Protocol

Mapping the Evidence for Opioid-Mediated Changes in Malignancy and Chemotherapeutic Efficacy: Protocol for a Scoping Review

Jonathan E Constance[1], PhD; Mary M McFarland[2], BSc; Tallie Casucci[3], MLIS; Michael W Deininger[4,5], MD, PhD; Elena Y Enioutina[1], MD, PhD; Kathleen Job[1], PhD; Richard S Lemons[6], MD, PhD; Carol S Lim[7], PhD; Robert M Ward[1], MD; Venkata Yellepeddi[1], PhD; Kevin M Watt[1], MD, PhD

[1]Division of Clinical Pharmacology, Department of Pediatrics, University of Utah, Salt Lake City, UT, United States

[2]Spencer S. Eccles Health Science Library, University of Utah, Salt Lake City, UT, United States

[3]J Willard Marriott Library, University of Utah, Salt Lake City, UT, United States

[4]Versiti Blood Research Institute, Milwaukee, WI, United States

[5]Division of Hematology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, United States

[6]Division of Hematology and Oncology, Department of Pediatrics, University of Utah, Salt Lake City, UT, United States

[7]Department of Molecular Pharmaceutics, College of Pharmacy, University of Utah, Salt Lake City, UT, United States

Corresponding Author:
Jonathan E Constance, PhD
Division of Clinical Pharmacology
Department of Pediatrics
University of Utah
295 Chipeta Way
Salt Lake City, UT, 84108
United States
Phone: 1 8017128088
Email: jonathan.constance@utah.edu

Abstract

Background: Numerous reports contend opioids can augment or inhibit malignancy. At present, there is no consensus on the risk or benefit posed by opioids on malignancy or chemotherapeutic activity. Distinguishing the consequences of opioid use from pain and its management is challenging. Additionally, opioid concentration data is often lacking in clinical studies. A scoping review approach inclusive of preclinical and clinical data will improve our understanding of the risk-benefit relationship concerning commonly prescribed opioids and cancer and cancer treatment.

Objective: The aim of the study is to map diverse studies spanning from preclinical to clinical regarding opioids with malignancy and its treatment.

Methods: This scoping review will use the Arksey six stages framework to (1) identify the research question; (2) identify relevant studies; (3) select studies meeting criteria; (4) extract and chart data; (5) collate, summarize, and report results; and (6) conduct expert consultation. An initial pilot study was undertaken to (1) parameterize the extent and scale of existing data for an evidence review, (2) identify key factors to be extracted in systematic charting efforts, and (3) assess opioid concentration as a variable for its relevance to the central hypothesis. Six databases will be searched with no filters: MEDLINE, Embase, CINAHL Complete, Cochrane Library, Biological Sciences Collection, and International Pharmaceutical Abstracts. Trial registries will include ClinicalTrials.gov, Cochrane CENTRAL, International Standard Randomised Controlled Trial Number Registry, European Union Clinical Trials Register, and World Health Organization International Clinical Trials Registry. Eligibility criteria will include preclinical and clinical study data on opioids effects on tumor growth or survival, or alteration on the antineoplastic activity of chemotherapeutics. We will chart data on (1) opioid concentration from human subjects with cancer, yielding a "physiologic range" to better interpret available preclinical data; (2) patterns of opioid exposure with disease and treatment-related patient outcomes; and (3) the influence of opioids on cancer cell survival, as well as opioid-related changes to cancer cell susceptibility for chemotherapeutics.

Results: This scoping review will present results in narrative forms as well as with the use of tables and diagrams. Initiated in February 2021 at the University of Utah, this protocol is anticipated to generate a scoping review by August 2023. The results of the scoping review will be disseminated through scientific conference proceedings and presentations, stakeholder meetings, and by publication in a peer-reviewed journal.

Conclusions: The findings of this scoping review will provide a comprehensive description of the consequences of prescription opioids on malignancy and its treatment. By incorporating preclinical and clinical data, this scoping review will invite novel comparisons across study types that could inform new basic, translational, and clinical studies regarding risks and benefits of opioid use among patients with cancer.

International Registered Report Identifier (IRRID): PRR1-10.2196/38167

(JMIR Res Protoc 2023;12:e38167) doi: 10.2196/38167

KEYWORDS

opioid; opioid receptor; drug; cocaine; crack; prescription opioid; opium; war on drug; cancer; chemotherapy; drug-drug interaction; malignancy; treatment; oncology; tumor; survival; antineoplastic; cancer cell; scoping; chemotherapeutic; librarian; library science; antineoplast; cancer cell survival; cancer cell growth; addict; addiction

Introduction

This project stems from a multidisciplinary team approach to better understand the consequences of drug interactions known to occur commonly in the management and care of patients with cancer. In contrast with typical scoping review methodology comprised exclusively of clinical data, this study incorporates a more comprehensive mapping of the literature, inclusive of preclinical data. In many clinical studies, it is difficult or impossible to disambiguate patient outcomes related to opioid use from the consequence of pain or pain management. This is because opioid use is often the measure by which pain is assessed. Therefore, our approach will enable a new perspective on an old and controversial problem.

Opioid analgesics are among the most frequently administered drugs for patients with cancer, and their use often coincides with active chemotherapeutic regimens [1]. The intended target for opioid analgesics is the μ-opioid receptor (μOR) expressed within the central nervous system [2]. However, the μOR is also present in diverse cancer types [3]. In cancer cells, μOR activity can stimulate intracellular signal cascades that regulate processes of cell survival and death and can coincide with the same signal cascades triggered by cytotoxic chemotherapy [3-12]. Some clinical studies for specific cancer types have identified the μOR as a negative prognostic factor and associated with chemotherapy resistance [3,13-23].

Paradoxically, opioids have demonstrated potential to both augment and inhibit cancer cell growth and survival as well as chemotherapeutic activity. For some types of cancers, opioid use is linked to metastasis, proproliferative effects, and decreased patient survival, while in other cancer types, opioids are associated with improved cancer cell killing and improved patient outcomes [16-19,21-47]. At present, there is no consensus on the risk or benefit posed by opioids in the context of malignancy and its treatment.

While multiple clinical studies have been conducted to evaluate the relationship between malignancy and its treatment with the μOR and analgesic opioid use, interpreting the risks or benefits of opioid use on tumor growth remains challenging and often confusing. Public response to some literature reports has led to surges in demand for opioids as potential antineoplastics. In contrast, other published data have led to concern that opioids will be withheld in the presence of suffering for fear of promoting malignancy [11,48,49]. Therefore, an improved understanding of the effects routinely prescribed opioids can have on any neoplasm, cancerous lesion, or malignancy and its treatment is an urgent public health need. A scoping review approach can help meet this need by organizing the existing clinical and preclinical evidence in a manner suitable to better distinguish clinically meaningful patterns and identify key knowledge gaps.

By examining both clinical and preclinical evidence together, 3 major challenges found in interpreting the clinical literature can begin to be addressed. First, clinical studies typically have a small n and focus on a specific cancer subtype, and among these, they differ in experimental design, intervention (eg, type, timing, and route of opioid administration), and patient population. Second, clinical opioid concentration data are lacking. Opioid concentration data are critical to establish the consequences of opioid use in the context of malignancy. As opioids are characterized by high inter- and intraindividual pharmacokinetic (PK) variability, the common practice of using opioid dose as a surrogate is a highly flawed means of estimating tumor tissue concentrations [50,51]. Finally, clinical studies seeking to assess the risks and benefits of opioids related to disease progression are frequently confounded by the role of pain and pain management on patient outcomes [41,52]. Preclinical studies have the potential to fill gaps in knowledge regarding opioid effects for certain cancer models at known concentrations and are not influenced by pain.

It is to be expected that the relationship between heterogeneous forms of cancer, μOR expression, and the clinical use of various analgesic opioids (routes of administration, formulations, and patterns of use) will be complex. Nonetheless, a scoping study approach can map evidence from both clinical and preclinical studies that will augment one another in the detection of meaningful associations between analgesic opioid exposure and the potential risks or benefits to patients with cancer.

Our objective is to map preclinical and clinical study data on therapeutically relevant concentrations of opioids effects on tumor growth or survival, or alteration on the antineoplastic activity of chemotherapeutics. We will map and evaluate published evidence regarding (1) opioid concentration data from human subjects with cancer, yielding a “physiologic range” to better interpret available preclinical data, (2) patterns of opioid exposure and disease and treatment-related patient outcomes, and (3) the influence of opioids and μOR activity on cancer cell survival and growth, as well as changes in susceptibility to

clinically used chemotherapeutics. Apparent contradictions and clinically relevant knowledge gaps concerning the risks or benefits of analgesic opioid use in the context of malignancy can be better understood and clarified by using a systematic approach to catalog and examine existing literature from a pharmacologic perspective.

