Nonmedical Use of Opioids Following Short Term Therapeutic Exposure in Children and Youth: A Systematic Review and Qualitative Study of Decision Maker Information Needs

by

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Abstract

Introduction

Healthcare visits, hospitalizations, and deaths due to opioid-related harms continue to rise for children, despite an overall decline in opioid prescriptions. Decision-makers (including patients, families, clinicians, and policy-makers) require high quality syntheses to inform decisions regarding therapeutic opioid use. Further, previous research has identified that how systematic review results are presented may influence uptake by decision-makers. Evidence summaries may be appealing to decision-makers as they provide key messages in a succinct manner.

Objectives

1) To conduct a systematic review examining the association between short-term therapeutic exposure to opioids in children and youth and development of opioid use disorder (OUD) or nonmedical use, and 2) to gain perspectives from policy decision-makers on the usability and presentation of results through the form of an evidence summary.

Methods

We conducted a systematic review following methods recommended by Cochrane. A medical librarian conducted a comprehensive search and two reviewers were involved in study selection, data extraction and quality assessment. Studies were eligible if they reported primary research in English or French, participants had short-term therapeutic exposure to opioids before age 18 years, and outcomes related to nonmedical use of opioids and/or OUD. Results were described narratively.

For the qualitative study, decision makers were recruited through purposive and snowball sampling methods and participated in interviews to discuss an evidence summary based on the systematic review. Interviews were transcribed and data were analyzed using thematic analysis. Ethics approval was obtained for the qualitative study.

Results

Twenty-one American studies involving 49,944,602 participants were included. One study demonstrated that short-term therapeutic exposure may be associated with opioid abuse. Four others showed an association without specifying duration of exposure. Other studies reported on prevalence or incidence of nonmedical use after medical exposure to opioids. Identified risk factors were contradictory and remain unclear.

Interviews showed that decision makers had mixed preferences for the presentation of evidence, depending on their degree of involvement in research versus practice. A majority preferred having methods and key characteristics of studies included in the first page of the evidence summary. They noted that the summary should not be text-heavy and details should be appended. They commented on the need for and how to present recommendations in light of uncertain evidence.

Conclusions

A number of studies suggest there is an association between lifetime therapeutic opioid use (of unknown duration) and future nonmedical opioid use; however, there is limited evidence to determine whether short-term exposure is specifically associated with these outcomes. Policy

and decision-makers prefer a succinct evidence summary for this systematic review, with study-specific details provided as an appendix.

Preface

This thesis is an original work by Malema Ahrari.

Chapter 2 of this thesis has been submitted to a peer-reviewed journal as: Malema Ahrari, Samina Ali, Lisa Hartling, Kathryn Dong, Amy L. Drendel, Terry P. Klassen, Kurt Schreiner, and Michele P. Dyson, "Nonmedical Opioid Use Following Short-Term Therapeutic Exposure in Children and Youth: A Systematic Review".

I was involved in the study design and responsible for the acquisition, analysis and interpretation of data. I conducted the statistical analysis, led the drafting and critical revision of the manuscript, 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. Dyson and Hartling obtained funding, were involved in the study concept and design, provided study supervision, were involved in the acquisition, analysis, interpretation of data, provided support with statistical analysis, the drafting and critical revision of the manuscript, 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.

Dr. Ali obtained funding, was involved in the study concept and design, provided study supervision, was involved in the analysis and interpretation of data, and the drafting and critical revision of the manuscript.

Drs. Dong, Drendel, Klassen and Mr. Schreiner were involved in the study concept and design. All authors engaged in a critical revision of the manuscript for intellectual content, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

The research project under chapter 3 of this thesis received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Decision-maker Perspectives on Usability of Systematic Review Results: A Qualitative Study", No. 00095233, January 7, 2020.

Chapter 3 of this thesis may be submitted for publication as Ahrari, M., Dyson, M., Ali, S., and Hartling, L., "Short-term use of therapeutic opioids for children and future opioid use disorders: a qualitative study of decision-maker information needs." I was responsible for concept formation, data collection and analysis, and manuscript composition. Drs. Hartling, Dyson and Ali assisted with concept formation, data verification, and manuscript edits, with Dr. Hartling as the supervisory author.

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List of Abbreviations

aOR = adjusted odds ratio

CI = confidence interval

IQR = interquartile range

NMUPO = nonmedical use of prescription opioids

NR = not reported

OR = odds ratio

OD = overdose

OUD = opioid use disorder

RD = risk difference

RR = risk ratio/relative risk

SD = standard deviation

Chapter 1: Introduction

Opioids for Pain

Acute pain occurs suddenly, is sharp in nature, is typically caused by a specific event, such as surgery, burns, cuts and broken limbs; and is often temporary.[1,2] In contrast, chronic pain is considered a disease on its own, it is ongoing in nature and diagnosed if it persists or recurs for at least three months.[1] Experiences of pain can be influenced by social, biological, psychological and spiritual factors which ultimately influence diagnosis and treatment options.[1]

There is a broad range of acute pain therapies including: nonpharmacological therapies (e.g. heat, ice, massage, rest and psychological therapy); opioid pharmacotherapy; non-opioid pharmacotherapy (e.g. acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), some anticonvulsants and antidepressants); and multimodal therapy, which can include a combination of interventions and different opioid and/or non-opioid pain medications.[3]

Treating pain with non-opioid medication and nonpharmacological interventions can be successful in most post-operative, dental and primary care settings.[3] However, when first-line, non-opioid interventions do not provide adequate pain relief, opioids are then recommended and used for the effective management of acute moderate to severe pain.[4,5] The American Academy of Pediatrics' consensus statement on the assessment and management of children's pain recommends adding opioids to the pharmacologic management of acute pain, after acetaminophen and ibuprofen.[6] While non-opioid alternatives such as acetaminophen and NSAIDs are sufficient for managing mild pain, these medications are considered to be less potent analgesics than opioids and can offer inadequate pain relief for acute moderate to severe pain, where opioids are frequently needed.[7,8] The type of opioids that are prescribed vary by individual circumstances.

Opioid Crisis

The opioid epidemic, referring to the high rates of opioid-related overdoses, hospitalizations, and deaths, has been considered a national public health crisis in both Canada and the United States.[9,10] In 2020, 6,214 apparent opioid toxicity deaths were reported in Canada, claiming

approximately 17 lives per day.[11] Canadian youth and young adults have also been considered the fastest growing groups to be hospitalized as a result of an opioid overdose.[12]

In the first decade of the opioid crisis, a majority of deaths and overdoses were related to the nonmedical use of prescription opioids, mainly hydrocodone and oxycodone.[13,14] In the more recent decade, a majority of opioid related deaths have been caused by the use of heroin and illicit synthetic opioids due the lower cost and greater availability.[15,16,17]

Emergency department visits for opioid overdose have increased significantly during the COVID-19 pandemic.[18] Many communities across Canada experienced record high numbers of opioid-related hospital visits, emergency calls and deaths,[19] with a majority having occurred in the Territories, British Columbia, Alberta and Ontario.[11] Canadian data show a 23% increase in opioid-related poisoning hospitalizations when comparing a 9-month period in 2020 to the same period in 2019.[11] Comparably, data from the United States showed an increase by approximately 30% when comparing an 8 month period in 2020 to the same period in 2019.[20]

Given the deaths and morbidity recently associated with the opioid crisis, decreasing the use of prescription opioids has been recommended due to the risks of accidental death and overdose.[21] Further, emerging evidence suggests that for many conditions, NSAIDs may be sufficient, if dosed appropriately.[22-24] Health care providers have been under immense pressure to reduce opioid prescriptions, with Canada seeing an 18% decline in the overall quantity of opioids prescribed between 2012 and 2017.[25] The opioid crisis has created much controversy around the link between prescription opioids for acute pain and illicit drug use, to the extent that the concept of opioid-free emergency departments has also emerged.[26] At the same time, researchers have suggested that illicit opioids are causing the alarming opioid overdose rates, not prescription opioids, and that the decline of prescription drugs comes at a greater cost for some patients who are experiencing devastating effects of not being adequately treated for their pain.[27]

Pain Management in Children

It is now well understood that postoperative pain is experienced similarly in adults and children and that not treating children's pain in a quick and effective manner can lead to long-term adverse outcomes, both physically and psychologically.[7] However, managing pain in children

can be more challenging than in adults, with time constraints, lack of resources, knowledge gaps and concerns over safety resulting in consistent reports of suboptimal care.[28] While of opioids, oral morphine has the largest evidence base for children, the evidence base for other oral opioids is lacking, and optimal strategies for oral use, including for morphine, are contraversial.[29,30] Further, the risk of therapeutically exposing children to opioids for a short-term period remains unknown. The need for more studies on pain management for children has been consistently reported.[29,31]

Adolescents in particular, are a high risk group for nonmedical use of opioids, with higher rates of nonmedical opioid use, overdose, and opioid related deaths, in comparison to the general adult population.[3] Adolescents demonstrate greater risk-taking and novelty-seeking behaviours due to their still maturing brains. These behaviours may increase their risk of drug use and drug related problems.[32,33] With growing attention on the opioid epidemic, many parents express concerns about having their children exposed to prescription opioids due to the potential risk of nonmedical use or addiction.[34] This issue is unique to pediatrics, where parental factors, such as beliefs, can have a significant role in children's access to opioid medication. According to a National Survey conducted by the American Society of Anesthesiologists, more than half of parents expressed concerns of opioid addiction in relation to their children using opioids in a medical situation, however, a majority still thought that opioids were the best option for managing pain.[34] With the current stigma around opioid use, the under-treatment of pain and its associated short and long-term consequences cannot and should not be ignored.[35]

Gaps in Research

Currently, clinical and public opinions regarding the therapeutic use of opioids in children are polarized, and it is unknown if short-term therapeutic exposure is associated with later opioid use disorder (OUD) or nonmedical use.[36-43] Without this knowledge, clinicians and families are unable to weigh risks and benefits in an evidence-informed manner, and decision-makers lack reliable facts to inform decisions during an opioid crisis. Additionally, risk factors for misuse have not been examined in the context of short-term therapeutic exposure to opioids in childhood.[44,45-48,49,50] To date, studies focusing on the use of opioids for acute pain have looked

closely at the implications for persistent use. One study determined that 4.8% of opioid naïve youth and young adults who were prescribed opioids had persistent use after surgery.[51]

Filling the Gaps

In order to fill the current knowledge gaps relating to short-term exposure to opioids in childhood, we planned to conduct a systematic review, understand the best way to deliver the knowledge we gained and to effectively mobilize our findings for policy decision-makers to help inform policy, practice and/or potential future research investments.

Systematic reviews are one of the most robust methods of synthesizing evidence [52] and have been described as "the most reliable source of evidence to guide clinical practice."[53] They aim to provide a comprehensive synthesis of all relevant studies related to a specific research question through an extensive screening, data extraction, quality appraisal, validity assessment, and synthesis process. By following a precise and transparent methodology, systematic reviews aim to minimize bias through reproducible findings and therefore enhance the reliability of conclusions that are made.[53] Research funders often require systematic reviews for understanding the state of evidence and knowledge on a specific research topic.[53]

With respect to knowledge mobilization, the length and complexity of systematic reviews are often barriers for decision-makers who want to readily access research findings and use them to inform policies.[54] Evidence has shown that policy decisions are typically made without research evidence when time and resources are limited, when decision-makers lack research literacy or cannot access clear and relevant findings at the time they are needed, or when findings are not adequately contextualized.[55,56] Without being informed by research and evidence, public health policy decisions are at risk of being ineffective and may potentially have negative consequences. In order to evaluate how to mobilize knowledge effectively, we planned to develop an evidence summary and gather feedback from policy decision-makers using qualitative research methods.

Objectives

The objectives of this work were to conduct two studies: 1) a systematic review exploring the association between short term therapeutic opioid exposure in children and youth and

nonmedical opioid use that may follow; and 2) a qualitative study evaluating decision-maker perspectives on an evidence summary and their information needs.

Research Questions

The research questions addressed in the two studies presented in this thesis are as follows:

I. Systematic Review:

1) Is short-term therapeutic use of opioids in children and youth associated with future development of OUD or nonmedical use over their lifespan?

2) Are there high-risk predictive variables associated with the development of OUD or nonmedical use following short-term therapeutic opioid use in children and youth?

II. Qualitative Study:

3) What are decision-maker perspectives on the usability of an evidence summary?

4) What are decision-maker information needs?

Thesis Outline

This thesis includes two studies. Chapter 2 is the systematic review, which is undergoing journal peer-review. Chapter 3 is the qualitative study which has also been formatted as a stand-alone manuscript, with an intention to submit for publication in the near future. Overall, the goal of this work is to help provide an understanding of the association between short term opioid use in children's healthcare and nonmedical opioid use, and how to translate systematic reviews into a more user-friendly format for healthcare decision makers.

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Chapter 2: Systematic Review

Title: Nonmedical Opioid Use After Short-Term Therapeutic Exposure in Children: A Systematic Review

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Abstract

Context

Opioid-related harms continue to rise for children and youth. Analgesic prescribing decisions are challenging as the risk for future nonmedical opioid use or disorder is unclear.

Objectives

To synthesize research examining the association between short-term therapeutic exposure to opioids and future nonmedical opioid use or development of opioid use disorder (OUD) and identify associated risk factors.

Data Sources

11 electronic databases.

Study Selection

Two reviewers screened studies. Studies were included if: published in English or French; participants had short-term (≤14 days) or an unknown duration of therapeutic exposure to opioids before 18 years; and reported OUD or misuse.

Data Extraction

Data were extracted and methodological quality was assessed by two reviewers. Data were summarized narratively.

Results

We included 21 observational studies (49,944,602 participants). One study demonstrated that short-term therapeutic exposure may be associated with opioid abuse; 4 showed an association between medical and nonmedical opioid use without specifying duration of exposure. Other studies reported on prevalence or incidence of nonmedical use after medical exposure to opioids. Risk factors were contradictory and remain unclear.

Limitations:

A majority of studies did not specify duration of exposure, were of low methodological quality and participants may not have been opioid-naïve.

Conclusions:

Some studies suggest an association between *lifetime* therapeutic opioid use and nonmedical opioid use. Given the lack of clear evidence regarding short-term therapeutic exposure, healthcare providers should carefully evaluate pain management options and educate patients and caregivers about safe, judicious, and appropriate use of opioids and potential signs of misuse.

Introduction

Opioids are recommended and used for the effective management of acute moderate to severe pain not otherwise relieved by first-line interventions.[1,2,3] Between 1999 and 2019, nearly 450,000 Americans died from overdoses involving illicit and prescription opioids.[4,5] Emergency department visits for opioid overdose have increased by approximately 30% during the COVID-19 pandemic, when comparing an 8 month period in 2020 to the same period in 2019.[6]

Persistent use of opioids following therapeutic exposure among opioid naïve patients is an outcome that has been widely researched in recent years.[7-11] For example, Harbaugh et al., found that 4.8% of opioid-naïve youth and young adults had persistent opioid use after surgery.[7] Shah et al. determined that 5.3% of opioid-naïve adolescents and adults who filled an opioid prescription were likely to continue using opioids for one year or more; 3.6% had a probability of continued use if chronic non-cancer pain patients were excluded.[9] Still, risk factors for nonmedical use have not been examined in the context of short-term therapeutic exposure to opioids in childhood, to date having focused on personal and environmental characteristics.[12,13-16,17,18]

Currently, clinical and public opinions regarding the therapeutic use of opioids in children are polarized, and it is unknown if short-term therapeutic exposure is associated with later nonmedical use or opioid use disorder (OUD).[19-26] Without this knowledge, clinicians and families are unable to weigh risks and benefits in an evidence-informed manner, and decision-makers lack reliable facts to inform decisions during an opioid crisis. While nonmedical use of opioids and OUD are different entities, behaviours related to nonmedical use , such as taking opioids in greater quantities and durations than prescribed, have been recognised as precursors for the development of OUD.[27]

The purpose of this systematic review was to address 2 key questions: 1) Is short-term therapeutic use of opioids in children associated with future nonmedical use or the development of OUD over their lifespan?; and 2) Are there high-risk predictive variables associated with the development of nonmedical use or OUD following short-term therapeutic opioid use in children?

Methods

This systematic review was conducted according to methodological standards defined by Cochrane[28] and the protocol was registered (PROSPERO registration #: CRD42019122681). This study was exempt from ethics approval.

Search Strategy

A medical research librarian developed the search strategy, which was peer reviewed by a second librarian. Eleven databases were searched from inception to May 12, 2019 (updated September 4, 2020), 5 of these were key grey literature sources (supplement e-methods 1 and e-table 1). Reference lists of relevant and included studies were checked and primary authors were contacted as necessary. Scopus and Google Scholar were used to conduct a forward citation search based on included studies.

Study Selection

Screening forms were developed and piloted by the review team (MA, MD and LH) (Appendix 1). Two reviewers (MA and a research assistant/MD) independently assessed all titles and abstracts, and potentially relevant full-texts, for inclusion. Discrepancies were resolved through discussion, and with a third reviewer (MD/LH) when needed. Eligibility criteria included: 1) publication in English or French; 2) report of quantitative primary research; 3) study participants had short-term (≤14 days) therapeutic exposure to opioids before the age of 18 or during school years (K-12); and 4) studies reported on OUD (encompassing the older terms opioid addiction and abuse)[29] or misuse (See Table 1 for definitions). Through discussion and consensus, the review team included one study with short-term exposure for a median of 17 days.[30] Where the duration of exposure was unclear, studies were included provided there was no definitive language confirming long-term therapeutic exposure to opioids.

Data Extraction

Data were extracted by 1 reviewer (MA) using a standardized form (Appendix 2) and verified by a second reviewer (research assistant/MD). Discrepancies were discussed and resolved by a third party when necessary (MD/LH). Data were extracted on study and population characteristics

(e.g., setting, age, ethnicity/race), exposure characteristics (e.g., duration, dose), risk factors, and outcomes and results (e.g., timing, follow up period, effect estimate).

Quality Assessment

Methodological quality of included studies was independently assessed by 2 reviewers (MA and LH/MD) using the National Institute of Health (NIH) Quality Assessment Tool for Observational and Cross Sectional studies.[31] Disagreements were resolved through discussion.

Synthesis of Results

Studies were grouped into comparative and non-comparative designs. Odds ratios, risk ratios and risk differences were extracted from comparative studies or calculated using Review Manager 5.3 to provide consistent measures across studies. Data were not pooled due to methodological, clinical and statistical heterogeneity; as a result, data were summarized narratively.[28] Prevalence and incidence rates from the non-comparative studies are presented. Risk factors were extracted as reported by authors and summarized narratively; where available, measures of association were included.

Results

Study Selection

We identified 5,219 unique citations, of which 21 studies reported in 22 publications met our inclusion criteria (Figure 1). Reasons for exclusion are described in Figure 1.

Study characteristics

Table 2 provides a summary of included studies; details for each study are provided in Tables 3 and 4. Based on studies reporting sample size, sex distribution and age, 49,944,602 children and youth were analyzed (young adults were also included in the total population count where the youth population could not be separated)[32]; 48.4% were female and the mean age was 15.7 years. Fifteen studies were conducted exclusively in pediatric or high school populations (including 18-year olds),[19,22-24,30,33-43] while 6 studies included both children/youth and adults.[32,44-48]

Methodological Quality

A majority of the included studies were assessed as having lower methodological quality; however, they were largely designed to address different types of research questions. Quality scores ranged from 6 of 14 to 13 of 14 (see Tables 3, 4 and Supplement e-table 2). Common methodological limitations were self-reporting of exposures and outcomes, no specification of the duration of exposure, and cross-sectional designs.

Comparative Studies

Of the 5 comparative studies, 1 explored the association between short-term therapeutic exposure and opioid abuse:[45] individuals (including adults and youth; mean age 21.8 [standard deviation: 2.4] years) who were prescribed opioids were significantly more likely to have a diagnosis of abuse within 365 days than those who were not exposed (adjusted absolute risk difference 5.3%, 95% CI 5.0%-5.7%; [a]RR 15.1, 95% CI 12.4-18.3). Within the opioid-exposed cohort, those aged 22 to 25 were less likely to be diagnosed with opioid abuse at 1 year than those aged 16 to 18 years ([b]aOR 0.8 (95% CI 0.7-1.0)). Asian race was associated with lower odds of abuse compared with White race ([b]aOR 0.3 (95% CI 0.2-0.6)); female sex ([b]aOR 11.5 (95% CI 9.4-14.8)) and previous non-opioid substance abuse ([b]aOR 4.5 (95% CI 3.4-5.9)) were associated with higher odds of abuse.

The other 4 studies did not specify the duration of therapeutic exposure to opioids; however, each reported an association between therapeutic opioid exposure and future nonmedical use of opioids. McCabe et al. (2013a)[22] found that adolescents who reported past year medical exposure to opioids in year 1 were significantly more likely to have subsequent nonmedical opioid use in year 2, compared to those with no medical exposure ([a]RR 2.36, 95% CI 1.28-4.37). McCabe et al. (2016)[19] showed that those who had any medical use of opioids by age 18 were significantly more likely to have past-year nonmedical opioid use at age 35 compared to those who had no medical or nonmedical use at age 18 ([a]RR 1.83, 95% CI 1.15-2.89; [b]aOR 1.74, 95% CI 1.10-2.76). Miech et al. reported a significant association between receipt of a prescription opioid by grade 12 and future opioid misuse by age 23 ([b]RR 1.33, 95% CI 1.04-1.7); this association was strongest among individuals generally considered to be at lower risk for opioid misuse (i.e., those with little or no prior drug use, and who disapproved of marijuana use).[33] Osborne et al. found that youth who indicated that they had lifetime medical use of prescription

opioids had an increased risk of past 30-day nonmedical opioid use (i.e., use of their own opioids in a manner other than directed or opioids from another person) ([a]RR 2.72, 95% CI 1.76-4.22)[34] (Table 3).

