


Scoping Review of Off-Label Topical Analgesia in Palliative, Hospice and Cancer Care: Towards Flexibility in Evidence-Based Medicine

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Purpose: Scoping reviews address the nature of the literature per se rather than inferring evidence-based treatment guidelines. Scoping reviews of the published literature are intended to describe the aggregated nature of the evidence surrounding some agent or intervention, in contrast to systematic reviews that seek when possible to guide clinical practice. We conducted a scoping review to identify reports of potential clinical utility of off-label topical analgesics and adjuvants when FDA-approved treatments have proven inadequate.

Methods: We performed a comprehensive search of three databases (PubMed, Web of Science and Embase) for articles dating from 1947 to the present. Mindful that FDA-approved and WHO-recommended analgesic medications often prove inadequate for individual patients in extremis with palliative, hospice or cancer pain, we used broad, structured inclusion criteria to retrieve articles.

Results: We retrieved 12,100 articles; after screening, we had 39 reports addressing 19 different topical agents out of the 32 chemical entities. Our scoping review disclosed evidence about agents that might not have met inclusion criteria for clinical practice guidelines.

Discussion: Although generally considered lower quality evidence, case reports or series present suggestions for diverse topical medications to manage pain in challenging circumstances when high-quality evidence for agents and routes of administration is lacking.

Conclusion: Patients with the greatest need for evidence to identify and guide lesser-used agents during aggressive pain management are the most difficult to enroll and follow in standardized, controlled and/or blinded clinical trials. This scoping review identifies medications, dosages, and routes of topical agents reported to be effective in these often-challenging circumstances. Until larger and higher quality studies are completed, we must rely on the best available evidence even if of lower quality.

Keywords: topical medications, pain, analgesia, palliative care, hospice, cancer, evidence-based medicine, personalized medicine

Introduction

“Where there is pain, there the medicine goes” [Rumi, 13th century Sufi polymath and poet]

Uncontrolled pain is a significant problem in hospice and palliative medicine, and cancer care.¹ A recent meta-analysis reported a pain prevalence in 38.9% of all patients with cancer and 66.4% of those with advanced, metastatic or terminal disease.² Often, standard therapies and guidelines prove inadequate and physicians turn to adjuvant pain medications,³ alternative routes of delivery, or interventional⁴

methods of pain control. Thus, the use of topical medications for acute, chronic and cancer-related pain has grown increasingly popular. Scoping reviews of the published literature are intended to describe the aggregated nature of the evidence surrounding some agent or intervention, in contrast to systematic reviews that seek when possible to guide clinical practice.⁵ However, regulatory or quasi-governmental, eg, WHO, guidance concerning topical agents for hospice, palliative and cancer care pain regimens is hampered by a dearth of randomized and blinded controlled studies.⁶ A committee recently convened by the US National Academies of Science, Engineering and Medicine (NASEM) undertook a broad review of the use of topical medications for the treatment of pain.⁷ Their recommendations (published in 2020) spanned standard treatments in patients with acute (eg, musculoskeletal) or chronic (eg, neuropathic or inflammatory) noncancer pain. Also included in the NASEM review were patients whose neuropathic pain resulted from prior chemotherapy, but not from ongoing progression of underlying malignancies for which chemotherapy would be given. The patients assessed in the NASEM report included those studied in the context of clinical trials designed to minimize bias, or case reports if no higher quality evidence were available. The NASEM participants' desire to minimize methodological bias intentionally excluded multiple reports from consideration. Importantly, the focus of the NASEM report was upon patients or subjects whose skin was intact, thereby excluding patients whose pain arose from ulcerated cutaneous lesions, ie, who would be included in the present review.

Thus, we performed a comprehensive scoping review to focus upon patients receiving topical agents in the context of hospice, palliative or cancer-related care – few if any of whom would have been discussed in the NASEM report. Our goal was not to winnow down the articles retrieved during a comprehensive literature search. Instead, we wanted to be as inclusive as possible to call clinicians' attention to agents with which they might be less familiar and that are not FDA-approved for the treatment of cancer pain. Such topical agents might be considered for patients who had failed standard guidelines and who were running out of analgesic options as they approached life's end.