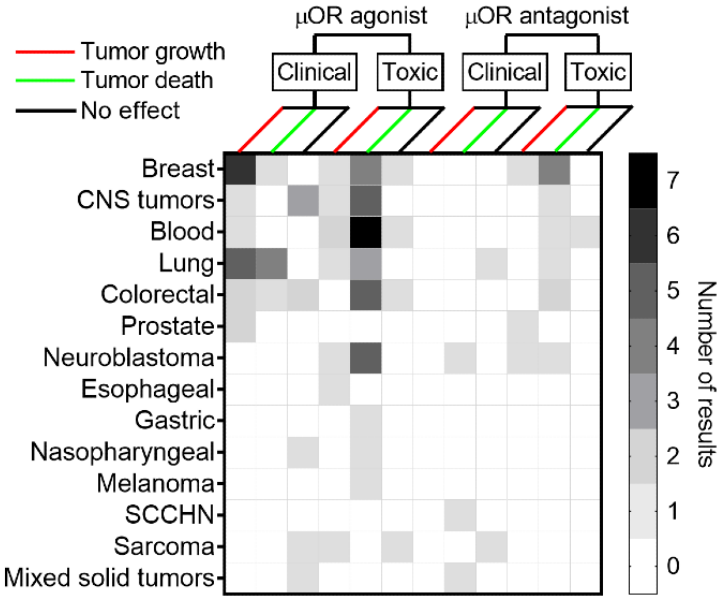
A search for existing evidence reviews or protocols on topic has been conducted (TC) in PROSPERO and MEDLINE (Ovid) on February 6, 2021. None were identified by the team as being on topic.

Prior to developing the scoping methodology protocol, a pilot study was undertaken to evaluate existing clinical and preclinical data concerning the effects of analgesic opioids on malignancy and its treatment (JEC). The central research question proposed for this study has been sought before and remains the source of much controversy. However, as the pilot study demonstrated, harnessing both clinical and preclinical information can bring into focus central concepts, such as the use of physiologic versus supraphysiologic opioid concentrations and biologic context. These concepts are often absent in the broader discussion of opioids and malignancy yet essential to solving some of the seeming contradictions. As this prestudy data, using an inclusive approach, revealed novel and informative patterns, we anticipate, a full scoping review will provide a new framework to view existing evidence and therefore, its interpretation.

The pilot study used MEDLINE (Ovid) for years 1946-2021, titles and abstracts were screened for inclusion (full publication). References of included studies were additionally assessed for relevancy and potential inclusion. Study data were collected and managed using Excel (Microsoft Corp) and GraphPad Prism (version 9; GraphPad Software, Inc). Data elements extracted were manuscript information (journal, title, authors, and year), study type (clinical [human subjects], including ex vivo), preclinical (in vivo [animal model] or in vitro), malignancy (type, subtype, model, or cell line), ligand (μOR agonist [ie, most analgesic opioids], antagonist, and partial agonist) and concentration information (eg, IC_{50}), any coinciding antineoplastic treatment, and predominant effect reported (ie, promotion or inhibition of tumor growth or chemotherapeutic activity). For ex vivo or in vitro data, "clinical" concentrations of μOR agonists were based on human subject studies reporting maximal peak concentrations experienced by adult patients with cancer receiving opioids as part of the standard of care: morphine (≤350 nM), fentanyl (≤10.8 nM), methadone (≤3.2 μM), and oxycodone (≤320 nM), and antagonists: nalmefene, methylnaltrexone, naltrexone, and naloxone (≤1 μM).

Data were extracted from 94 studies found to meet the pilot study criteria. From each study, findings were categorized as "tumor growth," "tumor death," or "no effect." A given study could report multiple findings, for instance, morphine (μOR agonist) could be found to stimulate cancer cell proliferation in a breast cancer cell line, while naloxone (a μOR antagonist) may be found to induce cancer cell apoptosis. Aggregated findings of opioid-associated effects on cancers are presented in Figure 1 [7-10,12,17-23,30,31,33-40,42,46,52-121].

Figure 1. Summary data from in vitro, in vivo, and clinical studies of opioids at "clinical" or "toxic" concentrations grouped by cancer type. μOR: μ-opioid receptor; CNS: central nervous system; SCCHN: squamous cell carcinoma of the head and neck.



The following conclusions have been drawn:

- The magnitude of the literature makes a scoping approach feasible, with fewer than 100 total clinical and preclinical studies found to meet the pilot study criteria for inclusion.
- Clinical studies evaluating opioid effects on malignancy are typically retrospective, and opioid concentration data among patients with cancer are scant.
- Preclinical studies often use opioids at concentrations exceeding those considered safe for humans. Additionally, preclinical studies which use opioid concentrations reflecting physiologically relevant concentration ranges for humans, on the basis of comparison with existing clinical concentration data, can offer important dose-response information but pose challenges for clinical interpretation.

- Important patterns emerged, including confirming the hypothesis that for cancer tissue, opioid concentration is a critical dimension to understand the effect. Clinically relevant μOR agonist concentrations were often associated with cancer growth, while "toxic" or supraphysiologic concentrations were associated more often with cancer cell killing. Concentration is a critical, but often overlooked, dimension of opioid influence on malignancy and emphasizes the need for PK data in patients with cancer.
- The expression profiles of the μOR are poorly understood for many cancer types.

Methods

Study Design

We will conduct our scoping review with guidance from the latest version of the *JBI Manual for Evidence Synthesis* [122]. Using the framework as outlined by Arksey [123] and expanded by Peters [124], we will conduct our scoping review with Arksey's [123] six stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) expert consultation involving oncologists, pain management specialists, and basic and translational scientists with expertise in pharmacology and cancer biology. Consultations will be held to inform the process of project conception, protocol development, study design and conduct, and finally, the interpretation of data, including discovery and description of key knowledge gaps [123,124]. For transparency and reproducibility, we will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) reporting guidelines in reporting our results [125].

We will use Covidence (Veritas Health Innovation), a web-based systematic reviewing platform, to screen and select studies. Citation management and duplicate detection and removal will be accomplished with EndNote (Clarivate Analytics). Research Electronic Data Capture (REDCap) tools hosted at the University of Utah will be used for data capture and charting [126].

Literature Searching

Overview

A librarian (TC) will develop and translate search strategies for the web-based databases using a combination of keywords and controlled subject headings unique to each database. Peer review of the strategies will be conducted by an information specialist (MMM) using the Peer Review of Electronic Search Strategies guidelines [127]. Preliminary searches by 2 reviewers (JEC and VY) resulted in pilot data of 94 studies, which will be used by the librarian to harvest search terms.

Electronic Sources

We will search the following databases: MEDLINE (Ovid) 1946-2022, Embase 1974-2022, CINAHL Complete (Ebscohost) 1937-2022, Cochrane Library 1898-2022 including CENTRAL 1898-2022, Biological Sciences Collection (ProQuest) 1946-2022, and International Pharmaceutical Abstracts (Ovid) 1970-2022.

Other Sources

Trial registries will include ClinicalTrials.gov, Cochrane CENTRAL Register of Controlled Trials (Wiley), International Standard Randomised Controlled Trial Number registry, European Union Clinical Trials Register, and World Health Organization International Clinical Trials Registry.

No gray literature will be designated for searching. For studies meeting inclusion criteria, references will also be evaluated for relevancy and potential inclusion.

Study Selection (Eligibility Criteria)

Inclusion Criteria

Participants

Patients in clinical studies diagnosed with any type of malignancy will be included.

Concept

We will assess the use of therapeutic opioids or assessment, direct or indirect, of opioid receptors or any other proposed mechanism for opioid action.

Context

For preclinical studies, any investigation involving any cancer cell lines, xenografts, ex vivo specimens, or relevant in vitro models of cancer related to clinically used opioids, opioid receptors, opioids purported to act upon, bind to, or influence cell processes via known or unknown targets will be included.

For clinical studies, patients diagnosed with, or survivors of, any type of cancer may or may not have received opioids at any time. Studies including patients with cancer but without opioid exposure will be included, if the study concerns biomarkers, outcomes, or other parameters related to opioid receptor or opioid influence on a malignancy or its treatment.

English-language studies will be preferred. We will chart non–English-language studies meeting or appearing to meet inclusion criteria.

Exclusion Criteria

Conference abstracts, studies exclusive to the topic of opioid addiction and abuse and not involving a cancer diagnosis or containing opioid concentration data, and those exclusive to the topic of pain and pain management and do not involve a cancer diagnosis or contain opioid concentration data will be excluded.

