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Topical therapy for pain management in malignant fungating wounds: a scoping review

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Research data (full-text protocol and database) will be available with as few restrictions as possible. Additional requests should be sent to the corresponding author.

CRediT authorship contribution statement

Suzana Aparecida da Costa Ferreira: study conception, project administration, design, data collection, data curation, data interpretation, manuscript writing, and final approval. **Carol Viviana Serna González:** design, data collection, data curation, data interpretation, manuscript writing, and final approval. **Magali Thum:** data collection, data analysis, manuscript writing, and final approval. **Adriane Aparecida da Costa Faresin:** data collection, data analysis, manuscript writing, and final approval. **Kevin Woo:** design, data collection, data curation, data interpretation, manuscript writing, and final approval. **Vera Lúcia Conceição de Gouveia Santos:** conception and project administration, design, data collection, data curation, data interpretation, manuscript writing, and final approval.

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Suzana da C. Ferreira declares having no funding or conflicts of interest to disclose.

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Terapia Tópica para el manejo del dolor en heridas neoplásicas malignas: revisión de alcance

Resumen

Objetivos: Mapear y sintetizar la literatura existente sobre las terapias tópicas para el manejo del dolor en heridas neoplásicas malignas y los vacíos en investigación.

Introducción: La mayoría de los pacientes con heridas neoplásicas malignas sienten dolor relacionado con la herida, que afecta su calidad de vida. Desafortunadamente, apesar de que el dolor es un síntoma relevante tanto en el cuidado de personas con cancer como en cuidados paliativos, poco se sabe actualmente sobre la disponibilidad de tratamientos tópicos y su impacto en el manejo del dolor.

Diseño: Revisión de escopo según la metodología de la JBI®.

Métodos: fueron realizada búsquedas en las bases de datos CINAHL, LILACS, Embase, Web of Science, PubMed, Cochrane, NICE, Scopus, JBISRIR, y literatura gris; en inglés, español y portugués, sin límite de tiempo. Dos autores revisaron todas las citaciones independientemente. Estudios en adultos con heridas neoplásicas malignas que reportaran intervenciones tópicas para el dolor fueron incluidos. Adicionalmente, un instrumento para extracción de datos fue desarrollado para la síntesis y análisis del tema. Este estudio siguió la lista de chequeo para el reporte de revisiones de alcance PRISMA-ScR de la red Equator.

Resultados: 70 Publicaciones fueron seleccionadas de 796 identificadas en las bases de datos. Los estudios incluyeron principalmente revisiones no sistemáticas y estudios de caso; solo seis fueron ensayos clínicos. Según la síntesis narrativa realizada, fueron identificadas veinte terapias, que incluyeron el uso de apósitos (58.6%), drogas analgésicas (55.7%), antimicrobianos tópicos (25.7%), protectores de piel (15.7%), crioterapia (5.7%), y terapia por presión negativa (4.3%). Las diversas terapias tópicas fueron recomendadas para el el lecho de la herida y el área perilesional. En el 68.5% de los estudios, no fue descrita la aplicación de instrumentos para la valoración del dolor.

Conclusiones: fueron identificadas terapias tópicas aplicadas al lecho de las heridas neoplásicas malignas o al área perilesionar, para el manejo del dolor. Sin embargo, la efectividad de las intervenciones fue analizada por pocos estudios clínicos, indicando la necesidad por más estudios primarios que informen la prácica clínica basada en la evidencia.

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Implicaciones para la práctica: se destacan para aplicación clínica, el uso de opioides, anestésicos y antimicrobianos, con resultados positivos en ensayos clínicos randomizados. Este estudio no incluyó pacientes.
Palabras claves: Neoplasia; Heridas y Lesiones; Manejo del Dolor; Cuidado centrado en el Paciente; Administración Tópica; Revisión; Enfermería; Enfermería basada en la evidencia; Enfermería Oncológica.

Terapia tópica para controle da dor em feridas neoplásicas malignas: revisão de escopo

Resumo

Objetivos: Mapear e sintetizar a literatura existente sobre terapias tópicas para o manejo da dor em feridas neoplásicas malignas e as lacunas de pesquisa.

Introdução: A maioria dos pacientes com feridas neoplásicas malignas sente dor relacionada à ferida, o que afeta sua qualidade de vida. Infelizmente, apesar da dor ser um sintoma relevante tanto no tratamento oncológico quanto nos cuidados paliativos, pouco se sabe atualmente sobre a disponibilidade de tratamentos tópicos e seu impacto no controle da dor.

Desenho: Revisão do escopo de acordo com a metodologia JBI®.

Métodos: CINAHL, LILACS, Embase, Web of Science, PubMed, Cochrane, NICE, Scopus, JBISRIR e bases de dados de literatura cinzenta foram pesquisados; em inglês, espanhol e português, sem limite de tempo. Dois autores revisaram todas as citações de forma independente. Estudos em adultos com feridas neoplásicas malignas relatando intervenções tópicas para dor foram incluídos. Adicionalmente, foi desenvolvido um instrumento de extração de dados para a síntese e análise do tema. Este estudo seguiu a lista de verificação do relatório de revisão de escopo PRISMA-ScR da rede Equator.

Resultados: Foram selecionadas 70 publicações dentre 796 identificadas nas bases de dados. Os estudos incluíram principalmente revisões não sistemáticas e estudos de caso; apenas seis eram ensaios clínicos. De acordo com a síntese narrativa realizada, foram identificadas vinte terapias, que incluíram o uso de curativos (58,6%), analgésicos (55,7%), antimicrobianos tópicos (25,7%), protetores cutâneos (15,7%), crioterapia (5,7%). , e terapia com pressão negativa (4,3%). Várias terapias tópicas foram recomendadas para o leito da ferida e a área periferida. Em 68,5% dos estudos não foi descrita a aplicação de instrumentos para avaliação da dor.

Conclusões: foram identificadas terapias tópicas aplicadas no leito de feridas neoplásicas malignas ou na área perilesional, para controle da dor. No entanto, a eficácia das intervenções foi analisada por poucos estudos clínicos, indicando a necessidade de mais estudos primários que informem a prática clínica baseada em evidências.

Implicações para a prática: o uso de opioides, anestésicos e antimicrobianos se destaca pela aplicação clínica, com resultados positivos em ensaios clínicos randomizados. Este estudo não incluiu pacientes.

Palavras-chave: Neoplasia; Ferimentos e Lesões; Gestão da dor; Cuidado Centrado no Paciente; Administração Tópica; Revisão; Enfermagem; Enfermagem baseada em evidências; Enfermagem Oncológica.

Topical therapy for pain management in malignant fungating wounds: a scoping review

Abstract

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Aims and objectives: To map and synthesize the existing literature on topical therapies for Malignant Fungating Wounds pain management and the gaps involved.
Background: Most cancer patients with Malignant Fungating Wounds suffer from wound-related pain, affecting their quality of life. Unfortunately, even though pain is a relevant symptom in cancer and palliative care, little is currently known about topical treatments' availability and impact on pain management.
Design: A scoping review following JBI® methodology
Methods: Searches were performed in CINAHL, LILACS, Embase, Web of Science, PubMed, Cochrane, NICE, Scopus, JBISRIR, and gray literature, in English, Portuguese and Spanish, with no time limit. Two authors independently reviewed all citations and a third was called in case of divergence, and studies in adults with Malignant Fungal Wounds reporting topical pain interventions were included. In addition, a data extraction tool for synthesis and thematic analysis was developed. This study followed the PRISMA-ScR Checklist.
Results: 70 publications were selected from 796 records retrieved from databases. The studies mainly included non-systematic reviews and case studies with only six clinical trials. According to the narrative synthesis, twenty therapies were identified, including the use of wound dressings (58.6%), analgesic drugs (55.7%), topical antimicrobials (25.7%), skin barriers (15.7%), cryotherapy (5.7%), and Negative Pressure Wound Therapy (4.3%). Therapies were recommended to be applied to the wound bed or the periwound skin. In 68.5% of the studies, a standardized assessment for pain was not described.
Conclusions: Topical therapies applied to Malignant Fungating Wounds or periwound areas had been examined for pain management. However, their effectiveness was analyzed in a few interventional studies, indicating the need for further primary studies to inform evidence-based practice.
Implication for Practice: Highlighted topical therapies for clinical practice consideration are opioids, anesthetics, and antimicrobials, with positive results described in randomized clinical trials.
This study did not include patients.
Keywords: Neoplasms; Wounds and injuries; Pain Management; Patient-Centered Care; Topical Administration; Review; Nursing; Evidence-based Nursing; Oncology Nursing.

