



The Role of Unconventional Topical Agents in First-Line Pain Management: Capsaicin, TCAs, Menthol, and More

Ashmeet Bedi¹, Arya Kermanshah², Garine Kalaydjian²

¹Lake Erie College of Osteopathic Medicine, ²Department of Internal Medicine St. John's Riverside Hospital



Abstract

Chronic pain affects nearly 63 million Americans, yet opioid therapy, despite its risks, remains widely used, with an estimated 22% using a prescription opioid for chronic pain management. This narrative review evaluates topical analgesics (TAs) as safer, effective alternatives. Using PubMed and Cochrane Library searches from the past 10 years, we examined evidence on topical anesthetics, NSAIDs, capsaicin, Tricyclic antidepressants, clonidine, cannabinoids, and permeation enhancement methods. Across conditions such as postoperative pain, postherpetic neuralgia, diabetic neuropathy, and osteoarthritis, TAs showed meaningful pain reduction with fewer adverse events than systemic analgesics. Advances in permeation enhancers have improved transdermal absorption, expanding therapeutic potential. Despite strong safety and efficacy data, TAs remain underutilized due to cost, access, and awareness barriers. Our findings support wider adoption of topical agents as first-line, opioid-sparing therapies for acute and chronic pain.

Problem

The scope of this study includes a general review of topical and transdermal approaches to pain management, including our understanding of the physiology behind different treatment options and how to enhance their efficacies. In addition to expanding our understanding on current guidelines, we seek to understand potential barriers to the use of topical anesthetics and reasons they are not already recommended first-line agents. In the United States, chronic pain is widespread, yet opioids remain common despite safer, effective alternatives.

UPDATED PAIN LADDER

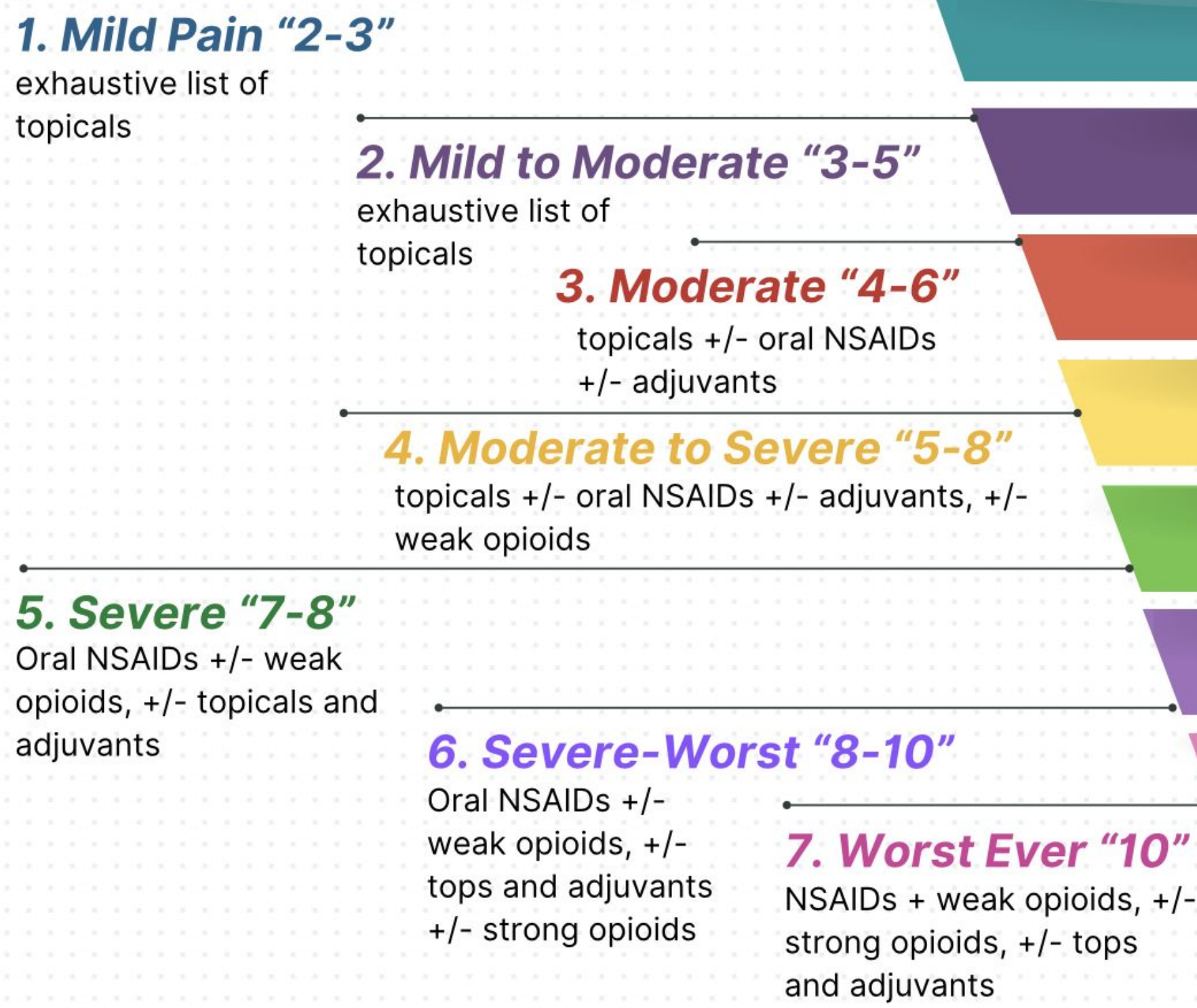


Figure 3. Updated Pain Ladder

Introduction

Topical anesthetics remain an underutilized option in the management of acute and chronic pain, despite strong evidence supporting their safety and efficacy. The CDC recommends nonopioid therapies as equally or more effective than opioids for most acute pain conditions, yet nearly 8 million Americans continue to rely on opioids for chronic pain, contributing to an estimated \$630 billion annual economic burden. Chronic pain affects nearly one-third of the U.S. population and accounts for a majority of disability cases, underscoring the urgent need for safer, more accessible alternatives. When not contraindicated, nonsteroidal anti-inflammatory drugs (NSAIDs) are often first-line and may outperform opioids in specific scenarios. In addition, nonopioid modalities such as capsaicin, lidocaine, and topical tricyclic antidepressants are recommended for subacute and chronic pain management, reflecting a growing recognition of localized, multimodal analgesic strategies.

We reviewed current clinical guidelines from major organizations, including the Centers for Disease Control and Prevention (CDC), American College of Physicians (ACP), American Academy of Family Physicians (AAFP), American College of Rheumatology (ACR), and Osteoarthritis Research Society (ORS), to assess the role of topical anesthetics in pain management. Our analysis reveals a consistent underuse / underreporting of these agents despite strong evidence of efficacy, favorable safety profiles, and cost-effectiveness. Advances in topical formulations and delivery systems continue to enhance clinical utility and patient adherence, particularly in populations at risk for systemic side effects or opioid misuse. We argue that topical anesthetics should be considered first-line options for acute, subacute, and chronic pain in adults and that both clinicians and patients can benefit from increased awareness of their expanding over-the-counter availability.

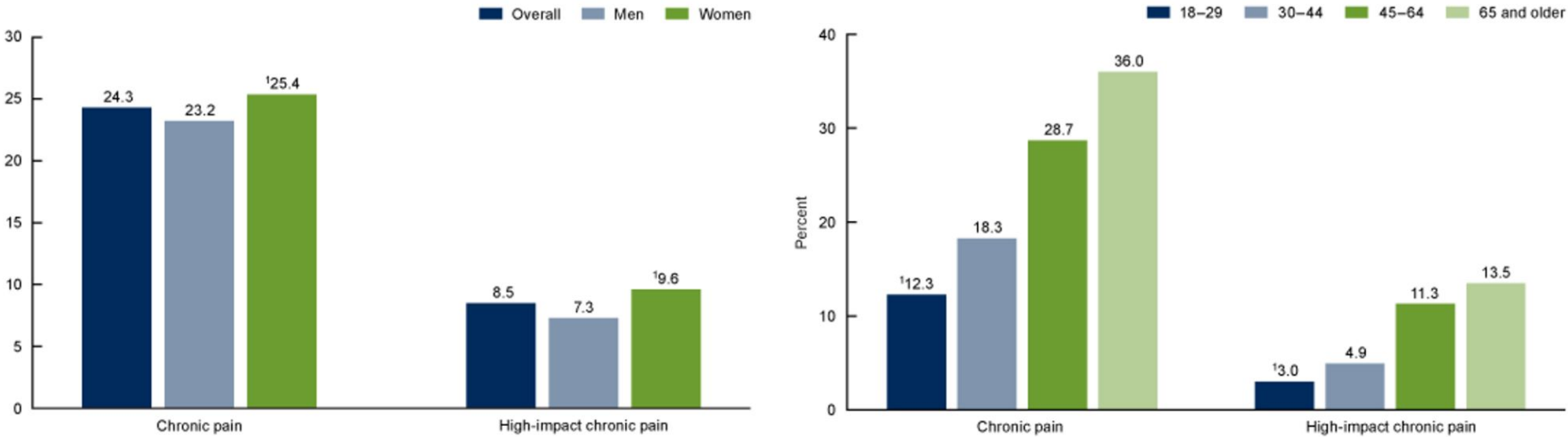


Figure 2. Percentage of adults age 18 and older with chronic pain and high-impact chronic pain in the past 3 months, overall and by sex: United States, 2023 [1]

Methods

The design of this project is a thematic synthesis of the literature regarding topical anesthesia, local anesthetics, current guidelines, adverse effect profiles, and permeation enhancement of various topical choices. We reviewed peer-reviewed articles from the past 15 years using keywords such as "topical anesthetics," "transdermal anesthetics," "enhancing topical anesthetics," "topical NSAIDs," "topical tricyclic antidepressants," and related terms. Non-peer reviewed work, and work that did not fit our search criteria were excluded.

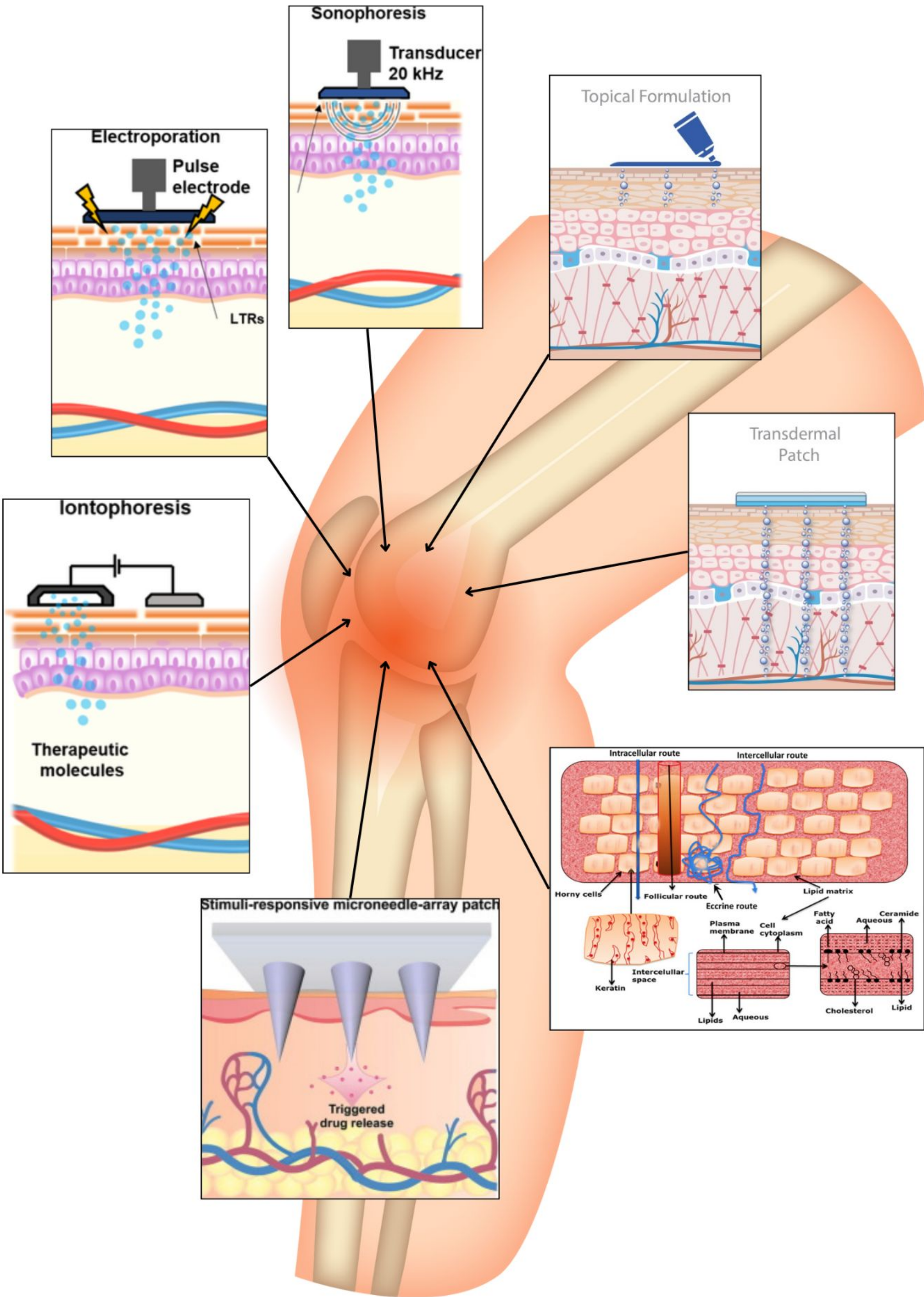


Figure 4. Advanced transdermal delivery mechanisms for topical anesthetics. Schematic illustrating the major pathways and technologies enhancing dermal and transdermal drug delivery for local analgesia. Collectively, these technologies expand the therapeutic potential of topical anesthetics by improving onset, duration, and bioavailability while minimizing systemic exposure and adverse effects.

Results

Our narrative review of the literature describes that topical anesthetics, including choices beyond NSAIDs and opioids, are efficacious in treating a host of pains related to disease. We reviewed classic anesthetics of the amino amides and amino esters classes, EMLA creams, lidocaine patches, lidocaine gels, capsaicin patches, capsaicin ointments, rubefacients, tricyclic antidepressant ointments, nitrates, clonidine patches, and cannabinoids. Based on a variety of studies describing the use of each treatment option, a range of pains related to disease were treated.

These treated diseases include: acute pain in surgery (minor excisions, IV line management, biopsies, peripheral neuropathic pain, postherpetic neuralgia, central pain due to spinal cord compression and metastases to subarachnoid space, diabetic neuropathy, diabetic polyneuropathy, intercostal neuralgia, persistent postoperative pain, meralgia paresthetica, generalized low back pain, coccydynia, bone metastases, muscle-fascial pain, neuropathic facial pain, trigeminal neuralgia, mucosal pain, chemotherapy induced mucositis, burning mouth syndrome, HIV neuropathy, osteoarthritis, Guillain-Barre Syndrome, fibromyalgia, post-mastectomy pain syndrome, reflex sympathetic dystrophy, carpal-tunnel syndrome, atopic dermatitis related intractable itch, rheumatologic conditions including rheumatoid arthritis, ankylosing spondylitis, complex regional pain syndrome, bursitis, vulvodynia, venous leg ulcers, and migraines.