Team

Reviewers (JEC, VY, and KJ) will screen, independent of each other, the titles and abstracts of search results. Reviewers will then review the full text, also independent of each other's vote. Consensus will be reached through discussion among the reviewers. Any ties will be decided by a fourth independent reviewer (KMW, CSL, EYE, or RSL).

Quality Assessment

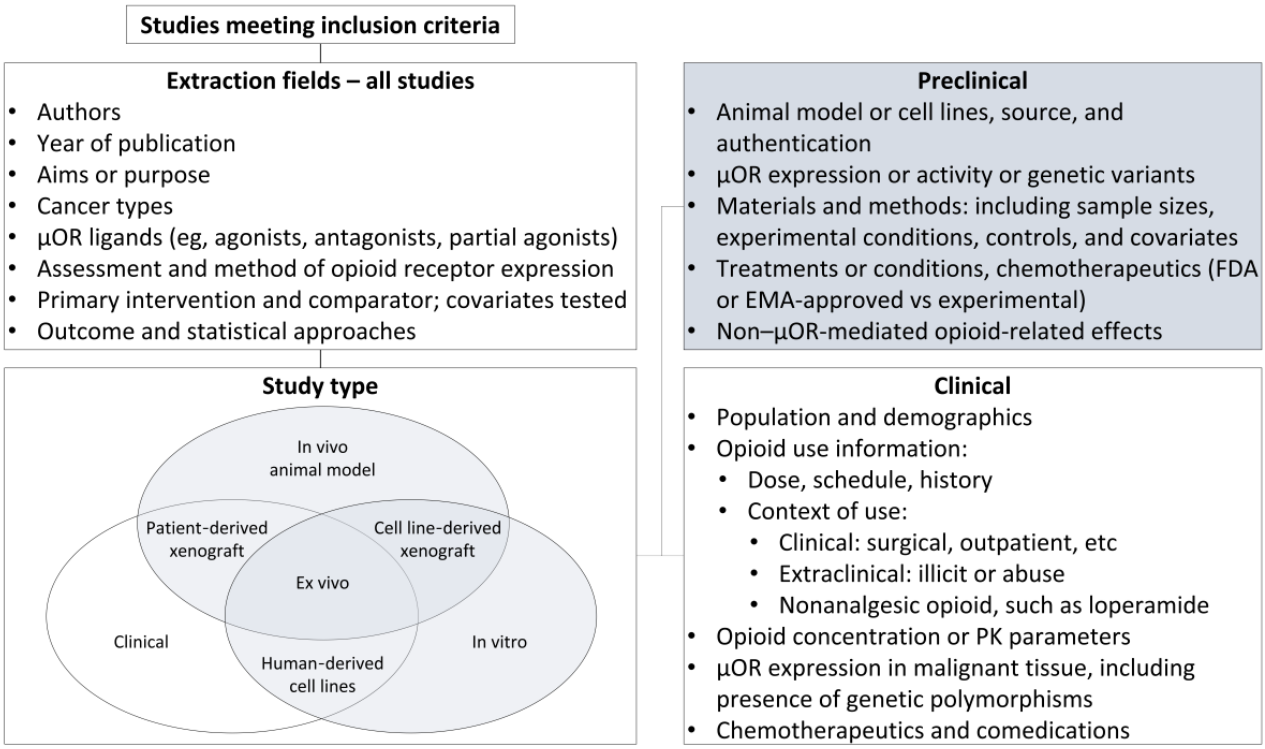
In compliance with scoping review methodology, no quality assessment of included studies will be performed as our goal is to rapidly map the literature.

Data Extraction: Charting the Data

Study data will be collected and managed using REDCap tools hosted at the University of Utah [126]. REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources [126].

Extraction fields were developed based on the initial prescoping review pilot study to adequately address the primary research question (Figure 2). This includes extraction and charting of general manuscript information as well as adopting strategies to facilitate disaggregation of studies dependent upon data type (eg, clinical vs preclinical) for analysis.

Figure 2. Data extraction and charting. Studies concerning the influence of clinically used opioids on malignancy and its treatment do not align with a strictly "clinical" versus "basic" science dichotomy. Capturing data elements from across the spectrum of study types will provide a more holistic view to benefit the goals of this scoping review and distinguishes it from other reviews. µOR: µ-opioid receptor; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; PK: pharmacokinetic.



Analysis of Evidence

Overview

A descriptive analysis will be used across all studies (eg, retrospective, clinical trial, and in vitro) and be inclusive of reported outcomes. For each cancer subtype, a descriptive synopsis of opioid-related data will be compiled, including conditions or variables associated with opioid or µOR activity influencing malignancy or its treatment. The analysis will be split into 2 main components based on the "Research question."

Component 1: Do Therapeutically Relevant Concentrations of Opioids Affect Tumor Growth and Survival?

Data extracted from clinical and basic research studies will be aggregated by µOR ligand and cancer type. µOR ligands will be categorized by class (agonist, antagonist, and partial agonist) as well as by individual entity (morphine, oxycodone, etc) and by measures of µOR ligand exposure (eg, concentrations, PK parameter estimates, dosage, and route of administration) or exposure-response (eg, IC_{50}).

For basic (animal, in vitro) study results, µOR ligands will be categorized according to effect on malignancy (ie, no effect, promotes, or inhibits malignancy), and for clinical study results, µOR ligands will be categorized according to effect on malignancy, chemotherapeutic activity via clinical indices, or patient outcome (eg, minimal residual disease and progression-free survival). Clinical data will be further categorized by covariates such as sex, age range (pediatric vs adult), new diagnosis, or relapse.

Due to differences in study design, direct comparisons between studies are not feasible. Data will be aggregated by category, and a count of results will be conducted. An illustration: consider a study that demonstrates that morphine administered in high doses, generating supraphysiologic blood concentrations (considered toxic for humans), stimulated metastases, as compared to controls, in a xenograft murine model of breast cancer. This study result would be tabulated as breast cancer,

μOR agonist, supraphysiologic exposure, promotes cancer. If, in addition, to the experimental conditions above, morphine was administered to generate clinically relevant blood concentrations, and these were associated with diminished tumor growth, this would be tabulated as breast cancer, μOR agonist, physiologic exposure, inhibits cancer.

Component 2: Do Therapeutically Relevant Concentrations of Opioids Alter the Antineoplastic Activity of Chemotherapeutics?

Data extracted from clinical and basic research (preclinical) studies, incorporating μOR ligand use coinciding with chemotherapeutics used to induce malignant cell death will be aggregated by μOR ligand, cancer type, and chemotherapeutic class.

Chemotherapeutics and μOR ligands will be classified by class as well as by individual entity. Chemotherapeutics will include conventional (anthracyclines, antimetabolites, alkylating agents, mitotic spindle inhibitors, topoisomerase inhibitors, antitumor antibiotics, platinum-based agents, corticosteroids, biologicals [enzymes], or nitrosoureas), targeted (kinase inhibitors, proteasome inhibitors, and antibodies), and agents undergoing clinical trials or considered experimental.

Measures of chemotherapeutic agent or μOR ligand exposure (eg, concentrations, PK parameter estimates, dosage, and route of administration) or exposure-response (eg, IC_{50}) will be considered.

For basic (animal, in vitro) study results, μOR ligands will be categorized according to effect on chemotherapeutic activity (ie, no effect, antagonism, or synergism). For clinical study results, μOR ligands will be categorized according to the effect on chemotherapeutic activity via clinical indices and patient outcomes studies attribute to or suggest as being related to changes in treatment efficacy. Clinical data will be further categorized by covariates such as sex, age range (pediatric vs adult), new diagnosis, or relapse.

As with component 1, it is anticipated that differences in study design and experimental conditions will preclude direct comparisons between data generated across studies. As above, data will be tabulated by category, including chemotherapy type, and a count of results will be conducted.

Ethical Considerations

This study does not require ethical approval as data and information collected, using scoping review methodology, has previously been made available through publication. The results of this scoping review will be submitted for publication in a relevant peer-reviewed journal as well as disseminated through presentations at scientific conferences. Any changes from our protocol during the conduct of the scoping review will be acknowledged and defined in the manuscript.

Results

The results of this scoping review will be presented using a descriptive narrative form as well as graphical and tabular representations. The results will be structured, as appropriate, to emphasize the effects of prescription opioids by cancer classification as well as chemotherapy type. Additionally, study results concerning data classified as preclinical, translational, and clinical will be presented distinctly to facilitate comparison. The protocol for the scoping review was initiated in February 2021 at the University of Utah and is expected to be completed in August 2023. The results of the scoping review will be disseminated through regional and national scientific conference proceedings and presentations, stakeholder meetings, and by publication in a peer-reviewed journal.