What does this paper contribute to the broader global clinical community?

- Patients with Malignant Fungating Wounds experience physical, mental, social, and spiritual pain, as conceptualized by Cecily Saunders in "total pain". Pain may be related to tumor infiltration and be of a nociceptive, neuropathic origin, caused by moisture-associated periwound skin damage or wound dressing manipulation.
- Systemic treatments for pain management in patients with cancer ineffectively manage malignant fungating wound-related pain due to its etiopathogenic characteristics and poor superficial tissue perfusion. In addition, there is no clarity about available topical options for pain control in these wounds.
- This scoping review found 20 potential topical therapies for Malignant Fungating Wound-associated pain, documented mainly in non-systematic reviews, case reports, and a few interventional studies. Eleven studies recommended the use of topical therapies applied to the peri-wound skin that act by promoting a protective barrier.

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- Topical products were categorized as anti-adherent, antimicrobial, anti-inflammatory, absorbent dressings, analgesic drugs (gel based on anesthetic, opioid, and oil with cannabinoids), negative pressure wound therapy or cryotherapy, and careful irrigation and removal of dressings.
- Most of the included studies (69%) did not formally assess pain using the appropriate tools.
- This study's comprehensive mapping of the literature on topical MFW pain therapies highlights different treatments worldwide, opening the door for urgent primary research and evidence-based implementation projects. Furthermore, the results included herein may guide future studies and support the revision of local protocols.

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Introduction

According to the Globocan 2020 report, one in five people will develop cancer. The report estimated that 19.3 million people across the globe were living with cancer at the time of the publication, and 10 million had died from the disease (Sung et al., 2021). Advancements in cancer diagnosis and treatments have led to prolonged survival time in recent decades (Sung et al., 2021; Tsichlakidou et al., 2019)~~;~~ , putting cancer survivors at risk for chronic complications from the progression of the disease and treatments, including the emergence of Malignant Fungating Wounds (MFWs) (Hoshi et al., 2019; Tilley et al., 2020).

MFWs are complex chronic wounds that originate from uncontrolled proliferation of infiltrating malignant cells, disrupting skin integrity. Over time, these wounds evolve and deteriorate, becoming more extensive and invasive (Hoshi et al., 2019; Tilley et al., 2020; Young, 2017). Approximately 4% -15% of cancer patients develop this type of injury (Firmino et al., 2020) that predominately involve breasts (62 to 66%), head and neck (24%), and the chest due to the proximity of the compromised tissue to the skin (EONS, 2015; Firmino et al., 2020; Neves Duarte Lisboa, 2016; O'Neill et al., 2022). According to the Haisfield-Wolfe and Baxendale-Cox staging system, people with MFWs in their advanced stages are beleaguered by debilitating symptoms, including odor, exudate, itching, bleeding, and pain (Haisfield-Wolde ME, 1999). These symptoms can present significant challenges to patients, caregivers, and health professionals (Santos & Fuly, 2015; Tilley et al., 2020).

Pain is the most common concern of all symptoms related to people living with MFWs. However, pain is a subjective experience that is difficult to assess objectively; evaluation relies on self-reported measures (Raja et al., 2020). Therefore, using validated instruments to evaluate pain

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systematically is essential to monitor and benchmark the efficacy of pain treatment over time (Caraceni & Shkodra, 2019).

Mechanism involved in MFW-related pain is complex and multifactorial because of the omnipresence of infection due to high local microbial load (Vardhan et al., 2019), irritation of exposed nerve endings (trauma at dressing changes), tumor growth (pressure compressing on body structures), and edema (impaired lymphatic and capillary drainage). In consequence, patients may experience nociceptive, neuropathic, inflammatory, or mixed pain, depending on the trigger (EONS, 2015; Naylor, 2001).

Current literature regarding topical interventions for the management of MFWs is inconsistent with the use of different topical substances with varying analgesic effects, such as opioids, anti-inflammatory drugs, anesthetics, and non-adherent dressings (EONS, 2015). Topical pain treatment may be preferred over systemic use of medication linked to many devastating side effects. In addition, the bioavailability of systemic pain medication can be unpredictable for controlling MFW-related pain due to altered circulation caused by malignant infiltration (LeBon et al., 2009).

A previous systematic review examined the efficacy of topical MFW treatments for local infection, odor, and pain. The review included four studies, three randomized controlled trials, and a pre and post-test survey on odor and infection management; In the end, the authors recommended new intervention studies for the control of MFW-related pain (Finlayson et al., 2017a).

Aims

This study aimed to map and synthesize the existing literature on topical therapies for MFW pain management and identify the existing gaps.

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Methods

A scoping review was conducted according to the JBI® approach developed to map key concepts, clarify definitions, define boundaries of a subject, summarize information, and describe research and clinical gaps (Peters et al., 2020). Unlike a systemic review that focuses on treatment effectiveness, a scoping review is a rigorous undertaking to conduct a comprehensive search for all the available literature about a subject without stringent methodological restriction.

The title of this review was recorded in the JBI® database (JBI, 2019). The protocol is on the Open Science Framework (OSF) platform (da Costa Ferreira et al., 2020) and was published in the Journal Wound Care (JWC) (Ferreira et al., 2021).

This study entailed secondary methodology (review of the literature); therefore, an ethical review was not necessary.

Review question

What types of topical therapies and/or treatments are available for pain management in patients with MFWs?

Inclusion criteria

Participants

This review considered studies of patients who were 18 years of age and above with painful MFWs.

Concept

The key concept of this review was to map any topical therapy for MFW-related pain management. Topical therapy was defined as applying a product to the wound and periwound skin, as previously described (Mayba & Gooderham, 2018).

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The secondary concept was to identify and describe how topical therapies are used for MFW-related pain management and the instruments used to assess pain.

Context

This study considered all types of care settings for patients with MFWs, such as hospitalization, outpatient and/or home care, long-term care, and palliative care support institutions.

Types of sources

For this review, we considered all qualitative, quantitative, and review studies describing the use of topical therapies to manage MFW-related pain in adult patients.

Any study with a qualitative theoretical and methodological framework was considered for qualitative studies. Any experimental (controlled trials with or without randomization, quasi-experimental, before and after) and observational studies (descriptive, cohort, cross-sectional, case, and case series) were considered for quantitative studies. Systematic, non-systematic, meta-analyzes, meta-synthesis, and clinical practice guidelines were considered. In addition, unpublished studies (gray literature) in English, Portuguese, and Spanish without time limits were also considered.

Search strategy

Searches were performed in three steps: 1. An initial search was done on the MEDLINE and CINAHL databases using the terms "Wounds and Injuries; Neoplasms; Pain Management; Administration, Topical" to identify new keywords. 2. A new search was applied using all keywords and descriptors identified in the included databases. 3. Additionally, with the support of a librarian, a search equation was built for each database. The search strategy for CINAHL (EBSCO) is detailed in Table 1. No time limit was applied in the search equations conducted from

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2019 to 2020 which was then updated in March 2022. Finally, an active search in the reference lists of selected studies was performed to identify additional studies of interest.

Table 1: Search Strategy Example on CINAHL database through EBSCO platform[†]

Search	Descriptors	Records retrieved
1	(MH "Wounds and Injuries/TH") [Mesh]	38,896
2	(MH "Fungating Wounds/TH")	57
3	(MH "Fungating Wounds/TH") OR TI “malignant fungating wounds” OR AB “malignant fungating wounds”	87
4	(MH "Neoplasms") [Mesh]	72,428
5	(MH "Neoplasms") [Mesh] OR TI cancer OR AB cancer OR TI oncol* OR AB oncol*	392,223
6	1 AND 5	28
7	3 OR 6	217

[†]Search carried out until March 22,2022. Filters: no time or language limit
Abbreviations: TI, Title; AB, Abstract; MH, Major Headings

Information sources

CINAHL (EBSCO), LILACS (VHL Regional Portal), Embase, Scopus, Web of Science, Medline (PubMed), Cochrane, NICE, JBISRIR, as well as unpublished studies on the Open Access Scientific Repository (Canada), Canadian Dissertation and Thesis Portal, *Tesis Doctorales Database* -Teseo (Spain), CAPES Thesis Bank (Brazil), Google Scholar (including Textbooks and Congress Proceedings), and the European Thesis and Dissertation Database-Dart-E.