[a]Calculated by review team, [b]Calculated by study authors

Non-Comparative Studies

A majority of the non-comparative studies reported prevalence of nonmedical opioid use following past therapeutic exposure of unknown duration; 2 of the 16 studies indicated that the study sample had short-term therapeutic exposure to opioids.[30,35,42] Bell et al. found that within a cohort of adolescent trauma patients, 11% of patients discharged with a prescription for opioids received an opioid antagonist injection and 8% were given an overdose diagnosis over the five year study period.[35] Chung et al. identified 437 opioid-related adverse events (emergency department visit, hospitalization, or death) out of 1,362,503 prescriptions in children aged 2 to 17 years (cumulative incidence 38.3 of 100,000 prescriptions); 71 of the events (0.005% of total prescriptions dispensed and 16% (71 of 437) of total adverse events) were attributed to abuse or self-harm (all in youth aged 12 to 17).[30]

Across non-comparative studies, nonmedical use prevalence rates among those with medical exposure to opioids ranged from 0.005% to 36%, with a median of 27.8% (IQR: 20.1% - 30.7%; Table 4). However, this corresponds to a wide range of circumstances. Three studies measured nonmedical use of opioids among those who had been prescribed opioids (20.1%-36%);[23,24,36] 1 assessed the proportion of past-year nonmedical misusers whose only source of misuse was their prescription (14.4%).[37] Wei et al. examined 10-year trends in incident cases of OUD/OD, and reported annual rates of individuals who had received a prescription in the year prior (22.6%-34.1%).[46] There was a significant decrease in the proportion of youth receiving prescription opioids prior to being diagnosed with OUD/OD between 2006 and 2016 (P value for trend = 0.001). The lowest value (0.005%) represents adverse events (emergency department visit, hospitalization, or death) as a result of abuse or self-harm from opioid prescriptions dispensed over a 5 year follow-up period.[30] Bell et al. also reported on opioid overdoses, with prevalence rates of 7.6% for an overdose diagnosis and 10.8% for an opioid antagonist injection over a 5 year period after being prescribed an opioid.[35] These values can be contrasted with prevalence

rates among samples including individuals who were and were not medically exposed to opioids: median 2.6% (IQR 1.3%-4.3%).

Risk Factors

Age, sex/gender, race/ethnicity and previous substance abuse were commonly explored risk factors within the studies we included; however, results were inconsistent across and sometimes within studies. The impact of age was most constant, with 3 studies reporting that older adolescents were at higher risk of nonmedical opioid use than younger children and young adults.[30,35,45] Two studies determined that females were more likely to have nonmedical use than males,[34,37] although 6 did not find a difference.[24,30,32,33,35,43] Four studies examined previous substance abuse as risk factors for nonmedical prescription opioid use, but differed markedly in variables measured and analytic approaches used. Miech et al.[33] determined that students who were at lower risk for opioid misuse (i.e., had the least experience with illegal drug use and strongly disapproved of the use of marijuana) had the strongest association between prescription opioid use and nonmedical use after high school, while Schroeder et al.[45] found that those with previous non-opioid substance abuse were at higher risk of opioid abuse. Bell et al. found no association with a positive drug or alcohol screen upon admission.[35] All studies examining race/ethnicity found a significant effect, although findings differed: three studies found that Caucasians were more likely to misuse opioids than Asians[45], African-Americans,[24] and racial/ethnic minorities,[33] while two others found that African-Americans were more likely to misuse than Caucasians.[35,39] Currently, the evidence related to risk factors for nonmedical opioids use or OUD following short-term therapeutic exposure is unclear (Figure 2 and e-table 3).

Discussion

Summary of evidence

There is limited evidence to determine whether *short-term* therapeutic exposure to opioids in childhood is definitively associated with future nonmedical opioid use or development of an OUD; however, this review suggests a link between *lifetime* therapeutic opioid use (unknown duration) and nonmedical opioid use. The existing evidence on risk factors for nonmedical opioid use or OUD following short-term therapeutic exposure is unclear, however, older

adolescents with short-term therapeutic exposure during their lifetime may be at higher risk of nonmedical use than younger children.

Clinical implications

There is a great deal of emerging research related to the harms associated with the therapeutic use of opioids; however, we were unable to clearly answer our original question. Current research has focused on the use of opioids in adult populations, where the evidence suggests that a prescription for opioids for a long duration put adults at risk of future nonmedical opioid use.[49] Data specific to pediatrics is scarce, and to date, has largely relied upon cross-sectional, self-reported evaluations of usage patterns. Prospective studies are urgently needed in the area of acute pain, to help inform decisions in emergency departments, ambulatory clinics and following surgeries.

The study by Miech et al. has been widely cited and has generated much controversy, as the group at most risk for opioid misuse following therapeutic exposure were those who would typically be least expected of being at risk: those with little to no history of prior drug use and with strong disapproval of illegal drug use. Miech et al. acknowledge that "their results do not support legitimate opioid prescription use, by itself, as a major contributor to chronic opioid misuse".[33] Hence, healthcare providers should not use these conclusions as a basis for limiting prescribing where opioids are needed, but rather, ensuring some risk screening (i.e. for pre-existing OUD at minimum), judicious prescribing and disposal mechanisms are in place. With the current stigma around opioid use, the under-treatment of pain and its associated short and long-term consequences cannot and should not be ignored.[50]

A broad framework for evidence-based prescribing post-surgery identifies 3 key areas of responsible opioid prescribing: recognizing that prescription opioid use is associated with short and long-term risks; optimizing pain management in the peri-operative phase using alternative non-opioid medication where possible; and educating families and patients about managing pain and using opioids safely before and after surgery.[51] While evidence-based guidelines and validated risk screening tools for the use of opioids for children of all ages with acute pain are lacking, other resources may help guide decision-making on the use of opioids such as Health

Quality Ontario guidelines for prescribing opioids for acute pain for ages 15 and older[52] and the World Health Organization's guidelines for prescribing opioids for chronic pain.[53] The use of resources by caregivers and prescribers (e.g., brochures developed by the Institute for Safe Medication Practices Canada)[54] may help navigate the challenging conversations with patients and families around opioid risks and use.

Our systematic review captures studies published up until September 4, 2020 and as a result, would not take into consideration the evidence based on any newly published studies. For example, we did not include the 2021 study by Hadland et al. that reported on incidence rates of OD and OUD ranging from 0.1% to 0.3% among youth and adults who had acutely painful conditions and were therapeutically exposed to opioids.[55] Nonetheless, these new findings would fall within the nonmedical use prevalence and incidence rates that we observed in our sample, which ranged from 0.005% to 36%.

This review provides a rigorous and comprehensive synthesis of the current literature, however there were few studies that directly addressed our research question. Further, there were a number of limitations with the existing evidence. First, study samples may not have been opioid-naïve. Only 3 studies evaluated short-term exposure to opioids, of which, only 1 had a non-exposed comparison group.[45] None of these studies were able to fully control for opioid-naivety. Studies that did not specify the duration of exposure were also included, unless there were clear indications of long-term exposure, such as long-term use of opioids for chronic conditions; therefore, our sample may have included some participants with longer term exposure, or excluded those who had chronic pain and were opioid-naïve. Many studies focused on past year medical exposure rather than lifetime exposure and did not have measures in place to ensure that therapeutic exposure preceded opioid misuse at any point during one's lifetime.

A second limitation is that exposure may have occurred during adulthood. Many of the surveys were conducted in high schools, where some of the participants were already 18 years old and therefore could have been exposed therapeutically in adulthood.[19,22-24,33,34,36,37,41] Similarly, the most robust comparative study reported on associations for the entire sample, which included youth and adults, and was not broken down by age group.[45] A third challenge in synthesizing this

literature was inconsistency in outcome measurement and terminology. Some studies only captured past year or past 30-day misuse, potentially underreporting the prevalence of opioid misuse. Studies also reported a number of outcomes such as addiction, abuse, overdose, self-harm, nonmedical use, medial misuse, diversion, opioid specific substance use disorder and opioid use disorder. While a majority fall under the umbrella terms misuse and nonmedical use, they capture variable information. Fourth, a majority of the studies were considered of poor quality due to their cross-sectional design, reliance on self-reporting, inadequate measures for ensuring short-term therapeutic exposure preceded outcome, lack of controlling for confounders, and not having a comparator group.

Finally, our included studies may be limited with respect to their generalizability. Some studies using clinical samples relied on commercial[45] and/or Medicaid[30,46] insurance claims. Data from other service providers (such as Emergency Medical Services and the police), or opioid-related adverse events where medical attention was not sought were not routinely reported. Further, the risk of misuse may vary based on location of exposure (e.g., within a controlled hospital setting versus going home with prescribed opioids). None of the included studies reported risk of nonmedical opioid use following short-term exposure in a controlled setting.

Research Implications

In order to assess potential harms from short-term therapeutic opioid use, future research is needed in which studies: reliably assess and report duration of opioid exposure, dosage, preparation type, and setting; compare those exposed to an unexposed group; control for opioid-naivety at baseline (i.e., no prior long- or short-term therapeutic and/or non-therapeutic exposure); differentiate between reasons for nonmedical use (e.g., for pain or pleasure); rigorously assess risk factors; and evaluate the potential misuse associated with exposure to different opioids, as some may put patients at higher risk of misuse than others.[56] Existing administrative data may be more effectively utilized via record linkage to help construct more comprehensive datasets. The use of artificial intelligence, including machine learning, may also provide an opportunity to identify risk factors for misuse.[57]

Conclusions

There is limited evidence to determine whether short-term exposure is specifically associated with OUD or nonmedical use of opioids; however, a number of studies suggest an association between lifetime therapeutic opioid use and nonmedical opioid use. There is also limited evidence to identify risk factors for OUD or nonmedical use following short-term therapeutic exposure. Rigorous studies are needed to examine the association between short-term therapeutic exposure in children and nonmedical opioid use or the development of an OUD. Until the risks are more clearly defined, it is recommended that prior to prescribing short-term opioids, healthcare providers carefully consider the risks, benefits and alternatives, and educate patients and caregivers about safe, and appropriate use and when to seek reassessment.

Figures and Tables

Figure 1. PRISMA flow diagram

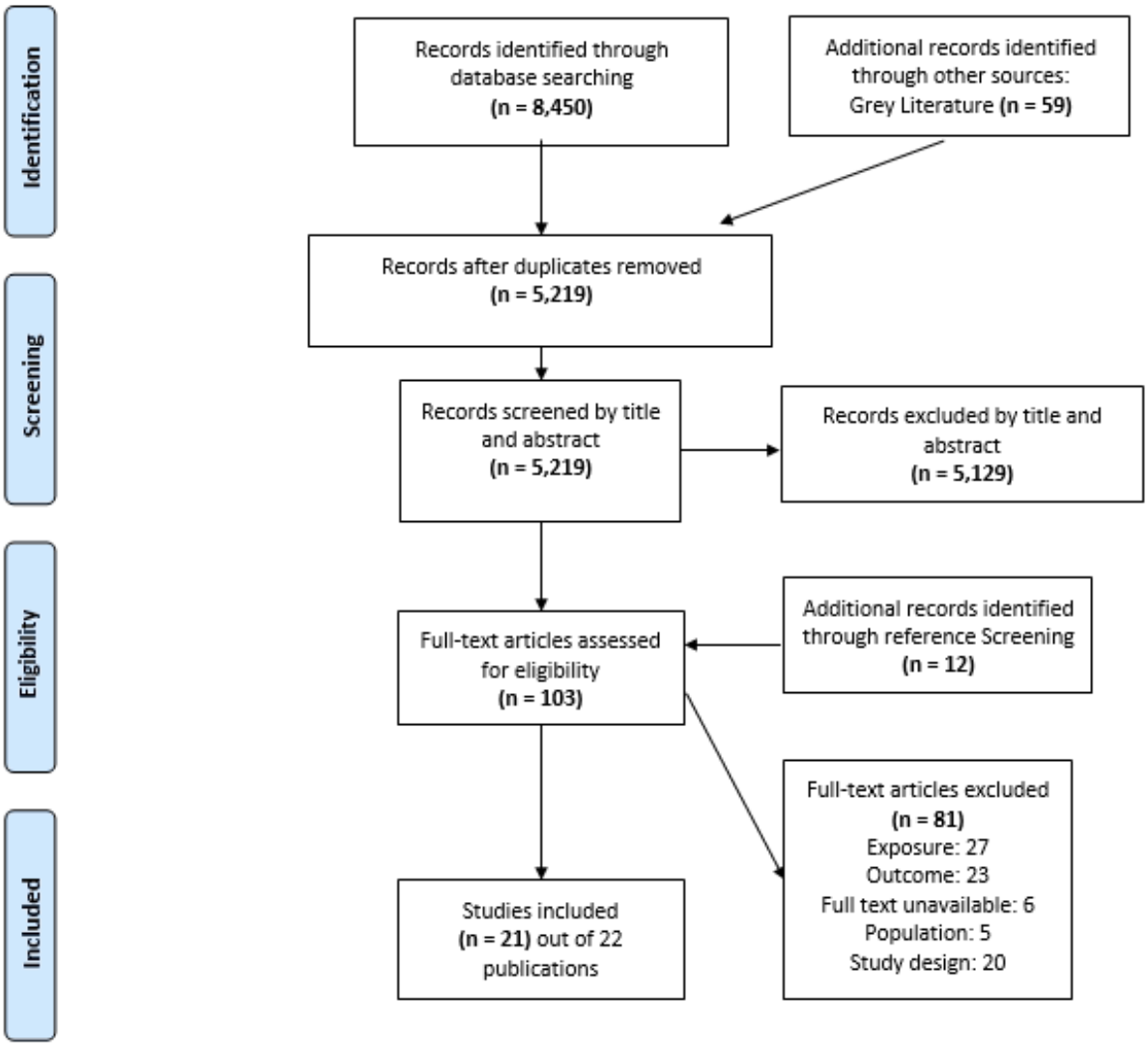
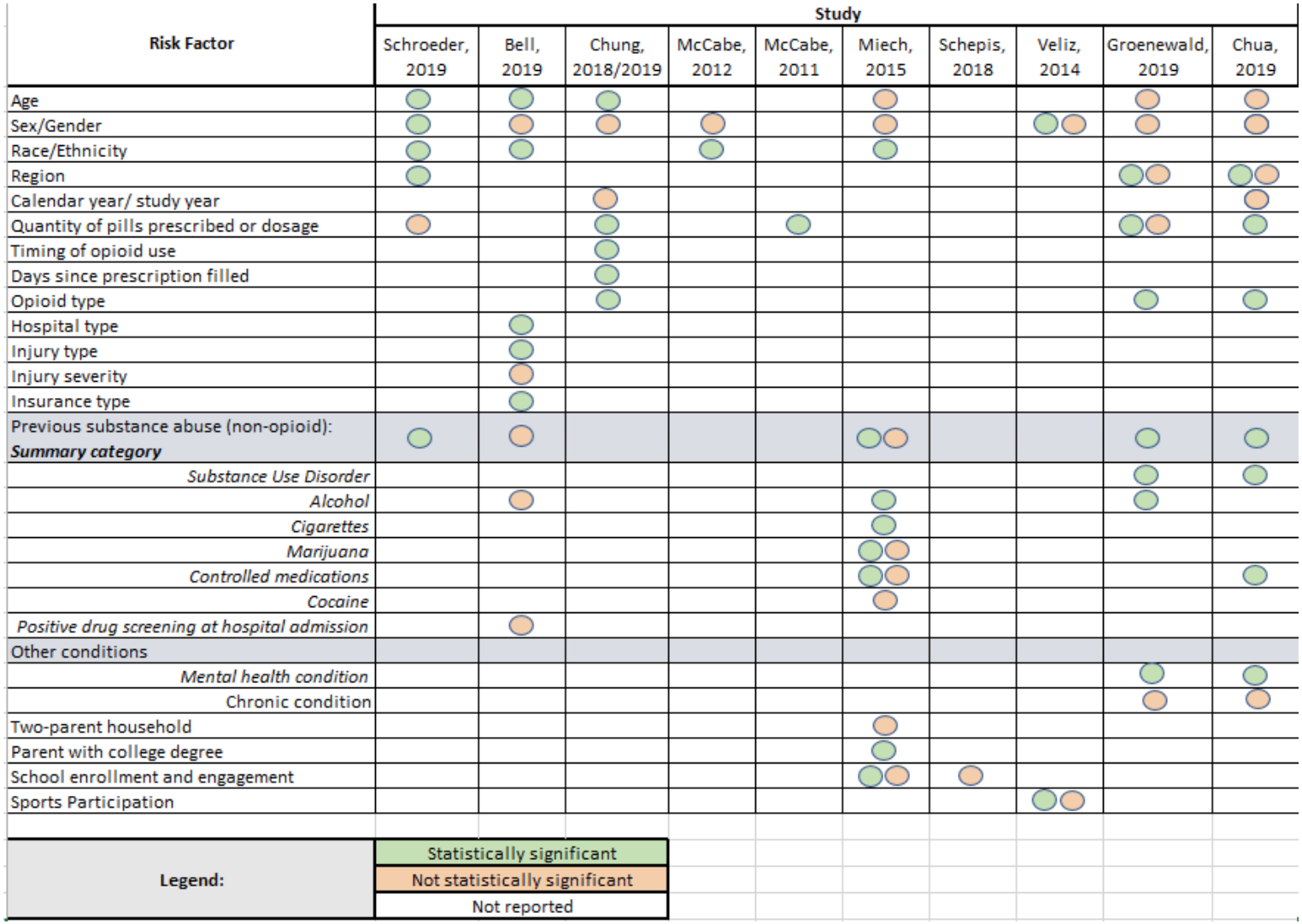


Figure 2: Risk Factors for Nonmedical Prescription Opioid Use by Statistical Significance



The substance abuse summary row includes the data from each of the seven rows below.
Additional details available in supplemental e-table 4.

Table 1: Glossary

Term	Definition
Opioid use disorder (OUD)	OUD is defined in the DSM-5 as a problematic pattern of opioid use leading to clinically significant impairment or distress.[27] The presence of at least two symptoms indicates an OUD.
Opioid addiction	"Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases."[58]
Opioid dependence	"A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist."[59]
Opioid misuse	"Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not."[60]
Opioid abuse	"The intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness, e.g., getting high."[60] This term is no longer used, however it is referenced here and used in the manuscript when it was the outcome of interest in one of the included studies.[61]
Nonmedical use of prescription opioids	The use of opioids "without a prescription or use that occurs simply for the experience or feeling the drug causes"[62]

Table 2: Summary of Included Studies (n=21)

Study Characteristics	N	%
Study Design		
Non-comparative	16	76.2
Prospective Cohort	4	19.0
Retrospective Cohort	5	23.8
Cross-Sectional	12	57.1
Gender		
Female[a]	N/A[a]	48.4[a]
Mean Age[b]	15.5	N/A[b]
Study Setting		
School	9	42.9
Home	2	9.5
Dental	1	4.8
Trauma centre	1	4.8
Entertainment venues	1	4.8
Other	7	33.3
Duration of Opioid Exposure Specified	3	14.3
Outcomes Reported		
Misuse/Nonmedical Use	12	57.1
Overdose	6	28.6
Abuse	1	4.8
Opioid Use Disorder	2	9.5
Country - USA	21	100

[a] Sex breakdown reflects 12 studies and includes some adult populations as some studies did not present the sex distribution by age.
[b] Mean age was calculated across eight studies where such a calculation was possible.