Methods

For the reasons described above, a “scoping review” (also called “mapping review” or “scoping study”) seemed a more appropriate technique than the conventional

systematic review to approach this still-growing, marginal literature. Scoping studies are “meant to ‘map’ relevant literature in a field of interest”.^{6,8} Arksey and O'Malley⁸ describe two “main differences between a systematic review and a scoping study”:

- “A systematic review might typically focus on a well-defined question where appropriate study designs can be identified in advance, whilst a scoping study tends to address broader topics where many different study designs might be applicable.”
- “The systematic review aims to provide answers to questions from a relatively narrow range of quality assessed studies, whilst a scoping study is less likely to seek to address very specific research questions nor consequently, to assess the quality of included studies.”

To the above distinction, Peters et al⁹ add;

... scoping reviews are commonly used for ‘reconnaissance’ – to clarify working definitions and conceptual boundaries of a topic or field. Scoping reviews are therefore particularly useful when a body of literature has not yet been comprehensively reviewed, or exhibits a complex or heterogenous nature not amenable to a more precise systematic review of the evidence.

To accomplish our scoping study, we enlisted the support of a co-author (AL) with extensive experience as a research librarian supporting literature reviews. We went through six iterations of search terms before arriving at the final version ([Appendix 1](#)), based on the need to be comprehensive without generating an unmanageably large group of articles to screen and extract. We searched 32 active ingredients identified as chemical entities of interest for topical analgesia from the NASEM monograph (see below for search strategy). Following our initial review, we identified an additional five agents captured in the portion of our search that addressed pain control in palliative and hospice settings. These included menthol, sevoflurane, hyaluronic acid (Dermafill), hydrocolloid dressings and turmeric/curcumin. We included only English-language reports. We excluded articles that used iontophoresis, injection or any other methods of cutaneous drug administration other than having the medication applied onto the surface of the skin, wound or mucosa. In contrast to the NASEM methodology, we did not require that the skin be intact. We did not address agents' absorption through the skin

nor their comparative effectiveness. Such analysis falls outside the framework of a scoping review, though the body of literature addressing mechanisms of action is increasing and may permit their future inclusion.¹⁰

Based upon our motive to assess novel or little-used agents, we excluded any articles about agents already United State Food and Drug Administration (USFDA)-approved to treat cancer-related pain and in common everyday use, eg, lidocaine-impregnated gauze, transdermal fentanyl or buprenorphine patches. We excluded articles that did not involve patients in hospice, palliative or cancer care or where it could not be discerned whether such patients were among the treated cases or groups. Grey literature was sought by employing broad inclusion criteria. Our search strategy resulted in identification of primary clinical data from case reports, case series, retrospective studies and prospective trials reported in

journals, organizational newsletters, and program books of abstracts from scientific meetings. We excluded systematic or narrative reviews that lacked primary descriptions of palliative patients receiving non-US FDA approved medications.

We followed the PRISMA methodology¹¹ (Figure 1) in which the successive phases of a systematic review are identification, screening, confirmation of eligibility, and inclusion. The initial search strategy (see [Appendix 1](#)) generated 12,100 “hits” after removal of duplicate entries from the three databases searched: PubMed, Embase and Web of Science. The titles and abstracts of each report were screened by two independent reviewers to confirm their relevance and suitability for more detailed screening. Each screened article was examined by two independent reviewers to confirm that it met primary inclusion/exclusion criteria. Data extracted from each of the screened