Discussion

This scoping review will map diverse studies spanning from preclinical to clinical regarding the intersection of opioids with malignancy and its treatment. The interpretation of opioid-malignancy interactions within a clinical context is often confounded by pain and its management. It is therefore both novel and necessary to include preclinical study data to identify key knowledge gaps, begin to reconcile seeming conflicting data (eg, opioids foment cancer growth vs opioids kill cancer cells) by setting a context to parse the biologic and molecular complexities of opioid impact on malignancy and its treatment, and ultimately, inform patient treatment algorithms to optimize outcomes. The knowledge presented in the scoping review will help to inform and improve the design of studies to assess the unmet medical need to understand the risks and benefits associated with opioids extending to the potential to impact cancer and its care.

This scoping review study has several strengths. First, our scoping review approach will be inclusive of studies spanning the spectrum of published data available from clinical to in vitro. Popular opinion and clinical judgment regarding the potential for opioids to affect malignancy have been deeply influenced by the publication of basic (in vitro or ex vivo) studies. Therefore, expanding this review to include both clinical and preclinical studies provides a new perspective on the topic, acknowledges that basic studies impact clinical care and shape patients' attitudes, and addresses limitations specific to the opioid-malignancy question in the context of clinical studies. Current clinical studies examining the opioid-malignancy question, often retrospective, are confounded by pain and the management of pain. Adequate pain management is associated with improved patient survival; therefore, interpretation of the potential effects of opioid use on the malignancy itself is challenging to interpret. Finally, despite the intense attention the topic has received, the key dimension of opioid concentration is often not addressed. Therefore, incorporating data from clinical and preclinical studies into this review with an emphasis on systemic opioid exposures (concentration) is warranted, and based on the preliminary data collected, aids in clarifying seemingly contradictory findings pointed to in existing reviews.

This scoping review also has limitations. Specifically, no quality assessment of the included studies will be performed. Relevant data may be missed, as we are searching for published studies only. We selected several sources and developed sensitive search strategies to increase the discovery of eligible studies.

The topic of opioid impact on cancer and its treatment is not new but remains controversial and clinically relevant. This scoping review seeks to encompass preclinical and clinical studies to generate a comprehensive landscape for interpreting the existing literature within pathophysiologic and pharmacologic contexts. We hope this study will be used to identify key knowledge gaps and advance future studies aimed at improving patient outcomes.

Acknowledgments

Research reported in this publication was supported by the Primary Children's Hospital Foundation and the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002538 (JEC) and the National Cancer Institute of the National Institutes of Health under Award Number K22CA258671 (JEC). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

Data sets will be presented in the main manuscript and as additional supporting files or made available upon request.

Authors' Contributions

JEC wrote the manuscript and provided data, VY conceptualized the project as a scoping review, TC aided in methodologic approach for scoping protocol development, and MMM provided oversight for scoping review protocol development. All authors helped in the preparation, critical review, and revision of the scoping protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer review reports.
[PDF File (Adobe PDF File), 144 KB-Multimedia Appendix 1]

References

1. Biltaji E, Enioutina EY, Yellepeddi V, Rower JE, Sherwin CMT, Ward RM, et al. Supportive care medications coinciding with chemotherapy among children with hematologic malignancy. Leuk Lymphoma 2020;61(8):1920-1931 [FREE Full text] [doi: 10.1080/10428194.2020.1749604] [Medline: 32264729]
2. Pasternak GW. Mu opioid pharmacology: 40 years to the promised land. Adv Pharmacol 2018;82:261-291 [FREE Full text] [doi: 10.1016/bs.apha.2017.09.006] [Medline: 29413524]
3. Lennon FE, Moss J, Singleton PA. The μ-opioid receptor in cancer progression: is there a direct effect? Anesthesiology 2012;116(4):940-945 [FREE Full text] [doi: 10.1097/ALN.0b013e31824b9512] [Medline: 22357347]
4. Good Z, Sarno J, Jager A, Samusik N, Aghaeepour N, Simonds EF, et al. Single-cell developmental classification of B cell precursor acute lymphoblastic leukemia at diagnosis reveals predictors of relapse. Nat Med 2018;24(4):474-483 [FREE Full text] [doi: 10.1038/nm.4505] [Medline: 29505032]
5. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, et al. Drug resistance in cancer: an overview. Cancers (Basel) 2014;6(3):1769-1792 [FREE Full text] [doi: 10.3390/cancers6031769] [Medline: 25198391]
6. Gullaksen S, Skavland J, Gavasso S, Tosevski V, Warzocha K, Dumrese C, et al. Single cell immune profiling by mass cytometry of newly diagnosed chronic phase chronic myeloid leukemia treated with nilotinib. Haematologica 2017;102(8):1361-1367 [FREE Full text] [doi: 10.3324/haematol.2017.167080] [Medline: 28522574]
7. Gupta K, Kshirsagar S, Chang L, Schwartz R, Law P, Yee D, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res 2002;62(15):4491-4498 [FREE Full text] [Medline: 12154060]
8. Lennon F, Mirzapoiazova T, Mambetsariev B, Salgia R, Moss J, Singleton PA. Overexpression of the μ-opioid receptor in human non-small cell lung cancer promotes Akt and mTOR activation, tumor growth, and metastasis. Anesthesiology 2012;116(4):857-867 [FREE Full text] [doi: 10.1097/ALN.0b013e31824babe2] [Medline: 22343475]
9. Lin X, Li Q, Wang YJ, Ju YW, Chi ZQ, Wang MW, et al. Morphine inhibits doxorubicin-induced reactive oxygen species generation and nuclear factor kappaB transcriptional activation in neuroblastoma SH-SY5Y cells. Biochem J 2007;406(2):215-221 [FREE Full text] [doi: 10.1042/BJ20070186] [Medline: 17542780]
10. Panagiotou S, Bakogeorgou E, Papakonstanti E, Hatzoglou A, Wallet F, Dussert C, et al. Opioid agonists modify breast cancer cell proliferation by blocking cells to the G2/M phase of the cycle: involvement of cytoskeletal elements. J Cell Biochem 1999;73(2):204-211 [FREE Full text] [doi: 10.1002/(sici)1097-4644(19990501)73:2<204::aid-jcb6>3.0.co;2-v] [Medline: 10227383]