Table 3: Key Characteristics and Results of Comparative Studies (n=5)

Author, publication year Study Years	Study design Clinical setting	No. of participants analyzed (% female) Age, y Duration of exposure	Measurement/definition of OUD or misuse Timing of outcome assessment	Misuse Prevalence	Main Results: Exposed vs unexposed group comparison	Quality Assessment Score (NIH tool)[a]
Short-term exposure						
Schroeder, 2019[45] 2015	Retrospective cohort (with age- and sex-matched controls) Dental	44,664 (53%) 16-25 (included subgroup analysis for ages 16-18) 3 days (IQR 3 to 5)	ICD-9 or ICD-10 codes associated with opioid abuse within medical records Within 12 months after exposure	115 of 1814 (6.3%) subjects aged 16-18 who were prescribed opioids were diagnosed with opioid abuse within 365 days. (All therapeutically exposed to opioids)	Opioid abuse-related diagnosis (total sample): • Opioid exposed: 866 of 14,888 (5.8%) • Opioid non-exposed: 115 of 29,776 (0.4%) Adjusted absolute RD: 5.3% (95% CI, 5.0%-5.7%; P<0.001) [Estimates adjusted for race/ethnicity and previous non-opioid substance abuse] RR=15.1 (95% CI, 12.4-18.3)[b]	13/14
Unknown duration of exposure						
McCabe, 2016[19] 1976-2013	Prospective cohort Surveys at school (*Monitoring the Future*); follow-up questionnaires at age 35	4,072 (57%) Modal age 18 NR	Survey question on lifetime NMUPO 17 years later (at age 35)	Past-year prevalence of NMUPO at age 35 among those with: No medical use or NMUPO at 18: 72/3,014 (2.4%) Appropriate medical use only at 18: 23/527 (4.4%). (All therapeutically exposed to opioids)	Nonmedical use at age 35: • No medical use or NMUPO at 18: 1.0 (reference) • Medical use only at 18: aOR 1.74 (95% CI, 1.10-2.76; P<0.05) Adjusted for race/ethnicity, sex, geographic region, urbanicity, parental education, substance use, and cohort year (age 18) RR: 1.83 (95% CI, 1.15-2.89)[b]	9/14

					RD: 1.98% (95% CI, 0.15%-3.80%) [b]	
McCabe, 2013a[22] 2009-2011	Prospective cohort Online survey (Secondary Student Life Survey) administered in two Southeast Michigan school districts	1,928 (50% at time of enrollment) Grades 7-11 NR (ranges from 0 to ≥40 occasions)	Survey question on occasions of misuse in past 12 months	Of those who had appropriate medical use of prescription opioids in year 1, 7.0% (12/172) reported any NMUPO in year 2. (All therapeutically exposed to opioids)	NMUPO in Year 2: • No use in Year 1: 46 of 1,556 (3.0%) • Medical use in Year 1: 12 of 172 (7.0%) RD= 4.0% (95% CI, 0.1%-7.9%) [b]; RR=2.36 (95% CI, 1.28-4.37)[b]	10/14
Miech, 2015[33] 1990-2012	Prospective Cohort Survey/questionnaires (*Monitoring the Future*) administered in classrooms	6,220 (NR) Grade 12 NR	Survey question on opioid misuse in past 12 months Annually from age 19 to 23	502/6220 (8.1%) reported opioid misuse. (Includes opioid exposed and unexposed group)	Risk of opioid misuse at 23 years following opioid prescription in grade 12: RR 1.33 (95% CI, 1.04-1.7; P<0.01) [Adjusted for sex, race, parent education, use of other substances, course marks, and disapproval of marijuana use] Based on a stratified analysis, the association varied based on predicted probability of opioid misuse, where the largest association was in lower risk strata.	7/14
Osborne, 2019[34] 2008-2011	Cross-sectional 10 US Metropolitan areas; recruited from entertainment centers for survey that took place at same venue (National Monitoring of	10,965 youth provided responses to the survey (52%) 10 to 18 NR	Survey question on misuse in past 30 days Past 30 days	22/526 (4.1%) of those who reported lifetime medical use of prescription opioids also reported past 30-day NMUPO. (All therapeutically exposed to opioids)	Past 30-day NMUPO: • No lifetime medical use of prescription opioids: 153 of 9,955 (1.5%) • Lifetime medical use of prescription opioids: 22 of 526 (4.1%) RR 2.72 (95% CI, 1.76-4.22)[b]	6/14

	Adolescent Prescription Stimulants Study)				RD 2.65% (95% CI, 0.92%-4.37%)[b]	

[a] Questions that were not applicable to the study or its design did not count negatively towards the score, more details available in Supplemental e-table 2.
[b] Calculated by review authors
Abbreviations: aOR = adjusted odds ratio, CI= confidence interval, IQR = interquartile range, NMUPO = nonmedical use of prescription opioids, NR = not reported, OR = odds ratio, OUD = opioid use disorder, RD = risk difference, RR = risk ratio/relative risk

Table 4: Key Characteristics and Results of Non-Comparative Studies (n=16)

Author, publication year Study Years	Study design Clinical setting	No. of participants analyzed[a] (% female)[b] Age, y Duration of Exposure	Measurement/definition of OUD or misuse Timing of outcome assessment	Results: Opioid Misuse Incidence or Prevalence [c]	Quality Assessment Score (NIH tool)[d]
Short-term exposure					
Bell, 2019[35] 2011-2013	Retrospective Cohort Level I trauma centers (1 pediatric and 1 adult center)	736 (26%) 12 to 18 (mean age: 14.6) NR (included patients hospitalized for injury; 88% had length of stay ≤7 days)	Overdose based on ICD-9/10 codes; opioid antagonist administration measured using medical record data Measured within 5 years after exposure	51 of 668 (7.6%) were given an overdose diagnosis over the 5-year follow-up period 72 of 668 (10.8%) had an opioid antagonist injection. (All therapeutically exposed to opioids)	11/14
Chung, 2018 & 2019[30,42] 1999-2014	Retrospective Cohort State Medicaid files; indications for opioid prescriptions were: 31% dental, 25% outpatient procedure/surgery, 18% trauma, 17% minor infections	1,362,503 outpatient prescriptions for opioids filled (52%) 2 to 17 Median 17 days (IQR 16-19)	Medical records with coded diagnoses indicating adverse event or symptoms consistent with opioid overdose Assessed all prescriptions filled between 1999 and 2011 Minimum of 1 year after exposure	Opioid-related adverse events: 437 of 1,362,503 (0.03%). Adverse events include opioid-related emergency department visit, hospitalization, or death (71.2% were not related to misuse). 71 of 437 (16%) cases of adverse events were attributed to abuse or self-harm; all occurred among adolescents (ages 12-17). Total misuse prevalence: 71 events of 1,362,503 (0.005%) prescriptions. (All therapeutically exposed to opioids)	11/14
Unknown duration of exposure					
Boyd, 2006[36] 2003	Cross-sectional Online survey, administered to a Detroit public school district	1,017 (50%) 10 to 18 (mean age: 13.7) NR	Survey question on occasions of nonmedical use in past 12 months.	94 of 262 (36%) with prescribed use also had nonmedical use. Past year nonmedical use (lifetime medical use of pain medication vs. no medical use): aOR: 9.80 (95% CI, 5.86-16.39). [Adjusted for gender, race, grade level]	7/14

Burke, 2020[47] 2011 - 2014	Retrospective Cohort Massachusetts Chapter 55 data set (includes a variety of databases, registry records, and toxicology reports)	27,745 (ages 11-17) (55.3% - includes adult sample) 11 to 85+ (mean age: 49.1) (included subgroup analysis for age 11- 17, which is the data used for this review) 66.4% (across entire population) received opioids for <1 month	Medical claims and emergency department records for OUD or OD, pharmacy claims for medications. 12 months to 4 years	OUD Hazard ratio for ages 11 to 17: 0.35 (0.28–0.43); P<0.001 Non-fatal OD hazard ratio: 0.29 (0.09–0.89); P=0.03 Fatal OD hazard ratio: 0.23 (0.03–1.65); P=0.14 *Reference group: 45-54 years Results were considered significant by study authors at P<0.007	11/14
Chua, 2019[32] 2009 - 2017	Retrospective Cohort IBM MarketScan Commercial Claims and Encounters database	14,399,799 person-days (reflects "no recent opioid use group" (52.8% female - reflects total population of study, including recent use group) 12 to21 (mean age: 17.2, SD 2.5) – reflects total population of study	Medical claims with ICD-CM 9 or 10 codes for OD Within study years	Overdose occurred on 119 person-days of 14,399,799 person-days (0.001%) contributed by the "no recent opioid use" group. (All therapeutically exposed to opioids)	12/14
Groenewald, 2019[43] 2007 - 2015	Cross-sectional US commercially insured population (Truven MarketScan databases of Commercial Claims and Encounters database)	1,146,412 (50.6%) 11 to 17 (modal age: 17) NR (up to 90 days of exposure)	ICD 9 codes for OD Median period of observation: 1.75 years (IQR 0.7-6.7 years)	725 individuals of 1,146,412 (0.06%) had an opioid overdose event Cumulative incidence rate of opioid overdose for the total sample: 28 overdose events (95% CI, 26–31) per 100,000 observed person-years (All therapeutically exposed to opioids)	12/14

Hudgins, 2019[48] 2015 and 2016	Cross-sectional National US survey, computer-assisted with interviewer, in residence (National Survey on Drug Use and Health)	27,857 adolescents (52% - includes adult sample)[63] 12 to 25 (included subgroup analysis for adolescents 12 – 17, providing the data used for this review) NR	Survey questions on nonmedical use and sources of prescription opioids (DSM-IV criteria used for substance specific SUD) Past year nonmedical use	19.2% (95% CI, 16.4–22.1) of adolescents who were misusing opioids had obtained them from a single physician source and 2.2% (95% CI, 1.3%–3.2%) obtained them from multiple physicians (based on extrapolated population estimates)	7/14
McCabe, 2013b[37] 2007-2010	Cross-sectional National US survey (Monitoring the Future study), paper-based surveys administered in classrooms	8,888 (53%) Modal age: 18 NR (ranges from 0 to ≥40 occasions)	Survey questions on occasions of misuse in past 12 months and in lifetime.	104 (14.4%) of those with nonmedical use of opioids indicated use from previous prescriptions only. (Calculations were based on weighted samples)	7/14
McCabe, 2012[24] 2007-2009	Cross-sectional National US Survey (Monitoring the Future Study), paper-based surveys administered in private and public high schools	6,673 (48%) Modal age: 18 NR (ranges from 0 to ≥40 occasions)	Survey questions on occasions of misuse during lifetime (before age 18)	287 of 6,673 (4.3%) reported lifetime medical exposure to prescription opioids prior to nonmedical use (total sample includes opioids exposed and unexposed). 287 of 908 (31.6%) reported lifetime medical exposure to prescription opioids prior to nonmedical use (all were therapeutically exposed to opioids). 621 of 6,673 (9.3%) reported receiving a prescription for opioids and only using it for medical purposes.	7/14

McCabe, 2011[23] 2009-2010	Cross-sectional Internet survey administered to two Southeastern Michigan school districts	2,597 (51.1%) 11 to 19 (mean age: 14.8, SD 1.9) NR (ranges from 0 to ≥40 occasions)	Survey question on occasions of medical misuse	74 of 369 (20.1%) individuals that were prescribed opioid pain medication in the past-year reported past year medical misuse. 67 of 369 (18.2%) reported taking too much and 34 of 369 (9.2%) reported that they intentionally got high or used to increase alcohol or other drug effects.	7/14
Schepis, 2019[38] 2009-2014	Cross-sectional National US Survey, audio computer-assisted self-interviewing, site of administration not specified (National Survey on Drug Use and Health)	103,920 (49%) 12 to 17 NR	Survey questions on nonmedical use in past 30 days (DSM-IV criteria used for substance-specific SUD)	447 of 103,920 (0.4%) reported misusing prescription opioids from a physician source only (total sample includes opioid exposed and unexposed group). Of those who misused opioids from physician sources only, 12.9% (95% CI, 9.5%-17.4%) had an opioid specific substance use disorder, 5.2% (95% CI, 2.9%-9.0%) had opioid abuse and 7.7% (95% CI, 5.5%-10.8%) had opioid dependence.	7/14
Schepis, 2018[44] 2015	Cross-sectional National US survey, computer-assisted self-interviews, site of administration not specified (National Survey on Drug Use and Health)	13,585 adolescents (49%) 12 to 25 (included subgroup analysis for ages 12 to 17, providing the data for this review) NR	Survey question on medical misuse in past 12 months	165 of 12,738 (1.3%) had reported opioid misuse in the past year. (Includes opioid exposed and unexposed sample)	7/14
Schepis, 2009[39] 2005-2006	Cross-sectional National US survey, administered in homes (National Survey on Drug Use and Health)	36,992 (NR) 12 to 17 NR	Survey questions on medical misuse at any point during lifetime	477 of 36992 (1.3%) of the total sample (opioid exposed and unexposed) reported opioid misuse from a physician source. 22.2% of those who misused opioids had obtained them from a physician, the remainder had obtained opioids from non-physician sources.	7/14
Veliz, 2014[40]	Prospective cohort	1,494 (50.3%)	Survey question on occasions of medical misuse	Medical misuse (using too much): ≥1 occasion: 74 of 1,494 (5.0%) ≥3 occasions: 27 of 1,494 (1.8%)	9/14

2009-2012	Web-based survey administered within 2 middle schools and 3 high schools in Michigan	Year 1: 11 to 17, mean age: approximately 14 NR (ranges from 0 to ≥40 occasions)	Measured annually over a three-year period	Medical misuse (to get high): ≥1 occasion: 40 of 1,494 (2.7%) ≥3 occasions: 10 of 1,494 (1.8%) (Includes opioid exposed and unexposed sample)	
Vosburg, 2016[41] NR	Cross-sectional Massachusetts Recovery High Schools (in classroom)	31 (29%; reflects 28 participants) Mean age: 18 (+/- 2 years) NR	Self-report on opioid abuse and addiction Entire sample had outcome of interest (i.e., students all had a lifetime history of prescription opioid abuse)	3 of 31 (9.7%) who had prescription opioid abuse (i.e., used medication to get high) and 3 of 18 (16.7%) who had prescription opioid addiction (i.e., inability to stop using) reported that they first obtained the prescription opioids therapeutically	6/14
Wei, 2019[46] 2005-2016	Cross-sectional US commercially insured population (Truven MarketScan databases of Commercial and Medicare supplement claims)	46,921,461 (≤18) (40.8% - reflects those with OUD and OD, not entire under 18 sample) 0 to 65+ (included subgroup analysis for ≤18 group, providing the data used for this review) NR	ICD 9 and 10 codes for OUD and OD (having at least one) Measured within one year of exposure	Among incident cases of OUD/OD in youths, 29.4% received a prescription opioid in the year prior in 2006 and 22.6% in 2016 (P-trend = 0.001). (All were therapeutically exposed to opioids)	11/14

[a] Sample analysed reflects those included in the analysis of the study who were within the age group of interest (children and youth). Total population count for the SR does not double count studies using the same sample across same years or Chung et al. where total sample size was not reported.

[b] Where the sex was not reported by age group, the percentage of females will include the entire population and not just the age group of interest.

[c] Burke 2020 did not report on prevalence or incidence of nonmedical opioid use and reported hazard ratios.

[d] Questions that were not applicable to the study or its design did not count negatively towards the score, more details available in Supplemental e-table 2.

Abbreviations: aOR = adjusted odds ratio, CI = confidence interval, IQR = interquartile range, NMUPO = nonmedical use of prescription opioids, NR = not reported, OR = odds ratio, OD = overdose, OUD = opioid use disorder, RD = risk difference, RR = risk ratio/relative risk, SD = standard deviation

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Supplementary Content

E-table 1: Databases Searched

Databases	Grey Literature
Ovid MEDLINE, Ovid Embase, Cochrane Library, Ovid PsycINFO, CINAHL Plus with Full Text via EBSCOhost, and Child Development & Adolescent Studies via EBSCOhost	Web of Science Core Collection, Proquest Dissertations and Thesis, OCLO PapersFirst, clinical trial registries (ClinicalTrials.gov), and the Conference Proceedings Citation Index (Clarivate Analytics)

E-methods 1: Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to May 10, 2019>

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1 exp Narcotics/ or (opiate* or opioid* or codeine* or morphine or fentanyl or hydrocodone* or hydromorphone* or oxycodone* or oxy-codone or oxycontin or oxy-contin or vicodin or meperidine or demerol* or tramadol* or percocet or oxymorphone or narcotic*).ti,ab,kf. (194599)

2 exp child/ or exp infant/ or (child or children or childhood or p?ediatric* or boy* or girl* or toddler* or infant* or newborn* or neonat* or baby or babies or preschool* or adolescen* or teen* or youth).ti,ab,kf. or (pediatric* or paediatric* or child or children or childhood or adolescen* or infan* or neonat*).jw,nw. (3241895)

3 1 and 2 (17466)

4 Pain Management/ or Postoperative pain/ or exp "Wounds and Injuries"/ or exp Dentistry/ or Pain/dt or tu.fs. or (((therap* or treat* or manag*) adj4 pain) or analges* or sedation or an?esth* or pharmacotherap* or surg* or postsurg* or postoperative* or post-operative* or short-term or injur* or orthop?edic* or dentist* or dental).mp. (6838816)

5 3 and 4 (12865)

6 substance-related disorders/ or exp opioid-related disorders/ or Prescription Drug Misuse/ or ((opiate* or opioid* or codeine* or morphine or fentanyl or hydrocodone* or hydromorphone* or oxycodone* or oxy-codone or oxycontin or oxy-contin or vicodin or meperidine or demerol* or tramadol* or percocet or oxymorphone* or narcotic*) and (dependen* or addict* or abus* or misuse or non-medic* or nonmedic* or recreational or illicit)).ti,kf. or ((opiate* or opioid* or codeine* or morphine or fentanyl or hydrocodone* or hydromorphone* or oxycodone* or oxy-codone or oxycontin or oxy-contin or vicodin or meperidine or demerol* or tramadol* or percocet or oxymorphone or narcotic*) adj5 (dependen* or addict* or abus* or misuse or non-medic* or nonmedic* or extra-medic* or extramedic* or recreational or illicit)).ab. or (nmupo or nupo or nmupd or nmpo).ti,ab,kf. (122831)

7 (Prescription Drugs/ or (prescription* or prescribed).ti,ab,kf.) and (non-medic* or nonmedic* or extra-medic* or extramedic* or long-term).ti,ab,kf. (12702)
8 (correlat* or associat* or incidence or prevalence or predict* or risk*).ti,ab,kf. (7618436)
9 7 and 8 (7993)
10 6 or 9 (129759)
11 5 and 10 (1618)
12 limit 11 to (english or french) (1555)
13 remove duplicates from 12 (1545)

Segment : Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to September 04, 2020>
Date run : 2020-09-06 (updated search)

#	Searches	Results
1	exp Narcotics/ or (opiate* or opioid* or codeine* or morphine or fentanyl or hydrocodone* or hydromorphone* or oxycodone* or oxy-codone or oxycontin or oxy-contin or vicodin or meperidine or demerol* or tramadol* or percocet or oxymorphone or narcotic*).ti,ab,kf.	208813
2	exp child/ or exp infant/ or (child or children or childhood or p?ediatric* or boy* or girl* or toddler* or infant* or newborn* or neonat* or baby or babies or preschool* or adolescen* or teen* or youth).ti,ab,kf. or (pediatric* or paediatric* or child or children or childhood or adolescen* or infan* or neonat*).jw,nw.	3437903
3	1 and 2	19121
4	Pain Management/ or Postoperative pain/ or exp "Wounds and Injuries"/ or exp Dentistry/ or Pain/dt or tu.fs. or (((therap* or treat* or manag*) adj4 pain) or analges* or sedation or an?esth* or pharmacotherap* or surg* or postsurg* or postoperative* or post-operative* or short-term or injur* or orthop?edic* or dentist* or dental).mp.	7263148
5	3 and 4	14042
6	substance-related disorders/ or exp opioid-related disorders/ or Prescription Drug Misuse/ or ((opiate* or opioid* or codeine* or morphine or fentanyl or hydrocodone* or hydromorphone* or oxycodone* or oxy-codone or oxycontin or oxy-contin or vicodin or meperidine or demerol* or tramadol* or percocet or oxymorphone* or narcotic*) and (dependen* or addict* or abus* or misuse or non-medic* or nonmedic* or recreational or illicit)).ti,kf. or ((opiate* or opioid* or codeine* or morphine or fentanyl or hydrocodone* or hydromorphone* or oxycodone* or oxy-codone or oxycontin or oxy-contin or vicodin or meperidine or demerol* or tramadol* or percocet or oxymorphone or narcotic*) adj5 (dependen* or addict* or abus* or misuse or non-medic* or nonmedic* or extra-medic* or extramedic* or recreational or illicit)).ab. or (nmupo or nupo or nmupd or nmpo).ti,ab,kf.	131026
7	(Prescription Drugs/ or (prescription* or prescribed).ti,ab,kf.) and (non-medic* or nonmedic* or extra-medic* or extramedic* or long-term).ti,ab,kf.	14387
8	(correlat* or associat* or incidence or prevalence or predict* or risk*).ti,ab,kf.	8370322

9	7 and 8	9203
10	6 or 9	138912
11	5 and 10	1941
12	limit 11 to (english or french)	1877
13	remove duplicates from 12	1863
14	(201905* or 201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020*).dt.	1841821
15	13 and 14	180

E-table 2: NIH Quality Assessment

Author, Year	1. Was the research question or objective in this paper clearly stated?	2. Was the study population clearly specified and defined?	3. Was the participation rate of eligible persons at least 50%?	4. Were all subjects selected or recruited from the same/similar populations (and time period)? Were inclusion & exclusion criteria for being in the study prespecified and applied uniformly to all?	5. Was a sample size justification, power description, or variance and effect estimates provided?	6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?	9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	10. Was the exposure(s) assessed more than once over time?	11. Were outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	12. Were the outcome assessors blinded to the exposure status of participants?	13. Was loss to follow-up after baseline 20% or less?	14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	**Score (out of 14)**
Bell, 2019	yes	yes	yes	yes	no	yes	yes	NA	yes	NA	yes	no	yes	no	**11**
Schroeder, 2019	yes	yes	yes	yes	no	yes	yes	NA	yes	NA	yes	yes	yes	yes	**13**
Chung, 2018/19	yes	yes	yes	yes	no	yes	yes	NA	yes	NA	yes	no	yes	no	**11**
Schepis, 2018	yes	yes	yes	yes	no	no	no	NA	no	NA	no	no	yes	no	**7**
McCabe, 2016	yes	yes	yes	yes	no	yes	yes	NA	no	NA	no	no	no	yes	**9**
Miech, 2015	yes	no	yes	yes	no	yes	yes	NA	no	NA	no	no	no	no	**7**
Veliz, 2014	yes	yes	yes	yes	no	yes	yes	NA	no	NA	no	no	yes	no	**9**
McCabe, 2013	yes	yes	yes	yes	no	yes	yes	NA	no	NA	no	no	yes	yes	**10**
McCabe, 2013	yes	yes	yes	yes	no	no	no	NA	no	NA	no	no	yes	no	**7**
Schepis, 2009	yes	yes	yes	yes	no	no	no	NA	no	NA	no	no	yes	no	**7**
Boyd, 2006	yes	yes	yes	yes	no	no	no	NA	no	NA	no	no	yes	no	**7**
Schepis, 2019	yes	yes	yes	yes	no	no	no	NA	no	NA	no	no	yes	no	**7**
Vosburg, 2016	yes	yes	CD	yes	no	no	CD	NA	no	NA	no	no	yes	no	**6**
McCabe, 2012	yes	yes	yes	yes	no	no	no	NA	no	NA	no	no	yes	no	**7**
McCabe, 2011	yes	yes	yes	yes	no	no	no	NA	no	NA	no	no	no	yes	**7**
Osborne, 2019	yes	yes	yes	yes	no	no	no	NA	no	NA	no	no	no	no	**6**
Wei, 2019	yes	yes	yes	yes	no	yes	yes	yes	Yes	NA	yes	no	yes	no	**11**
Hudgins, 2019	yes	yes	yes	yes	no	no	no	N/A	no	NA	no	no	yes	no	**7**
Burke, 2020	yes	yes	yes	yes	no	yes	yes	yes	Yes	NA	yes	no	yes	no	**11**
Groenewald, 2019	yes	yes	yes	yes	no	yes	yes	yes	Yes	NA	yes	no	yes	yes	**12**
Chua, 2019	yes	yes	yes	yes	no	yes	yes	yes	yes	NA	yes	no	yes	yes	**12**

