Medical and Clinical Research: Open Access

Review Article

Topical Opioids in Pain Management - A Brief Review

James K Rotchford*

Medical Director of Olympas Medical Services LLC, Port Townsend, Washington State, USA.

Keywords

Chronic Pain, Pain Management, Opioid receptors, Dermal receptors,Topical medications, Neurosensitization, Synergy.

Corresponding Author Information

James K Rotchford

Medical Director of Olympas Medical Services LLC, Port Townsend, Washington State, USA.

Received: May 25, 2025; **Accepted:** June 29, 2025; **Published:** July 07, 2025

Citation: James K Rotchford. Topical Opioids in Pain Management - A Brief Review. Med Clin Res Open Access. 2025; 6(2):1-5.

Introduction

This article is an informal review of the potential clinical applications of topical opioids. Combinations of Western pharmaceuticals, along with topical opioids, have had positive results. This paper intends to encourage the widespread use of topical opioids in acute and chronic pain management. More research will better delineate the role of topical opioids and other topical substances in pain management.

Background

The need for safe and effective pain management prompted the Joint Commission in the early 2000s to include pain as a fifth vital sign. Fears about opioids and their abuse have interfered with ensuring effective pain management. In addition to their other highly published risks, their chronic use can lower pain thresholds. Nonetheless, the chronic use of opioids remains foundational for effective pain management in a subset of patients [1,2]. It is crucial for healthcare professionals to feel empowered in their practice to provide safe and effective individualized care.

Providers and patients commonly assume that pain is a symptom of pathology related to structure or something observable by standard imaging. It is not the pain itself, but rather the reason for the pain, that warrants attention. These common clinical assumptions are helpful and pragmatic, especially when the pain is relatively new (acute pain), and safe and effective therapy for the diagnosed condition is available. When pain persists and is considered chronic (having lasted several months or more), the "pathology" involves complex mechanisms that regulate pain. With chronic pain, the pain itself becomes the primary "pathology" and not only the symptom of another diagnosis. Unfortunately, providers still commonly reinforce common assumptions by explaining that chronic pain is due solely to structural and observable explanations, such as an injury, osteoarthritis, inflammation, tight muscles, pinched nerves, infection, or scoliosis, among others.

These explanations are oversimplifications, especially when pain has become chronic. Chronic pain is largely limited when the central nervous system (the brain and spinal cord) functions optimally. The exception might be with certain forms of chronic pain, such as with cancer, where ongoing acute tissue damage contributes to chronic "nociception," the medical term related to the pain mechanisms associated with tissue damage.

Treating symptoms and not addressing the underlying cause is rarely the best solution. In addition to ongoing nociception, the primary reasons for chronic pain often involve a combination of factors that affect both the central nervous system (CNS) and the peripheral nervous system (PNS). When one sleeps or is under general anesthesia, one should not feel pain. This lack of felt pain is due to blocked pain pathways at the level of the brain's thalamus.

In addition to various circuits in the brain, pain-inhibitory circuits also operate within the spinal cord and peripherally. One dramatic example is the spinal pathway that blocks the input of pain at the spinal level. This pathway is activated in some cases following acute and severe injuries, when victims may be pain-free for some time despite the presence of overwhelming tissue damage. This lack of pain, given serious injury, likely has complex explanations but is purportedly primarily a result of activation of descending inhibitory circuits that, similar to spinal anesthesia, block sensory input at the spinal level. Indeed, when inhibitory circuits function "properly," they effectively limit inputs from tissue damage (nociception). When this occurs, it reflects our nervous system doing its "job" to ensure both short and long-term well-being and function. Even with severe joint destruction, as in some cases of rheumatoid arthritis and osteoarthritis, some patients commonly do not feel pain.

No one can accurately predict, regardless of imaging studies, the amount of pain, if any, that will be associated with chronic structural or inflammatory issues. The underlying structural problems may help us better understand and appreciate pain and promote more effective solutions. Still, as with myocardial infarctions, where the heart muscle lacks blood, some patients feel no pain even in the presence of significant "tissue damage." Using the "metaphor" of heart disease and angina, besides the surgical interventions used for improving blood flow to the heart, for the best results, a competent clinician will also address blood pressure, cholesterol, diabetes, exercise, sleep, etc. As with addressing factors that contribute to atherosclerosis and subsequent angina, similar attention to factors that improve CNS function and its inhibitory capacity is most productive in managing chronic forms of pain.