11. Kreye G, Masel E, Hackner K, Stich B, Nauck F. Methadone as anticancer treatment: hype, hope, or hazard?: a series of case reports and a short review of the current literature and recommendations of the societies. Wien Med Wochenschr 2018;168(7-8):159-167 [FREE Full text] [doi: 10.1007/s10354-018-0623-5] [Medline: 29460263]
12. Friesen C, Roscher M, Hormann I, Fichtner I, Alt A, Hilger RA, et al. Cell death sensitization of leukemia cells by opioid receptor activation. Oncotarget 2013;4(5):677-690 [FREE Full text] [doi: 10.18632/oncotarget.952] [Medline: 23633472]
13. Liang X, Liu R, Chen C, Ji F, Li T. Opioid system modulates the immune function: a review. Transl Perioper Pain Med 2016;1(1):5-13 [FREE Full text] [Medline: 26985446]
14. Hu N, Yu T, Chen J, Zheng S, Yan H, Duan J. Oxycodone stimulates normal and malignant hematopoietic progenitors via opioid-receptor-independent-β-catenin activation. Biochem Biophys Res Commun 2020;533(4):1457-1463 [FREE Full text] [doi: 10.1016/j.bbrc.2020.10.031] [Medline: 33268026]
15. Li Y, Li G, Tao T, Kang X, Liu C, Zhang X, et al. The μ-opioid receptor (MOR) promotes tumor initiation in hepatocellular carcinoma. Cancer Lett 2019;453:1-9 [FREE Full text] [doi: 10.1016/j.canlet.2019.03.038] [Medline: 30928385]
16. Zhang XY, Liang YX, Yan Y, Dai Z, Chu HC. Morphine: double-faced roles in the regulation of tumor development. Clin Transl Oncol 2018;20(7):808-814 [FREE Full text] [doi: 10.1007/s12094-017-1796-x] [Medline: 29127594]
17. Singleton P, Mirzapoiazova T, Hasina R, Salgia R, Moss J. Increased μ-opioid receptor expression in metastatic lung cancer. Br J Anaesth 2014;113(suppl 1):i103-i108 [FREE Full text] [doi: 10.1093/bja/aeu165] [Medline: 24920011]
18. Yao Y, Yao R, Zhuang L, Qi W, Lv J, Zhou F, et al. MOR1 expression in gastric cancer: a biomarker associated with poor outcome. Clin Transl Sci 2015;8(2):137-142 [FREE Full text] [doi: 10.1111/cts.12246] [Medline: 25441763]
19. Bortsov A, Millikan RC, Belfer I, Boortz-Marx RL, Arora H, McLean SA. μ-Opioid receptor gene A118G polymorphism predicts survival in patients with breast cancer. Anesthesiology 2012;116(4):896-902 [FREE Full text] [doi: 10.1097/ALN.0b013e31824b96a1] [Medline: 22433205]
20. Bimonte S, Barbieri A, Cascella M, Rea D, Palma G, Del Vecchio V, et al. The effects of naloxone on human breast cancer progression: in vitro and in vivo studies on MDA.MB231 cells. Onco Targets Ther 2018;11:185-191 [FREE Full text] [doi: 10.2147/OTT.S145780] [Medline: 29379300]
21. Xu X, Mao B, Wu L, Liu L, Rui J, Chen G. A118G polymorphism in μ-opioid receptor gene and interactions with smoking and drinking on risk of oesophageal squamous cell carcinoma. J Clin Lab Anal 2017;31(1):e22018 [FREE Full text] [doi: 10.1002/jcla.22018] [Medline: 27373278]
22. Zylla D, Gourley BL, Vang D, Jackson S, Boatman S, Lindgren B, et al. Opioid requirement, opioid receptor expression, and clinical outcomes in patients with advanced prostate cancer. Cancer 2013;119(23):4103-4110 [FREE Full text] [doi: 10.1002/cncr.28345] [Medline: 24104703]
23. Kang SM, Rosales JL, Meier-Stephenson V, Kim S, Lee KY, Narendran A. Genome-wide loss-of-function genetic screening identifies opioid receptor μ1 as a key regulator of L-asparaginase resistance in pediatric acute lymphoblastic leukemia. Oncogene 2017;36(42):5910-5913 [FREE Full text] [doi: 10.1038/onc.2017.211] [Medline: 28650467]
24. Ondrovics M, Hoelbl-Kovacic A, Fux DA. Opioids: modulators of angiogenesis in wound healing and cancer. Oncotarget 2017;8(15):25783-25796 [FREE Full text] [doi: 10.18632/oncotarget.15419] [Medline: 28445930]
25. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiology 2008;109(2):180-187 [FREE Full text] [doi: 10.1097/ALN.0b013e31817f5b73] [Medline: 18648226]
26. Exadaktylos A, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006;105(4):660-664 [FREE Full text] [doi: 10.1097/00000542-200610000-00008] [Medline: 17006061]
27. Lin L, Liu C, Tan H, Ouyang H, Zhang Y, Zeng W. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. Br J Anaesth 2011;106(6):814-822 [FREE Full text] [doi: 10.1093/bja/aer055] [Medline: 21436156]
28. Wang K, Qu X, Wang Y, Shen H, Liu Q, Du J. Effect of mu agonists on long-term survival and recurrence in nonsmall cell lung cancer patients. Medicine (Baltimore) 2015;94(33):e1333 [FREE Full text] [doi: 10.1097/MD.0000000000001333] [Medline: 26287418]
29. Singleton PA, Moss J, Karp DD, Atkins JT, Janku F. The mu opioid receptor: a new target for cancer therapy? Cancer 2015;121(16):2681-2688 [FREE Full text] [doi: 10.1002/cncr.29460] [Medline: 26043235]
30. Onken J, Friesen C, Vajkoczy P, Misch M. Safety and tolerance of D,L-methadone in combination with chemotherapy in patients with glioma. Anticancer Res 2017;37(3):1227-1235 [FREE Full text] [doi: 10.21873/anticanres.11438] [Medline: 28314286]
31. Zylla D, Kuskowski M, Gupta K, Gupta P. Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer. Br J Anaesth 2014;113(suppl 1):i109-i116 [FREE Full text] [doi: 10.1093/bja/aeu351] [Medline: 25303989]
32. Connolly C, Madden SF, Buggy DJ, Gallagher HC. Expression of anaesthetic and analgesic drug target genes in excised breast tumour tissue: association with clinical disease recurrence or metastasis. PLoS One 2017;12(5):e0177105 [FREE Full text] [doi: 10.1371/journal.pone.0177105] [Medline: 28558008]

33. Tai Y, Wu H, Chang W, Tsou M, Chen H, Chang K. Intraoperative fentanyl consumption does not impact cancer recurrence or overall survival after curative colorectal cancer resection. Sci Rep 2017;7(1):10816 [FREE Full text] [doi: 10.1038/s41598-017-11460-1] [Medline: 28883624]
34. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer. Ann Oncol 2017;29(4):1076 [FREE Full text] [doi: 10.1093/annonc/mdx776] [Medline: 29253076]
35. Lennon FE, Mirzapoiazova T, Mambetsariev B, Poroyko VA, Salgia R, Moss J, et al. The mu opioid receptor promotes opioid and growth factor-induced proliferation, migration and epithelial mesenchymal transition (EMT) in human lung cancer. PLoS One 2014;9(3):e91577 [FREE Full text] [doi: 10.1371/journal.pone.0091577] [Medline: 24662916]
36. Zhang Y, Xu Q, Liao L, Xu X, Wu J, Wu Z, et al. Association of mu-opioid receptor expression with lymph node metastasis in esophageal squamous cell carcinoma. Dis Esophagus 2015;28(2):196-203 [FREE Full text] [doi: 10.1111/dote.12165] [Medline: 24428760]
37. Bimonte S, Barbieri A, Rea D, Palma G, Luciano A, Cuomo A, et al. Morphine promotes tumor angiogenesis and increases breast cancer progression. Biomed Res Int 2015;2015:161508 [FREE Full text] [doi: 10.1155/2015/161508] [Medline: 26064880]
38. Singh A, Jayanthan A, Farran A, Elwi AN, Kim SW, Farran P, et al. Induction of apoptosis in pediatric acute lymphoblastic leukemia (ALL) cells by the therapeutic opioid methadone and effective synergy with Bcl-2 inhibition. Leuk Res 2011;35(12):1649-1657 [FREE Full text] [doi: 10.1016/j.leukres.2011.06.035] [Medline: 21798596]
39. Friesen C, Hormann I, Roscher M, Fichtner I, Alt A, Hilger R, et al. Opioid receptor activation triggering downregulation of cAMP improves effectiveness of anti-cancer drugs in treatment of glioblastoma. Cell Cycle 2014;13(10):1560-1570 [FREE Full text] [doi: 10.4161/cc.28493] [Medline: 24626197]
40. Friesen C, Roscher M, Alt A, Miltner E. Methadone, commonly used as maintenance medication for outpatient treatment of opioid dependence, kills leukemia cells and overcomes chemoresistance. Cancer Res 2008;68(15):6059-6064 [FREE Full text] [doi: 10.1158/0008-5472.CAN-08-1227] [Medline: 18676827]
41. Zylla D, Steele G, Gupta P. A systematic review of the impact of pain on overall survival in patients with cancer. Support Care Cancer 2017;25(5):1687-1698 [FREE Full text] [doi: 10.1007/s00520-017-3614-y] [Medline: 28190159]
42. Owusu-Agyemang P, Hayes-Jordan A, Van Meter A, Williams UU, Zavala AM, Kapoor R, et al. Assessing the survival impact of perioperative opioid consumption in children and adolescents undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Paediatr Anaesth 2017;27(6):648-656 [FREE Full text] [doi: 10.1111/pan.13146] [Medline: 28419679]
43. Ninković J, Roy S. Role of the mu-opioid receptor in opioid modulation of immune function. Amino Acids 2013;45(1):9-24 [FREE Full text] [doi: 10.1007/s00726-011-1163-0] [Medline: 22170499]
44. Sathornviriyapong A, Nagaviroj K, Anothaisintawee T. The association between different opioid doses and the survival of advanced cancer patients receiving palliative care. BMC Palliat Care 2016;15(1):95 [FREE Full text] [doi: 10.1186/s12904-016-0169-5] [Medline: 27871265]
45. Xie N, Matigian N, Vithanage T, Gregory K, Nassar ZD, Cabot PJ, et al. Effect of perioperative opioids on cancer-relevant circulating parameters: mu opioid receptor and toll-like receptor 4 activation potential, and proteolytic profile. Clin Cancer Res 2018;24(10):2319-2327 [FREE Full text] [doi: 10.1158/1078-0432.CCR-18-0172] [Medline: 29511031]
46. Montagna G, Gupta HV, Hannum M, Tan KS, Lee J, Scarpa JR, et al. Intraoperative opioids are associated with improved recurrence-free survival in triple-negative breast cancer. Br J Anaesth 2021;126(2):367-376 [FREE Full text] [doi: 10.1016/j.bja.2020.10.021] [Medline: 33220939]
47. Du KN, Feng L, Newhouse A, Mehta J, Lasala J, Mena GE, et al. Effects of intraoperative opioid use on recurrence-free and overall survival in patients with esophageal adenocarcinoma and squamous cell carcinoma. Anesth Analg 2018;127(1):210-216 [FREE Full text] [doi: 10.1213/ANE.0000000000003428] [Medline: 29757780]
48. Theile D, Mikus G. Methadone against cancer: lost in translation. Int J Cancer 2018;143(8):1840-1848 [FREE Full text] [doi: 10.1002/ijc.31356] [Medline: 29516505]
49. Sekandarzad MW, Doornebal C, Hollmann MW. Opiophobia in cancer biology—justified?—The role of perioperative use of opioids in cancer recurrence. Curr Pharm Des 2019;25(28):3020-3027 [FREE Full text] [doi: 10.2174/1381612825666190703163329] [Medline: 31269880]
50. Constance JE, Campbell SC, Somani AA, Yellepeddi V, Owens KH, Sherwin CMT. Pharmacokinetics, pharmacodynamics and pharmacogenetics associated with nonsteroidal anti-inflammatory drugs and opioids in pediatric cancer patients. Expert Opin Drug Metab Toxicol 2017;13(7):715-724 [FREE Full text] [doi: 10.1080/17425255.2017.1329415] [Medline: 28490206]
51. Altamimi MI, Choonara I, Sammons H. Inter-individual variation in morphine clearance in children. Eur J Clin Pharmacol 2015;71(6):649-655 [FREE Full text] [doi: 10.1007/s00228-015-1843-x] [Medline: 25845657]
52. Steele G, Dudek AZ, Gilmore GE, Richter SA, Olson DA, Eklund SP, et al. Impact of pain, opioids, and the mu-opioid receptor on progression and survival in patients with newly diagnosed stage IV pancreatic cancer. Am J Clin Oncol 2020;43(8):591-597 [FREE Full text] [doi: 10.1097/COC.0000000000000714] [Medline: 32482952]
53. Aylsworth CF, Hodson CA, Meites J. Opiate antagonists can inhibit mammary tumor growth in rats. Proc Soc Exp Biol Med 1979;161(1):18-20 [FREE Full text] [doi: 10.3181/00379727-161-40479] [Medline: 108682]