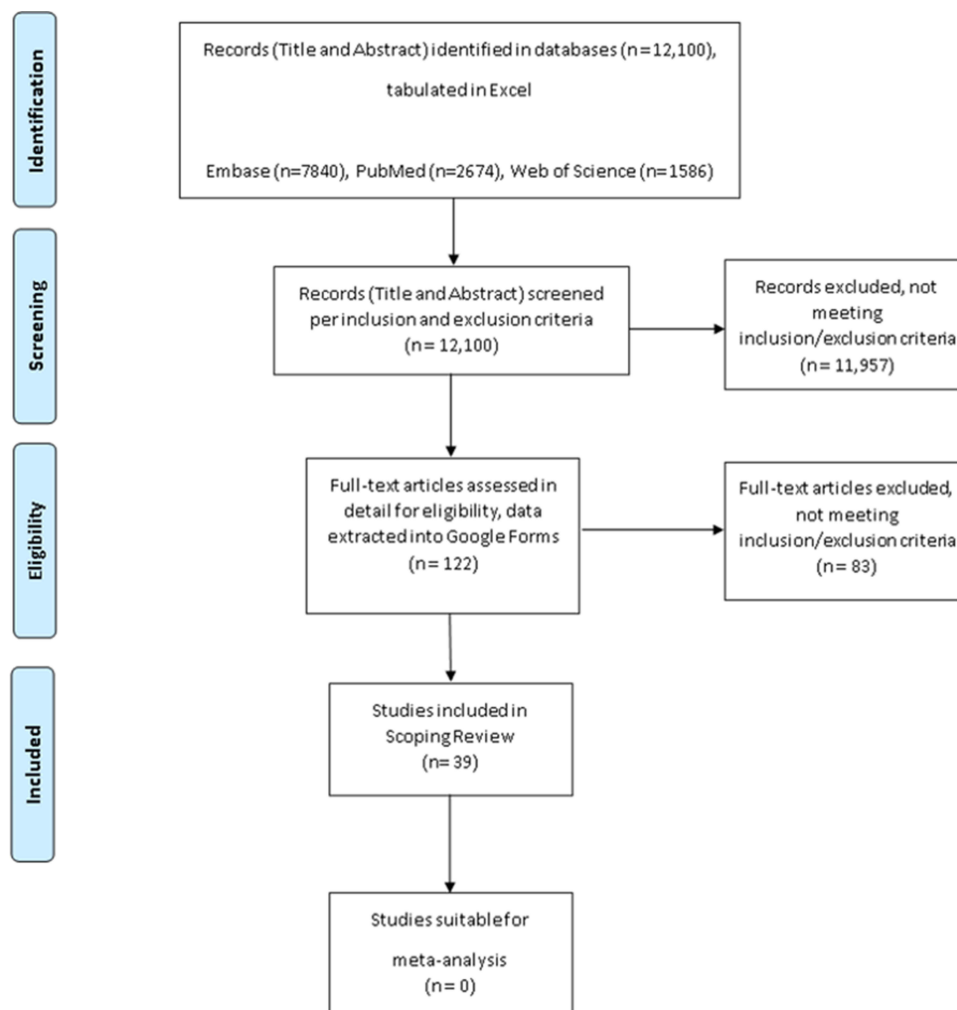


Figure 1 PRISMA 2009 Flow Diagram.

Notes: Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *PLoS Med*. 2009;6(7):e1000097.¹¹

reports was tabulated in an Excel spreadsheet created for this purpose. A third reviewer was enlisted in case of disagreement between the two independent screening authors. If the third reviewer could not decisively state “include/exclude”, the article was included in keeping with our motivation to include all studies whose results might benefit clinicians and patients in often dire circumstances.

The screening phase applied these inclusion criteria:

1. A primary or secondary end-point of the report was pain control.

2. The reported participants were (at least in part) receiving hospice or palliative care, and/or being treated for cancer-related pain. Our search terms included “hospice care,” “hospice,” “terminal care,” “palliative therapy,” “palliative nursing,” “end of life,” “terminal,” and “palliative.”

