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Compounded Topical Pain Creams

Review of Select Ingredients for Safety, Effectiveness, and Use

Debra A. Schwinn and Leigh Miles Jackson, *Editors*

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

Board on Health Sciences Policy

Health and Medicine Division

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COMMITTEE ON THE ASSESSMENT OF THE AVAILABLE SCIENTIFIC DATA REGARDING THE SAFETY AND EFFECTIVENESS OF INGREDIENTS USED IN COMPOUNDED TOPICAL PAIN CREAMS

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **ELI Y. ADASHI,** Brown University, and **DAVID L. EATON,** University of Washington. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Preface

Pain is complex and often hard to treat. Acute and/or chronic pain affects millions of individuals each year and is associated with morbidity and increased health care use. Once pain became regarded as the "fifth vital sign," clinicians, patients, hospitals, and health systems began to more vigorously treat all types of pain in order to meet a "no pain" patient satisfaction standard, often with increasing use of medications (e.g., opioid analgesics, nonsteroidal anti-inflammatories, adjuvants) and other modalities. In retrospect, return to functional activity is a better goal because zero pain is unrealistic in many medical situations.

Clinicians who treat pain recognize that elucidation of the specific mechanism underlying an individual's pain is essential for rational pain therapy. As a result, a variety of oral medications have been developed over the years to target various pain mechanisms. However, not everyone can tolerate specific oral medications, given coexisting diseases and age-related changes, and there is a general desire to limit systemic effects of drugs whenever possible. In addition, currently available oral medications do not effectively treat all pain scenarios. In recent years this has led to emergence of a host of alternative approaches to treating pain (providing analgesia). One such approach is topical analgesia.

Topical application of analgesics has two possible roles. First, skin-based drug application provides an alternative approach to achieve systemic levels of medication, exemplified by the fentanyl patch; however, this first approach is not the focus of this report. A second role involves topical analgesics in the form of gels, patches, or creams applied to the skin to deliver pain medication to a localized area of the body. In theory, topically

applied pain medication provides analgesia near the skin (locally) while minimizing systemic absorption (uptake into the blood with circulation to the entire body). There are many potential advantages of using topical approaches to treating pain, although it would be an error to consider a drug safe simply because it is being delivered through the skin; this was elegantly demonstrated in a recent study showing sunscreen lotion chemicals applied to the skin are absorbed systemically at potentially high enough levels to be of concern,[1] as well as in an older study[2] that demonstrated how permeable skin can be to organic compounds. Nonetheless, skin does provide a formidable barrier to entry of active ingredients for pain therapy, so these drugs are often applied in much higher concentrations than would be used orally. While this is not a problem for healthy intact skin in most adults, it can create life-threatening situations in cases where pain therapies are topically applied to skin that is not normal (e.g., skin or diaper rash, thin skin at extremes of age, burns) or when applied to large areas relative to body size. Because skin is such a formidable barrier, topical pain creams often contain enhancers, or chemicals specifically designed to help move a drug from the surface through the skin (epidermis and dermis) to regional areas below with a goal of reaching a muscle group or joint for treating pain. Of note, when active drug ingredients move beyond the skin to subdermal regional locations, they are brought in contact with the systemic circulation and some amount of drug will be absorbed into the central circulation.

Because the U.S. Food and Drug Administration (FDA) has only approved a few topical analgesics, pharmacies have filled in the gap by providing compounded topical pain creams. Compounding is a traditional part of pharmacy practice where pharmacists prepare drugs in alternate dosages or vehicles to support the specific clinical need of individual patients; for example, a cancer patient who cannot swallow tablets or capsules might have a pharmacist produce or compound a liquid form of the drug that could be swallowed more easily. Because of the long historical roots centered on small independent compounding pharmacies, the U.S. Congress has permitted most compounded preparations to be made with minimal FDA oversight, as compared to FDA-approved drug products.[3]

[1] Matta, M. K., R. Zusterzeel, N. R. Pilli, V. Patel, D. A. Volpe, J. Florian, L. Oh, E. Bashaw, I. Zineh, C. Sanabria, S. Kemp, A. Godfrey, S. Adah, S. Coelho, J. Want, L. A. Furlong, C. Ganley, T. Michele, and D. G. Strauss. 2019. Effect of sunscreen application under maximal use conditions on plasma concentration of sunscreen active ingredients: A randomized clinical trial. *JAMA* 321(21):2082–2091.