Understanding Chronic Pain Mechanisms Helps Explain How Topical Opioids Work

Topical opioids act primarily by "blocking" the transmission of signals from nociceptive receptors in the periphery. Common local anesthetics, such as lidocaine, generally work by blocking the transmission of all sensory impulses. The elegant aspect of topical opioids is that they impede the transmission, as with conventional local anesthetics. However, in contrast to local anesthetics that block all sensory transmission, they work by blocking local mu receptors that initiate the transmission of nociception to the central nervous system (CNS). The targeted blockage or stimulation of receptors is a cornerstone of "allopathic" pharmaceutical medicine.

Further Explanations for the Effectiveness of Topical Pain Creams

As previously noted, when attempting to understand the effects of pharmaceuticals, we generally explain the mechanism through allopathic mechanisms, that is, through a substance directly influencing an established physiological process. In homeopathic models, one describes the benefits of therapy mainly by the ability of an intervention to elicit homeostatic responses; in other words, interventions intended to stimulate the body's homeostatic mechanisms. Homeopathic, Chinese, and Ayurvedic models of medicine also acknowledge the influence of electromagnetic fields in and around the body, as well as within their remedies. Western medicine also recognizes the importance of electromagnetic fields. For example, it acknowledges the damage or destruction of tissue from intense electromagnetic interventions, as in the case of radiation therapy. It also recognizes effective homeostatic mechanisms, such as cold laser therapy and ultrasound, as well as the therapeutic effects of sunlight and music. Some therapeutic explanations, such as the placebo effect and prayer, suggest that significant healing mechanisms remain outside our standard medical models.

In review, topical opioids penetrate the skin and inhibit or block receptors (mu receptors in C fibers) in the dermis and subdermis of the skin. The observed and relatively immediate reaction to the topical opioids suggests a local effect, especially since negligible amounts of the cream enter the bloodstream. The regional impact on the mu receptors in the dermis and sub-dermis likely influences feedback loops involving spinal cord circuits that modulate pain thresholds [3-5]. Substances are also known to migrate up nerve sheaths to the central nervous system. These mechanisms help explain the effects of topical opioids and other topical substances on spinal and higher inhibitory circuits, even without any of the substances entering the bloodstream or penetrating deeply into underlying structures. In summary, topical opioids likely work by altering pain thresholds and, in doing so, mitigate the "suffering" associated with nociception.

Potential Risks of Topicals

The primary benefit of topical pain creams is their relative safety and accessibility, especially given their seemingly broad effectiveness [6]. Since little, if any, of the pharmaceuticals in creams enter the bloodstream, the possibility of systemic side effects is negligible. There is always a risk of an unusual allergic response to elements of the cream and its contents; however, if such a response were to occur, it is likely to be minor and readily manageable.

Another drawback of topical opioid creams is that applying the creams up to eight times daily can be laborious and inconvenient. If the topicals are highly effective, they could potentially interfere with patients' willingness to engage in healthier, more active modalities, such as exercise, sleep hygiene, an informed diet, addressing other comorbidities, maintaining good posture, practicing yoga, meditation, and improving relationships. Might one also develop tolerance or dependence on opioids or other substances in the topical pain cream? There are likely individual risks that we remain unaware of, but they are likely to be rare. It is best to address unknown risks by acknowledging the risks associated with inadequately managed conditions, as well as the risks of established treatments.

Since we are managing pain from what, in some cases, reflects conditions that require additional attention, symptom reduction could be a concern; as with other pain relievers, as noted above,

topical opioids are allopathic and a relatively passive intervention, the treatment of chronic diseases is often most effective when active modalities are used rather than relying solely on passive ones. Active modalities enable individuals to "learn" new responses that lead to improved outcomes over time. These new ways of responding are often not apparent, and some "learning" is reflected in neural circuits outside our conscious awareness, as in the already-referenced phenomenon of neurosensitization. In the case of topical opioids, when one limits pain for some time, the central nervous system (CNS) often does a better job of "inhibiting the nociception. In this regard, topical opioids have potential active properties; that is, over time, the creams might "teach" and condition the system to be less sensitive to pain and, in so doing, effectively mitigate neurosensitization.

On a clinical and pragmatic note, online prescription programs used by American clinicians make the prescribing of synergistic topical pain creams challenging. Some pharmacists hesitate, and some have even refused to fill prescriptions that involve compounding, whether by the patient or another professional. These hesitant responses by pharmacists are even more likely when the prescriptions involve scheduled drugs and are not paid for by third parties. Indeed, not having ready access and coverage through third parties can be considered a downside of topical opioids, especially for those with limited financial means.