*CD = Cannot Determine (counts negatively towards score), NA = Not Applicable (does not count negatively towards score)

E-table 3: Risk Factors for Nonmedical Prescription Opioid Use Reported Within Included Studies

Study	**Association of Interest** **Statistical Method**	**Statistically Significant Variables**	**Measure of Association**	**Variables Examined but not Statistically Significant or Unknown Significance**
Short-term exposure				
Schroeder, 2019[45]	Short-term opioid exposure and diagnosis of opioid abuse within 365 days Multivariable logistic regression (adjusted odds ratio, 95% CI)	Age: 16-18 19-21 22-25 Sex: Male Female Race/ethnicity: White Asian Black Hispanic Unknown US Region: South Northeast North Central Mountains Pacific Previous non-opioid substance abuse: No Yes	 1.0 (reference) 1.1 (0.9-1.4) 0.8 (0.7-1.0) 1.0 (reference) 11.5 (9.4-14.8) 1.0 (reference) 0.3 (0.2-0.6) 1.0 (0.7-1.3) 0.9 (0.7-1.1) 1.0 (0.8-1.5) 1.0 (reference) 1.1 (0.9-1.4) 1.2 (1.0-1.4) 0.8 (0.6-1.0) 1.2 (0.9-1.5) 1.0 (reference) 4.5 (3.4-5.9)	Prescribed more than 20 pills vs. ≤20 pills
Bell, 2019[35]	Short-term therapeutic exposure and overdose diagnosis Proportions (%)	Age: ≤14 ≥15 Race: White Black	 3.5% 12.9% 5.7% 15.0%	Gender Injury severity (major vs. minor/moderate)

		Other Hospital type: Pediatric Adult Injury type: Blunt Penetrating Other Insurance type: Medicaid Self-pay Private Other	0.0% 5.5% 18.2% 4.2% 26.3% 0.0% 10.8% 8.6% 3.2% 22.2%	Positive alcohol screening at hospital admission Positive drug screening on admission
Chung, 2018 & 2019[30,42]	Short-term therapeutic exposure and opioid-related adverse events (includes those who had adverse events that were not related to misuse) Poisson regression (incidence rate ratio, 95% CI)	Age: 2-5 6-11 12-17 Timing of use: Recent (14 days after end of supply) Current (time between prescription fill and end of supply) Days since prescription filled: ≥8 days 4-7 days 1-3 days Dose (mg/kg per d) tertile: Low Intermediate High	 1.0 (reference) 0.94 (0.66-1.33) 2.22 (1.67-2.96) 1.0 (reference) 2.09 (1.58-2.76) 1.0 (reference) 1.51 (1.13-2.02) 3.31 (2.41-4.53) 1.0 (reference) 1.59 (1.23-2.04) 1.86 (1.45-2.39)	Sex Calendar year (1999–2003, 2004–2007, and 2008–2011)
	Short-term therapeutic exposure and opioid-related adverse events associated with self-harm or substance abuse Hazard ratios			Opioid type (hydrocodone, codeine, oxycodone, tramadol)

Unknown duration of exposure				
McCabe, 2012[24]	Nonmedical use following medical use Proportions (%)	White African-American Hispanic	5.6% 1.9% 1.6% P<0.001	Gender
McCabe, 2011[23]	Taking too much or medical misuse of prescribed pain medication Proportions (%)	Frequent users of pain medications: 1 to 2 occasions 3 to 9 occasions ≥10 occasions	 14.4% 19.8% 36.4% P<0.01	
Miech, 2015[33]	Therapeutic use of opioids and future opioid misuse after high school Predictive modelling (relative risk, 95% CI)	Lifetime marijuana use occasions by 12th grade: None 1-2 3-5 6–9 10–19 20–39 40+ Cigarette smoking history by 12th grade: Never Once or twice Occasionally but not regularly Regularly in the past Regularly now Lifetime prescription opioids misuse occasions by 12th grade: None 1-2 3-5 6-9 10-19 20-39 40+ Lifetime misuse prescription barbiturates/ sedatives occasions by 12th grade: None 1–2 3–5 6-9 10–19	 1.0 (reference) 1.43 (0.97-2.11) 1.31 (0.83-2.08) 2.21 [b] (1.43–3.43) 2.74 [b] (1.88-3.99) 2.56 [b] (1.69–3.89) 2.92 [b] (2.09–4.08) 1.0 (reference) 1.56 [b] (1.15–2.13) 1.73 [b] (1.25–2.4) 2.08 [b] (1.4–3.09) 1.78 [b] (1.26–2.52) 1.0 (reference) 1.97[b] (1.4-2.77) 2.8[b] (1.83-4.29) 3.2[b] (2.06-4.96) 3.58[b] (2.26-5.65) 5.88[b] (3.19-10.8) 4.63[b] (2.79-7.67) 1.0 (reference) 1.63[a] (1.01–2.65) 1.97[b] (1.19–3.26) 1.57 (0.85-2.89) 2.56[a] (1.2–5.45)	Gender School truancy Number of evenings out per week Two-parent household Age at survey Perceived risk of regular marijuana use Number of occasions of misuse of prescription amphetamines Number of occasions of misuse of prescription tranquilizers Number of occasions of lifetime cocaine use

		20–39 40+ Binge drinking in last 2 weeks: None Once Twice 3–5 6-9 10+ Disapproval of regular marijuana use: No disapproval Disapproval Strong disapproval Average course marks in 12th grade Racial/ethnic minority Parent with college degree	2.93[b] (1.61–5.33) 1.04 (0.53-2.01) 1.0 1.16 (0.86-1.55) 1.05 (0.77-1.44) 1.44[a] (1.06–1.97) 0.83 (0.48-1.42) 0.86 (0.42-1.74) 1.0 (reference) 0.72[a] (0.56-0.93) 0.52[b] (0.39–0.69) 0.95[a] (0.95-1.0) 0.62[b] (0.48–0.8) 1.23[a] (1.02–1.48)	
Schepis, 2018[44]	Medical exposure to opioids and past year medical misuse of opioids Proportions (%) (95% CI) (Analyses controlled for age, race/ethnicity, and sex)			Educational status (home schooled; in school, good school adjustment; in school, poor school adjustment; not in school)
Veliz, 2014[40]	Past year medical misuse of opioid medication Proportions (%)	Males Females	3.6% 6.3% P<0.05	
	Past year medical misuse of opioid medication (used to get high) Proportions (%)			Gender

	Past year medical misuse (males) Multivariable logistic regression (adjusted odds ratio, 95% CI; analyses controlled for grade-level at study initiation, parent education, race, DAST-10 results, and time)	Males with medical misuse (used too much) on ≥1 occasion: Did not participate in organized sports Participated in organized sports Continual sports participation over 3 years Males with medical misuse (used to get high) on ≥1 occasion: Did not participate in organized sports Participated in organized sports Continual sports participation over 3 years	 1.0 (reference) 2.99 (1.22–7.41)[b] 10.5(2.42–45.5)[a] 1.0 (reference) 1.32 (0.492-3.52) 4.01 (1.13-14.2) [b]	
	Past year medical misuse (females) Multivariable logistic regression (adjusted odds ratio, 95% CI; analyses controlled for grade-level at study initiation, parent education, race, DAST-10 results, and time)			Sports participation (did not participate in organized sports, participated in organized sports, continuously participated in organized sports)
Groenewald, 2019[43]	Opioid overdose following medical exposure **Opioid-related overdose includes incidences unrelated to nonmedical use.* Cox Proportional Hazard Models (hazard ratio)	Anxiety: No Yes Mood disorders: No Yes Substance-related disorders: No Yes Alcohol-related disorders: No Yes US Region: North central Northeast South West Unknown	 1.0 (reference) 1.65 (1.33–2.06) [d] 1.0 (reference) 2.77 (2.26–3.34)[d] 1.0 (reference) 3.09 (2.27 – 3.39)[d] 1.0 (reference) 2.45 (1.65-3.60)[d] 1.0 (reference) 0.98 (0.75–1.26) 0.99 (0.81–1.20) 1.39 (1.13–1.71)[c] 1.29 (0.75–2.24)	Age Sex Metropolitan Statistical Area Complex chronic condition Morphine equivalent daily dose

		Type of opioid prescribed: Oxycodone Codeine Hydrocodone Tramadol Other opioids No. opioid prescriptions during study period 1 2 ≥3 Quantity of opioid tablets supplied 0-18 19-30 >30	 1.0 (reference) 0.94 (0.70–1.27) 1.13 (0.90–1.44) 2.67 (1.90–3.75)[d] 2.55 (0.81–8.08) 1.0 (reference) 1.05 (0.86–1.27) 1.54 (1.29–1.82) [d] 1.0 (reference) 1.09 (0.91-1.30) 1.35 (1.05-1.73)[e]	
Chua, 2019[32]	Opioid overdose following medical exposure Multivariable logistic regression (adjusted odds ratio, 95% CI)	Daily opioid dosage category Concurrent benzodiazepine use Extended-release or long-acting opioid use US census region (vs Northeast): Midwest South West Mental health disorder Substance use disorder	1.26 (1.06-1.50) 2.86 (1.52-5.40) 4.31 (1.92-9.67) 2.20 (1.12-4.32) 1.78 (0.93-3.42) 1.77 (0.86-3.64) 2.85 (1.93-4.21) 6.79 (4.40-10.47)	Age, in single y Sex Urban residence Study year Other chronic condition

[a]P<0.01, [b]P<0.05, [c]P=0.002, [d]P<0.0001, [e]P=0.02
DAST-10: Drug Abuse Screening Test, Short Form

E-table 4: Detailed Risk Factors Matrix

Risk Factor	Study													
	Schroeder, 2019	Bell, 2019	Chung, 2018 & 2019	McCabe, 2012	McCabe, 2011	Miech, 2015		Schepis, 2018	Veliz, 2014		Groenewald, 2019		Chua, 2019	
Age	16-18 19-21 22-25	≤14 ≥15	2-5 6-11 12-17			Age at survey					11-17		Age, in single y	
Sex/Gender	Male Female	Male Female	Male Female	Male Female		Men Women			Male Female (Using too much of medication)	Male Female (Using medication to get high)	Male Female		Male Female	
Race/ Ethnicity	White Asian Black Hispanic Unknown	White Black Other		White African-American Hispanic		Racial/ethnic minority								
Region	South Northeast North Central Mountains Pacific										North central Northeast South West Unknown	Metropolitan statistical area	Midwest South West	Urban residence
Calendar year/ Study year			1999–2003 2004–2007 2008–2011										Study year (vs 2009)	
Quantity of pills prescribed or dosage	>20 pills ≤20 pills		Low Intermediate High		1 to 2 occasions 3 to 9 occasions						No. of opioid prescriptions during	Morphine equivalent daily dose:	Daily opioid dosage category	

					≥10 occasions					study period: 1, 2, ≥3 Quantity of opioids prescribed: 0-18 tablets 19-30 tablets >30 tablets	<0.5, 0.5-0.9, >0.9	
Timing of opioid use			Recent Current									
Days since prescription filled			1-3 4-7 ≥8									
Opioid type			Hydrocodone Codeine Oxycodone Tramadol							Hydrocodone Codeine Oxycodone Tramadol Other opioids		Extended-release or long-acting opioid use
Hospital type		Pediatric Adult										
Injury type		Blunt Penetrating Other										
Injury severity		Minor/ Moderate Major										
Insurance type		Medicaid Self-pay Private Other										

Previous substance abuse (non-opioid) *Summary category*	Yes No	Positive alcohol screen at admission (yes/no) Positive drug screen at admission (yes/no)				Lifetime marijuana use Lifetime misuse of prescription barbiturates and sedatives Binge drinking Cigarette smoking	Perceived risk of marijuana use Lifetime misuse of prescription amphetamines Lifetime misuse of prescription tranquilizers Lifetime cocaine use				Substance-related disorders (yes/no) Alcohol-related disorders (yes/no)	Substance use disorder
Substance Use Disorder											Substance-related disorders (yes/no)	Substance use disorder
Alcohol		Positive alcohol screening at hospital admission				Binge drinking in last 2 weeks: None 1 2 3-5 6-9 ≥10					Alcohol-related disorders (yes/no)	

Cigarettes						History by 12th grade: Never Once or twice Occasionally but not regularly in the past Regularly now						
Marijuana						Lifetime marijuana use (occasions by 12th grade): 0 1-2 3-5 6-9 10-19 20-39 ≥40 Disapproval of marijuana use: No disapproval Disapproval Strong disapproval	Perceived risk of regular marijuana use					

Controlled medications						Lifetime prescription opioids misuse Lifetime misuse of prescription barbiturates and sedatives Both measured as occasions by 12th grade: 0 1-2 3-5 6-9 10-19 20-39 ≥40	Lifetime misuse of prescription amphetamines (occasions) Lifetime misuse of prescription tranquilizers (occasions)					Concurrent benzodiazepine use
Cocaine						Lifetime cocaine use (occasions)						
Other Conditions												
Mental health conditions											Anxiety (none/yes) Mood disorders (no/yes)	Mental health disorder

Chronic conditions											Complex chronic conditions (none/yes)	Other chronic condition
Positive drug screening at hospital admission		Yes No										
Two-parent household						Yes No						
Parent with college degree						Yes No						
School enrollment and engagement						Average course marks in 12th grade	School truancy Number of evenings out per week	Home schooled In school, good school adjustment In school, poor school adjustment Not in school				
Sports Participation									No sports participation Sports participation Continuous sports participation (Males;	No sports participation Sports participation Continuous sports participation (Females;		

								used too much or to get high)	used too much or to get high)		

Legend:	Statistically significant
	Not statistically significant
	Not reported

Appendices

Appendix 1: Screening Forms

Screening Criteria (Title and Abstract)

Reviewer: _____ Reference ID: _____

Criteria	Yes	No	Unclear
1. LANGUAGE Study is in English or French Exclude: studies in other languages			
2. PUBLICATION TYPE Report of quantitative primary research Exclude: qualitative research, opinion pieces, letters, editorials, commentaries			
3. POPULATION Study population includes children (<18 years) at the time of exposure measurement			
4. EXPOSURE Short-term (≤14 days) therapeutic opioid exposure. Opioids include: • codeine • fentanyl (Actiq, Duragesic, Fentora) • hydrocodone (Hysingla ER, Zohydro ER) • hydrocodone/acetaminophen (Lorcet, Lortab, Norco, Vicodin) • hydromorphone (Dilaudid, Exalgo) • meperidine (Demerol) • methadone (Dolophine, Methadose) • morphine (Astramorph, Avinza, Kadian, MS Contin, Ora-Morph SR) • oxycodone (OxyContin, Oxecta, Roxicodone) • oxycodone/acetaminophen (Depalgos Endocet, Percocet, Roxicet, Tylox) • oxycodone/aspirin (Percodan) • oxycodone/naloxone (Targiniq ER) • tramadol (Ultram, Zytram)			
5. OUTCOMES Primary Outcome: Opioid use disorder Inclusion of opioid use disorder or at least one of the following: • Opioid addiction • Opioid dependence • Opioid abuse • Opioid misuse • Nonmedical use of opioids Comments:			

REVIEWER'S DECISION: **Include** ☐ **Exclude** ☐ **Unsure** ☐

Inclusion Criteria (Full Text)

Reviewer: _____ Reference ID: _____

Criteria	Yes	No	Unclear
1. POPULATION Study population includes children (<18 years) at the time of exposure measurement			
2. EXPOSURE Short-term (≤14 days) therapeutic opioid exposure. Opioids include: • codeine • fentanyl (Actiq, Duragesic, Fentora) • hydrocodone (Hysingla ER, Zohydro ER) • hydrocodone/acetaminophen (Lorcet, Lortab, Norco, Vicodin) • hydromorphone (Dilaudid, Exalgo) • meperidine (Demerol) • methadone (Dolophine, Methadose) • morphine (Astramorph, Avinza, Kadian, MS Contin, Ora-Morph SR) • oxycodone (OxyContin, Oxecta, Roxicodone) • oxycodone/acetaminophen (Depalgos Endocet, Percocet, Roxicet, Tylox) • oxycodone/aspirin (Percodan) • oxycodone/naloxone (Targiniq ER) • tramadol (Ultram, Zytram)			
3. OUTCOMES Primary Outcome: Opioid use disorder Inclusion of opioid use disorder or at least one of the following: • Opioid addiction • Opioid dependence • Opioid abuse • Opioid misuse • Nonmedical use of opioids Comments:			

REVIEWER'S DECISION: **Include** ☐ **Exclude** ☐ **Unsure** ☐

Appendix 2: Data Extraction Form

<table>
<tr><th colspan="4">Non-Medical Opioid Use in Pediatrics</th></tr>
<tr><td>RefID:</td><td>First Author:</td><td>Year of Publication:</td><td>Date of Data Extraction:</td></tr>
<tr><td colspan="2">Reviewer 1 (DE):</td><td colspan="2">Reviewer 2 (DV):</td></tr>
<tr><td colspan="4">Study Characteristics</td></tr>
<tr><td colspan="2">Country:</td><td>Study dates:</td><td>Publication type:
- Journal article
- Abstract
- Dissertation
- Conference paper/presentations</td></tr>
<tr><td colspan="2">Funding source:</td><td colspan="2">Possible conflict of interest:</td></tr>
<tr><td colspan="2">Study design:
- RCT
- NRCT
- Prospective cohort
- Retrospective cohort
- Cross-sectional
- Other (specify):</td><td colspan="2">Method of data collection (e.g., survey):</td></tr>
<tr><td colspan="4">Study objectives:</td></tr>
<tr><td colspan="4">Population Characteristics</td></tr>
<tr><td colspan="4">Condition or disease studied:</td></tr>
<tr><td colspan="4">Clinical/study setting:</td></tr>
<tr><td>Socioeconomic factors:
- Education:
- Income:
- Occupation:</td><td>Sample size (n):
- Enrolled:
Male: n:__;____%
Female: n:_____;_____%

- Analyzed:
Male: n:__;____%
Female: n:_____;_____%

- Completed:
Male: n:__;____%
Female: n:_____;_____%</td><td>Age:
- Mean, SD:
- Median:
- Range:
- Other:</td><td>Ethnicities (n):</td></tr>
</table>

Inclusion criteria:	Exclusion criteria:	
Exposure Characteristics		
Opioid(s) prescribed:	Comparator(s), if applicable:	
Describe intervention: - Duration of treatment: - Dose: - Route of administration:	Describe comparator(s), if applicable:	
Outcomes Reported		
Opioid use disorder	Definition:	
Opioid addiction	Definition:	
Opioid dependence	Definition:	
Opioid misuse	Definition	
Opioid abuse	Definition:	
Nonmedical opioid use	Definition:	
Other outcomes & risk factors, specify:		
How were outcomes measured?	Timing of outcome measurement:	Length of follow-up period:
Results		
• Effect size • P-value • Mean • Median • Risk ratio	• Odds ratios • Adjusted odds ratios: o What was adjusted: • Confidence intervals:	
Risk of Bias Assessment		
Study Design and Tool • Follow National Institute of Health Quality Assessment Tool for Observational and Cross Sectional studies		
Conclusions		
Describe authors' conclusions:		
Additional comments:		

DE = data extraction; DV = data verification

Chapter 3: Qualitative Study

Title: Short-term therapeutic use of opioids for children and youth and future nonmedical use: a qualitative study of decision-maker information needs

Authors: Malema Ahrari MSc Candidate, Michele P. Dyson PhD, Samina Ali MD, and Lisa Hartling PhD

Abstract

Background

Despite an overall decline in opioid prescriptions in Canada, healthcare visits, hospitalizations, and deaths due to opioid-related harms continue to rise for children. Decision-makers (including patients, clinicians, and policy-makers) require high quality syntheses to inform decisions regarding opioid use for children. Previous research has found that how systematic review results are presented may influence uptake by decision-makers. Evidence summaries can be appealing to decision-makers as they provide key messages in a succinct manner.

The objective of this study was to gain perspectives from policy decision-makers on the usability and presentation of results from a systematic review through the form of an evidence summary. The purpose of the systematic review was to explore the association between short term therapeutic opioid exposure in children and nonmedical opioid use that may follow.

Methods

Decision-makers were recruited through purposive and snowball sampling methods. They participated in one-on-one interviews to discuss an evidence summary based on the findings of the systematic review. Interviews were transcribed and data were analyzed using thematic analysis.

Results

Eleven decision-makers who influence children's health policies were included in our sample. Four major themes emerged from the data: 1) Content, 2) Format, 3) Expertise, and 4) Actionability. Decision-makers shared their preferences for the format of evidence summaries; this included having a single-page document, key messages, tables, figures, infographics, links, bolding, colours, and white space. They shared perspectives on actionability of the recommendations in the summary that was reviewed and discussed limitations of systematic reviews as a whole. Finally, they commented on the role of experts and trusting those who developed the summary, as well as their reliance on experts for making judgements and decisions in the absence of strong evidence.

Conclusions

While a systematic review can contribute evidence to guide clinical practice and future research, these qualitative findings help in understanding the type of information needed by policy decision-makers and their preferences for how it is presented. Overall, decision-makers want clear, succinct and actionable evidence summaries with the key messages on the first page and details on subsequent pages. In general, evidence summaries will only ever be as useful and influential as the findings of the review and their strength/certainty.

Keywords: evidence summary, knowledge mobilization, nonmedical use of opioids, systematic review, decision-makers, children

Background

Policy decisions are typically made without research evidence when time and resources are limited, when decision-makers lack research literacy or cannot access clear and relevant findings at the time they are needed, or when findings are not adequately contextualized.[1,2] While systematic reviews are one of the most robust methods of synthesizing evidence,[3] their length and complexity are often barriers for decision-makers wanting to readily access research findings and use them to inform policies.[4] Without being informed by evidence, health policy decisions are at risk of being ineffective and may potentially have negative consequences.