Inclusion of the studies

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After conducting the searches, all identified records were grouped and registered on Mendeley® (Mendeley Ltd., Elsevier, The Netherlands) for management and duplicate removal. Two independent reviewers reviewed titles and abstracts based on the inclusion criteria for evaluation. Potentially relevant documents were retrieved in full text. Two independent reviewers evaluated the full text of the selected citations in detail, based on the inclusion criteria. A third reviewer decided on disagreements between reviewers at any stage of the selection process.

Data extraction

Two independent reviewers extracted the data using a data extraction tool developed by the authors and previously tested on three articles to assess their adequacy. After the test, we added the variables: "trade name of the therapy," "formulation," and "application form" (Table 2).

Table 2: Data extraction instrument

General data
Article n°: _____ Database: _____
Title of article: _____
Authors: _____
Author's main training: Nursing ( ) Medicine ( ) others ( )_____
Journal: _____ Year: _____ Vol: _____
Publication language ( ) English ( ) Spanish ( ) Portuguese ( ) Other: _____
Country of publication: USA ( ) Brazil ( ) Other ( )_____
Type of study: _____ Objective: _____
Sample: _____Sex: _____ Age: _____
Methodological design: _____
Topical MFW Pain Therapy: _____
Results: _____

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Conclusion: _____
Specific data
Primary tumor: _____ Tumor Staging: _____
Metastasis: ( ) No ( ) Yes metastasis location: _____
Wound location: _____ Wound Staging: _____
Wound Pain Rating: ( ) No ( ) Yes
Assessment Instrument: _____
Wound pain classification:_____
Location of wound pain: _____
Description of wound pain: _____
Duration and moment of feeling the wound pain: _____
Taking wound pain control medication: ( ) No ( ) Yes Specify: _____

Extracted data included general data regarding the author(s), year of publication, origins, objectives, methods, topical therapies used, and results. In addition, specific data regarding tumor type, staging, wound location and stage, pain evaluation with an assessment tool, pain classification, location and duration of pain, and the use of medication to control wound pain were extracted. The authors of one of the included articles were contacted to request additional data (Ciałkowska-Rysz & Dzierżanowski, 2019). As seen in the methodology of scoping reviews, a critical evaluation of the included articles was not carried out.

Data presentation

Extracted information from the included articles was summarized using narrative synthesis to delineate all available strategies in the literature, identify possible gaps and limitations in the

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current knowledge, and guide future primary studies that can respond to the challenges of topical MFW-related pain management.

According to the objectives and the review question, the narrative synthesis is presented in suitable key conceptual categories and specific subgroups created after the data extraction process. The synthesis followed the guidelines of the EQUATOR checklist called the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Supplementary File 1) (Tricco et al., 2018). Results were categorized and refined to describe the characteristics of the interventions using figures and tables.

Results

Study characteristics

Among the 796 identified studies, 564 articles did not meet the inclusion criteria. Eighty-seven were considered eligible for a full-text reading after excluding 145 duplicates, from which 24 were further discarded (Supplementary Table 3) as they did not meet the inclusion criteria.

Table 3. Excluded Articles Description[†]

Exclusion motive 1: the articles did not meet the inclusion criteria (do not present a proposal for pain management therapy in Malignant Fungating Wounds). n=18		
Year	**Title of the article**	**Authors**
2019	Applying honey dressings to non-healing wounds in elderly persons receiving home care	R Zeleníková, D Vyhlídalová
2018	Management of Non-Healing Wounds with Honey Dressings: A Literature Review	Vyhlídalová D, Kozáková R, Zeleníková R.
2017	Topical Opioids and Antimicrobials for the Management of Pain, Infection, and Infection -Related Odors in Malignant Wounds: A Systematic Review	Finlayson, Kathleen; Teleni, Laisa; McCarthy, Alexandra L.
2017	Systemic antibiotics for treating malignant wounds.	Ramasubbu DA1, Smith V, Hayden F, Cronin P.

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2016	The relationship between malignant wound status and pain in breast cancer patients	Tamai, N., Mugita, Y., Ikeda, M., Sanada, H.
2015	Management of signs and symptoms in malignant wounds: An integrative review (congress summary)	Vasques C.I., Sacramento C.
2014	Feridas malignas: caraterística e qualidade de vida	Ázera, Joana Vaz
2014	Enfermeiras no atendimento ambulatorial a mulheres com feridas neoplásicas malignas	Firmino, Flávia; Alcântara, Laísa Figueiredo Ferreira Lós
2013	Patient story 3:1 Fungating wound	British Journal of Community Nursing
2013	A Gestão da ferida maligna em cuidados paliativos: práticas de enfermagem (dissertação	Moreira, Cátia Regina Lima
2012	Home nursing care of a woman with a malignant wound in a primary health care setting	Romero-Collado A.
2011	Management of a fungating wound	Watret L.
2011	Fungating wounds - Multidimensional challenge in palliative care	Merz T., Klein C., Uebach B., Kern M., Ostgathe C., Bükki J.
2010	Caring for a patient with a fungating malignant lesion in a hospice setting: reflecting on practice	Maureen Hawthorn
2007	Revisão sistemática sobre tratamento tópico de lesões vegetantes malignas	Cristina Mamedio da Costa Santos
2005	Qualitative and quantitative evaluation of a new regimen for malignant wounds in women with advanced breast cancer	Lund-Nielsen, B., Müller, K., Adamsen, L.
2003	Palliative wound management: the use of a glycerine hydrogel	Burns J1, Stephens M.
2001	Malignant wound management: what dressings do nurses use?	Wilkes, L., White, K., Smeal, T., Beale, B.
Exclusion motive 2: the articles did not meet the exclusion criteria (language different than English, Portuguese, and Spanish) (n=6)		
2018	Malignant wounds: A scab which no longer heals (German)	Witte F.
2015	Malignant wounds in palliative care (French)	Fromantin I, Rollot F, Nicodeme M, Kriegel I.
2013	History and care of malignant wounds in breast câncer (French)	Fromantin I1, Alran S2, Cassoux N2.
2009	Nurse's experience caring for a patient with malignant fungating wound with enterocutaneous fistula (Chinese)	Chuang W, Hsieh S.
2009	Palliative care for patients with malignant non-healing wounds (Croatian)	Kloke, M., Pinbauer, M.

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2007	Care of patients with fungating malignant wounds. (French)	Grocott P1.
[†]Papers excluded after the confirmation of at least two researchers.		

After actively searching the references of the included articles, seven extra papers were added, thus totaling 70 articles for this scoping review analysis (Figure 1).