54. Page G, Ben-Eliyahu S, Yirmiya R, Liebeskind JC. Morphine attenuates surgery-induced enhancement of metastatic colonization in rats. Pain 1993;54(1):21-28 [FREE Full text] [doi: 10.1016/0304-3959(93)90095-7] [Medline: 8378099]
55. Maneckjee R, Biswas R, Vonderhaar BK. Binding of opioids to human MCF-7 breast cancer cells and their effects on growth. Cancer Res 1990;50(8):2234-2238 [FREE Full text] [Medline: 2156613]
56. Hatzoglou A, Bakogeorgou E, Castanas E. The antiproliferative effect of opioid receptor agonists on the T47D human breast cancer cell line, is partially mediated through opioid receptors. Eur J Pharmacol 1996;296(2):199-207 [FREE Full text] [doi: 10.1016/0014-2999(95)00703-2] [Medline: 8838457]
57. Tegeder I, Grösch S, Schmidtko A, Häussler A, Schmidt H, Niederberger E, et al. G protein-independent G1 cell cycle block and apoptosis with morphine in adenocarcinoma cells: involvement of p53 phosphorylation. Cancer Res 2003;63(8):1846-1852 [FREE Full text] [Medline: 12702572]
58. Nguyen J, Luk K, Vang D, Soto W, Vincent L, Robiner S, et al. Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer. Br J Anaesth 2014;113(suppl 1):i4-i13 [FREE Full text] [doi: 10.1093/bja/aeu090] [Medline: 24861561]
59. Farooqui M, Li Y, Rogers T, Poonawala T, Griffin RJ, Song CW, et al. COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. Br J Cancer 2007;97(11):1523-1531 [FREE Full text] [doi: 10.1038/sj.bjc.6604057] [Medline: 17971769]
60. Afsharimani B, Baran J, Watanabe S, Lindner D, Cabot PJ, Parat M. Morphine and breast tumor metastasis: the role of matrix-degrading enzymes. Clin Exp Metastasis 2014;31(2):149-158 [FREE Full text] [doi: 10.1007/s10585-013-9616-3] [Medline: 24072419]
61. Ustun F, Durmus-Altun G, Altaner S, Tuncbilek N, Uzal C, Berkarda S. Evaluation of morphine effect on tumour angiogenesis in mouse breast tumour model, EATC. Med Oncol 2011;28(4):1264-1272 [FREE Full text] [doi: 10.1007/s12032-010-9573-5] [Medline: 20567944]
62. Kocak N, Ozen F, Yildirim IH, Duran Y. Fentanyl inhibits tumorigenesis from human breast stem cells by inducing apoptosis. Asian Pac J Cancer Prev 2017;18(3):735-739 [FREE Full text] [doi: 10.22034/APJCP.2017.18.3.735] [Medline: 28441707]
63. Brawanski K, Brockhoff G, Hau P, Vollmann-Zwerenz A, Freyschlag C, Lohmeier A, et al. Efficacy of D,L-methadone in the treatment of glioblastoma in vitro. CNS Oncol 2018;7(3):CNS18 [FREE Full text] [doi: 10.2217/cns-2018-0006] [Medline: 29916277]
64. Oppermann H, Matusova M, Glasow A, Dietterle J, Baran-Schmidt R, Neumann K, et al. D,L-Methadone does not improve radio- and chemotherapy in glioblastoma in vitro. Cancer Chemother Pharmacol 2019;83(6):1017-1024 [FREE Full text] [doi: 10.1007/s00280-019-03816-3] [Medline: 30888463]
65. Sueoka N, Sueoka E, Okabe S, Fujiki H. Anti-cancer effects of morphine through inhibition of tumour necrosis factor-alpha release and mRNA expression. Carcinogenesis 1996;17(11):2337-2341 [FREE Full text] [doi: 10.1093/carcin/17.11.2337] [Medline: 8968046]
66. Sueoka E, Sueoka N, Kai Y, Okabe S, Suganuma M, Kanematsu K, et al. Anticancer activity of morphine and its synthetic derivative, KT-90, mediated through apoptosis and inhibition of NF-kappaB activation. Biochem Biophys Res Commun 1998;252(3):566-570 [FREE Full text] [doi: 10.1006/bbrc.1998.9695] [Medline: 9837747]
67. Sergeeva MG, Grishina ZV, Varfolomeyev SD. Morphine effect on proliferation of normal and tumor cells of immune origin. Immunol Lett 1993;36(2):215-218 [FREE Full text] [doi: 10.1016/0165-2478(93)90055-7] [Medline: 8394283]
68. Ishikawa M, Tanno K, Kamo A, Takayanagi Y, Sasaki K. Enhancement of tumor growth by morphine and its possible mechanism in mice. Biol Pharm Bull 1993;16(8):762-766 [FREE Full text] [doi: 10.1248/bpb.16.762] [Medline: 8220322]
69. Maneckjee R, Minna JD. Opioid and nicotine receptors affect growth regulation of human lung cancer cell lines. Proc Natl Acad Sci U S A 1990;87(9):3294-3298 [FREE Full text] [doi: 10.1073/pnas.87.9.3294] [Medline: 2159143]
70. Maneckjee R, Minna JD. Nonconventional opioid binding sites mediate growth inhibitory effects of methadone on human lung cancer cells. Proc Natl Acad Sci U S A 1992;89(4):1169-1173 [FREE Full text] [doi: 10.1073/pnas.89.4.1169] [Medline: 1311082]
71. Tian M, Jin L, Li R, Zhu S, Ji M, Li W. Comparison of oxycodone and morphine on the proliferation, apoptosis and expression of related molecules in the A549 human lung adenocarcinoma cell line. Exp Ther Med 2016;12(2):559-566 [FREE Full text] [doi: 10.3892/etm.2016.3346] [Medline: 27446244]
72. Heusch WL, Maneckjee R. Effects of bombesin on methadone-induced apoptosis of human lung cancer cells. Cancer Lett 1999;136(2):177-185 [FREE Full text] [doi: 10.1016/s0304-3835(98)00335-8] [Medline: 10355747]
73. Koodie L, Ramakrishnan S, Roy S. Morphine suppresses tumor angiogenesis through a HIF-1alpha/p38MAPK pathway. Am J Pathol 2010;177(2):984-997 [FREE Full text] [doi: 10.2353/ajpath.2010.090621] [Medline: 20616349]
74. Mathew B, Lennon FE, Siegler J, Mirzapoiazova T, Mambetsariev N, Sammani S, et al. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. Anesth Analg 2011;112(3):558-567 [FREE Full text] [doi: 10.1213/ANE.0b013e31820568af] [Medline: 21156980]
75. Simon RH, Arbo TE. Morphine increases metastatic tumor growth. Brain Res Bull 1986;16(3):363-367 [FREE Full text] [doi: 10.1016/0361-9230(86)90057-2] [Medline: 3708390]