Evidence summaries are a promising method of disseminating information to decision-makers. A study exploring strategies to enhance the uptake of systematic reviews and understand the best format for health care managers and policy-makers found that participants preferred a high-level, plain language summary that focused more on the interpretation of results and the impacts to healthcare practice and policy and less on review methodology. Policy makers preferred having background and key messages on one page and methods and limitations on another.[2]

Our team previously conducted a systematic review exploring the association between short-term therapeutic exposure to opioids in children and youth and nonmedical opioid use. There has been a lack of clarity regarding the balance between potential benefits and risks of exposing children to opioids for a short-term period in a medical setting. Therefore, we compiled the available

evidence to support the decision-making processes of patients, caregivers, clinicians, and decision-makers. Our systematic review determined that there is limited evidence to determine whether *short-term* therapeutic exposure to opioids in childhood is definitively associated with future nonmedical opioid use or development of an OUD; however, the review suggests a link between *lifetime* therapeutic opioid use (unknown duration) and nonmedical opioid use. The existing evidence on risk factors for nonmedical opioid use or OUD following short-term therapeutic exposure is unclear, however, older adolescents with short-term therapeutic exposure during their lifetime may be at higher risk of nonmedical use than younger children.

The goals of this study were to: 1) develop an evidence summary to help communicate the findings of the systematic review to decision-makers in child health; and 2) to conduct qualitative interviews to understand decision-maker perspectives on the usability of the evidence summary.

Methods

Development of the Evidence Summary

An evidence summary was developed using the layout proposed in the Development and Usability Testing of EPC Evidence Review Dissemination Summaries for Health Systems Decision-makers.[5] This template was selected because it targeted health system decision-makers as the end user group. The first page of the summary included a short background section, summary of review findings and implications for practice and research. The second page included the methods and PRISMA flow diagram. Summary of results tables followed on pages 3-5. The evidence summary can be found under Appendix A.

Research Team

Personal Characteristics and Relationship with Participants

The research team consisted of four females: two PhDs, one MD and one Master's student. The researcher conducting the interviews (MA) had formal training in qualitative research methods. She did not have a direct relationship with the participants; however, members of the research team who made the referrals did, through their research and clinical networks (LH, SA). Aside from the recruitment emails, no relationship was established between the interviewer and

participants prior to commencement of the interviews. Participants were provided information on the researcher's goals to complete her thesis research and to translate the findings of the systematic review into the most usable format for decision-makers.

Study Design

Theoretical Framework

The methodology that was used in this study was qualitative description. Qualitative description is an approach used for studies which are descriptive in nature, particularly for examining health care and nursing-related phenomena.[6] Qualitative description is a widely cited research tradition and has been identified as important and appropriate for research questions that focus on discovering the who, what, and where of events or experiences and gaining insights from informants regarding a poorly understood phenomenon.[6] It is also the method of choice when a straight description of a phenomenon is desired or information is sought to develop and refine questionnaires or interventions.[6,7] Brink and Wood (2001) describe it as exploratory research.[8]

The use of qualitative description is particularly relevant where information is required directly from those experiencing the phenomenon under investigation, where time and resources are limited and perhaps as part of a mixed methods approach.[8,9] Our systematic review provides new knowledge on a question that to date, has not been widely understood. We wanted to ensure that end-users had the opportunity to access out findings and sought to develop an effective knowledge mobilization tool that could inform policy, practice, and/or future investments in research.

Understanding the world of the potential end-user enhances the likelihood that an evidence summary would be used.[10] The qualitative study was intended to allow us to gain insights from policy decision-makers on their experiences with understanding health-related information, the context of their decision-making, and their information needs and in turn, help inform what an effective knowledge dissemination tool could look like.

Ethics

The plan for this study was reviewed and approved by the University of Alberta's Research Ethics Board on January 7, 2020 under the project name "Decision-maker Perspectives on Usability of Systematic Review Results: A Qualitative Study", No. 00095233. The plan outlined the researchers' commitment to ensuring that the rights of research participants are respected and how they will be protected from harm. An information sheet and consent form were shared with participants ahead of time to ensure they were able to make an informed decision about participating.

Participant Selection

The inclusion criteria for decision-makers were people in high-level leadership positions (e.g., Directors or higher), working in a children's health care organization or a branch within a larger organization such as a regional public health authority/administrator, and responsible for making or influencing children's health policy outcomes.

Sampling of decision-makers was based on a combination of purposive and snowball methods, facilitating the selection of participants whose qualities or experiences are required for the study[8], and who may not otherwise be easily identifiable without a referral.

Thirteen prospective participants were emailed directly by the researcher for recruitment, of which 10 participated, and 3 did not respond. Those receiving the initial recruitment email were known to members of the research team as individuals who influenced children's health policies and were asked to forward the email to others who would also fit the inclusion criteria. Three additional participants reached out confirming they were willing to participate. Nobody dropped out or explicitly refused to participate. One on one interviews were conducted with a total of 13 participants.

Setting

Three interviews took place in person, and the remainder took place over the phone due to geographic location. Aside from the interviewer and participant, nobody else was present during the interviews.

Data Collection

A semi-structured interview guide was used to avoid limiting responses and to encourage participants to express themselves freely (Appendix B).[11] The interview guide was pilot tested with a member of the interviewer's research group and adjusted based on feedback prior to commencing interviews.

Interviews were recorded and then transcribed. Field notes were made during some of the interviews. Interviews were scheduled for one hour and took an average of 45 minutes. Interviewees were asked a series of questions about their experience and background and were then provided with ten minutes to review the evidence summary, which they had also received in advance of the interview. Following the ten-minute review of the evidence summary, they were asked to provide feedback through a series of open-ended questions.

It became evident that data saturation was reached when new codes were no longer being developed and new themes were not emerging towards the 11th and 12th interviews, therefore, no additional participants were recruited. Transcripts were not returned to participants for comment and/or correction.

Analysis and Findings

Data Analysis

Data were analysed by one researcher (MA) using thematic analysis. Data were first coded and categorized within NVivo and then split into themes. Excerpts from each category were cross checked by LH and MD to ensure that they fit the category. Categories were assessed for internal homogeneity and external heterogeneity to confirm whether data within categories made sense and to ensure that categories were distinct from each other. Four themes were formed and derived from the data to identify the relationship between the different categories. In some cases, there was some overlap between the overarching themes that categories fell under, which limited the external heterogeneity. The coding tree can be found under Appendix C. Participants did not provide feedback on the findings.

Rigor

In order to ensure rigor, strategies were implemented throughout the entire research process. To increase rigor and trustworthiness of results, the criteria proposed by Lincoln and Guba on credibility, transferability, dependability and confirmability were followed.[12] To enhance credibility, a second review was conducted by LH or MD on the findings and decision process to reduce the risk of interpretive bias. To enhance transferability of results, descriptions of the interview setting and characteristics of participants are included, these are intended to increase the reliability of generalizations that are made about the group under study. To enhance dependability and confirmability, an audit trail is included under Appendix D so that decisions made to identify and develop themes can be traced and defended. To increase confirmability, reflexivity was also practiced throughout the data analysis stage, to ensure that the researcher/interviewer was engaging in an ongoing process of self-reflection and requesting peer reviews to take notice of how one's own social background, positioning, assumptions, and behaviour can influence the research process.[8] The reflections can be found in Appendix E. Where contradictions in the data were discovered, these have been noted in the results summary, for example, contradictions in preferences for the use of statistics and level of detail. While measures were taken to minimize the potential for bias within the research process, fully eliminating the possibility of bias was not possible given the interpretive nature of qualitative research and the potential influence that may come from a researcher's own beliefs and background.

Results

Two participants were excluded from the results as they did not meet the inclusion criteria for the study. One did not identify as a decision-maker and the other did not have a role that influenced children's health policies but did have a role that influenced health outcomes. The details of their respective roles and whether they identify as someone who influences policy decisions became evident throughout the interview and were not apparent during the recruitment phase. Characteristics of the included participants are described in Table 1.

Of the included participants, most had research and clinical education and training (n=10), one had clinical training only, and one had training only in business administration. Six (55%) were

male and five (45%) were female. Nine (82%) represented or influenced policy decisions for more than one type of organization/institution.

Table 1: Characteristics of Group

Participant #	Educational Training	Sex	Involvement in conducting Systematic Reviews	Years in Decision Making Role	Type of organization/institution they represent/influence decisions for
1	Clinical and Business	Male	None	10-15 years	National Association
2	Clinical	Female	A few	10-15 years	Hospital/Clinic
3	Research and Clinical	Male	A few	5-10 years	Hospital/Clinic and a National Society
4	Research and Clinical	Female	Many	5-10 years	Government (provincial and national) and University
5	Research and Clinical	Male	Many	5-10 years	Government (provincial), University, National Network
6	Research and Clinical	Female	Many	0- 5 years	University, Government (federal), National Network
7	Research and Clinical	Male	Many	5-10 years	University, National Network and International Involvement
8	Not included				
9	Research and Clinical	Female	A few	15 - 20 years	Hospital/Clinic and University
10	Research and Clinical	Male	Many	0- 5 years	Hospital/Clinic and University
11	Research and Clinical	Male	Many	More than 20 years	Hospital/Clinic, University, Health Innovation Centre
12	Research and Clinical	Female	Many	More than 20 years	Hospital/Clinic and Government (federal and Provincial)
13	Not included				

Through conducting a thematic analysis, 4 major themes emerged from the data: 1) content, 2) format, 3) expertise, and 4) actionability.

Decision-makers commented on a number of factors relating to preferences in the type of content included in a summary and the way a summary is formatted. They shared perspectives on the

actionability of the recommendations in the summary they reviewed and other summaries in general. Finally, they commented on the role of experts in the context of trusting a summary and those who engaged in the process of creating it, as well the reliance on experts for making judgements and decisions in the absence of strong evidence. The details below elaborate on some of the codes that emerged under the four themes; these are also summarized in Tables 2-5. Appendix F outlines the size of each theme and codes.

Content

As anticipated, the content of an evidence summary was of great importance to decision-makers. Specific categories related to content are detailed in Table 2 with supporting quotes. Clarity and conciseness were very important, including having clear key messages with no unnecessary text, ensuring clear and consistent terminology, and providing definitions as needed. We found variability with respect to presentation of statistics: while some, particularly those with more familiarity with research, wanted to see the data, others found this to be "extra noise" distracting from the key messages. Participants highlighted the need for sufficient context or background information to understand the problem and set the stage for decision-making. With respect to the evidence provided, participants often expressed wanting more details about the individual studies. Further, participants wanted information on quality of the evidence, including risk of bias or methodological concerns of individual studies and overall quality of the body of evidence (e.g., GRADE assessments).

Table 2: Content

Category	Number of participants who discussed this	Number of times this was coded	Summary	Quotes
Clarity and Conciseness	10	29	Clarity and conciseness were very important. This applied to: Having clear key messages and ensuring they are straightforward and there is no ambiguity in what is being said, no unnecessary words. Terminology ensuring definitions were clear and that there was consistent use of terms – misuse, non-medical use, NMUPO, abuse etc.	**Key messages:** P10: "If the message is that even the little evidence that we have sort of raises alarm bells around short-term opioid use for questionable indications that maybe it should just be a more straightforward statement to that effect." P12: "It needs to be really clear with no unnecessary kind of words on the page." P9: "In general, I do think that less is more. You want to deliver your message. There's only so much that people can digest and then you can take them or let them know where to go to get more details." **Terminology:** P3: "You guys really need to get some sort of definition in there early, because lifetime implies almost lifelong." P11: "You do vary your terminology somewhat. Like you go from nonmedical use of opioids in the title and then I guess for instance, you have disorders that kind of came out under key message one, but then key message two, you determine opioid use disorder or opioid misuse. And is that the same as nonmedical?"

Use of statistics in summary	9	11	Decision-makers had mixed preferences for the use of statistics in a summary. While some with extensive research experience and familiarity with statistics found comfort in the reporting of statistics, the general message was that they added extra noise into the summary but could be incorporated in the tables for those who want it.	P12: "I would get rid of that. For me it's kind of extraneous noise and for most people who don't have research backgrounds, they find it like messy and takes away from the flow of the sentence." P2: "I'm not a statistician so when you start to get into RR's, an RR 1.33 means nothing to me. Absolutely nothing to me… I think some of these can come out and be in the tables instead, because the front page is really busy." P6: "I'm always very suspicious of evidence summaries that don't have any numbers or data. But also, you don't want so much that you can't digest it easily, you know?"
Background Specific to Issue	8	14	Decision-makers commented on the need for more information to understand the problem and set the stage for decision making. For example, decision-makers wanted information about: 1) age and sex differences and why adult evidence cannot be applied to children, as well as differences between children and adolescents; 2) the importance of ensuring pain is adequately treated and the risks of not treating it adequately and the effectiveness of opioids vs non-opioids; 3) commenting	**Age and sex differences:** P2: **"**It would be nice to especially put in a bit of neurobiology, of what's happening in the brain to understand why that risk is higher in an adolescent population than it is for a 35-year-old population." P3: "Whenever you look at this research, age groups in pediatrics is a huge issue. There's a significant difference in a two-year-old and a 12-year-old. Not only in maturity but in actual behaviour." P7: "Is there any additional research that suggest why these findings in adults, which are quite worrisome would not translate into a young adult or late teenager population?" P2: "Did we ask the sex question, or did we ask the gender question? Because those are two very, very

			on the current state of the literature, and what influential studies are already stating about patients and drug factors influencing risk of opioid misuse; and 4) context of opioid exposure within the studies, e.g. setting and dosage	different questions. And that's something we are very aware of, in Peds, because of genetic, sex differences in pain, and understanding a bit more about them." **Treating pain** P7: "I think that basic piece as to how the comparative effectiveness of opioids versus non opioids for pediatric pain, I think is worth covering." **Current state of literature and known risk factors:** P12: "You could say that historically these other publications have found that opioid naive people who are given a prescription opioid have a 5.3% likelihood of still taking it at one year and here were the risk factors. I mean, that Shah study really gives a nice overarching context to begin with, but they didn't comment on whether that was misuse." P12: "The dose of the opioid hasn't, wasn't really well described and we know that low doses are associated with low risk and the number of doses and the prescriptions. So, duration of prescription is another risk factor that we know is associated with long-term use." **Context of exposure** P3: "Is there any differentiation between children who had short-term exposure to opioids while in hospital versus a short-term exposure while at home?"
Quality and Strength of evidence	6	12	Two participants commented on wanting to see GRADE being used to assess the	P4: "I think it was, it's important to know from a grading perspective, you know, high, medium or low impact."

			strength of evidence, and four commented on the quality of the studies and better capturing risk of bias concerns.	P11: “I don't know if you deliberately didn't put a lot of risk of bias or that in there, you'd use the term insufficient evidence maybe.” P2: “It would be nice to even have a... how did you determine it was good vs fair vs poor. And even if it could be a brief "these were the three characteristics of a good study."

Format

With respect to the format of the evidence summary, decision-makers commented on the following: the usefulness of tables to reduce overcrowding the summary and accessing supplemental information; the importance of having brief, one page summaries that are not text heavy; their preferences for seeing infographics and other visual depictions of information, e.g. bolding, font and colours; hyperlinks for accessing studies; having a step by step display of the systematic review methodology; and finally, the importance of providing enough information in an easily digestible format. Preferences for detail also varied depending on the end user, where those with strong research backgrounds typically liked having access to more details. Specific categories related to format are detailed in Table 3 with supporting quotes.

Table 3: Format

Category	Number of participants who discussed this	Number of times this was coded	Summary	Quotes
Use of tables	11	16	Decision-makers commented on the usefulness of tables for those who wanted more details about the studies and highlighted the potential role tables can play in making the summary less crowded. Two participants also mentioned that they would have liked to see links to the actual studies within the tables.	P9: "I certainly wouldn't put less than this within the table. I think what's, what's in the table now is currently quite good, Um, I was trying to think if you could summarize what's in first page and those bullet points in a table somewhere else so that someone could just look at it and scan it if they want to." P5: "I like this first table. It's very good for somebody like myself. Most of my questions were answered. I still am curious enough. I'd love to click on the specific manuscript for example, to be able to look at some of the details. But I don't think the answer is to put more detail in your table."
Infographics and Visual Representation	10	24	The text heaviness of the evidence summary was frequently commented on, finding the right balance between providing information and not overloading decision-makers with text is a key element of effective evidence summaries. A majority of decision-makers commented on the use of infographics as an effective way of doing this. Participants also appreciated	P2: "It's really busy, so if I were handed this on a busy shift, I'd be looking for words you need to know now, as a way to decrease the amount in the summary. Yeah, because when I look at it. This is the key message; do I need all this additional information to back up the key message in the front page." P2: "I like the use of the colour because then it makes it easier to read." P6: "The only thing that occurred to me was, I mean, it is very text heavy. By the time you get to the second page, there's really effective use of tables and figures,

			seeing colour in the evidence summary, highlighted the importance of using larger font size, bolding to draw attention to key items and the use of hyperlinks to access included studies. Preferences for detail also varied depending on the end user, where those with strong research backgrounds typically liked having access to more details.	which I found really useful. I just wondered if there was some way on the first page to summarize some of that, you know, in more of an infographic method?" P9: "Mm hmmm, it's almost even, you know, it's the type of decision-makers you're talking about as well. Like if you're talking about an executive team in a hospital that's way too much detail and way too much medical detail and statistics. Um, but if you're talking about, um, you know, a clinical group that's going to write policy, uh, specifically, you know, from pharmacy on how to use opioids, they want that detail. So, it's like there isn't one size that fits all." P11: "I would say the things I look for or I've heard would be you know, fewer words is better, use of infographics or pictures to illustrate clarity around what does it really tell you because I think the problem with evidence people is, they often are so methodologically driven and detail is so important to them and the nuance is so critical."
Single-page documents	8	15	Having a one-page document that was quick and brief was also a preferred format. Decision-makers did not mind having an appendix to accompany it with further details, however they preferred to have the main summary as one page.	P12: "So, I would say it needs to be in one page. Like otherwise people aren't going to read it. It needs to be very clearly laid out. It's good if it can have some white space on the page that you, people don't want to pick up something that's really cluttered and I think bullet points are more helpful than narrative. P9: "I think I find a general approach is to have, you know, one page that has the very high-level summary. This is what you need to know. And then for people that

				want more details, they can, they know where to go and find it.”
Showing methodology	4	4	Four decision-makers commented on the display of methodology and that they liked seeing the visual explaining all the steps.	P9 “I really liked your slide two or your page two of the systematic review methods where you basically say, this is how we did it. So I know I can trust your conclusions because you had a very rigorous methods, you detailed everything, you have your flow diagram that tells me how many you started with and the whole process to go through in terms of um, what papers you're drawing the conclusions from and the quality of those papers that you've ended up with. So, all that's really helpful.”

Actionability

The actionability of the results and recommendations was a main topic of discussion. In general, decision-makers found that there was a lack of actionability or ability to prompt any major change because of the insufficient evidence from the systematic review. The issue of insufficient evidence from systematic reviews was also raised where decision-makers recognized that when the quality of relevant primary studies included within the systematic reviews and resources for conducting systematic reviews is limited, they must turn to other sources and move forward with decision-making. Specific categories related to actionability are detailed in Table 4 with supporting quotes.

Table 4: Actionability

Category	Number of participants who discussed this	Number of times this was coded	Summary	Quotes
Actionability of results and recommendations	10	24	In general, decision-makers found that there was a lack of actionability or ability to prompt any major change due to insufficient evidence. However, they found that the evidence indicated that some caution is needed when prescribing opioids, even for a short-term period.	P4: "But I would feel it would be difficult to, for me to make a recommendation to my decision-maker, which is the CEO about something, if the evidence was weak. It would be hard to change policy that way." P7: "Yeah, I mean, you know, if you're suggesting all this caution, then you are essentially endorsing the possibility of a connection, but you're also seemingly and also espousing shared decision making and, uh, that's all fine, but it would be nice to, you know, I guess maybe this is part of the KT, but just some kind of guidance or tool and what that might look like. Should pharmacists or a prescriber use specific tools prior to prescribing opioids in this age category…that would be more specific and actionable." P9: "You know what, I don't know that there really is enough to actually change anything at this point. I mean, you're certainly raising the issue. But if I'm thinking as a clinician, you know, how do I interpret this? How do I, how am I going to use this? Am I going to not prescribe an opioid for an acute painful injury or episode because I'm worried, they're going to go on and have long-term opioid use? No, I wouldn't not use it because we need to treat the pain that's happening at present. "

				P2: “But again, its insufficient evidence, but at least it's giving us food for thought as to how we address these issues. And certainly, the guidance for future research.”
Evidence beyond SRs and SR shortcomings	4	10	There were some discussions on the actionability of systematic reviews in general, and that often evidence from systematic reviews can be limited based on the quality of the studies being synthesized and the process for undertaking one can be so time consuming that decision-makers need to turn to other resources in order to move forward with decision-making.	P9: “The problem is usually that there's limited information to be able to make the kind of decisions that you want to. So, I mean systematic reviews are only as good as the papers that actually informed the systematic reviews. And sometimes by the time you actually sort that out and really remove any papers that are of lower quality, you're really not able to have robust recommendations for decision making or, or intervention. So that's the bigger challenge with systematic review, but where there is good evidence, it's very helpful.” P2: “So we’ve changed for example, several of our policies over the years as new evidence emerges, and it’s not necessarily coming out of the systematic reviews because someone doesn’t necessarily have time to redo all of that based on the new evidence, but it’s certainly up to people who do the systematic reviews to update them on a regular basis.” P3: “I’ve always been one of those people who’s like “I know there’s a problem because I’m a clinician, and I don’t know what the solution is. But I can synthesize the number of possible solutions and can start testing”, whereas, especially in the last 10 or 12 years, there seems to have been a move towards “we think there’s a problem, so we’re going to perform a systematic review to state whether or not there’s a problem and then we’re going to start thinking about if there are any solutions… And so, to me, that is

				quite slow moving… Many times, we know there's a problem and we just need to move ahead and try to sort it out."
Knowledge mobilization	8	22	While there was insufficient evidence to prompt any change towards children's health policies, decision-makers acknowledged the importance of mobilizing knowledge about opioid safety amongst parents and patients and the need for clinicians to have these tools and knowledge to pass information along.	P12: "So you've said that patients and parents should be educated on using prescribed medication correctly. So, I think that's correct, but I think even more fundamental than that is that the healthcare professionals need the knowledge and skills to be able to do that. Maybe that's implicit, but I think it's such a strong thing that needs mentioning. So, I think we really need to raise the just raise awareness that this is absolutely critical that healthcare providers need to have the knowledge and tools to be able to provide this information to the children and families." P4: "So, for decision-makers, I would think one of the things I'd want to worry about is does my facility or my, um, whatever I'm managing, do I have a return opioid policy? Do I have accurate, you know, education tools and things to rely on to create high reliability and safety? What information am I providing parents or patients? And then the third implication that came, bounced out at me is, a lot of the studies are within adolescence. Adolescents don't necessarily listen to their parents. So, what information do we need to think for schools or you know, social media or something like that. Are there implications for that?"

SR = Systematic Review

Expertise

Expertise was another major theme that was raised in the interviews, where decision-makers identified barriers to accessing research and systematic reviews, particularly due to the length and complexity of the reviews, as well as restrictions front-line workers have with accessing research databases. Further, they noted that a degree of trust typically needs to be given to those who are developing an evidence summary, and that this trust could reduce the amount of detail needed within the summary. Additionally, they commented on their reliance on experts and consensus when tasked with decision making in the context of weak evidence. Specific categories related to expertise are detailed in Table 5 with supporting quotes.

Table 5: Expertise

Category	Number of participants who discussed this	Number of times this was coded	Summary	Quotes
Clinician Research Barriers	4	8	Decision-makers who identified as clinicians also commented on some barriers for accessing research, such as; 1) access to databases (specifically for front-line health care providers), and 2) length and complexity of systematic reviews. This emphasizes the importance of needing evidence summaries to mobilize knowledge from systematic reviews.	P2: "The issue is having access to them as a clinician is at times difficult because I use my university sign on and get onto the university library, am I'm able to find data because of that. but front line care providers don't have that access, and so, the more we have open access, the more someone is able to find it but then that's why we rely on people like your group, to come up with the evidence summary that we can then trust and be able to review and look at the KT or dissemination of that information." P3: "And the systematic reviews that I would've read in the past, they are tough reads. It's a long read, it's not what a lot of clinicians find and go out and look for." P6: "Uh, I would say that sometimes they're far too long, uh, and it's hard to extract the key messages. So that's been a barrier in the past. But in terms of actually accessing the reviews, no, I have had no problem."
Prescribing habits and other options	9	19	Decision-makers commented on the overprescribing of opioids and the need for clinicians to consider alternative non-opioid pain medications, where possible, while also considering patient	**Other non-opioid options:** P5: "There's been a trend toward using less and less as we have understood that things like ibuprofen… medication like ibuprofen is really very effective and maybe almost as effective as opioids in some circumstances. So, I guess the bigger, so I think… what do we know? This review is only part of the picture. So

			safety, values and preference when making a decision.	that broad question is…. kids who have fractures with substantial amount of pain over several days thereafter… do we really need to incorporate narcotics in that to get maximum effect? P12: "So, if there is evidence, it should inform what we do, if there's no evidence then we should be trying to do the right thing and the right thing for me when it comes to opioids is doing everything that we can to avoid using opioids. But if other non-opioid pharmacotherapy and physical strategies and psychological strategies together are not working, then we should be prepared to have a trial of opioids that are linked to specific goals around pain and function and that we should be monitoring patients with regards to achieving those goals. And if those goals are not met, then we should have a plan for tapering and discontinuation." P10: "You know, in a sense you go back to your Hippocratic oath of do no harm. I mean you sort of do your best to make an evidence informed decision and, and you know, I think that we're all about what are the priorities, like it probably is patient safety, and patient comfort is obviously a really important consideration as well."
Trusting Experts	8	16	Decision-makers acknowledged the importance of being able to trust those who developed the evidence summary to a large degree to avoid being overloaded with information.	**Trusting those who developed the summary** P1: "I consider myself more of a typical end user, where I have to go by the opinion of the experts, and their position and knowing that it's credible." P2: "But the most important thing is trusting that whoever has created the evidence summary has the

			Additionally, many decision-makers mentioned that they would rely on expert consensus in the absence of clear evidence.	background and knowledge to stand behind the summary and say, "trust me and what I have created".” P11: “I think the problem with evidence people is, they often are so methodologically driven and detail is so important to them and the nuance is so critical. And usually the reader, or as a policy person or as a clinician, who doesn't really care about systematic… you want to trust whoever's put this together, but you do want to know, well, what is the sense of things.” **Trusting expert consensus when evidence is weak** **P9: “**Yeah, I mean that's, that's very common, especially in pediatrics where there really isn't good evidence for a lot of things. You have to make the best, informed decision that you can, so you have to look to see what the evidence is and what the basis for that evidence is. And then there's, unfortunately, you have to rely on expert opinion or expert discussion, consensus, being very mindful of what the limitations of that are. So, I think whenever you rely on expert opinion, you always have to keep an open mind, you have to have a plan to revisit it should new evidence emerge. You can't be as much of a stickler on following that because it is based on opinion as opposed to evidence.” P5: “So I guess that's the way, you see in developing guidelines, pathways, a committee needs to make a decision, but the degree to which they jump up and down about it, say emphatically, clinicians, thou shalt do this or that, that should be reserved for those things for which there's absolute certainty. And for those things that aren’t, that you are honest, you admit limitations

				and you say, “this seems reasonable based on consensus and whatever else you can come up with”. But you, you would never expect somebody to absolutely conform. That's the way I guess I typically think of it.”

Discussion

This qualitative study provided rich data to understand what decision-makers want in an evidence summary. The themes that emerged from the data were: content; format; expertise; and actionability. Decision-makers included researchers, clinicians and policy-makers and as a result, there is no "one size fits all" approach for an evidence summary because information needs vary depending on the type of decision-maker and the participant's background and interests, as well as the nature of the decision and resulting output.

The results of this study reinforce previous findings on content and format preferences. For example, a scoping review that looked at barriers and facilitators for the use of systematic reviews among policy makers and health care managers also identified the importance of one page summaries, white space, clear and concise key messages, findings that are tailored to different types of decision-makers, and summaries that contextualize findings for decision-makers by outlining implications of findings.[13] Similarly, others have commented on decision-maker preferences for having colours, tables to present results, hyperlinks, single page summaries, white space and key messages in plain language. [2, 5 14,] The findings also reinforce the importance of trust in the research process and that when limited information is presented to decision-makers (e.g. through the form of an evidence summary), they will default to trusting the experts who developed the summary rather than relying on the entire review as a basis for influencing policy.

A majority of decision-makers commented on the issue of insufficient evidence and how this becomes a barrier for action and decision-making. In the case of our review, there was insufficient evidence to answer our research question about the association between short-term therapeutic opioid use in children and subsequent nonmedical opioid use. Under these circumstances, decision-makers suggested that recommendations for safe practice are outlined; for example, that clinicians need to consider alternative non-opioid pain medications, where possible, while balancing this with careful consideration of not leaving pain untreated or undertreated. In the absence of clear evidence on the association between short-term exposure to

opioids in childhood and nonmedical use, decision-makers emphasised the importance of patient safety, values and preferences informing prescribing practices.

The feedback from decision-makers offers new insight about the usability of our systematic review findings and how best to package our results for end-users. Participants in the study generally agreed that the insufficient evidence from the systematic review could not prompt any major changes, however, the evidence was enough to raise caution around the use of opioids for children and provide new knowledge that could be mobilized, not only for policy decision-makers, but for future researchers, health care providers, patients, and families. While the findings may not prompt specific policy changes, they provide a useful basis for decision-makers to evaluate whether further investment in research is needed to better understand the risks of short-term exposure to opioids in childhood.

A significant portion of the feedback received through these interviews was specific to our systematic review; however, there were key findings from our qualitative study that could be interpreted more generally and applied to evidence summaries as a whole. Table 6 offers general considerations that researchers could refer to when developing evidence summaries for healthcare decision-makers.

Table 6: Considerations for Developing an Evidence Summary

Category	Action Items
Content	
Clarity and conciseness	Provide clear key messages that are straightforward with no unnecessary words. Provide definitions and use terms consistently.
Incorporating statistics	Avoid overuse of statistics; consider including data/results tables as an appendix for those who want this detail.
Context and background info	Include sufficient background information to help readers understand the problem and set the stage for decision making, this should include the state of the literature and details of exposure/intervention within included studies.
Quality and strength of evidence	Include risk of bias considerations for the individual studies, as well as assessments of certainty of evidence for key findings.
Format	
Use of tables	Use of appendices with tables to avoid overcrowding the summary is essential. Consider links to studies referenced in tables.
Infographics and visual representation instead of too much text	Use infographics, colours, bolding, larger font, white space and hyperlinks.
One pagers, quick and brief	Limit to one page (or include key take-away messages on first page) with other information in appendix.
Describing methodology	Provide brief explanation or visual demonstration of systematic review methodology to increase credibility.
Actionability	
Clear action items	Describe clear action items for decision-makers as they relate to healthcare practices, research and policy.
Expertise	
Trusting the experts	Assume that decision-makers have already given researchers a degree of trust. Minimize excessive or unnecessary information or details.

Limitations

Given that there was no "one size fits all" for an evidence summary, the applicability of these findings for all decision-makers is limited. Our inclusion criteria were broad and included decision-makers who influenced children's health policies in varying degrees and settings. Furthermore, some participants were very familiar with the topic of discussion (i.e. use of opioids in children's health), whereas others were more familiar with systematic reviews and/or may have been generalists in the field of children's health. Decision-makers' backgrounds could have influenced the extent of information that they looked for relating to context for the systematic review, terminology used, methodology of the systematic review and the use of tools such as Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

Further, the study reinforces the challenge of making very specific recommendations for policy decision-makers when evidence is weak or lacking. The insufficiency of the evidence being presented limited the overall value that the evidence summary could bring for healthcare decision makers, however, the summary does identify an important gap in the scientific evidence that requires prioritization and investment from funders.

This study focused primarily on the information needs of decision-makers who influence children's health policies, however, a majority were clinicians who highlighted the need for knowledge mobilization tools targeted for front-line workers and families as well. Our evidence summary includes some general recommendations for these groups but in order to be more usable, the summary would need to be modified and designed in a way that resonates with these different groups. Feedback was not obtained from decision-makers following the modified evidence summary (Appendix G); as a result, it is possible that further changes would be suggested if a second opportunity for feedback was available.

Conclusion

Overall, decision-makers want clear, succinct and actionable evidence summaries with the key messages on the first page and details on subsequent pages. For the most part, methodological

details can be limited or appended as decision-makers typically trust the experts who have completed a systematic review. Study details and statistics/analyses should be limited or contained within an appendix. Finally, evidence summaries will only ever be as useful and influential as the findings of the review and their strength/certainty.

Our evidence summary, which has been tailored to the needs and preferences of decision-makers, can be used to contribute to a provincial and national dialogue on how to manage children and adolescents with pain in the acute care system. Such dialogues may lead to actions and further research aimed to improve care and ensure the best possible outcomes for patients. Further, the information within the evidence summary could be repurposed for other audiences such as patients, parents and health-care providers.

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Appendices

Appendix A: Evidence Summary

Non-medical Use of Opioids following Short-term Therapeutic Exposure in Children: Summary of Results from a Systematic Review

Background

- Despite an overall decline in opioid prescriptions in Canada, healthcare visits, hospitalizations, and deaths due to opioid-related harms have continued to rise for children and youth.
- Healthcare providers are facing significant challenges when making analgesic prescribing decisions as the risks of misuse associated with short-term therapeutic opioid use remain unclear.
- Given these concerns, researchers at the University of Alberta conducted a systematic review to evaluate the evidence available to support this decision-making.
- The purpose of this document is to summarize the findings of a comprehensive systematic review.
- This summary may **assist informed decision-making by clinicians and policy makers and guide future research**.

Summary of Findings

Key Message 1: Preliminary evidence suggests a link between lifetime therapeutic opioid use and opioid use disorder and/or misuse; however, there is <u>insufficient</u> evidence available to determine whether <u>short-term</u> therapeutic exposure to opioids in childhood is definitively associated with developing these disorders.

- Only one study specifically examined the association between short-term therapeutic exposure to opioids and misuse. This dental study showed that individuals with therapeutic opioid use had 15 times higher risk of non-medical use within 365 days than the non-exposed group (RR 15.1, 95% CI 12.4, 18.3). Caution: these results included those who were exposed in early adulthood and those who potentially had prior lifetime opioid exposure.
- Four studies did not specify duration of therapeutic exposure to opioids. One study showed that those with therapeutic exposure were more likely to have subsequent non-medical use within 1-2 years (RR 2.36, 95% CI 1.28, 4.27). Another study showed that a legitimate prescription for opioids in 12th grade independently increased risk of future opioid misuse by 33% (RR 1.33, $p<0.05$). A longitudinal study showed that those exposed by age 18 were more likely to have past-year nonmedical use of prescription opioids at age 35 (aOR 1.74, 95% CI 1.10, 2.76). The fourth study showed that among youth who reported past 30-day nonmedical use of prescription opioids, 6.4% reported lifetime medical use while 44.4% reported never having used legitimate prescription opioids.
- Eleven non-comparative studies reported prevalence of misuse following therapeutic exposure. Only two studies of clinical populations indicated that the study sample had short-term therapeutic exposure to opioids. One study found that 11% of trauma patients had an opioid antagonist injection and 8% were given an overdose diagnosis over the 5-year follow-up period. The other study showed that one of every 2611 study opioid prescriptions was followed by an opioid-related emergency department visit, hospitalization, or death, with more than two thirds being unrelated to misuse and approximately one quarter (23%) of adolescent cases being attributed to opioid abuse or self-harm.

Key Message 2: Currently, there is insufficient evidence to confirm <u>risk factors</u> for opioid use disorder or opioid misuse following short-term therapeutic exposure.

- One study that examined short-term therapeutic exposure found that females, those with previous non-opioid substance abuse, and those between 16-18 years (vs. 22-25 years) had higher risks, while those of Asian race/ethnicity had lower risk (relative to whites).
- Age, sex/gender, and race/ethnicity have been the mostly commonly explored risk factors in other studies; however, results are often contradictory across studies, and the majority of included studies did not specify duration of therapeutic opioid exposure.

Implications for Practice and Research

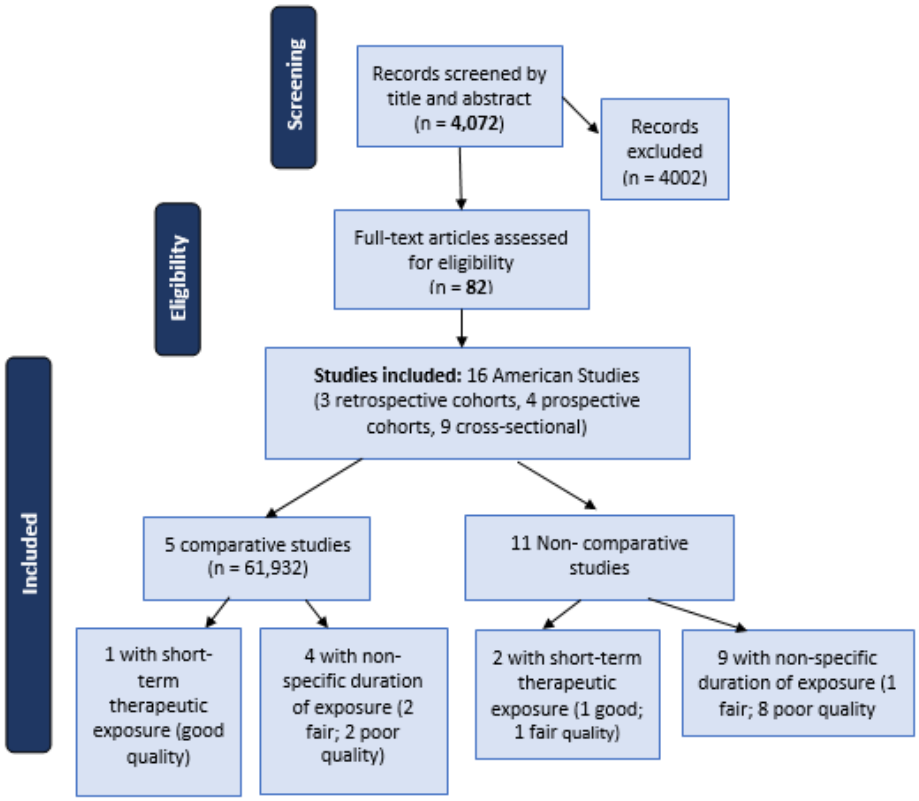
Practice: Patients and parents should be educated on using prescribed medication correctly, how to dispose of or manage unused medication, and the potential risks of deviating from the prescribed regimen (i.e. potential risk of opioid misuse or lack of therapeutic effect). Careful consideration of the risks and benefits of opioid use should be undertaken prior to prescribing short-term opioids; if prescribed, close follow up for the development of complications is warranted.
Research: More rigorous studies are needed to examine the association between short-term therapeutic exposure in children and misuse. Studies should: report duration of exposure; compare those exposed to an unexposed group; and control for whether the opioid-exposed group is opioid-naïve at baseline (i.e., no prior therapeutic or non-therapeutic exposure).

Systematic Review Methods

Search Strategy
1. A medical librarian searched online databases from inception to May 2019 2. Reviewers scanned reference lists of included studies
Study Selection
Two reviewers independently screened titles and abstracts, then full text of potentially relevant studies using pre-established criteria.
Quality Assessment
Quality was assessed using the National Institute of Health Quality Assessment tool. Two reviewers assessed quality and resolved discrepancies through discussion.
Data Analysis
Due to clinical and methodological heterogeneity we did not combine data. Results are reported narratively.

Criteria Used to Select Studies		
Criteria	Included	Excluded
Population	18 or below at time of exposure	Over age 18 at time of exposure
Intervention	Short-term therapeutic exposure to opioids or therapeutic exposure for undefined period	Non-therapeutic exposure to opioids, or evidence of long-term exposure (i.e. more than 30 days)
Comparator Group	Any control strategy, include even if no control strategy was in place	-
Outcomes	Opioid use disorder, opioid misuse, abuse, dependence or addiction	All other outcomes
Setting	Any setting	-
Language	French and English	All other languages
Study Design	Publications reporting quantitative primary research	All others

PRISMA Flow Diagram



Evidence Summary Tables

Table 1. Summary of Results from Comparative Studies

The following table summarizes key characteristics and results of the comparative studies included in this review.

Author, publication year	Study design Clinical setting	No. of participants analysed (% female) Age, y	Misuse prevalence within opioid exposed group	Exposed vs unexposed group comparison
Schroeder 2019	Retrospective cohort Dental	44,664 (53%) 16-25	115 (**6.3%**) of 1814 subjects aged 16-18 were **diagnosed with opioid abuse within 365 days**	Among entire sample, 866/14,888 (5.8%) exposed and 115/29,776 (0.4%) non-exposed had at least one diagnosis of abuse at the time of outcome assessment. Overall **RD=5.3 (95% CI 5.0 to 5.7); RR=15.1 (12.4, 18.3)**
McCabe 2013	Prospective cohort Online survey, administered in two Southeast Michigan school districts	2,050 (50%) NR (grades 7-11)	Of those who had appropriate use in year 1, 7% (12/172) reported any NMUPO in year 2.	7% (12/172) of those with appropriate medical use only in year 1 had NMUPO in year 2. Whereas, 3% (46/1,556) of those with no use in year 1 had NMUPO in year 2. **RD=4% (95% CI 0.1, 7.9); RR=2.36 (1.28, 4.37)**
Miech 2015	Prospective Cohort Survey/questionnaires administered in classrooms	6,220 (NR) 17 to 18	Not reported	**RR 1.33 (P<0.01)** (95% CI 1.04, 1.7); a legitimate medical prescription for opioids in 12th grade is independently associated with a 33% increase in risk of future opioid misuse (association concentrated among individuals who have little to no history of drug use and/or a strong disapproval of illegal drug use at baseline).
McCabe 2016	Prospective cohort Surveys at school and then questionnaires at age 35	4,072 (57%) 17 to 18	**4.4% of those with medical use at age 18 reported NMUPO at age 35**.	At age 35, the past-year prevalence of NMUPO was 2.4% among individuals who reported no medical use or NMUPO at age 18 and 4.4% for medical use only (**aOR of nonmedical use at age 35 was 1.74 (95% CI 1.10, 2.76)** for those who had medical use only at baseline (age 18).
Osborne 2019	Cross-sectional US Metropolitan areas	11,048 youth completed the survey (48%) 10 to 18	Of 345 that reported past 30-day non-medical use of prescription opioids, 22 (6.4%) reported lifetime medical use of prescription opioids.	**Among 345 that reported past 30-day NMUPO, 22 (6.4%) reported lifetime medical use of prescription opioids**, and 153 (44.4%) reported never having used legitimate prescription opioids.

NMUPO = non-medical use of prescription opioids; OR = odds ratio; OUD = opioid use disorder; RD = risk difference; RR = risk ratio; NR= not reported

Table 2. Summary of Results from Non-Comparative Studies

The following table summarizes key characteristics and results of the non-comparative studies included in this review.