3. The active ingredient was one of the 32 agents examined in the NASEM report: amitriptyline, baclofen, benzhydrocodone, bupivacaine, cannabidiol, capsaicin, carbamazepine, clonidine, codeine, cyclobenzaprine, dexamethasone, doxepin, gabapentin, hydrocodone, hydromorphone, ketamine, levorphanol, meloxicam, memantine, meperidine, methadone, morphine, naltrexone, naproxen, nifedipine, orphenadrine, oxycodone, oxymorphone, pentoxifylline, tapentadol, topiramate, and tramadol. To these specific items, we added the search terms “analgesic agent,” “analgesia,” “pain,” and “drug combination,” to increase the sensitivity of our search.

4. The active agent was applied topically. Our search terms included “topical,” “dermal,” “skin,” “transcutaneous,” “rubs,” “lotion,” “gel,” “patch,” “cream,” “transdermal,” “transdermal drug administration,” “percutaneous,” “transmucosal,” and “compound.”

Exclusion criteria during this second phase of screening were:

1. The topical agent was already in customary, widespread daily use in dose regimens as approved for marketing by US or other nations’ FDAs to treat cancer-related pain (fentanyl, lidocaine and buprenorphine).

2. The topical agent was applied using iontophoresis, phonophoresis or percutaneous injection.

3. The topical agent was administered intradermally or by percutaneous injection.

All articles identified during screening were retrieved in full except for three. The full texts of two of these were obtained through an international, interlibrary loan program; one of these¹² was eligible for and included in

subsequent data extraction. The article that could not be located in full was deemed ineligible on the basis of the information provided in its abstract. The data from all eligible articles was extracted using a Google Forms data sheet drafted for this study. This data included title, last name of first author, year of publication, type of study, endpoint(s), patient population, medication(s) used, medication formulation, application technique, medication concentration/dose/frequency, comparator medication/placebo, initial participant number, final participant number, reasons for participant withdrawal, main results, and side effects. Once again, each article was assessed by two independent reviewers. The reports that were included are summarized in [Appendix 2](#). It was obvious upon inspection that no quantitative syntheses, or pooling of results, was possible due to the heterogeneity in agents and diversity of the reports (including varied study designs and regimens tested). Across all agents, the durations of treatment were brief, reflecting clinical trial design and/or the limited life expectancy of many of the participants.

Results

Our initial literature search ([Appendix 1](#)) generated a total of 12,100 articles after being adjusted for duplications and incomplete citations. These articles were sourced from three databases: Embase (7840), PubMed (2674), and Web of Science (1586). A separate search for grey literature yielded no further studies, not surprising given how broad our initial search and inclusion criteria were. Each of the 12,100 articles was reviewed by two independent researchers who assessed their titles and abstracts. After this initial review, we applied our inclusion and exclusion criteria, resulting in 125 eligible articles. Two independent readers scrutinized each of these eligible articles, applied secondary exclusion and inclusion criteria, and extracted the data from the included articles onto a specially designed Google Forms extraction sheet. After confirming their eligibility, there remained a total of 39 reports^{6,12–49} that were included ([Appendix 1](#)). These addressed 19 ([Table 1](#)) different topical agents out of the 32 chemical entities identified in the NASEM report as relevant to topical analgesia. The number of available studies and their generally weak nature are shown in [Table 1](#). [Appendix 2](#) provides specifics on the nature of the studies reported for individual agents according to their pharmacologic class.

Table 1 Agents and Corresponding Evidence from Studies Included in This Scoping Review (Listed in Descending Order by Number of Studies)

Agent(s)	Number of Reports	Number of Reports by Subgroup
Capsaicin	9	2 RCT, 1 PCS, 3 CS, 3 CR
Morphine	9	2 RCT, 1 PCS, 3 CS, 3 CR
Methadone	6	1 RCT, 4 CS, 1 PCS
Cannabis	3	2 PCS, 1 RCS
Gabapentin	2	2 CS
Ketamine	2	1 CR, 1 CS
Sevoflurane	2	2 CR
ABHR (Ativan/Benadryl/Haldol/Reglan)	1	1 CR
Acetylsalicylic acid (ASA)	1	1 RCS
Amitriptyline	1	1 RCS
Bupivacaine	1	1 CS
Cellulose	1	1 CS
Clonidine	1	1 CS
Diamorphine hydrochloride	1	1 RCS
Dexamethasone	1	1 CR
Hydrocolloid	1	1 CR
Methanol	1	1 CR
Tetracaine	1	1 CS
Turmeric or curcumin	1	1 CS

Abbreviations: RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective comparative study; CS, case series; CR, case report.