76. Fujioka N, Nguyen J, Chen C, Li Y, Pasrija T, Niehans G, et al. Morphine-induced epidermal growth factor pathway activation in non-small cell lung cancer. Anesth Analg 2011;113(6):1353-1364 [FREE Full text] [doi: 10.1213/ANE.0b013e318232b35a] [Medline: 22003224]
77. Yeager MP, Colacchio TA. Effect of morphine on growth of metastatic colon cancer in vivo. Arch Surg 1991;126(4):454-456 [FREE Full text] [doi: 10.1001/archsurg.1991.01410280056007] [Medline: 2009060]
78. Wu Q, Chen X, Wang J, Sun P, Weng M, Chen W, et al. Nalmefene attenuates malignant potential in colorectal cancer cell via inhibition of opioid receptor. Acta Biochim Biophys Sin (Shanghai) 2018;50(2):156-163 [FREE Full text] [doi: 10.1093/abbs/gmx131] [Medline: 29267844]
79. Xu YJ, Li SY, Cheng Q, Chen WK, Wang SL, Ren Y, et al. Effects of anaesthesia on proliferation, invasion and apoptosis of LoVo colon cancer cells in vitro. Anaesthesia 2016;71(2):147-154 [FREE Full text] [doi: 10.1111/anae.13331] [Medline: 26669824]
80. Zagon IS, McLaughlin PJ. Opioids and the apoptotic pathway in human cancer cells. Neuropeptides 2003;37(2):79-88 [FREE Full text] [doi: 10.1016/s0143-4179(03)00007-6] [Medline: 12747939]
81. Nylund G, Pettersson A, Bengtsson C, Khorram-Manesh A, Nordgren S, Delbro DS. Functional expression of mu-opioid receptors in the human colon cancer cell line, HT-29, and their localization in human colon. Dig Dis Sci 2008;53(2):461-466 [FREE Full text] [doi: 10.1007/s10620-007-9897-y] [Medline: 17680363]
82. Zhang XL, Chen ML, Zhou SL. Fentanyl inhibits proliferation and invasion of colorectal cancer via β-catenin. Int J Clin Exp Pathol 2015;8(1):227-235 [FREE Full text] [Medline: 25755709]
83. Zhang XL, Chen ML, Zhou SL. Fentanyl increases colorectal carcinoma cell apoptosis by inhibition of NF-κB in a Sirt1-dependent manner. Asian Pac J Cancer Prev 2014;15(22):10015-10020 [FREE Full text] [doi: 10.7314/apjcp.2014.15.22.10015] [Medline: 25520062]
84. Harimaya Y, Koizumi K, Andoh T, Nojima H, Kuraishi Y, Saiki I. Potential ability of morphine to inhibit the adhesion, invasion and metastasis of metastatic colon 26-L5 carcinoma cells. Cancer Lett 2002;187(1-2):121-127 [FREE Full text] [doi: 10.1016/s0304-3835(02)00360-9] [Medline: 12359359]
85. Wurster EF, Pianka F, Warschkow R, Antony P, Brenner T, Weigand MA, et al. Peridural analgesia does not impact survival in patients after colon cancer resection: a retrospective propensity score-adjusted analysis. Int J Colorectal Dis 2019;34(7):1283-1293 [FREE Full text] [doi: 10.1007/s00384-019-03315-0] [Medline: 31172261]
86. Moon TD. The effect of opiates upon prostatic carcinoma cell growth. Biochem Biophys Res Commun 1988;153(2):722-727 [FREE Full text] [doi: 10.1016/s0006-291x(88)81154-9] [Medline: 2898243]
87. Börner C, Höllt V, Kraus J. Mechanisms of the inhibition of nuclear factor-κB by morphine in neuronal cells. Mol Pharmacol 2012;81(4):587-597 [FREE Full text] [doi: 10.1124/mol.111.076620] [Medline: 22258905]
88. Perez-Alvarez S, Iglesias-Guimarais V, Solesio ME, Melero-Fernandez de Mera RM, Yuste VJ, Galindo MF, et al. Methadone induces CAD degradation and AIF-mediated necrotic-like cell death in neuroblastoma cells. Pharmacol Res 2011;63(4):352-360 [FREE Full text] [doi: 10.1016/j.phrs.2010.12.001] [Medline: 21145398]
89. Zagon IS, McLaughlin PJ. Naltrexone modulates tumor response in mice with neuroblastoma. Science 1983;221(4611):671-673 [FREE Full text] [doi: 10.1126/science.6867737] [Medline: 6867737]
90. Kugawa F, Ueno A, Aoki M. Apoptosis of NG108-15 cells induced by buprenorphine hydrochloride occurs via the caspase-3 pathway. Biol Pharm Bull 2000;23(8):930-935 [FREE Full text] [doi: 10.1248/bpb.23.930] [Medline: 10963298]
91. Wang N, Zhang Z, Lv J. Fentanyl inhibits proliferation and invasion via enhancing miR-302b expression in esophageal squamous cell carcinoma. Oncol Lett 2018;16(1):459-466 [FREE Full text] [doi: 10.3892/ol.2018.8616] [Medline: 29928433]
92. Wang S, Li Y, Liu X, Zhao C, Yang K. Polymorphism of A118G in μ-opioid receptor gene is associated with risk of esophageal squamous cell carcinoma in a Chinese population. Int J Clin Oncol 2013;18(4):666-669 [FREE Full text] [doi: 10.1007/s10147-012-0441-5] [Medline: 22752309]
93. Wu W, Wei N, Jiang C, Cui S, Yuan J. Effects of sufentanil on human gastric cancer cell line SGC-7901 in vitro. Cent Eur J Immunol 2014;39(3):299-305 [FREE Full text] [doi: 10.5114/ceji.2014.45939] [Medline: 26155139]
94. Lu J, Liu Z, Zhao L, Tian H, Liu X, Yuan C. In vivo and in vitro inhibition of human liver cancer progress by downregulation of the μ-opioid receptor and relevant mechanisms. Oncol Rep 2013;30(4):1731-1738 [FREE Full text] [doi: 10.3892/or.2013.2640] [Medline: 23900681]
95. Cao L, Li H, Lin W, Tan H, Xie L, Zhong Z, et al. Morphine, a potential antagonist of cisplatin cytotoxicity, inhibits cisplatin-induced apoptosis and suppression of tumor growth in nasopharyngeal carcinoma xenografts. Sci Rep 2016;6:18706 [FREE Full text] [doi: 10.1038/srep18706] [Medline: 26729257]
96. Kawase M, Sakagami H, Furuya K, Kikuchi H, Nishikawa H, Motohashi N, et al. Cell death-inducing activity of opiates in human oral tumor cell lines. Anticancer Res 2002;22(1A):211-214 [FREE Full text] [Medline: 12017290]
97. Boehncke S, Hardt K, Schadendorf D, Henschler R, Boehncke WH, Duthey B. Endogenous μ-opioid peptides modulate immune response towards malignant melanoma. Exp Dermatol 2011;20(1):24-28 [FREE Full text] [doi: 10.1111/j.1600-0625.2010.01158.x] [Medline: 20955200]
98. McLaughlin PJ, Stucki JK, Zagon IS. Modulation of the opioid growth factor ([Met(5)]-enkephalin)-opioid growth factor receptor axis: novel therapies for squamous cell carcinoma of the head and neck. Head Neck 2012;34(4):513-519 [FREE Full text] [doi: 10.1002/hed.21759] [Medline: 21584896]