Study	Study Design Setting	No. of Participants Analysed (% female) Age at baseline, y	Opioid Misuse Prevalence
Clinical samples			
Bell 2019	Retrospective Cohort Trauma centres	736 (26%) 12-18	11% of patients with opioid exposure had an opioid antagonist injection and 8% were given an overdose diagnosis over the 5-year study period
Chung 2018	Retrospective Cohort Various clinical settings	401,972 children with 1,362,503 filled outpatient prescriptions for opioids, Medicaid population (52%) 2-17	One of every 2611 study opioid prescriptions was followed by an opioid-related ED visit, hospitalization, or death. 71% of adverse event were related to therapeutic use and not misuse. However, approximately 1/4 of adolescent cases of adverse events were attributed to abuse or self-harm. (71/310 = 23%)
Select high school samples			
Veliz 2014	Prospective cohort Survey in Michigan schools	1,540 (50%) 11-17	5.0% indicated using too much of their opioid medications on at least 1 occasion and 2.7% used their opioid medications to get high on at least one occasion during the 3-year study period. 1.8% indicated using too much of their prescribed opioid medication on 3 or more occasions and 0.7% indicated using their prescribed opioid medication to get high on 3 or more occasions during the 3-year study period.
Boyd 2006	Cross-sectional Online survey in Detroit public school district	1,017 (50%) 10-18	94/262 (36%) with prescribed use also had nonmedical use. Those with lifetime medical use of pain medication had a 9.80 aOR (95% CI 5.86,16.39; OR adjusted for gender, race, grade level) of past year nonmedical use relative to those with no medical use.
Vosburg 2016	Qualitative pilot study Massachusetts Recovery High School	31 (35%) Average 18	Of the 31 who had prescription opioid abuse, 3 reported that they first obtained the prescription opioids legally (i.e. therapeutically)
McCabe 2011	Cross-sectional Survey in two Southeastern Michigan school districts	2,597 (49%) Grades 7-12	Of the 369 individuals prescribed pain medication in the past-year, 74 (20.1%) reported past year medical misuse.
National samples			
Schepis 2018	Cross-sectional National survey	13,585 (49%) 12-17	3.5% of 81 (home-schooled) had medical misuse, 1.1% of 10,723 (in good school) had medical misuse, 2.0% of 1341 (in poor school) had medical misuse, 2.9% of 593 (not in school) had medical misuse
McCabe 2013	Cross-sectional National survey in classrooms	8,888 (53%) Average 18	647/8888 participants (7.3%) reported past-year nonmedical use of prescription opioids. Among these, 104 (14.4%) indicated they used opioids from their previous prescription only.
Schepis 2009	Cross-sectional National in-home survey	36,992 (NR) 12-17	Lifetime prevalence for misuse was 10.1% for opioids (includes all sources including those prescribed by a doctor). 22.2% of those who misused opioids had obtained them from a physician.
Schepis 2019	Cross-sectional National survey	103,920 (49%) 12-17	44/103,920 (0.4%) reported misusing drugs from a physician source only. Of those who misused opioids from physician sources only, 12.9% (CI= 95% 9.5-17.4) had an opioid specific substance use disorder, 5.2% had opioid abuse and 7.7% had opioid dependence.
McCabe 2012	Cross-sectional Surveys in high schools across US	7,374 (48%) Mode 18	287 of 6673 (4.3%) had prior medical exposure to prescription opioids before using them nonmedically. 12.9% of high school seniors reported lifetime nonmedical use of prescription opioids. The percentage of students who ever received a prescription for opioids and never used nonmedically in their lifetime was 9.3%.

NMUPO = nonmedical use of prescription opioids

Table 3. Summary of Results of Risk Factor Investigations

The table below summarizes risks factors that were identified as part of this review.

Study (quality)	Results for Risk Factor Analyses
Short-term therapeutic opioid exposure	
Schroeder 2019 (good)	□Youth ages 16-18 had higher odds of misusing opioids than the older age group (aOR for 22-25 years 0.8, 95% CI 0.7,1.0) □Females had higher odds of opioid abuse than males (aOR 11.5, 95% CI 9.4-14.8) □Asian race/ethnicity had lower odds compared to white race/ethnicity (aOR 0.3, 95% CI 0.2-0.6) □Previous non-opioid substance abuse was associated with higher odds of opioid abuse (aOR 4.5, 95% CI 3.4-5.9)
Duration of therapeutic opioid exposure unclear	
Miech 2015 (poor)	□Among 12th grade students who have little experience with illegal drug use and strongly disapprove of marijuana use, a legitimate opioid prescription predicts opioid misuse after high school.
Bell 2019 (good)	□ An opioid overdose diagnosis was more prevalent amongst the following groups: those who were of age 15 and over (in comparison to 14 and under), of black race (in comparison to white race), males, those in adult hospitals than pediatric hospitals, had a major injury (in comparison to a minor/moderate injury), had a penetrating injury (in comparison to a blunt or other type), and those who were insured by other insurers (in comparison to Medicaid, self-pay and private insurers).
Chung 2018 (fair)	Risk factors were reported for all patients with opioid-adverse events, including those who did not deviate from their prescribed regiment (i.e. did not misuse opioids): Ages 12-17 had a higher incidence rate ratio (IRR) (2.22) of opioid adverse events than ages 2-5, those with current use had a higher IRR (2.09) than those with recent use, those who used opioids for 1-3 days had a higher IRR (3.31) than those who used for 8 or more days, those with a high dose of opioids had a higher IRR (1.86) than those who had a low dose.
Schepis 2018 (poor)	□Among adolescents who were home-schooled 3.5% (95% CI 0.8, 14.2) reported past year medical misuse of opioids, which was higher than those in school with good school adjustment (1.1%, 0.9-1.4), in school with poor school adjustment (2.0%, 1.2-3.5), and not in school (2.9%, 1.7-5.0). However, statistical tests comparing the latter three groups showed no statistically significant difference. □Adolescents poorly engaged in school or not in school appear especially in need of interventions to limit PDM and associated SUD symptoms.
Veliz 2014 (fair)	□Males who were continual sports participants had higher odds of past-year medical misuse in order to 'get high' on at least 1 occasion (aOR = 4.01, 95% CI = 1.13, 14.2) when compared to males who did not participate in sports. Among females, no association was found between participation in organized sports and medical misuse.
McCabe 2013 (fair)	□NMUPO (from their previous prescription) was significantly higher for females compared with males (17.2 vs 11.5 p<0.001)
Schepis 2009 (poor)	□Of those who were prescribed by a physician (assuming medical use) and had reported misuse (n=432): 259 (17.5%) were Caucasian, 81 (27.2%) were Hispanic/Latino, and 92 (36.6%) were African-American (p<0.001 relative to Caucasian; p=0.041 relative to Hispanic/Latino). □African-American adolescents were more likely to misuse opioids obtained from a physician (n=36.6%) compared to Caucasians (17.5%, p<0.001) and Hispanic/Latinos (27.2%, p=0.041).
Boyd 2006 (poor)	□There were no differences between White and African American students in their reports of medical or nonmedical use of prescription pain medication. □As grade level increased so too did prevalence rates of substance use, including both medical and nonmedical use of pain medications.
Schepis 2019 (poor)	□28.3% of males reported prescription drug misuse from a physician source compared with 20.6% of females (p=0.0001).
McCabe 2012 (poor)	□Racial/ethnic differences with respect to history of medical use and NMUPO: white students had significantly higher rates (p<0.001) of medical use and NMUPO (12.3%, 5.6% respectively (n=4015)) compared to African-Americans (3.6%, 1.9% respectively (n=713)) and Hispanics (3.9%, 1.6% (n=993)). □Lifetime prevalence of NMUPO was 11.8% among females and 13.8% among males.

NMUPO = nonmedical use of prescription opioids

Appendix B: Interview Questions

General Questions

1. Please describe your role within the organization you work with and the types of decision-making you are typically tasked with (e.g., policies within local health systems/clinics, national policies, other, etc.).
2. How long have you been in a decision-making role?
3. What is your educational background (clinician-training, research training, management training) and the extent of your research experience?
4. What was the most memorable evidence summary you have read to date? And what stuck out in your mind, when thinking about that summary?
5. Have you even been involved in conducting a systematic review or being a clinical consult on a systematic review(s) (and if yes, how many)?
6. Systematic Reviews are generally considered the most robust method for synthesizing evidence. Have you ever referred to systematic reviews when using research to inform policy?
    a. If yes, were your past experiences with systematic reviews useful for informing your policy recommendations/decisions? Were there any barriers to accessing and using systematic reviews?
    b. If no, why don't you use them? Were there barriers to accessing and using systematic reviews in the past?
    c. If you don't use systematic reviews, what information do you use to inform policies?

Executive Summary Review

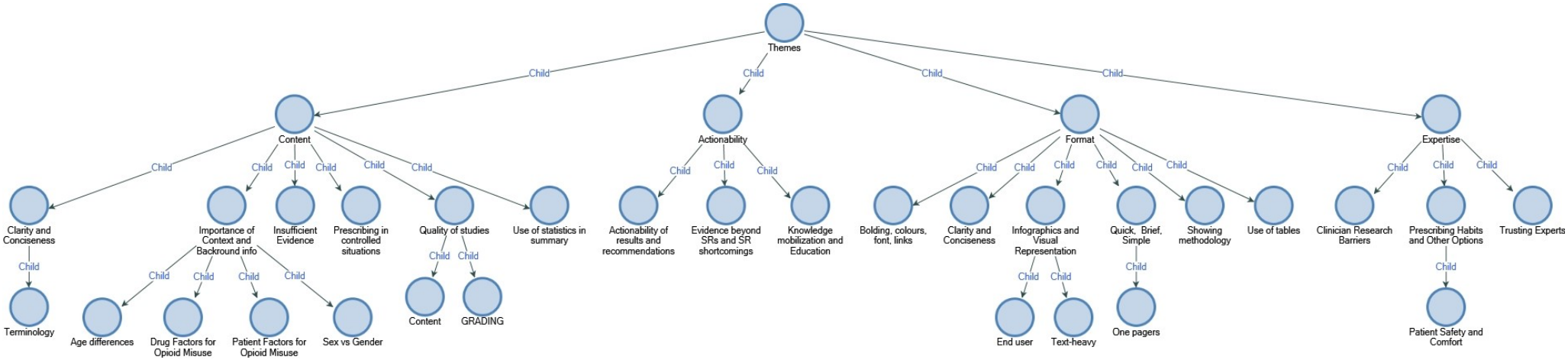
- Please take ten minutes to read through the executive summary and think about your role as a decision-maker or influencer and how these findings may or may not be usable for influencing decision-making with respect to children's health policies.

Questions on Evidence Summary

7. Please tell me in your own words, what the take home message was in the summary you read.
8. Was the information presented to you in the executive summary relevant to your job and the role you may have in influencing policies?
9. What key messages did you take away from the information that was presented to you? How did you interpret the results (e.g. do you think the evidence shows an association between short-term exposure to opioids and future misuse)? Why or why not?
10. Any suggestions for making it more useful/readable?
11. Did you identify any gaps that could prevent these findings from influencing policies/decisions with respect to the short-term therapeutic use of opioids in children's health?
    a. If not, would this information be usable for influencing policies?

12. Do you have any other preferences for how and what type of information should be presented in order to help inform policies (e.g., more/specific results, specific analysis such as risk ratios or others, more details about the individual studies, more interpretation and less number, etc.)?
13. What do you do if the evidence available to you is weak or lacking?
14. How likely are you to search for systematic reviews in the future, when looking for information that could influence children's health policies?

Appendix C: Coding Tree



Appendix D: Audit Trail – 3 phases

Phase 1 Node Export

Name	Files	References	Theme	Secondary Theme	Sub theme
Communicating with Teens	1	1	Actionability		
Patient Safety and Comfort	2	2	Actionability	Experts	
Lack of actionability	3	5	Actionability		
Evidence beyond SRs and SR shortcomings	3	6	Actionability	Experts	
Actionability of Recommendations	4	6	Actionability		
Knowledge mobilization	4	6	Actionability		
Having Standards and Guidelines for Prescribing	2	7	Actionability	Content	
Communicating with Parents and Patients	6	7	Actionability		
End user	7	11	Actionability	Experts	
Prescribing habits and other options	9	17	Actionability	Experts	
Patient Factors for Opioid Misuse	1	1	Content		
First Opioid Exposure	1	1	Content		
Prescribing in controlled situations	1	1	Content		
Sex vs Gender	1	1	Content		
Terminology	1	1	Content		
Drug Factors for Opioid Misuse	1	2	Content		
Applicability to Canadian Population	1	3	Content		Background
GRADE-ing	2	4	Content		
Quality of studies	4	5	Content		
Definition of opioid misuse	3	7	Content		
Age differences	5	8	Content		Background
Use of statistics in summary	7	8	Content		
Importance of Context and Background info	6	11	Content		
Insufficient Evidence	8	11	Content		
Clarity and Conciseness	8	15	Content	Format	
Lack of clarity	1	4	Content	Format	
Clinician Research Barriers	4	8	Experts		
Trusting Experts	8	11	Experts		
Showing methodology	3	3	Format		

One pagers	5	5	Format		
Bolding and colours	6	8	Format		
Text heavy	9	10	Format		
Quick, Brief, Simple	8	12	Format		
Use of tables	9	13	Format		
Infographics and Visual Representation	8	15	Format		

Phase 2 Node Export

Name	Files	References
Themes	0	0
Actionability	0	0
Actionability of results and recommendations	8	14
Applicability to Canadian Population	1	3
Communicating with Parents and Patients	6	9
End user	8	13
Evidence beyond SRs and SR shortcomings	4	10
Having Standards and Guidelines for Prescribing	2	7
Knowledge mobilization	4	6
Lack of actionability	6	8
Patient Safety and Comfort	2	2
Prescribing habits and other options	9	18
Returning unused opioids	2	4
Content	0	0
Age differences	5	8
Clarity and Conciseness	9	19
Definition of opioid misuse	3	7
Drug Factors for Opioid Misuse	1	2
GRADE-ing	2	4
Importance of Context and Background info	8	14
Insufficient Evidence	8	11
Patient Factors for Opioid Misuse	1	2
Prescribing in controlled situations	1	2
Quality of studies	5	8
Sex vs Gender	1	1
Terminology	3	5
Use of statistics in summary	9	11
Expertise	0	0
Clinician Research Barriers	4	8
End user	6	11
Evidence beyond SRs and SR shortcomings	3	6
Patient Safety and Comfort	2	2
Prescribing habits and other options	8	16
Trusting Experts	8	16
Format	0	0
Bolding, colours, font	6	9
Clarity and Conciseness	9	19
Infographics and Visual Representation	8	16
One pagers	5	5

Quick, Brief, Simple	8	12
Showing methodology	4	4
Text heavy	9	12
Use of tables	11	16

Phase 3 Node Export

Themes and Codes
Content
Clarity and Conciseness
Use of statistics in summary
Importance of Context and Background info
Quality and strength of studies
Format
Use of tables
Infographics and Visual Representation instead of too much text
One pagers, quick and brief
Showing methodology
Actionability
Actionability of results and recommendations
Evidence beyond SRs and SR shortcomings
Knowledge mobilization
Expertise
Clinician Research Barriers
Prescribing habits and other options
Trusting Experts

Appendix E: Reflections

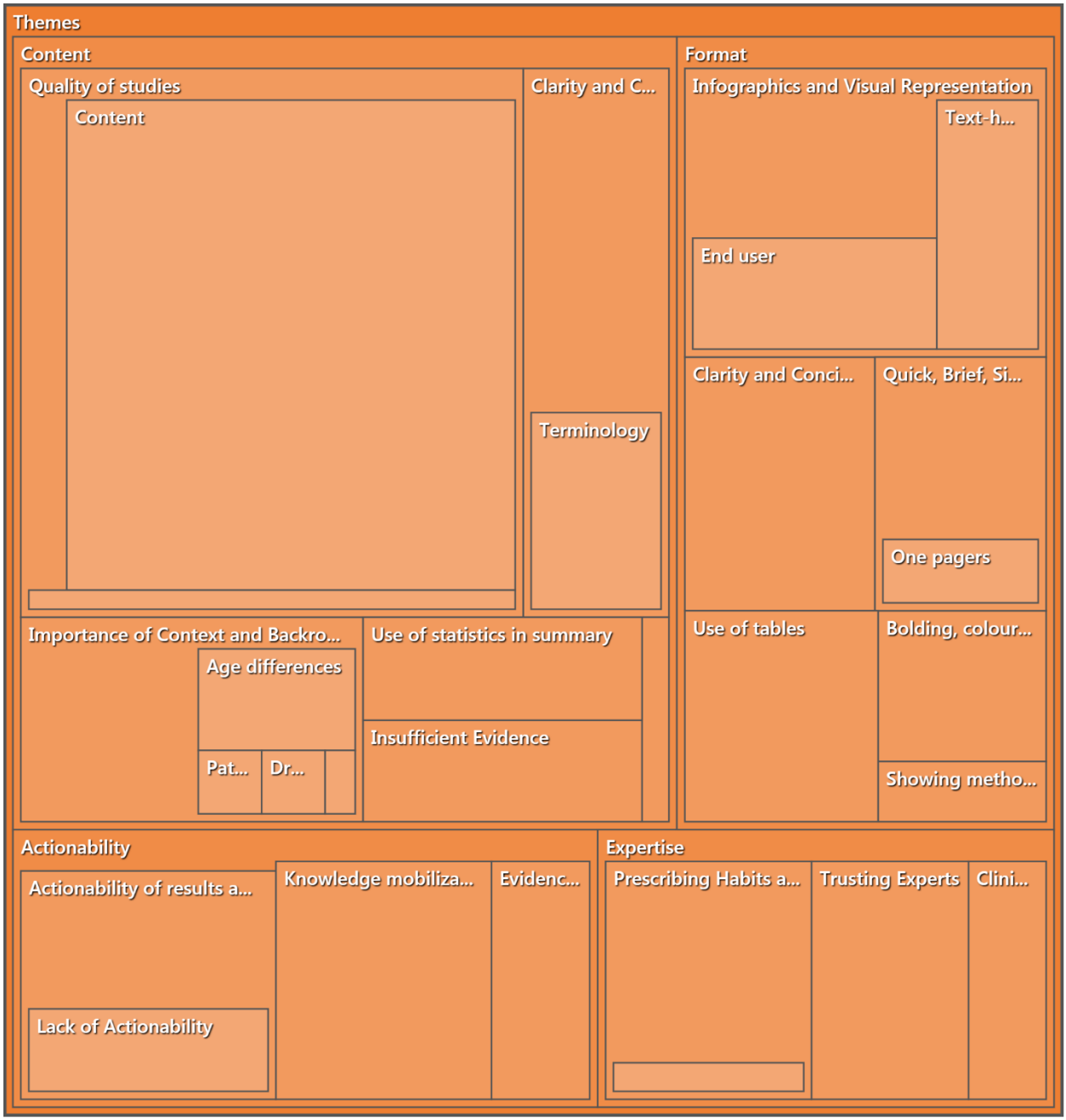
- Interviews, people brought a lot of important limitations: e.g., Canadian population, setting (drug administered in controlled setting vs at home), background (risks for addiction in adolescent vs adults), and non-medical use because of pain vs actual misuse is very different. We need to be able to differentiate that, which in most of the studies they do not (only the ones where they ask, to get high, etc.)
- Inclusion – Participant 8 and 13 do not meet inclusion criteria, will exclude.
- How to ensure I am not being too selective with codes – sought advice from research team and members of ARCHE. Attended workshop on qualitative research methods to expand knowledge of coding.
- Emerging themes:
    - Clarity and Conciseness – more that clarity and conciseness was missing
    - Infographics
    - Insufficient evidence – this is an obvious one, because it's already stated in the evidence summary
    - Actionability – more around lack of actionability of results and recommendations
    - End user, researchers like detail, policy-makers and front-line clinicians don't. Familiarity with SRs varies
    - Prescribing habits and other options/alternatives.
        - Encompasses over prescribing, considerations about alternatives, etc.
    - Bolding and Colours
    - Quick, brief and simple
    - Text Heavy/Too many words
    - Importance of Background and Context
        - E.g. does adult research apply to children, why and why not
    - Age differences came up as a subtheme as well.
        - Developing brain, etc.
    - Putting trust in experts – related t presenting methodology and stats and information to having expert consensus when making decisions in the absence of strong evidence.
    - Insufficient evidence – didn't feel like that's going to be a theme worth mentioning because it's kind of spelt out through the evidence summary
    - Use of tables – people liked that
    - Things that came up fewer times: GRADING, Quality of Evidence, One pager

- How do we develop evidence summaries for decision-makers in general, there are different types of decision-makers?
- 4 big areas:
    - Format – clarity, conciseness, tables, bolding, colours, text heaviness, infographics, elements that go into it.
    - Content – background (it's important to set the stage and demonstrate information about persistent use, different between children and adults, what we currently

know about risk factors, etc., context, information about prescribers, data itself (put actionability separate, quality, GRADE.

- Actionability:
  - Derives from simplicity and clear
  - Drawing that trust
- Experts: who's doing and preparing it for the SR, and then end users, relying on experts for consensus, decision making.

Appendix F: Size of themes and codes



Appendix G: Revised Evidence Summary

Key changes:

- Additional background includes: explicitly stating research question, and current knowledge around use of opioids.
- Less text under summary of findings, removal of stats such as relative risk and confidence intervals from key messages
- Larger fonts
- More colour
- Hyperlinking to text

Non-medical Use of Opioids following Short-term Therapeutic Exposure in Children: Summary of Results from a Systematic Review

Background

- Opioids are recommended and used for the effective management of acute moderate to severe pain not otherwise relieved by first-line interventions. Analgesic prescribing decisions are challenging as the risk of future nonmedical opioid use is unclear and opioid related deaths and overdoses continue to rise.
- Harbaugh et al. found that 4.8% of opioid-naïve youth and young adults had persistent opioid use after surgery[7].
- Nonmedical use is the use of opioids without a prescription or in a way other than prescribed (e.g. to get high).
- Researchers at the University of Alberta conducted a systematic review to determine whether:
  1) short-term therapeutic exposure to opioids in childhood is associated with the development of opioid use disorder or future nonmedical use; and
  2) risk factors associated with these outcomes.

Summary of Findings

Key Message 1: There is **limited evidence** to determine whether *short-term* therapeutic exposure to opioids in childhood is **definitively** associated with future nonmedical opioid use or development of an OUD; **however, this review suggests a link between *lifetime* therapeutic opioid use (unknown duration) and nonmedical opioid use.**

- We included 21 observational studies (49,944,602 participants).
- One study demonstrated that short-term therapeutic exposure may be associated with opioid abuse; 4 showed an association between medical and nonmedical opioid use without specifying duration of exposure. Other studies reported on prevalence or incidence of nonmedical use after medical exposure to opioids.