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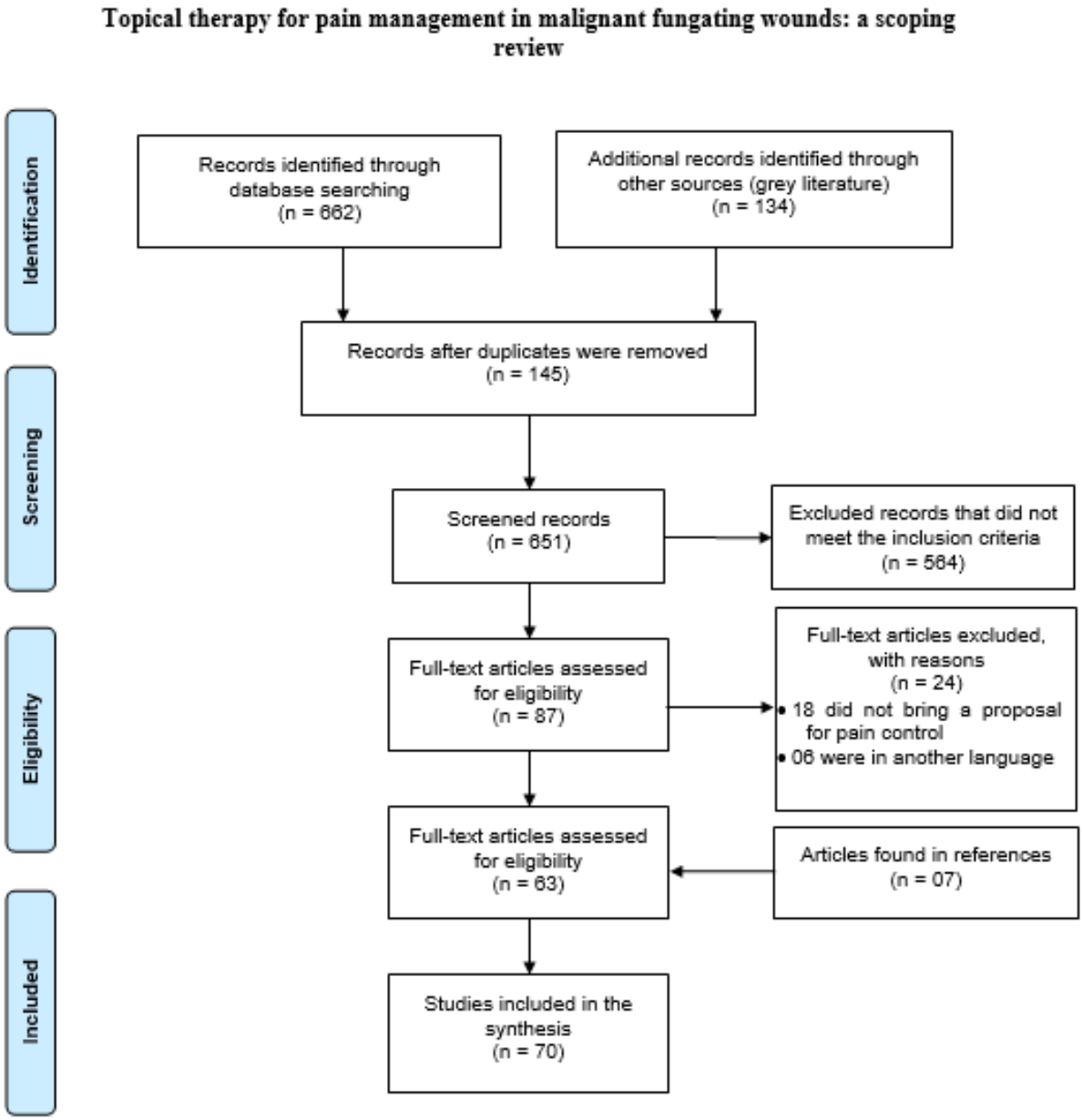

Figure 1: PRISMA flowchart for the scoping review process

The selected studies presented the following characteristics: 54 (88.6%) were published in English, four (5.7%) in Portuguese, and four (5.7%) in Spanish. England was the country with the largest number of publications (18 / 24.3%), followed by the USA (16 / 22.9%). Twenty-two studies (31.4%) were published in the last seven years (2015-2022). Nurses were the professional

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category that most published on the topic (54 / 77.1%), followed by physicians (15 / 24.1%) and pharmacists (1 / 1.4%).

Regarding the types of studies, 32 (45.7%) were non-systematic literature reviews, 20 (28.5%) case studies, and 18 (25.8%) the other methodologies (control trials, systematic reviews, cohorts, guidelines, and surveys) as detailed in the Table 4. Only seven MFW studies (10%) included pain management as a primary outcome. Study sample sizes ranged from 1 to 60 patients.

Table 4 - Distribution of the Study Types

Type of study	n	%
Non-systematic reviews	32	45.7
Case studies	20	28.5
Randomized clinical trials	6	8.6
Systematic reviews	3	4.3
Prospective cohorts	3	4.3
Guidelines	3	4.3
Surveys	2	2.9
Retrospective cohorts	1	1.4

Finally, 20 proposals were identified for the topical management of MFW-related pain. These are presented according to two general categories: Topical therapies applied in the wound and Topical therapies applied to periwound skin. Figure 2 shows the distribution of topical therapies in the 70 studies. Figure 3 summarizes the identified topical therapies grouped by MFW-derived sources of pain and the main research gaps.

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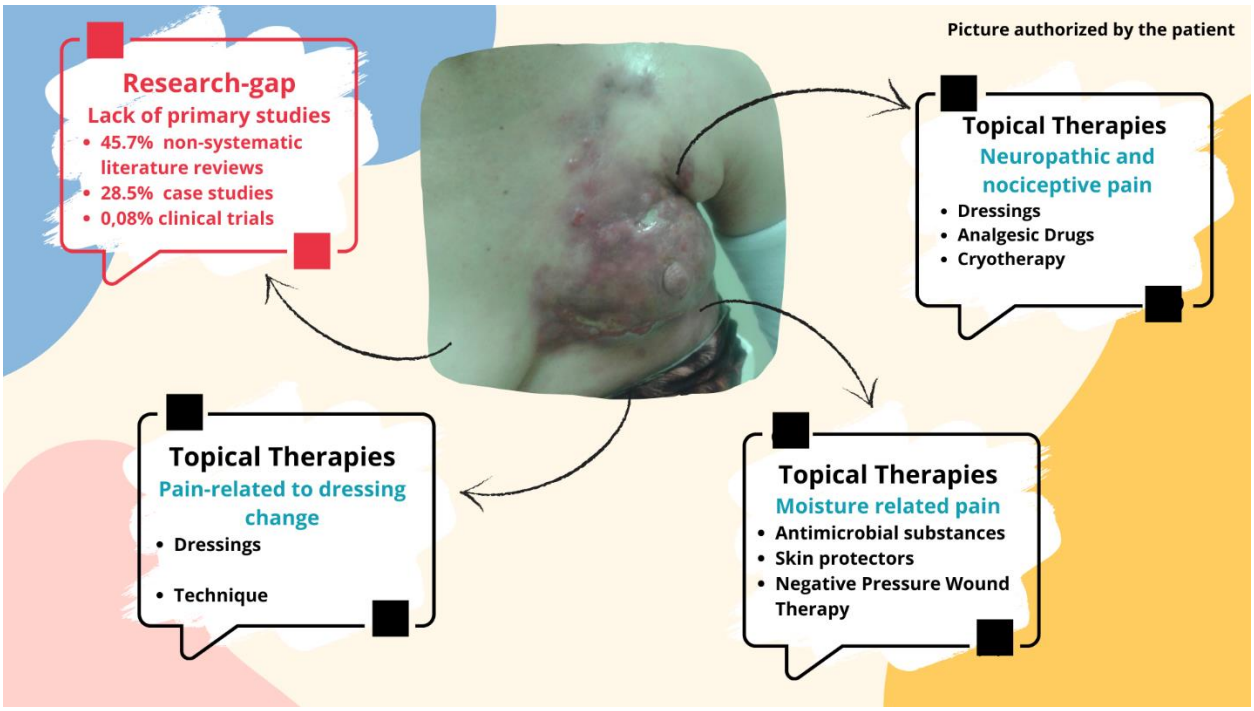

Figure 2: MFW-derived sources of pain and the main research gaps

Topical Therapies Applied in the wound

The topical therapies identified in this review included Analgesic Drugs, Antimicrobial Substances, Dressings, Negative Pressure Wound Therapy, and Cryotherapy. In addition, some studies presented more than one therapy, proposing an integrated approach for MFW-related pain management.

Dressings

This category included: Non-adherent dressings, Hydrogel, Absorbent dressings, and Anti-inflammatory dressings.

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Non-adherent Dressing

Twenty-six (37.1%) articles proposed non-adherent dressings for MFW-related pain management. The studies were non-systematic reviews (65.3%), case studies (19.8%), randomized clinical trials (3.8%), a guideline (3.8%), prospective cohorts (3.8%), and a Survey (3.8%). Twenty-five studies (35.7%) did not include pain management as a primary objective. All studies used dressings with other therapies such as opioids, anesthetics, and antiseptics. None of the studies mentioned a standardized way of using them or described the pain-related specific results from non-adherent dressings alone.

Hydrogel

Eleven out of the 70 studies (15.7%) recommended using hydrogels to manage MFW-related pain. The studies included non-systematic reviews (54.5%), case studies (36.3%), and systematic reviews (9.2%). Eight (72.7%) studies discussed hydrogel perfunctorily as an optional dressing for these patients to reduce pain by maintaining a moist wound environment. Discussions were brief without substantiation. The hydrogel was also mentioned as a vehicle to deliver other active substances such as opioids, anesthetics, and antibiotics in the included studies. None of the studies presented a standardized way of using this type of dressing, and no results were presented.