99. King T, Vardanyan A, Majuta L, Melemedjian O, Nagle R, Cress AE, et al. Morphine treatment accelerates sarcoma-induced bone pain, bone loss, and spontaneous fracture in a murine model of bone cancer. Pain 2007;132(1-2):154-168 [FREE Full text] [doi: 10.1016/j.pain.2007.06.026] [Medline: 17706870]
100. Abdel-Rahman O, Karachiwala H, Easaw JC. Outcomes of patients with advanced gastrointestinal cancer in relationship to opioid use: findings from eight clinical trials. J Natl Compr Canc Netw 2020;18(5):575-581 [FREE Full text] [doi: 10.6004/jnccn.2019.7382] [Medline: 32380454]
101. Barlass U, Deshmukh A, Beck T, Bishehsari F. Opioid use as a potential risk factor for pancreatic cancer in the United States: an analysis of state and national level databases. PLoS One 2021;16(1):e0244285 [FREE Full text] [doi: 10.1371/journal.pone.0244285] [Medline: 33406096]
102. Boland JW, Allgar V, Boland EG, Bennett MI, Kaasa S, Hjermstad MJ, et al. The relationship between pain, analgesics and survival in patients with advanced cancer; a secondary data analysis of the international European palliative care cancer symptom study. Eur J Clin Pharmacol 2020;76(3):393-402 [FREE Full text] [doi: 10.1007/s00228-019-02801-2] [Medline: 31865411]
103. Chancellor WZ, Mehaffey JH, Desai RP, Beller J, Balkrishnan R, Walters DM, et al. Prolonged opioid use associated with reduced survival after lung cancer resection. Ann Thorac Surg 2021;111(6):1791-1798 [FREE Full text] [doi: 10.1016/j.athoracsur.2020.09.015] [Medline: 33127403]
104. Dai S, Zhang X, Zhang P, Zheng X, Pang Q. Fentanyl inhibits acute myeloid leukemia differentiated cells and committed progenitors via opioid receptor-independent suppression of Ras and STAT5 pathways. Fundam Clin Pharmacol 2021;35(1):174-183 [FREE Full text] [doi: 10.1111/fcp.12581] [Medline: 32564393]
105. Gong S, Ying L, Fan Y, Sun Z. Fentanyl inhibits lung cancer viability and invasion via upregulation of miR-331-3p and repression of HDAC5. Onco Targets Ther 2020;13:13131-13141 [FREE Full text] [doi: 10.2147/OTT.S281095] [Medline: 33380803]
106. Haas B, Ciftcioglu J, Jermar S, Weickhardt S, Eckstein N, Kaina B. Methadone-mediated sensitization of glioblastoma cells is drug and cell line dependent. J Cancer Res Clin Oncol 2021;147(3):779-792 [FREE Full text] [doi: 10.1007/s00432-020-03485-3] [Medline: 33315125]
107. Lec PM, Lenis AT, Golla V, Brisbane W, Shuch B, Garraway IP, et al. The role of opioids and their receptors in urological malignancy: a review. J Urol 2020;204(6):1150-1159 [FREE Full text] [doi: 10.1097/JU.0000000000001156] [Medline: 32516030]
108. Lee J, Rosales JL, Byun HG, Lee KY. D,L-Methadone causes leukemic cell apoptosis via an OPRM1-triggered increase in IP3R-mediated ER Ca2+ release and decrease in Ca2+ efflux, elevating [Ca2+]i. Sci Rep 2021;11(1):1009 [FREE Full text] [doi: 10.1038/s41598-020-80520-w] [Medline: 33441856]
109. Lee S, Acharyya S, Tan A, Loh A. Anaesthetic modality and post-surgical oncological outcomes for paediatric tumours: is there a link? Singapore Med J 2021;62(1):20-28 [FREE Full text] [doi: 10.11622/smedj.2019123] [Medline: 33619573]
110. Lee YJ, Oh CS, Choi JM, Park S, Kim SH. mu-opioid receptor polymorphisms and breast cancer recurrence in adult Korean women undergoing breast cancer surgery: a retrospective study. Int J Med Sci 2020;17(18):2941-2946 [FREE Full text] [doi: 10.7150/ijms.49297] [Medline: 33173414]
111. Li C, Li L, Qin Y, Jiang Y, Wei Y, Chen J, et al. Exogenous morphine inhibits the growth of human gastric tumor. Ann Transl Med 2020;8(6):385 [FREE Full text] [doi: 10.21037/atm.2020.03.116] [Medline: 32355829]
112. Liu N, Ma M, Qu N, Wang R, Chen H, Hu F, et al. Low-dose naltrexone inhibits the epithelial-mesenchymal transition of cervical cancer cells in vitro and effects indirectly on tumor-associated macrophages in vivo. Int Immunopharmacol 2020;86:106718 [FREE Full text] [doi: 10.1016/j.intimp.2020.106718] [Medline: 32585612]
113. Liu W, Chen Y, Xu W, Wang W, Tang L, Xia R, et al. Fentanyl stimulates tumor angiogenesis via activating multiple pro-angiogenic signaling pathways. Biochem Biophys Res Commun 2020;532(2):225-230 [FREE Full text] [doi: 10.1016/j.bbrc.2020.08.038] [Medline: 32861420]
114. Lu H, Zhang H, Weng ML, Zhang J, Jiang N, Cata JP, et al. Morphine promotes tumorigenesis and cetuximab resistance via EGFR signaling activation in human colorectal cancer. J Cell Physiol 2021;236(6):4445-4454 [FREE Full text] [doi: 10.1002/jcp.30161] [Medline: 33184860]
115. Ma M, Wang X, Liu N, Shan F, Feng Y. Low-dose naltrexone inhibits colorectal cancer progression and promotes apoptosis by increasing M1-type macrophages and activating the Bax/Bcl-2/caspase-3/PARP pathway. Int Immunopharmacol 2020;83:106388 [FREE Full text] [doi: 10.1016/j.intimp.2020.106388] [Medline: 32171145]
116. Silagy AW, Hannum ML, Mano R, Attalla K, Scarpa JR, DiNatale RG, et al. Impact of intraoperative opioid and adjunct analgesic use on renal cell carcinoma recurrence: role for onco-anaesthesia. Br J Anaesth 2020;125(5):e402-e404 [FREE Full text] [doi: 10.1016/j.bja.2020.06.036] [Medline: 32703551]
117. Taniguchi Y, Tamiya A, Matsuda Y, Adachi Y, Enomoto T, Azuma K, et al. Opioids impair Nivolumab outcomes: a retrospective propensity score analysis in non-small-cell lung cancer. BMJ Support Palliat Care 2020:bmjspcare-2020-002480 [FREE Full text] [doi: 10.1136/bmjspcare-2020-002480] [Medline: 33293293]
118. Tripolt S, Neubauer HA, Knab VM, Elmer DP, Aberger F, Moriggl R, et al. Opioids drive breast cancer metastasis through the δ-opioid receptor and oncogenic STAT3. Neoplasia 2021;23(2):270-279 [FREE Full text] [doi: 10.1016/j.neo.2020.12.011] [Medline: 33465556]

119. Vatter T, Klumpp L, Ganser K, Stransky N, Zips D, Eckert F, et al. Against repurposing methadone for glioblastoma therapy. Biomolecules 2020;10(6):917 [FREE Full text] [doi: 10.3390/biom10060917] [Medline: 32560384]
120. Wang X, Zhang R, Wu T, Shi Y, Zhou X, Tang D, et al. Successive treatment with naltrexone induces epithelial-mesenchymal transition and facilitates the malignant biological behaviors of bladder cancer cells. Acta Biochim Biophys Sin (Shanghai) 2021;53(2):238-248 [FREE Full text] [doi: 10.1093/abbs/gmaa169] [Medline: 33410473]
121. Yu Y, Li DC, Duan J, Xu J, Li L, Tan D, et al. The pro- and anti-cancer effects of oxycodone are associated with epithelial growth factor receptor level in cancer cells. Biosci Rep 2020;40(2):BSR20193524 [FREE Full text] [doi: 10.1042/BSR20193524] [Medline: 31967294]
122. Aromataris E. Furthering the science of evidence synthesis with a mix of methods. JBI Evid Synth 2020;18(10):2106-2107 [FREE Full text] [doi: 10.11124/JBIES-20-00369] [Medline: 33038123]
123. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19-32 [FREE Full text] [doi: 10.1080/1364557032000119616]
124. Peters M, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015;13(3):141-146 [FREE Full text] [doi: 10.1097/XEB.0000000000000050] [Medline: 26134548]
125. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
126. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
127. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol 2016;75:40-46 [FREE Full text] [doi: 10.1016/j.jclinepi.2016.01.021] [Medline: 27005575]

Abbreviations

μOR: μ-opioid receptor
PK: pharmacokinetic
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
REDCap: Research Electronic Data Capture

Edited by A Mavragani;This paper was peer-reviewed by D Pessoa, J Rower, KT Bui, M Anderson; proposal externally peer-reviewed by the National Cancer Institute Special Emphasis Panel of the University of Utah. See the Multimedia Appendices for the peer-review reports; Submitted 21.03.22; accepted 05.04.23; published 22.05.23.

Please cite as:
Constance JE, McFarland MM, Casucci T, Deininger MW, Enioutina EY, Job K, Lemons RS, Lim CS, Ward RM, Yellepeddi V, Watt KM
Mapping the Evidence for Opioid-Mediated Changes in Malignancy and Chemotherapeutic Efficacy: Protocol for a Scoping Review
JMIR Res Protoc 2023;12:e38167
URL: https://www.researchprotocols.org/2023/1/e38167
doi: 10.2196/38167
PMID: