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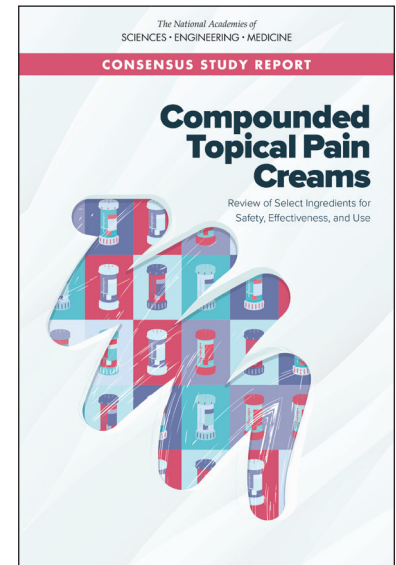
Compounded Topical Pain Creams

Review of Select Ingredients for Safety, Effectiveness, and Use

Pain is both a symptom and a disease. It manifests in multiple forms and its treatment is complex. The impact of pain at a population level is vast—according to one estimate from the Centers for Disease Control and Prevention, roughly 50 million U.S. adults live with chronic pain. In terms of pain’s global impact, estimates suggest the problem affects approximately 1 in 5 adults across the world, with nearly 1 in 10 adults newly diagnosed with chronic pain each year.

The complexity of pain management can increase when treating special populations for whom U.S. Food and Drug Administration (FDA) approved oral pain medications may be unsuitable, intolerable, or inadequate for a variety of reasons. To address the growing need for additional treatment options, use of topical pain medications—medications applied to intact skin—is often explored. Due in part to the limited number of FDA approved topical pain medications, the practice of creating compounded topical pain cream medications (medicines created to meet the unique clinical needs of an individual patient that otherwise cannot be met) has increased. Given its history as a small-scale, patient-specific, and ad hoc practice, compounded medications are not subject to the same level of extensive testing and stringent regulatory oversight as FDA approved medications. However, recent decades have seen an emergence of a type of compounding that is not patient specific, as well as greater volumes of compounded drugs sold across state lines, making the potential patient population for compounded topical pain creams much larger.

In response to the changing landscape in the compounding field, FDA asked the National Academies of Sciences, Engineering, and Medicine to convene an ad hoc committee that would assess available scientific data on the safety and effectiveness of ingredients commonly used in compounded topical pain creams. Based on this information, the committee was ultimately tasked with making recommendations for how the available scientific data on safety and effectiveness should inform the use of compounded topical pain creams to treat patients. This report addresses that charge.



SAFETY AND EFFECTIVENESS

To address the primary focus of the study charge, the committee reviewed 10 active pharmaceutical ingredients (APIs) of interest that were identified by FDA as high priority:

- muscle relaxant drugs with different mechanisms of action (baclofen, cyclobenzaprine, orphenadrine)
- opioid agonist (tramadol)
- NMDA receptor antagonist (memantine)
- alpha-2-adrenergic receptor agonist (clonidine)
- antiepileptics (gabapentin, topiramate)
- NSAID (meloxicam)
- antidepressant (amitriptyline)

To more fully assess compounding across pain mechanisms, the committee also examined an additional 10 ingredients that are commonly used in compounded topical pain creams:

- anesthetics (ketamine, bupivacaine, lidocaine)
- antiepileptic (carbamazepine)
- NSAID (naproxen)
- cannabinoid (cannabidiol)
- steroid (dexamethasone)
- calcium channel antagonist (nifedipine)
- antidepressant (doxepin)
- phosphodiesterase inhibitor (pentoxifylline)

This list does not represent every API used in compounded topical pain creams. The committee noted that omission of a category or mechanism does not imply safety or effectiveness of drugs in that category when used in compounded topical pain creams.