[2] Feldmann, R. J., and H. I. Maibach. 1970. Absorption of some organic compounds through the skin in man. *Journal of Investigative Dermatology* 54(5):399–404.

[3] This text has changed since the prepublication release of this report. Here and in other instances throughout the report, "commercially available product(s)" was replaced with "FDA-approved drug product(s)."

However, over the past two decades, there has been a substantial increase in both supply and demand for compounded medications. Consequently, an increasing fraction of drugs used in the United States are created without FDA oversight for quality, safety, efficacy, labeling, and/or postmarketing surveillance. Moreover, a growing number of reports of patients who have encountered harm using compounded preparations, including topical pain creams, highlights growing concerns.

Adding further complexity, given the global nature of drug and chemical production and distribution today, sources and quality of many products have become significant issues. As such, each individual compounding pharmacy is tasked with checking active ingredients used in compounded products for potency, quality, and lack of contaminants, a process that is impractical for many smaller pharmacies. Current compounded pain creams often contain more than one active ingredient, with many containing four to six drugs, creating the potential for combined toxicity and drug-to-drug interactions. It has been suggested by proponents of topical pain creams that combinations of active ingredients are present in order to target different underlying mechanisms of pain; however, it is interesting to note that some ingredients used today are primarily effective on central nervous system (CNS) pain pathways and not skin or localized regions near skin. Moreover, patients are often charged by the number of active ingredients included in their compounded preparations, which has led to insurance-related concerns regarding cost inflation and possible fraud.

In addition to considering active pharmaceutical ingredients to be compounded into a topical pain cream, the formulation of a topical product requires selection of an appropriate vehicle. There are a growing number of ointments and creams that can be used, with very little publicly available data to distinguish one from another. To facilitate ease of pharmacists compounding topical pain creams, several cream bases are now commercially available, some of which contain proprietary ingredients such as skin penetration enhancers and other chemicals designed to enhance ease of application and attractiveness of the final product to patients. The result is that pharmacists, prescribers, and patients are often not aware of all that is present in the cream and the potential side effects of its components. Because pain drug efficacy depends on relative penetration of active drugs through the skin, in addition to drug concentration, efficacy may vary depending on the cream base used. For best efficacy, each active ingredient concentration should be optimized and tested within a given cream base, an effort that would be costly and time consuming to do for every additional ingredient added to such a preparation.

Finally, given the interprofessional nature of clinical practice today, the pharmacist is often viewed by clinicians as the expert on the team in terms of drug therapy. So, when lists of prefilled prescription forms or

menus for compounded pain creams are faxed to clinicians for marketing purposes, there is a general expectation on the clinician's part that testing has occurred and that each combination has been shown to be effective. Even when this is not the case, once the clinician signs the form requesting a set of active ingredients and base cream for a patient, his or her signature provides the legal prescription that guides creation of the compounded pain cream; hence, ultimately it is the clinician who bears responsibility for having chosen to include specific or numerous ingredients. In this setting, there have also been cases of fraudulent prescribing.

Given this complicated backdrop, and the increasing use of these products, FDA requested that the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine (the National Academies) assess available scientific data regarding safety and effectiveness of ingredients used in compounded topical pain creams. Specifically, this committee was charged with identifying individual ingredients that scientific data support as being safe and effective to treat pain topically, describing concentrations and combinations of ingredients that may raise significant safety issues, and defining the level of expected benefit for various ingredients given their likelihood of being absorbed through the skin. Based on this information, the committee was ultimately tasked with making recommendations for how the available scientific data on safety and efficacy informs use of compounded topical pain creams to treat patients going forward. In making its deliberations, the committee specifically sought information and comments from the general public, as well as various stakeholders (including, but not limited to, patients, clinicians, compounding pharmacists, regulators, pain advocacy organizations, and government payers) as well as examining the scientific literature.

The committee is composed of an outstanding panel of national experts with broad related scientific expertise. In addition to the committee, such a detailed exploration of scientific literature and generation of the final consensus study report would not have been possible without the strong support of outstanding staff members from the National Academies, specifically Leigh Miles Jackson (study director), Claire Giammaria (associate program officer), Andrew March (research associate), Justin Jones (senior program assistant), and Anna Nicholson, our talented editor and writer. Thank you to everyone who participated in this timely and important report.