Typical Substances Used in Topicals and Their Actions

Morphine sulfate and methadone are potent opioids, and as referenced above, they inhibit mu receptors (opioid receptors) present in C fiber terminals, nerve fibers that transmit signals linked to pain. Indeed, these C fibers are the primary carriers of nociceptive signals into the central nervous system. There are also mu receptors on local immune cells. Therefore, it is possible that topical opioids could limit nociceptive transmission by inhibiting local inflammatory responses and their commonly associated nociception.

Carisoprodol is an FDA-approved muscle relaxant in the barbiturate class of pharmaceuticals. Barbiturates are effective anti-convulsants and can inhibit the activity of neurons, calming and sedating them. Whether gabapentin or other topical anti-convulsants would be more effective than carisoprodol, especially in a subgroup of patients, is worth studying [8].

Prednisone, when taken orally or through infusion or injection, is known to have a potent "shotgun" effect on quieting down inflammation. It is most effective when used systemically; however, it poses significant risks when it enters the bloodstream and produces substantial serum concentrations over time [9]. Given that a minimal amount (generally undetectable) of prednisone enters the bloodstream, topical prednisone is likely safe. Because prednisone is not a fluorinated corticosteroid, it is also unlikely to contribute to skin deterioration, as do topical fluorinated corticosteroids.

Other agents warrant exploration as potentially therapeutic for subgroups of patients. Topical ketamine has potential because it blocks NMDA receptors. These receptors, especially in the central nervous system, are most prominent in pathways that respond to and remember trauma. Peripheral NMDA receptors exist as well. Again, because of minimal, if any, levels present in the bloodstream, systemic side effects are expected to be absent when ketamine is applied topically to the skin. Ketamine is not commonly included in standard topical opioid formulas because it represents another controlled substance, it adds to the cost, and topical opioids are generally considered the most effective component of topical creams.

Hitting the mu receptors on the C-fibers, limiting inflammation, and stabilizing overly sensitive neural pathways provide an allopathic rationale behind adding prednisone and carisoprodol to opioid pain creams. As already noted, a subset of patients may also respond to other agents, such as topical ketamine. Topical lidocaine and NSAIDS found in the Lidoderm patch and Voltaren cream are already FDA-approved for pain management, but do not have the "desensitizing" potential of topical opioids. While they are occasionally quite effective and overall safe, these FDA-approved agents do not have the possibility of effectively addressing some of the "neurosensitization" that commonly occurs with chronic pain.

Synergy—Another Principle to Explain Therapeutic Responses

Synergy is a term that conveys the idea that a combination of interventions is often more effective than a single intervention. One should be cautious about assuming which ingredient in a topical pain cream is the most important for a specific patient. The opioid is likely the prime ingredient for most patients, with the other ingredients having a synergistic therapeutic effect. Methadone is now primarily used because it is a more effective opioid for "neuropathic" pain, is more fat soluble, and potentially influences other relevant receptors besides the mu receptors. It also has a longer half-life, at least when employed orally. It is plausible that opioids with a greater affinity for the mu receptors (hydromorphone, fentanyl) would, in some, have more potent and long-acting topical effects.

A well-conducted orchestra demonstrates metaphorically the above notion of synergy. The strings, horns, keyboard instruments, and percussion instruments can all be beautiful to listen to, independent of one another. However, there remains something special in the "synergy" of instruments harmoniously played together. Tailoring the "instruments" and the music to the score, the musicians, the theme, and other complex contextual factors remains a challenging task. It is consistent with the "Art" of medical care. This "art" clearly exists when using different ingredients in topicals. As in many areas of pharmacological management, a trial-and-error approach when using topical opioids and other substances, especially in a given individual, is likely to be associated with the best outcomes.

Unfortunately, there is little financial incentive to study synergistic effects, as the ability to recoup costs through patents and other means is limited, as is often the case with most FDA-approved pharmaceuticals. The administrative and regulatory burdens of dealing with a Schedule II substance such as morphine or methadone already accentuate financial and regulatory liabilities.

Areas for Further Research

The need for further research is apparent. Beyond the mechanistic research and case reports already referenced [9], the selection of substances to utilize, as well as doses, concentrations, frequency, duration, and specific painful conditions, are all worthy of formal study. What is the best vehicle for delivering the substance(s)? Are there dispensers, as with compounded hormone replacements, that would facilitate the application of the cream and dosing? Might other opioids be better than morphine or methadone? Would a more lipid-soluble opioid be more effective in an oil-based cream? Might buprenorphine work as well or even better than morphine or methadone? Buprenorphine is a longer-acting medication that binds to and inhibits kappa receptors. Buprenorphine is also only a Schedule III pharmaceutical. When might it be advantageous to add topical anti-convulsants, natural remedies such as CBD or other herbs, or ketamine, as previously mentioned? Can we predict which agents might work best for a given individual, let alone for the diagnoses associated with the pain? Are there contraindications to the use of topicals? What is their role in headaches and cancer-related pain? [10]. What are the best instructions for applying the cream? Is it possible to abuse professionally compounded topicals? The risk is surely relatively low yet feasible. What is the role of topical pain creams in acute settings with injuries or after surgery? What might help the appropriate implementation of more widespread use of topical opioids?