Key Message 2: The existing evidence on risk factors for nonmedical opioid use or OUD following short-term therapeutic exposure is **unclear**, **however, older adolescents with short-term therapeutic exposure during their lifetime may be at higher risk of nonmedical use.**

- Age, sex/gender, race/ethnicity and previous substance abuse were commonly explored risk factors in our sample; however, results were inconsistent across and sometimes within studies

Implications for Practice and Research

Practice:

- Until the risks are more clearly defined, it is recommended that prior to prescribing short-term opioids, healthcare providers carefully consider the risks, benefits and alternatives, and educate patients and caregivers about safe, and appropriate use and when to seek reassessment.

Research:

- More rigorous studies are needed to examine the association between short-term therapeutic exposure in children and nonmedical use.
- In order to adequately answer our question, studies should: reliably assess and report duration of opioid exposure, dosage, preparation type, and setting; compare those exposed to an unexposed group; control for opioid-naivety at baseline; differentiate between reasons for nonmedical use; rigorously assess risk factors; and evaluate the potential misuse associated with exposure to different opioids, as some may put patients at higher risk of misuse than others.

Systematic Review Methods

Search Strategy

1. A medical librarian searched online databases from inception to September 3, 2020
2. Reviewers scanned reference lists of included studies

Study Selection

Two reviewers independently screened titles and abstracts, then full text of potentially relevant studies using pre-established criteria.

Quality Assessment

Quality was assessed using the National Institute of Health Quality Assessment tool. Two reviewers assessed quality and resolved discrepancies through discussion.

Data Analysis

Due to clinical and methodological heterogeneity we did not combine data. Results are reported narratively.

Study Inclusion Criteria	
Population	Under age 18 or grade 12 and below at time of exposure
Intervention	Short-term therapeutic exposure to opioids or therapeutic exposure for undefined period
Comparator Group	Any control strategy, include even if no control strategy was in place.
Outcomes	Opioid use disorder, opioid misuse, abuse, dependence or addiction
Setting	Any setting
Language	French and English
Study Design	Publications reporting quantitative primary research

Results

PRISMA Flow Diagram

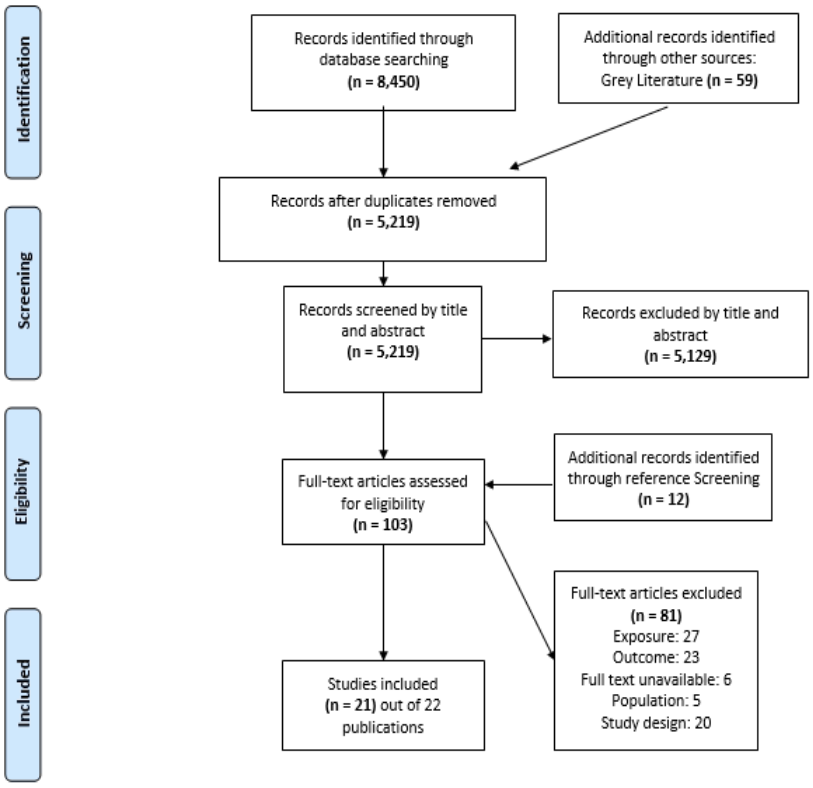


Table 1. Summary of Included Studies

Study Characteristics	N	%
Study Design		
Non-comparative	16	76.2
Prospective Cohort	4	19.0
Retrospective Cohort	5	23.8
Cross-Sectional	12	57.1
Gender		
Female[a]	N/A[a]	48.4[a]
Mean Age[b]	15.5	N/A[b]
Study Setting		
School	9	42.9
Home	2	9.5
Dental	1	4.8
Trauma centre	1	4.8
Entertainment venues	1	4.8
Other	7	33.3
Duration of Exposure Specified	4	19.0
Outcomes Reported		
Misuse/Nonmedical Use	12	57.1
Overdose	6	28.6
Abuse	1	4.8
Opioid Use Disorder	2	9.5
Country - USA	21	100

[a]Sex breakdown reflects 11 studies and includes some adult populations as some studies did not present the sex distribution by age.
[b]Mean age was calculated across seven studies where such a calculation was possible

Limitations

Limitations: A majority of studies did not specify duration of exposure, were of low methodological quality and samples may not have been opioid naïve.

Evidence Summary Tables

Table 1: Comparative Studies Results (N=5)

Author, publication year (Study Years)	Main Results: Exposed vs unexposed group comparison	Quality Assessment Score (NIH tool)[a]
Schroeder, 2019 (2015)	- Opioid abuse-related diagnosis (total sample): • Opioid exposed: 866 of 14,888 (5.8%) • Opioid non-exposed: 115 of 29,776 (0.4%) - Adjusted absolute **RD: 5.3%** (95% CI, 5.0%-5.7%; P<0.001) [Estimates adjusted for race/ethnicity and previous non-opioid substance abuse] **RR=15.1** (95% CI, 12.4-18.3)[b]	13/14
McCabe, 2016 (1976-2016)	- Nonmedical use at age 35: • No medical use or NMUPO at 18: 1.0 (reference) • Medical use only at 18: aOR 1.74 (95% CI, 1.10-2.76; P<0.05) - Adjusted for race/ethnicity, sex, geographic region, urbanicity, parental education, substance use, and cohort year. - **RR: 1.83** (95% CI, 1.15-2.89)[b] ; **RD: 1.98%** (95% CI, 0.15%-3.80%)[b]	9/14
McCabe, 2013a (2009-201)	- NMUPO in Year 2: • No use in Year 1: 46 of 1,556 (3.0%) • Medical use in Year 1: 12 of 172 (7.0%) - **RD= 4.0%** (95% CI, 0.1%-7.9%)[b] ; **RR=2.36** (95% CI, 1.28-4.37)[b]	10/14
Miech, 2015 (1990-2012)	- Risk of opioid misuse at 23 years following opioid prescription in grade 12: • **RR 1.33** (95% CI, 1.04-1.7; P<0.01) [Adjusted for sex, race, parent education, use of other substances, course marks, and disapproval of marijuana use] - Based on a stratified analysis, the association varied based on predicted probability of opioid misuse, where the largest association was in lower risk strata.	7/14
Osborne, 2019 (2008-2011)	- Past 30-day NMUPO: • No lifetime medical use of prescription opioids: 153 of 9,955 (1.5%) • Lifetime medical use of prescription opioids: 22 of 526 (4.1%) - **RR 2.72** (95% CI, 1.76-4.22)[b] - **RD 2.65%** (95% CI, 0.92%-4.37%)[b]	6/14

[a] Questions that were not applicable to the study or its design did not count negatively towards the score, more details available in Supplemental e-table 2.
[b] Calculated by review authors
Abbreviations: aOR = adjusted odds ratio, CI= confidence interval, IQR = interquartile range, NMUPO = nonmedical use of prescription opioids, NR = not reported, OR = odds ratio, OUD = opioid use disorder, RD = risk difference, RR = risk ratio/relative risk

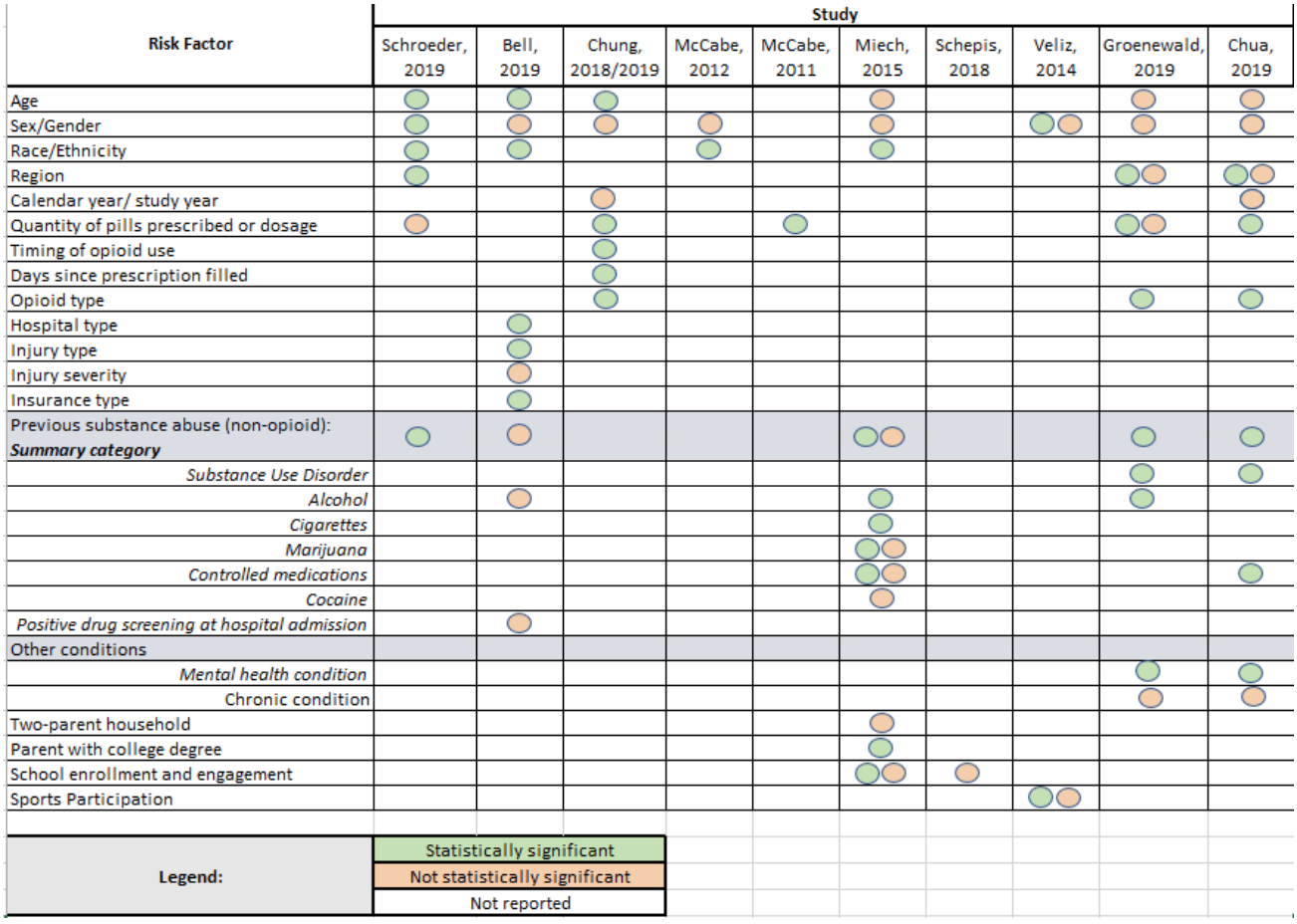
Table 2: Non-comparative Studies Results (N=16)

Author, Publication year (Study Years)	Results: Opioid Misuse Incidence or Prevalence [a]	Quality Assessment Score (NIH tool)[b]
Short-term exposure to opioids		
Bell, 2019 (2011-2013)	- 51 of 668 (7.6%) were given an overdose diagnosis over the 5-year follow-up period. - 72 of 668 (10.8%) had an opioid antagonist injection. - (All therapeutically exposed to opioids)	11/14
Chung, 2018&2019 (1999-2014)	- Opioid-related adverse events: 437 of 1,362,503 (0.03%). Adverse events include opioid-related emergency department visit, hospitalization, or death (71.2% were not related to misuse). - 71 of 437 (16%) cases of adverse events were attributed to abuse or self-harm; all occurred among adolescents (ages 12-17). - Total misuse prevalence: 71 events of 1,362,503 (0.005%) prescriptions. - (All therapeutically exposed to opioids)	11/14
Unknown duration of exposure to opioids		
Boyd, 2006 (2003)	- 94 of 262 (36%) with prescribed use also had nonmedical use. - Past year nonmedical use (lifetime medical use of pain medication vs. no medical use): aOR: 9.80 (95% CI, 5.86-16.39). [Adjusted for gender, race, grade level]	7/14
Burke, 2020 (2011 – 2014)	- OUD Hazard ratio for ages 11 to 17: 0.35 (0.28–0.43); P<0.001. - Non-fatal OD hazard ratio: 0.29 (0.09–0.89); P=0.03. - Fatal OD hazard ratio: 0.23 (0.03–1.65); P=0.14. - *Reference group: 45-54 years. Results were considered significant by study authors at P<0.007	11/14
Hudgins, 2019 (2015 and 2016)	- 19.2% (95% CI, 16.4–22.1) of adolescents who were misusing opioids had obtained them from a single physician source and 2.2% (95% CI, 1.3%–3.2%) obtained them from multiple physicians (based on extrapolated population estimates).	7/14
McCabe, 2013b (2007-2010)	- 104 (14.4%) of those with nonmedical use of opioids indicated use from previous prescriptions only. - (Calculations were based on weighted samples)	7/14
McCabe, 2012 (2007-2009)	- 287 of 6,673 (4.3%) reported lifetime medical exposure to prescription opioids prior to nonmedical use (total sample includes opioids exposed and unexposed).	7/14

	- 287 of 908 (31.6%) reported lifetime medical exposure to prescription opioids prior to nonmedical use (all were therapeutically exposed to opioids). - 621 of 6,673 (9.3%) reported receiving a prescription for opioids and only using it for medical purposes.	
McCabe, 2011 (2009-2010)	- 74 of 369 (20.1%) individuals that were prescribed opioid pain medication in the past-year reported past year medical misuse. - 67 of 369 (18.2%) reported taking too much and 34 of 369 (9.2%) reported that they intentionally got high or used to increase alcohol or other drug effects.	7/14
Schepis, 2019 (2009-2014)	- 447 of 103,920 (0.4%) reported misusing prescription opioids from a physician source only (total sample includes opioid exposed and unexposed group). Of those who misused opioids from physician sources only, 12.9% (95% CI, 9.5%-17.4%) had an opioid specific substance use disorder, 5.2% (95% CI, 2.9%-9.0%) had opioid abuse and 7.7% (95% CI, 5.5%-10.8%) had opioid dependence.	7/14
Schepis, 2018 (2015)	- 165 of 12,738 (1.3%) had reported opioid misuse in the past year. (Includes opioid exposed and unexposed sample)	7/14
Schepis, 2009 (2005-2006)	- 477 of 36992 (1.3%) of the total sample (opioid exposed and unexposed) reported opioid misuse from a physician source. - 22.2% of those who misused opioids had obtained them from a physician, the remainder had obtained opioids from non-physician sources.	7/14
Veliz, 2014 (2009-2012)	- Medical misuse (using too much): • ≥1 occasion: 74 of 1,494 (5.0%); ≥3 occasions: 27 of 1,494 (1.8%) - Medical misuse (to get high): • ≥1 occasion: 40 of 1,494 (2.7%); ≥3 occasions: 10 of 1,494 (1.8%) - (Includes opioid exposed and unexposed sample)	9/14
Vosburg, 2016 (NR)	- 3 of 31 (9.7%) who had prescription opioid abuse (i.e., used medication to get high) and 3 of 18 (16.7%) who had prescription opioid addiction (i.e., inability to stop using) reported that they first obtained the prescription opioids therapeutically.	6/14
Wei, 2019 (2005-2016)	- Among incident cases of OUD/OD in youths, 29.4% received a prescription opioid in the year prior in 2006 and 22.6% in 2016 (P-trend = 0.001) (All were therapeutically exposed to opioids).	11/14

[a] Burke 2020 did not report on prevalence or incidence of nonmedical opioid use and reported hazard ratios.
[b] Questions that were not applicable to the study or its design did not count negatively towards the score, more details available in Supplemental e-table 2.
Abbreviations: aOR = adjusted odds ratio, CI = confidence interval, IQR = interquartile range, NMUPO = nonmedical use of prescription opioids, NR = not reported, OR = odds ratio, OD = overdose, OUD = opioid use disorder, RD = risk difference, RR = risk ratio/relative risk, SD = standard deviation

Table 3: Risk Factors for Nonmedical Prescription Opioid Use by Statistical Significance



Chapter 4: Conclusions

This thesis was comprised of two studies to help inform the clinical prescribing of opioids for short-term pain management among children and youth. The first study was a systematic review that examined the association between short-term therapeutic exposure to opioids and nonmedical opioid use or the development of opioid use disorder (OUD) and associated risk factors. The second study sought to mobilize the findings of the systematic review into the most usable format for health policy decision-makers; this was done by interviewing policy decision-makers who influence children's health outcomes and understanding their information needs and preferences.

Overall, our systematic review provides a comprehensive synthesis of the existing primary research relating to our question, which to date, has not existed. The systematic review findings demonstrate that there is limited evidence to determine whether short-term exposure is specifically associated with OUD or nonmedical use of opioids; however, a number of studies suggest an association between *lifetime* therapeutic opioid use (for an unknown duration of exposure) and nonmedical opioid use. There is also limited evidence to identify risk factors for OUD or nonmedical use following short-term therapeutic exposure.

Key limitations of our systematic review are that a majority of studies did not specify the duration of therapeutic exposure to opioids and were of low methodological quality, due to their cross-sectional study design, reliance on self-reporting, inadequate measures for ensuring short-term therapeutic exposure preceded outcome, lack of controlling for confounders, and not having a comparator group. Most studies also sought to answer a different question than our own. In order to fully understand the association between short-term therapeutic exposure to opioids in childhood and nonmedical opioid use, and to inform decision-making at the policy and clinical level, additional studies are needed that reliably assess and report duration of opioid exposure, dosage, preparation type, and setting; compare those exposed to an unexposed group; control for opioid-naivety at baseline; differentiate between reasons for nonmedical use; rigorously assess risk factors; and evaluate the potential misuse associated with exposure to different opioids, as some may put patients at higher risk of misuse than others.

Further, our systematic review only reflects studies that were published up until September 4, 2020, and therefore could be missing other important and more up-to-date studies on this topic. For example, we did not include the 2021 study by Hadland et al. that reported on incidence rates of OD and OUD ranging from 0.1% to 0.3% among youth and adults who had acutely painful conditions and were therapeutically exposed to opioids.[1] Nonetheless, these new findings would fall within the nonmedical use prevalence and incidence rates that we observed in our sample, which ranged from 0.005% to 36%, and therefore would not change or strengthen our conclusions.

Until the risks for nonmedical opioid use following short-term therapeutic exposure are more clearly defined, it is recommended that prior to prescribing opioids for acute pain, clinicians should: conduct a comprehensive assessment (including an assessment for past or current OUD diagnosis at minimum); check patient's prescription history; offer a multi-modal therapy approach that only includes opioids when necessary; prescribe the lowest effective dose for 3 days or less, depending on circumstances; provide a verbal explanation and easily understood hardcopy of educational tools to patients, their families and caregivers on opioid benefits, harms, side effects and when to seek reassessment; and communicate and coordinate care with other clinicians if patients are already using opioids (e.g. for a chronic condition).[2] After opioids are prescribed, clinicians should have a plan in place to monitor, taper and discontinue medication for their patients while also staying up to date with the evidence base on appropriately treating acute pain.[2]

Additionally, it is recommended that prior to taking prescription opioids patients and/or their families and caregivers should: communicate information about their prescription and medical history with the clinician; understand their therapy options; and educate themselves about benefits, harms and side effects of opioids. After opioids are prescribed, patients, and/or their families and caregivers should safely store and dispose of unused medication,[2] monitor their condition and seek re-assessment if needed.

The second study on decision-maker information needs provided a valuable opportunity to examine how to mobilize our systematic review findings to help inform health-care policies, practice and guide considerations for future research investments on the use of opioids in children's health. Overall, decision-makers want clear, succinct and actionable evidence summaries with the key messages on the first page and details on subsequent pages. Study details and statistics/analyses should be limited or contained within an appendix.

The findings of the qualitative study reinforce the importance of trust in the research process and that when limited information is presented to decision-makers (e.g., through the form of an evidence summary), they will default to trusting the experts who developed the summary rather than relying on the entire review as a basis for influencing policy.

While the qualitative study provided an opportunity to understand the needs of decision-makers and tailor our evidence summary to meet their information needs (Appendix G), the evidence summary will not be able to support any major changes due to the insufficient evidence concluded by the systematic review. Nonetheless, Table 6 (in chapter 3) offers some considerations that researchers could refer to when developing evidence summaries for healthcare decision-makers.

Both the systematic review and the evidence summary can be used to contribute to a provincial and national dialogue on how to manage children and adolescents with pain in the acute care system. Examples of organizations that could be involved in this dialogue include but are not limited to: Translating Emergency Knowledge for Kids (TREKK); the Alberta Pain Network; Solutions for Kids in Pain (SKIP); and the Canadian Pain Task Force. Such dialogues may lead to further actions relating to opioid safety, while clarifying misconceptions about risks that are not yet fully understood. The dialogues may also prompt further research aimed to improve care and ensure the best possible outcomes for patients.

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