Debra A. Schwinn, *Chair*
Committee on the Assessment of the Available
Scientific Data Regarding the Safety and Effectiveness of
Ingredients Used in Compounded Topical Pain Creams

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Acronyms and Abbreviations

ACCP	American College of Clinical Pharmacy
API	active pharmaceutical ingredient
CBD	cannabidiol
CDC	Centers for Disease Control and Prevention
CIPN	chemotherapy-induced peripheral neuropathy
CNS	central nervous system
CRPS	complex regional pain syndrome
DESI	Drug Efficacy Study Implementation
DMSO	dimethyl sulfoxide
FAERS	FDA's Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
GTN	glyceryl trinitrate
HCl	hydrochloride
HHS	U.S. Department of Health and Human Services
MRI	magnetic resonance imaging
NABP	National Association of Boards of Pharmacy
NF	National Formulary

NPDS	National Poison Data System
NSAID	nonsteroidal anti-inflammatory drug
PCCA	Professional Compounding Centers of America
PLC	piroxicam, lidocaine, and cyclobenzaprine hydrochloride
PLO	pluronic lecithin organogel
PWT	paw withdrawal threshold
RCT	randomized controlled trial
THC	tetrahydrocannabinol
USP	United States Pharmacopeia
VAS	visual analog scale
w/w	weight per weight

Summary

Pain is both a symptom and a disease. It manifests in multiple forms and its treatment is complex. Physical, social, economic, and emotional consequences of pain can impair an individual's overall health, well-being, productivity, and relationships in myriad ways. The impact of pain at a population level is vast and, while estimates differ, the Centers for Disease Control and Prevention reported that 50 million U.S. adults are living in 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.

COMPLEXITY OF PAIN MANAGEMENT

While pain is encountered in all medical specialties, chronic pain management has become a distinct medical subspecialty. With the increasing recognition that pain care is dynamic and complex, interdisciplinary approaches have been encouraged to improve care. In spite of this, the percentage of clinician training time devoted to pain diagnosis and treatment is relatively small; furthermore, that training generally does not encompass today's full range of treatment modalities for pain. In addition, the large number of patients with chronic pain vastly exceeds the number that can be seen by pain specialists, leaving the difficult task of designing and maintaining pain management plans to other types of clinicians.

Pain management goals set forth by accrediting bodies call for achieving significant reduction in pain severity and, when feasible, elimination of pain. However, the complete elimination of pain is an unrealistic goal

in most situations. A more feasible aim is achieving a level of pain that is tolerable, that leads to improved function, enables return to productive living, and does not otherwise interfere with quality of life. Despite these more pragmatic treatment goals, attempts to eliminate pain have driven increasingly vigorous clinical treatment of all types of pain—through medications or other modalities—across U.S. health systems.

Pharmacological Approaches

Effective pain therapy hinges on targeting specific mechanisms underlying an individual's pain. Today, many commercially manufactured pharmacological therapies (analgesics) approved by the U.S. Food and Drug Administration (FDA) are available to treat acute and chronic pain conditions via targeting various systemic pain mechanisms. Commonly prescribed pain medications include opioid agonists, nonsteroidal anti-inflammatory drugs (NSAIDs), and other types of analgesics, such as muscle relaxants, antidepressants, and glucocorticoids. To personalize pain treatment, guidelines suggest that clinicians identify the likely mechanism of an individual's pain while also remaining cognizant of variability in response to pain treatment across individuals and groups. The complexity of pain management is further intensified in special populations for whom FDA-approved oral pain medications may be unsuitable, intolerable, or inadequate for a variety of reasons.[1] These groups include children, the elderly, women who are pregnant, those requiring palliative care, and individuals with coexisting conditions (e.g., spinal cord injury, kidney disease, renal failure). Furthermore, currently available oral medications cannot be used to treat all pain scenarios.