From its review of the relevant literature, the committee drew several conclusions on the effectiveness and safety risks of the 20 studied ingredients. Findings and conclusions include, but are not limited to:

- Out of the 20 APIs reviewed, 3 individual APIs and 1 two-drug combination demonstrate potential clinical effectiveness in compounded topical pain creams. Two ingredients, doxepin (tricyclic antidepressant) and lidocaine (local anesthetic), show evidence of effectiveness on their own. Naproxen (nonsteroidal) has inconsistent evidence on its own, but demonstrates potential effectiveness to treat certain types of pain. When combined, a high dose of pentoxifylline and clonidine (vasodilator/nerve receptor agonist) has limited evidence of effectiveness in one pain model, possibly due to absorption of its APIs throughout the body. However, additional studies are needed to better understand the effectiveness of these ingredients.
- There is inadequate data to support conclusions regarding safety and risks related to the use of compounded topical pain creams. Importantly, the committee noted that the absence of data does not prove safety or indicate that adverse events have not occurred, particularly where there is evidence of systemic absorption.
- As reflected in adverse event reports, high levels of systemic absorption (uptake into the blood) of certain APIs in topical pain creams have occurred, potentially enabled by excipient selection. Indiscriminant use over large skin areas, or use on non-intact skin, can have potentially life-threatening consequences.
- Substantial high-quality research is needed to identify effectiveness as well as the relative risk for adverse effects in response to local (skin-related), regional (muscle, joint, or deep-tissue), or systemic absorption of compounded topical pain creams.

ADDITIONAL AREAS OF CONCERN

Over the course of its research, the committee identified additional areas of concern and potential opportunities to avoid unintended harms related to the use of compounded topical pain creams. These areas include (1) inadequate federal and state level regulation and oversight, (2) data collection and surveillance, and (3) training and education for health care providers and individuals who compound.

Compounding has become an increasingly lucrative industry over the past two decades, but it is difficult to find verifiable estimates of the number of drugs compounded, types of compounded drugs, number of pharmacists who compound, or true size of the market. Compounded preparations have inadequate labeling requirements, and often there is no clear clinical rationale for specific combinations of APIs and dosages used. In addition, there is a lack of clinical guidelines and best practices for clinicians who prescribe compounding preparations or compound themselves. Coupled with limited regulatory oversight, the lack of data, clinical guidance, and standardized protocols and procedures pose challenges for accurate risk-benefit assessments and for changes to public health policy related to compounded drugs.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

From their research findings, the committee came to three overarching conclusions regarding the safety, effectiveness, and regulation of compounded topical pain creams:

- There is limited evidence to support the use of compounded topical pain creams to treat pain conditions in the general adult population. The few APIs that show potential effectiveness in compounded topical pain creams (doxepin (tricyclic antidepressant), lidocaine (local anesthetic), and naproxen (nonsteroidal)) are either already available in FDA approved topical products used to treat pain or in the case of naproxen, other NSAIDs (e.g., diclofenac) are in such FDA approved products.
- In context of the recent rise in supply and demand of compounded preparations, lack of evidence regarding systemic absorption of ingredients used in compounded topical pain creams gives rise to a substantial public health concern. It is important to consider the potential effects of all organic compounds (including APIs and excipients) that may permeate the skin.
- There is an opportunity for the U.S. Department of Health and Human Services to provide additional oversight to ensure the safety of compounded pain creams, with prioritized focus on those containing APIs that, when applied topically, cross the skin barrier to enter the bloodstream and act systemically within the body.

The committee also developed four recommendations regarding treatment and addressing public health concerns surrounding compounded topical pain creams (see Box 1). To review the specific directives within the committee's four recommendations, see the Recommendations Insert.

BOX 1. RECOMMENDATIONS

- **Recommendation 1:** Caution should be used when prescribing or dispensing compounded topical pain cream preparations.
- **Recommendation 2:** Strengthen and expand the evidence base on the safety and effectiveness of active pharmaceutical ingredients and excipients commonly used in compounded topical pain creams.
- **Recommendation 3:** Require continued training for clinicians who prescribe compounded pain medication, particularly pain management specialists. Revise current educational requirements for compounding pharmacists and nonpharmacists who compound.
- **Recommendation 4:** Additional state-level oversight of compounded topical pain creams is needed to improve safety and effectiveness.

**Committee on Assessment of the Available Scientific Data
Regarding the Safety and Effectiveness of Ingredients
Used in Compounded Topical Pain Creams**

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