Absorbent Dressing

Ten (14.2%) studies used absorbent dressings to manage MFW-related pain. The studies included non-systematic reviews (50%), case studies (20%), a guideline (10%), randomized clinical trials (10%), and a survey (10%). None (90%) of the studies aimed to test the absorbent dressing to control MFW-related pain. Some studies only cite them as a dressing option for patients

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with pain related to high exudate absorption, minimizing the possible dermatitis related-pain derived from periwound moisture. In all studies, these dressings are associated with other therapies such as opioids, anesthetics, and antiseptics. No study mentions a standardized way of using the dressings or of displaying their results on pain management without being combined with other products.

Anti-inflammatory Dressing

Anti-inflammatory dressings include absorbent polyurethane foam containing 0.5 mg/cm^2 of Ibuprofen homogeneously distributed throughout the foam matrix and a cream with essential oils.

- Foam with Ibuprofen

Eight (10%) out of 70 studies suggested using foam with Ibuprofen dressing as a therapy for MFW pain management. The studies were of the non-systematic reviews (87.5%) and survey (12.5%) types. None of the studies focused on evaluating the foam with Ibuprofen for MFW-related pain management, but only cited it as a dressing option for these patients. In addition, no study mentioned how to use the dressing or the results of its use.

- Cream with essential oils

Only one case study (1.4%) published in 2014 (Stringer et al., 2014) evaluated the use of a cream with essential oils in 12 patients (mostly women with breast cancer with ages between 40 and 81 years) for MFW symptoms. The cream contained 3% essential oils (without specifying ingredients). Without standardizing the dressings and reporting the cream's form and several

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applications on the wounds, the authors mentioned that six patients reported pain improvement (reducing the maximum score to zero on a Likert scale).

Analgesic Drugs

Topical opioids, topical anesthetics, and Medicinal Cannabis were categorized within analgesic drugs.

Topical Opioids

Thirty-one (44.2%) studies examined opioids applied topically to the wound bed to control MFW-related pain. The studies included non-systematic reviews (67.7%), case studies (16.1%), randomized clinical trials (.06%) (including a letter to the editor in which data from an unfinished trial was reported), guidelines (.03%), prospective cohorts (.03%) and systematic reviews (.03%). Of these 31 studies, just under a half mentioned specific opioids to treat MFW-related pain, specifically suggesting Morphine. Meanwhile, two of them also mentioned Oxycodone without describing its preparation or ways of applying these drugs, as shown in Table 5.

Table 5 - Topical Opioids and Related Results for Malignant Fungating Wound-related Pain Management (n = 18)

Citation	Country	Type of study	Type of opioid	Formulation	Form of application	Results[†]
Cornish L. Br J Community Nurs. 2019 Sep 1;24(Sup9):S19–23.	England	Non-systematic review	Injectable Diamorphine	6.25–15 mg of injectable Diamorphine (usually 10 mg) mixed with 8 g of an amorphous gel	Not described	Not described
Ciałkowska-Rysz & Dzierżanowski, T. Arch Med Sci.	Poland	Randomized clinical trial	Topical Morphine in .2% ointment form	.2 g of Morphine sulfate 3 g of Glycerol 100 g of Eucerin	Free application by patients without restrictions on	Visual Analogue Scale of 5.9 and 2.5 after morphine application (p <.001)

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2019;15(1):146–51.					the number of doses per day.	
Tilley et al. 2016;51(3):513–31.	USA	Case study	Morphine	10 mg of Morphine 8 g of hydrogel	Not described	Pain control
Probst et al. Eur J Cancer Suppl. 2009 Sep;7(2):232–3. 2009	Switzerland	Survey	Morphine	6.25-15 mg of Morphine (usually 10 mg) 8g of hydrogel	Not described	Not described
Woo et al., Adv Ski Wound Care. 2015;28(3):130–40.	Canada	Non-systematic review	.1% Morphine	25 mg of Morphine 25 g of hydrogel or use injection of 10 mg/ml Morphine sulfate or 10 mg of Morphine in 8 g of hydrogel (0.125%)	Apply 1 to 3 times a day	Not described
			.02% Hydromorphone	In 2% lidocaine gel or 5% ointment. It is recommended to use an injection volume of 50 mg/ml to minimize dilution of the base	Apply 1 to 3 times a day	Not described
			1% Powdered methadone	100 mg of Methadone 10 g of hydrocolloid powder or Carboxymethyl Cellulose gel	Sprayed on the wound with a 60 ml syringe once a day	Not described
Meaume et al., J Tissue Viability. 2013;22(4):122–30	France	Non-systematic review	Morphine	10 and/or 30 mg of Morphine 15 g of gel	Not described	It has been reported to be beneficial
Graham et al., Pain. 2013;154(10):1920–8.	England	Non-systematic review	Diamorphine, morphine sulfate, morphine hydrochloride, methadone	Varied doses and concentrations 1.6-15 mg of Diamorphine, Morphine sulfate, Morphine hydrochloride, or Methadone	Not described	The most common analgesic relief was achieved in patients with a pressure injury and MFWs

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				8 g of hydrogel		
Vaquer, LM. Rev Int Grup Invest Oncol. 2012 Feb;1(2):52–9.	Spain	Non-systematic review	.1% Morphine	1 mg of Morphine 1 g of hydrogel	Not described	Not described
Laird & Fallon, Clin Oncol. 2009;21(2):131–9.	Scotland	Non-systematic review	Gel Morphine	10 and 20 mg of Morphine	Not described	Not described
Alexander, J Wound Care. 2009 Oct;18(10):418–25.	Australia	Non-systematic review	.1% Morphine	1 mg of Morphine 1 g of hydrogel or 20 mg of Diamorphine 30 g of hydrogel	Not described	Not described
McDonald A & Lesage P. J Palliat Med. 2006;9(2):285–95	USA	Non-systematic review	.1% Morphine	1 mg of Morphine 1 g of hydrogel	Not described	Not described
Seaman S. Semin Oncol Nurs. 2006	USA	Non-systematic review	Diamorphine .08% Morphine Morphine sulfate	10 mg of Diamorphine added to an amorphous hydrogel 3.2 mg of Morphine 4 g of amorphous hydrogel 10 mg/ml of Morphine sulfate 8 g of gel	Daily application Daily application Not described	Improved pain control
Naylor, W. Nurs Stand. 2002. Sep 11;16(52):45–53	England	Non-systematic review	.1% Morphine or Diamorphine	1 mg of Morphine or Diamorphine to 1 g of hydrogel	Once per day	Not described
Naylor, World Wide Wounds. 2002	New Zealand	Non-systematic review	Morphine	1 mg of Morphine 1 g of hydrogel	Once per day	Not described

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Naylor, W. Br J Nurs. 2001 Dec 13;10(Sup5):S33–56	England	Non-systematic review	Morphine Diamorphine Diamorphine	1 mg of Morphine 1 g of hydrogel 10 mg of Diamorphine in an unspecified amount of hydrogel. 10 mg of Diamorphine to 15 g of hydrogel	Twice per day Once per day Once per day	Pain reduction
Twillman et al., J Pain Symptom Manage. 1999;17(4):288–92.	USA	Case study	Morphine	1-1.5 mg of Morphine 1 ml of amorphous hydrogel (Carboxymethyl cellulose polymer, propylene glycol and water)	Twice per day	Of the 9 patients, 8 reported significant improvements in Pain
Krajnik et al., Pain. 1999;80(1–2):121–5.	Poland	Case study	.1% Diamorphine	2500 mg of Morphine HCl 25 g of Carbomerum 974 2500 mg of Sodium EDTA 25 g of Trometamol 15% of propylene glycol / 25 g of Diamorphine 2500 ml distilled water	Doses ranged from 0.5 ml to 50 ml with an average application of twice per day	In all but one case, topical morphine provided rapid relief, which generally lasted 7 to 8 hours
Back & Finlay. Jounal pain Sympt Manag. 1995;10(7):493.	USA	Case study	Diamorphine	10 mg of Diamorphine added to hydrogel and a carboxymethyl cellulose dressing	Daily application	Pain relief

[†]Main results were literally extracted from papers.

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Topical Anesthetics

Regarding analgesic drugs, 20 (28.5%) studies proposed using topical anesthetics to manage MFW-related pain. The studies were non-systematic reviews (75%), case studies (5%), randomized clinical trials (5%), guidelines (5%), prospective cohorts (5%), and surveys (5%). Nine studies (45%) presented dosages and application guidelines for various topical anesthetics that are grouped and detailed in Table 6. Additionally, 11 (55%) mention using lidocaine, prilocaine, benzocaine, and a tricyclic anesthetic, without describing the formulation or mode of use.

Table 6- Topical Anesthetics and Related Results for Malignant Fungating Wound-related Pain Management (n = 9)

Citation	Setting	Type of study	Anesthetic	Formulation	Form of application	Results[†]
Cornish, L. Br J Community Nurs [Internet]. 2019 Sep 1;24(Sup9):S19–23.	England	Non-systematic review	Lidocaine patches	5% Lidocaine	Not described	Not described
Agra et al. Enferm Bras [Internet]. 2019 Mar 18;18(1):3.	Brazil	Non-systematic review	Lidocaine gel	2% Lidocaine gel	With each dressing	Not described

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Peng et al. Brazilian J Med Biol Res [Internet]. 2019;52(11): 1–5.	China	Randomized clinical trial	5 % lidocaine and prilocaine cream	2.5% Lidocaine 2.5% Prilocaine	Applied 10 minutes before dressing change Dose of 1.5 g / 10 cm^2	It had an analgesic effect. In pain relief, the effect of lidocaine was faster and greater than 10 mg of morphine tablets and maintained an almost painless state for a long time. Any *p*-value was informed
Young, T. Wounds UK EWMA Spec. 2017;1–6.	England	Non-sistematic review	5% lidocaine	5% Lidocaine	Not described	Not described
Tilley et al. Nurs Clin North Am. 2016;51(3):513–31.	USA	Case study	2% Lidocaine	2% Lidocaine gel	Not described	Pain control in MFWs
Woo et al., Adv Ski Wound Care. 2015;28(3):130–40.	Canada	Non-sistematic review	Lidocaine cream	2.5% Lidocaine 2.5% Prilocaine	Before wound debridement	Significantly reduces acute Pain induced by debridement
Sacramento et al., R Enferm Cent O Min [Internet]. 2015;5(1):1514–27.	Brazil	Non-systematic review	2% lidocaine	2% Lidocaine gel	Not described	Not described
Chrisman, CA. Int Wound J [Internet]. 2010 May 28;7(4):214–35.	USA	Non-systematic review	Lidocaine	2-75% Lidocaine in zinc oxide cream	30-45 minutes before debridement	Controls Pain quickly and lasts up to 4 hours

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INCA. Ministério da Saúde - Brasil - Série Cuidados Paliativos; 2009.	Brazil	Guidelines	2% lidocaine gel	2% Lidocaine gel	Apply on and around the MFWs, covering about 2 cm of healthy tissue	Not described
†Main results were extracted literally from papers.						

Medicinal Cannabis

Only one case study (1.4%) (Maida, 2017) proposed using medicinal cannabis as topical and vaporized oil as part of the MFW pain management armamentarium. The case focused on a 44-year-old male patient diagnosed with squamous cell cancer in the oral cavity, resulting in a MFW on the right hemiface. The patient rated the pain between 9 and 10/10 at baseline, and treatment included intravenous analgesia. After receiving the vaporized medicinal cannabis every 2 to 4 hours, and before changing the dressing or digitally applying and spreading 1-2 ml of the oil throughout the wound, externally and intra-orally, the patient reported significant pain relief, with his pain score was reduced to 3 and 4, this improvement allowed for a modification of the analgesic regimen. This is the first case report demonstrating the potential of topical medicinal cannabis for effective MFW pain management**.**

Antimicrobial substances

This scoping review categorized antimicrobial substances as topical antimicrobials, honey, and antiseptics. We consider any implications of antimicrobial substances if they present the ability

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to kill or inhibit the growth and development of a microorganism (bacteria, fungi, and viruses), including antibiotics, antiseptics, and disinfectants.

Topical antimicrobials

Ten (14.2%) studies proposed using topical antimicrobials such as Metronidazole, Nanocrystalline Silver, and Silver Sulfadiazine to manage MFW-related pain. These studies were case studies (40%), randomized clinical trials (20%), non-systematic reviews (10%), retrospective cohorts (10%), systematic reviews (10%), and surveys (10%). Six (60%) reported using antimicrobials, although pain was not their main focus, but did not present the form of use or the outcomes.

One randomized clinical trial (Lund-Nielsen et al., 2011) included in a systematic review (Adderley & Holt, 2014) reported positive results when using antimicrobials to control MFW odor, exudate, and pain. Three studies tested antimicrobials to manage MFW symptoms, including pain. Two were randomized clinical trials, and one was a retrospective cohort that included 192 patients with MFWs, mainly women aged between 47 and 90 years and primarily with breast cancer. Of these clinical trials, two used a verbal numeric scale and a visual analog scale, demonstrating improvement in pain; the third found no statistically significant effect on the pain outcome (Table 7).

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Table 7 - Topical Antimicrobials and Related Results for Malignant Fungating Wound-related Pain Management (Studies = 3 / patients = 192)

Citation	Setting	Type of study	Topical antimicrobials	Formulation	Form of application	Results[†]
Villela-Castro et al., J wound, ostomy, Cont Nurs Off Publ Wound, Ostomy Cont Nurses Soc. 2018;45(5):413–8.	Brazil	Randomized clinical trial	Antimicrobial solution Metronidazole Solution handled by the study hospital pharmacy	.2% of Polyhexamethylene Biguanide (PHMB) .8% of Metronidazole	30 ml of PHMB or metronidazole solution was applied to wash the wound, and then gauze was soaked in the solutions to cover the wound bed. Changed the dressing twice a day	Maintenance of pain score
Lund-Nielsen et al., Wound Repair Regen. 2011 Nov;19(6):664–70.	Denmark	Randomized clinical trial	Antiadherent Dressing with antimicrobial Silver coated absorbent dressing	Honey dressing Nanocrystalline silver dressing	Changed the dressing every two to three days	There was no statistical difference in pain control when comparing the honey dressing to the silver dressing (p = .733)
Signe-Picard et al., J Wound Care. 2010;19(9):369–78.	France	Retrospective cohort	1% of Silver Sulfadiazine and 2% of Ceric Nitrate	Silver Sulfadiazine (1g / 100g), Ceric nitrate (2g / 100g)	Daily application for the first seven days and then application every two days, ensuring a 3 mm layer of the product during the application	Improved pain control, decreased levels of exudate and odor

[†]Main results were extracted literally from papers.

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Honey

Five (7%) articles reported topical honey as a therapy for MFW-related pain management. None of the studies focused on pain management but on the general control of MFW symptoms, including pain. Two reviews (systematic and non-systematic) (Adderley & Holt, 2014; Praptiwi, 2017) included two primary studies in which authors obtained positive effects of using honey to control MFW odor, exudate, and pain. These studies analyzed 384 patients, mainly women, with an average age of 44 to 90 years, primarily with breast tumors. A visual analog scale was used just in one of the studies (Lund-Nielsen et al., 2011). (Table 8).

Table 8 - Topical Honey and Related Results for Malignant Fungating Wound-related Pain Management (Studies = 5 / patients = 384).

Citation	Setting	Type of study	Topical Honey	Formulation	Form of application	Results[†]
Tsichlakidou et al. . J BUON. 2019;24(3):1301–8.	Greece	Systematic review	Honey paste	Swab application, two times in the oral cavity	Decreased pain	Honey was safe for palliative treatment of MFW symptoms on skin and mucosa
			Honey in calcium alginate	Replacement of calcium alginate, in the external wound, according to need		
			Pure honey	Not described		
Woo et al., Adv Ski Wound Care. 2015;28(3):130–40.	Canada	Non-systematic review	Not described	Not described	Not described	Not described

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O'Brien, C. Can Fam Physician. 2012;58(3):272–4.	Canada	Case study	Honey	Not described	Not described	Not described
Lund-Nielsen et al., Wound Repair Regen. 2011 Nov;19(6):664–70.	Denmark	Randomized clinical trial	Non-adherent dressing with honey Coated silver absorbent dressing	Honey dressings Nano-crystalline silver dressings	Changed every two to three days	There was no statistical difference in pain control when comparing the honey dressing to the silver dressing (p = .733)
Segovia, D. Ostomy. 2010;5610):14–7.	USA	Case study	Active Honey Leptospermum (AHL)	The dressing was changed every three days	The anti-inflammatory properties of AHL provided an analgesic effect, reducing pain associated with the wound and dressing changes	Decreased pain associated with wound and dressing changes
†Main results were literally extracted from papers.						