Discussion

As described in the Introduction, there is a continuing unmet need for novel analgesic agents and routes of administration to improve patients' symptom control in hospice, palliative care, and cancer treatment.

Looking over the agents discussed in our present scoping review, it is possible that the benefit-to-risk ratio for topical analgesics in hospice, palliative or cancer care favors their wider use in patients whose concurrent medical conditions render them frail and prone to systemic toxicities from standard analgesic medications and routes of administration. We acknowledge that assays of blood levels of some topical agents may lack the sensitivity to detect them despite their apparent clinical effectiveness.^{50,51} It also appears evident that some agents, such as morphine, have greater analgesic effect when applied to areas of open skin compared with intact skin.

We undertook this scoping review to characterize the nature of the literature examining topical analgesics in these often challenging settings. We found that the small number of studies and the generally low quality of those studies limits the strength of evidence available upon which clinicians can rely.

This scoping review of off-label topical agents for pain control in patients in hospice, palliative or cancer care is distinct from NASEM's monograph on FDA-approved topical agents. This contrast exemplifies the tension between fundamentally different directions of evidence-based medicine. On one side are those who advocate for large trials designed to reduce bias associated with the investigators' or the participants' feelings and expectations, using statistical techniques and outcome measures deliberately applied to minimize the effect of outliers upon a study's conclusions. On the other side are those whose focus is on the personal (including individual biochemical, narrative and social) essence of the patient's experience – particularly where “total pain” is concerned. The NASEM white paper deliberately excludes many trials as prone to bias and relies upon a selected subset of retrieved literature to shape clinical guidance for treating chronic noncancer pain. Unfortunately, some of the most pressing needs for pain therapies involve patients who are often unsuited to participate in rigorous, prolonged clinical trials to assess the efficacy of such agents. Given this imperative need, we undertook this study to identify potentially valuable therapies that may be overlooked or require years of slowly accruing clinical trials to enter the therapeutic armamentarium. These therapies, eg, topical agents, are not included as first- or second-line therapy in most treatment guidelines for cancer pain, eg, the WHO method despite clues in the published literature that they might be better introduced early in patients' care.

Conclusion

“You must go on. I can't go on. I'll go on.” [The Unnamable (1953); Samuel Beckett, Nobel Laureate in Literature 1969]

Beckett's words express the dilemma faced by hospice, palliative and cancer care clinicians assessing the published evidence for guidance as to whether to try a topical agent for a patient with refractory severe pain. Our scoping review reveals a dearth of high-quality trials to provide such guidance. However, it is not acceptable to vacillate, waiting until the literature evolves sufficiently to permit accurate predictions of the effects and side effects of such therapies. Moreover, in recent years recognition that opioid-induced hyperalgesia and opioid use disorder have increased among the elderly⁵² has motivated a search for alternatives to systemic opioids – a longstanding pillar of palliative, hospice and cancer care.

Common sense dictates that, just as it is hazardous to generalize from clinical observations of small groups of patients to the treatment of large populations, it is also hazardous to take results derived from pooled group responses and expect they will apply to each individual. For some time, palliative clinicians have practiced individualized medicine as population-based therapies frequently fail to control pain symptoms. Our scoping review of topical pain medications to consider as supplements to FDA-approved medications and routes when needed may offer clinicians ideas to aid in the management of patients with refractory severe pain in hospice, palliative and cancer care settings.

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Disclosure

The authors have no financial disclosures or conflicts of interest to report.

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