Discussion / Conclusion

NSAIDs are consistently represented as superior or equivalent to opioids in the management of acute pain, with additional benefits in subacute and chronic pain contexts. Our review identified a broad range of topical anesthetic formulations, such as lidocaine, capsaicin, clonidine, and tricyclic antidepressant creams, that demonstrate clinically meaningful pain reduction, particularly when paired with permeation enhancers to improve dermal absorption. These agents offer a favorable balance between efficacy and safety, with minimal systemic exposure and reduced risk of dependence compared to opioid or systemic analgesic options.

Despite their proven effectiveness, topical anesthetics remain underutilized across many clinical settings. Barriers include limited prescriber familiarity, variable insurance coverage, and misconceptions about potency relative to systemic agents. As opioid-related morbidity continues to rise, expanding the role of topical anesthetics offers a practical, evidence-based strategy to reduce opioid exposure and improve multimodal pain management. Future research should focus on optimizing delivery systems, comparing head-to-head efficacy across formulations, and integrating these agents into standardized pain treatment algorithms. Other limitations include a general lack of randomized control trials. As clinicians advocating for safer pain control, promoting awareness and appropriate use of topical anesthetics may benefit a complex population.

References

- [1] Centers for Disease Control and Prevention. (2024, November 21). *Products - data briefs - number 518 - November 2024*. Centers for Disease Control and Prevention. <https://www.cdc.gov/nchs/products/databriefs/db518.htm>
- [2] Lee, J. H., Kim, J. H., Kim, J. H., Kim, H. S., Min, W. K., Park, Y. S., Lee, K. Y., & Lee, J. H. (2017). Efficacy and safety of Transdermal Buprenorphine versus oral tramadol/acetaminophen in patients with persistent postoperative pain after spinal surgery. *Pain Research and Management*, 2017, 1-11. <https://doi.org/10.1155/2017/2071494>
- [3] McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., Hawker, G. A., Henrotin, Y., Hunter, D. J., Kawaguchi, H., Kwoh, K., Lohmander, S., Rannou, F., Roos, E. M., & Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and Cartilage*, 22(3), 363-388. <https://doi.org/10.1016/j.joca.2014.01.003>
- [4] Jeong, W. Y., Kwon, M., Choi, H. E., & Kim, K. S. (2021). Recent advances in Transdermal Drug Delivery Systems: A Review. *Biomaterials Research*, 25(1). <https://doi.org/10.1186/s40824-021-00226-6>
- [5] An, Y., Park, M. J., Lee, J., Ko, J., Kim, S., Kang, D. H., & Hwang, N. S. (2020). Recent advances in the transdermal delivery of Protein therapeutics with a combinatorial system of chemical adjuvants and physical penetration enhancements. *Advanced Therapeutics*, 3(2). <https://doi.org/10.1002/adtp.201900116>
- [6] Makvandi, P., Jamaledin, R., Chen, G., Baghbantarghadari, Z., Zare, E. N., Di Natale, C., Onesto, V., Vecchione, R., Lee, J., Tay, F. R., Netti, P., Mattoli, V., Jaklencic, A., Gu, Z., & Langer, R. (2021). Stimuli-responsive transdermal microneedle patches. *Materials Today*, 47, 206-222. <https://doi.org/10.1016/j.mattod.2021.03.012>
- [7] Anjali Gurung, & Ashutosh Badola. (2023). An updated review on acne. *World Journal of Biology Pharmacy and Health Sciences*, 14(3), 300-317. <https://doi.org/10.30574/wjbphs.2023.14.3.0266>