Topical antiseptics

Only three (4%) studies proposed topical antiseptics such as Polyhexamethylene Biguanide, Octenidine, and other non-specified degerming agents for MFW pain management. The studies included randomized clinical trials (66.6%) and non-systematic reviews (33.4%). None of the studies had pain control as the primary aim but the control of general symptoms,

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including pain. The three studies analyzed 54 patients, predominantly women, between 24 and 92 years old, with primary tumors, mainly of the breast. Pain was assessed using verbal classification and visual analog scales in two of the studies. The use of topical antiseptics resulted in pain improvement in two studies and no changes in pain intensity scores in one study (Table 9).

Table 9 - Topical Antiseptics and Related Results for Malignant Fungating Wound-related Pain Management (Studies = 3 / patients = 54)

Citation	Setting	Type of study	Topical antiseptics	Formulation	Form of application	Results[†]
Villela-Castro et al., J wound, ostomy, Cont Nurs Off Publ Wound, Ostomy Cont Nurses Soc. 2018;45(5):413–8.	Brazil	Randomized clinical trial	Antimicrobial solution Metronidazole solution	.2% of Polyhexamethylene Biguanide (PHMB) .8% of Metronidazole	30 ml of PHMB or metronidazole solution was applied to wash the wound and then gauze was soaked in the solutions to cover the wound bed. Dressing was changed twice a day	Maintenance of pain score
Sopata et al., Adv Dermatology Allergo. 2013;4(4): 237–45.	Poland	Randomized clinical trial	Non-adherent silicone dressings, Gazes, and bandages	Octenidine dihydrochloride and non-adherent silicone dressing	The wounds were washed with saline solution three times a day and covered with non-adherent silicone dressings and	The decrease in pain experienced by patients was statistically significant ($p < .05$)

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					gauze saturated with octenidine dihydrochloride	
Langemo et al., Adv Skin Wound Care. 2007;20(6):312–4	England	Non-systematic review	Degerming agent	Not described	Not described	Can minimize pain

[†]Main results were literally extracted from papers.

Negative Pressure Wound Therapy

Three (4%) studies elucidated the use of Negative Pressure Wound Therapy (NPWT) to manage MFW-related pain. The studies were case studies (66.6%) and non-systematic reviews (33.4%). None of the studies focused primarily on pain management but on the general direction of MFW-associated symptoms; however, one of the studies did not mention the main objective. These studies analyzed data from six patients, women aged 56 to 62, with different primary tumors (sarcomas, breast cancer, melanoma, and sigmoid cancer). There was no quantitative or qualitative assessment of pain in any of the studies. Nevertheless, the studies reported an improvement in odor, exudate, and pain, thus impacting patients' quality of life (Table 10).

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Table 10 - Negative Pressure Therapy and and Related Results for Malignant Fungating Wound-related Pain Management (Studies = 3 / patients = 6).

Citation	Setting	Type of study	Negative pressure therapy	Formulation	Form of application	Results[†]
Beers, Surg Clin North Am. 2019 Oct;99(5):899–919.	USA	Non-systematic review	Not described	Not applicable	Not described	Reduction of exudate, odor, and pain
Riot et al., . Palliat Med. 2015;29(5):470–3.	France	Case study	Standard NPWT	Not applicable	Every five to seven days. Pressure 100 - 125 mmHg in continuous mode	Reduction of exudate, odor, and pain
Ford-Dunn, Palliat Med. 2006;20(4):477–8.	England	Case study	Standard NPWT	Not applicable	Change every three days	Control of exudate and pain

[†]Main results were literally extracted from papers.

Cryotherapy

In four studies (5%), topical cryotherapy was applied to control MFW-related pain without this being the primary focus, but rather the management of symptoms which included pain. The studies were non-systematic reviews (50%), surveys (25%), and guidelines (25%). The studies did not show the forms of use or results.

Topical therapies applied to periwound skin

Eleven (15.7%) studies discussed therapies for pain management in the periwound skin area. The studies were non-systematic reviews (63.7%), case studies (18.1%), guidelines (9.1%),

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and surveys (9.1%). The proposed therapies were zinc oxide (ointment and cream), silicone, dimethicone, petrolatum, acrylate and cyanoacrylate, hydrocolloid (paste and powder), and vitamin-rich ointment (A and D), all of which are part of pain-control protocols. All studies were coordinated by nurses and published in journals on wounds, palliative care, oncology, and general nursing. Two studies reported assessing pain, and one mentioned a Visual Analog Scale as the instrument used to measure pain. Positive results are reported, however, not further described (Table 11).

Table 11 - Topical Therapies Applied to Periwound Skin to Malignant Fungating Wound-related Pain Management (n = 11)

Citation	Setting	Type of study	Therapy	Formulation	Form of application	Results[†]
Agra et al., Enferm Bras. 2019 Mar 18;18(1):3.	Brazil	Non-systematic review	Zinc oxide	Ointment	At the edges and around the wound with each dressing	Not described
Tandler & Stephen-Haynes, Br J Nurs. 2017 Jun 22;26(12):S6–14.	England	Non-systematic review	Silicone	Adhesive remover	Not described	Not described
Woo et al., Adv Ski Wound Care. 2015;28(3):130–40.	Canada	Non-systematic review	Silicone Polymers Dimethicone Zinc oxide Petrolatum Acrylates and cyanoacrylate Hydrocolloid	1% to 5%	Not described	Not described

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Vaquer, LM. Rev Int Grup Invest Oncol. 2012 Feb;1(2):52–9.	Spain	Non-systematic review	Polymers (barrier cream) Polymers (barrier spray)	Barrier creams and spray barrier	Not described	Not described
Woo & Sibbald, Palliat Care. 2011;(September):223–39.	Canada	Non-systematic review	Silicone Zinc oxide Petrolatum Acrylates and cyanoacrylate Hydrocolloids	Not described	Not described	Not described
Chrisman, Int Wound J. 2010 May 28;7(4):214–35.	USA	Non-systematic review	Zinc oxide (cream)	Petrolatum-based skin ointment with different active principles	Not described	Not described
INCA. Ministério da Saúde - Brasil - Série Cuidados Paliativos; 2009.	Brazil	Guideline	Zinc oxide (ointment)		At the edges and around the wound	Not described
Benbow, J Community Nurs. 2009;23(11):12–8.	England	Non-systematic review	Polymer Plate hydrocolloid	Spray barrier film Not described	Not described	Not described

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Lo et al., J Wound Care. 2007;16(9):373–6.	Japan	Case study	Polymer Hydrocolloid (powder)	Spray barrier film Hydrocolloid in powder	Application of hydrocolloid powder, followed by application of a spray polymer layer	Wound healing in eight weeks
Poletti et al., Rev Bras Cancerol. 2002;48(3):411–7	Brazil	Non-systematic review	Vitamin A and D ointment	Not described	Not described	Not described
Collier, Nurs Stand. 2000 Nov 29;15(11):46–52.	England	Case study	Hydrocolloid	Not described	Not described	Not described
†Main results were literally extracted from papers.						

Technique

The dressing application and removal technique for MFW-related pain management was not categorized as a topical therapy. However, several studies alluded to various dressing application techniques and conditions and their effect on pain. Twenty-one (30%) studies proposed procedures related to the dressing technique to minimize pain. The studies were non-systematic reviews (66%), guidelines (14%), randomized clinical trials (10%), a case study (5%), and a survey (5%). In general, the authors proposed cleaning the wound with an appropriately warm solution, applying and removing dressings carefully, refraining from debridement due to the risk of bleeding,

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maintaining a moist environment in the wound bed, cleaning with soap with an appropriate pH, reducing the frequency of dressing changes, and providing analgesia before applying the dressing.

Discussion

This scoping review aimed to map and examine the literature available on topical MFW-related pain management, considering its relevance for oncology and palliative care clinicians. The synthesis of this body of literature may provide insights into treatments which could enhance quality-of-life, especially for patients with terminal cancer (Schmidt et al., 2020). This study is the first scoping review developed in its field to contribute to researchers seeking to advance research trends and elucidate the gaps in this field.

Cancer patients experience multiple symptoms, including pain that involves neurophysiological and affective components (Wood, 2021). Pain can be exacerbated, amplified, and contribute to loss of body functions, grief, a sense of doom, and other feelings, including anxiety, fear, and uncertainty within this population (Brant, 2017).