Summary

Topical opioids will be revolutionary in pain management. The benefit/risk ratio and potential accessibility provide significant advantages. Effective pain management is fundamental and is why many patients seek medical care. Safe and effective pain management remains essential for limiting morbidity and mortality.

Pain and the associated suffering remain primarily subjective. We use surrogate markers to attempt to objectify pain. The inattention to the subjective experiences of patients likely contributes to the relatively poor outcomes for chronic and high-impact pain. Third-party payers compensate relatively poorly for non-procedural pain management, and its provision is commonly associated with extra regulatory liabilities. It is both understandable and grievous that pain management commonly remains a low priority for providers and payers. Let us encourage politicians, advocacy groups, and healthcare leaders to further address the risks and costs associated with our current approaches, or lack thereof, to effective and safe pain management. Let us endeavor to implement a wider acceptance and use of safe and effective treatments, such as topical opioids.

Addendum

Based on clinical observations, patients who have been taking oral opioids for some time are especially likely to benefit from topical opioids, often in dramatic ways. Given the unmeasurable changes in serum opioid levels, the topicals are exceptionally safe and effective, likely especially so in patients who have been on chronic opioids and suffer from opioid-induced neurosensitization. It bears repeating that no therapy, especially therapies directed toward improving the function of our nervous systems, is effective for everyone. With almost all approaches, no shoe fits everyone.

On a final pragmatic note, prescriptions for patients to self-compound their topical medications are problematic. Patients who compound their medications, whether legitimately prescribed or directed to do so, do so illicitly based on Washington State's USP General Chapter <795>. Prescriptions involving controlled substances written by a DEA-registered prescriber are not illicit; however, the prescriptions could be interpreted as unprofessional, at least based on laws in Washington State. Regarding the expense, there are several distinct advantages to having prescriptions professionally compounded, particularly in terms of safety and possibly efficacy. These benefits may offset the higher costs associated with pharmacist-compounded prescriptions. Hopefully, most patients can afford the compounded prescriptions. Generally, they are currently under $100 for a trial, with significant cost savings for higher amounts.

References

1. Rotchford JK. Opioids in Chronic Pain Management: A Guide for Patients. CreateSpace Independent Publishing Platform. 2018; 66.
2. Rotchford JK. Agonist Therapy for Chronic Pain Management (COAT) - A Primer. https://docs.google.com/document/d/15a1UOtMiuKy4D5wJHNeUnicJFY9NoJZOKlbD6pzCsN0/edit?usp=sharing
3. Role of Topical Pain Creams in Pain Management. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on the Assessment of the Available Scientific Data Regarding the Safety and
4. Effectiveness of Ingredients Used in Compounded Topical Pain Creams; Jackson LM, Schwinn DA, editors. Compounded Topical Pain Creams: Review of Select Ingredients for Safety, Effectiveness, and Use. Washington (DC): National Academies Press. 2020; 13: 2. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560353/
5. Opioid Receptors on Peripheral Sensory Neurons - NIH Madame Curie Bioscience Database Austin (TX): Landes Bioscience. 2000-2013.
6. Krzysztof Nosek, Wojciech Leppert, Łukasz Puchała, Krzysztof Łon. Efficacy and Safety of Topical Morphine: A Narrative Review. MDPI Pharmaceutics. 2022; 14(7) : 1499; https://doi.org/10.3390/pharmaceutics14071499

7. Karudumpala Suresh, Sangeeetha G, Prakash K, Gnana Harikrishna G, Balaji G, et al. Formulation and Evaluation of Carisoprodol Topical Gel, Research Journal of Pharmacy and Technology; 2014; 7(1): 34–38.
8. Vyvey M. Steroids as pain relief adjuvants. Can Fam Physician. 2010;56(12): 1295-1297.
9. Tennant F. Topical Use of Morphine. Pract Pain Manag. 2008; 8(8): 1-7.
10. Ciałkowska-Rysz A, Dzierżanowski T. Topical morphine for treatment of cancer-related painful mucosal and cutaneous lesions: a double-blind, placebo-controlled crossover clinical trial. Arch Med Sci. 2019; 15(1): 146-151.