We reviewed 70 studies that explored 20 topical therapies such as dressings with different mechanisms of action, analgesic drugs, and antimicrobial substances, among others, with promising results to mitigate pain. However, only 31.4% of the studies applied standardized pain assessment tools: Visual Analogue Scale, Numerical Verbal Scale, McGill's Questionnaire, and the assessment by categories (no pain, weak, moderate, and severe). In addition, in a survey evaluating attitudes and knowledge about pain assessment and treatment among health care providers, demonstrated that nurses possessed a lower level of knowledge about pain assessment and management (Nuseir et al., 2016).

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In this review, the 20 topical treatments identified were grouped into five categories: dressings, analgesic drugs, antimicrobial substances, negative pressure therapy, and cryotherapy, with various products.

Studies on the use of dressings predominated as a proposal for topical therapy for MFW-related pain management. The treatment of pain that arises from changing dressings due to the adhesion of the product to the wound bed and the subsequent difficulty of removing it was highlighted. This demonstrates the benefits of protecting friable tissue in the wound bed in a malignant fungating wound. (Woo et al., 2015; Woo & Sibbald, 2010).

Non-adherent dressings, such as polyurethane foam, silicone foams, silicone hydrocellular foam, fibers, and hydrofibers, were recommended for promoting painless removal. However, there is still a need to clarify the best non-adherent therapy applied to MFWs due to changes in circulation and the presence of non-viable tissue. Absorbent dressings were also mentioned for MFW-related pain management, including the Pain of periwound dermatitis caused by excessive MFW exudation and the irritating components present in the exudate (Gozzo et al., 2014; Tamai et al., 2016a).

The use of a non-adherent and absorbent polyurethane foam covered with Ibuprofen was mentioned in 11% of the studies with positive results regarding MFW pain control. This was not surprising since this drug introduces anti-inflammatory and analgesic properties into the wound bed. However, new studies with the primary objective of evaluating this therapy to control MFW-related pain with an adequate description of the methodology would allow for a safer indication, considering its additional properties of nonadherence and absorbency (Gottrup et al., 2008).

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Topical opioids were another option. Opioid receptors are present in the peripheral nervous system, synthesized in the dorsal root ganglia, transported axonally to the peripheral terminals, and detectable after peripheral injuries and inflammation. An inflammatory process developed in the MFW beds could explain pain improvement using opioids (Vardhan et al., 2019). Future studies should consider more potent opioids such as fentanyl (Wang et al., 2017).

Medical cannabis was also explored as a potential analgesic drug in a case study that reported a reduction in MFW-related pain. Cannabinoids are substances derived from the *Cannabis sativa* plant. The expression and identification of cannabinoid receptors in peripheral neurons has contributed to studies exploring topical formulations based on cannabinoids. In animals, alone or in association with other analgesics, the analgesic effect of cannabinoids has been demonstrated and has even attributed to an increased in the antinociceptive effects of Morphine (Maida et al., 2021; Nielsen et al., 2017).

Antimicrobial substances, including honey, Octenidine, polyhexanide, and metronidazole, showed promising results in MFW-related pain management through decreasing local microbial load which is responsible for triggering pain as a classic indicator of infection (Swanson & Angel, 2022). In addition, the progressive nature of cancer makes MFWs sensitive to microbial growth, mainly with anaerobic microorganisms causing wound odor, exudate, and pain. Thus, the control of the microbial burden of MFWs through topical antimicrobial substances can explain the reduction of exudate, odor, and pain (Vardhan et al., 2019 ; Villela-Castro et al. 2018; Finlayson et al., 2017b;).

Case studies included in this review used NPWT to manage symptoms of MFWs and reported favorable results, increasing patients' quality of life. Although NPWT is contraindicated

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for MFWs, this therapy should be adequately studied in palliative care (Riot et al., 2015). Negative pressure creates a closed environment for the wound, thereby controlling moisture, removing excess exudate, reducing microbial load, promoting perfusion, stimulating mitosis, and granulation tissue formation. These latter actions are contraindicated for in patients with MFWs, because mitosis is not desired and granulation is not the primary objective for wound management (Cai et al., 2017). Furthermore, malignant cells can induce the formation of new blood vessels, which are friable, requiring careful evaluation and caution when using NPWT on MFWs due to the risk of bleeding (Firmino et al., 2021).

Cryotherapy promotes cold-induced vasoconstriction and causes muscle spasms that slow down nerve conduction, reducing pain (Farah et al., 2021). However, no primary studies have been found evaluating the effectiveness of cryotherapy in the past five years. Therefore, it is not included in the guideline for patients with MFWs published by the European Oncology Nursing Society (EONS, 2015). The lack of primary studies in cryotherapy may be the result of the development of new therapies and coverage for pain in MFW which demonstrate greater effectiveness and ease of application.

Wound-related pain is not limited to the wound bed area and may involve periwound skin. MFWs can evolve with high exudation, irritating to the periwound skin, and are characterized by inflammation with or without erosion, itching, pain, and potential skin damage secondary to infection (Tamai et al., 2016b). Due to constant moisture, periwound protection is recommended using a suitable barrier product that can repel excess moisture, protecting the skin from consequent damage (LeBlanc et al., 2021). However, there are few studies on using these products in patients with MFWs.

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Patients often experience pain during dressing changes. Careful application and removal, irrigation techniques, and the proper decision on the frequency of dressing changes can be easily modified to contribute to topical pain management (Woo, 2015).

Review Limitations

This review limited the languages for searching articles to Portuguese, English, and Spanish. However, search strategies brought up six articles in languages other than those cited, and they were not included in this review (supplementary table 3).

Conclusions

This scoping review of the available literature about topical therapies for topical MFW-related pain management included 70 studies with 20 topical therapies categorized as dressings (non-adherent dressing, hydrogel, absorbent dressing, and anti-inflammatory dressing); analgesic drugs (topical opioids, topical anesthetics, medical cannabis); antimicrobial substances (antimicrobials, honey, and antiseptics); cryotherapy; and negative pressure wound therapy. For periwound skin interventions: zinc oxide (ointment and cream), silicone (adhesive remover), dimethicone, petrolatum, acrylate, cyanoacrylate, hydrocolloid (plate and powder), and a vitamin-rich ointment (A and D) were identified. Some technical aspects related to MFW pain management included irrigating with a warm solution, careful application and the removal of the dressing, no debridement, maintaining a moist environment in the wound bed, cleaning with soap with an appropriate pH, reducing the frequency of dressing changes, and applying systemic analgesia before the dressing. However, there is a lack of studies describing the products' mode of use in detail and their effectiveness for evidence-based informed practice.

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Pain was not formally assessed in 68.5% of the studies. However, the following specific pain assessment instruments were mentioned in 22 studies: Visual Analogue Scale, Numerical Verbal Scale, McGill Questionnaire, and assessment by category (no pain, weak, moderate, and severe).

Relevance to Clinical Practice

This scoping review contributed with a systematized summary of the available topical treatments for MFW-related pain management. Topical therapies were identified for considerations in clinical practice, highlighting opioids, anesthetics, and antimicrobials; however, few prospective interventional studies described effectiveness. In addition, none explored cost-effectiveness or cost-benefits, which are relevant aspects for clinical implementation.

The topical therapies with positive results reported by randomized clinical trials were lidocaine/prilocaine 2.5%, morphine gel 0.2% as analgesics, metronidazole 0.8% solution, and polyhexamethylene biguanide (PHMB) with betaine 0.1% solution, octenidine solution, honey, and silver as antimicrobials. Moreover, the combination of topical therapies on the wound bed, periwound skin, and the application of techniques of dressing change aiming at pain prevention can potentially improve the painful experience in people with MFWs (Figure 3).

This review did not critically appraise the methodologies and studies' qualities due to the aims and method of a scoping review; consequently, the comments on the clinical practice should be considered carefully.

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	4-8
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	11-12
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	12-13
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	12
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status) and provide a rationale.	13
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	13-15
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	13-14
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	15
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	15-17
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	16-17
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	No
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	17

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SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	17-20 Figure 1 Table 1,3
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	17-22 Figure 2
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	No
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	17-41 Table 4-11
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	17-41 Table 4-11
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	17-41 Table 4-11
Limitations	20	Discuss the limitations of the scoping review process.	45
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	41-47
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Title page

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR):

Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

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