In recent years, these issues have contributed to increased demand for alternative strategies for treating pain. One such strategy is to expand use of topical pain medications—medications applied to intact skin. This report focuses on these topical medications, which are designed to deliver active pharmaceutical ingredients (APIs) to a localized area of the body. This nonoral route of administration for pain medication has the potential benefit, in theory, of local activity and fewer systemic side effects. Ideally, topical analgesics applied to the skin in the form of creams, gels, ointments, or lotions can provide local analgesia near the skin while also minimizing systemic absorption—meaning, uptake of APIs into the blood, which would then circulate to the entire body to have systemic effects. Transdermal medication delivery systems have been developed to move compounds through the skin to achieve systemic levels by an alternative route, such as a fentanyl

[1] This text has changed since the prepublication release of this report. Here and in other instances throughout the report, "commercially available product(s)" was replaced with "FDA-approved drug product(s)."

patch. However, this report does not focus on the design, effectiveness, or safety of systems designed intentionally to achieve systemic levels of analgesic medications. Instead it focuses on topical pain creams that are thought to act more locally as adjuvant pain medicine therapy.

FDA has approved several topical pain products with formulations that include lidocaine, hydrocortisone, dibucaine, capsaicin, and NSAIDs as APIs. All FDA-approved topical pain products have gone through rigorous safety and efficacy evaluations as part of their approval process. Other APIs determined to be effective in the treatment of pain can be found in FDA-approved oral or injectable formulations for systemic use, but they are not currently available as FDA-approved *topical* products. The limited number of FDA-approved topical analgesics, coupled with the growing interest in the field of personalized medicine, has led to increasing numbers of customized compounded formulations being prescribed by health care providers in an attempt to individualize and optimize pain management. Certain compounded topical pain creams include APIs that are approved by FDA for oral or systemic use to treat pain, others contain APIs that are used off-label to treat pain, and still others include APIs that have no demonstrated potential to treat pain at all.

Compounded Topical Pain Creams in Pain Management

Overview of Compounding

Compounding has a long history in the field of pharmacy, serving as the primary form of the practice until the advent of the commercial pharmaceutical industry in the mid-twentieth century. Today, compounding is primarily the process of altering or combining ingredients to create medications that are tailored to meet the specific clinical needs of an individual patient. These compounded drugs represent therapeutic alternatives for people with clinical needs that are not met by FDA-approved drug products. Custom formulations can be compounded to create alternate dosage forms, or strengths, or to omit inactive components included in an FDA-approved formulation to which a patient may have an allergy or otherwise cannot tolerate (e.g., lactose, dyes).

Traditional compounding, which primarily involves altering an FDA-approved drug into different dosage forms or strengths in response to a prescription written for an individual patient, has historically occurred in individual small-scale pharmacies, hospitals, or even physicians' offices. For example, a liquid form of a drug could be compounded for a person with cancer who cannot swallow tablets or capsules; a concentrated drug could be diluted for safer clinical use by a hospital pharmacy; or a specialized preparation or concentration of a drug could be compounded for a person

in hospice. However, recent years have seen an emergence of large-scale compounding pharmacies that produce and sell greater volumes of compounded preparations in preset formulations, sometimes across state lines. This change in the compounding landscape prompted Congress to create a separate category of compounding facility—called an "outsourcing facility"—that is subject to an increased level of federal oversight, although not as strict as FDA oversight for commercial products. (See below for an additional discussion of compounding pharmacies and outsourcing facilities.)

Benefits and Risks of Compounded Topical Pain Creams

Topical pain creams have a range of potential advantages, the most compelling being their nonsystemic route for administering pain medication. Furthermore, when not systemically absorbed, topical application of pain medications is thought to potentially avoid certain adverse side effects linked to oral analgesics. A few specific topical agents have presented sufficient evidence to FDA to be formally approved; however, no comprehensive reviews or evidence-based clinical guidelines have empirically demonstrated advantages of *compounded* topical pain creams in specific patient populations.

Among patients and clinicians, common misperceptions are that medications applied topically are safer or that local application may be more effective compared to oral or other systemic routes of delivery. Despite the many theoretical advantages of using topical approaches to treating pain, a drug is not inherently (or necessarily) safer or more effective simply because it is delivered through the skin. In principle, compounded pain creams can be formulated with enhancers, which are chemicals distinct from APIs, in order to (1) deliver APIs into cutaneous tissues (e.g., skin and dermal tissues) to produce local effects, or (2) drive APIs into subcutaneous tissue to produce regional effects, such as in muscles or joints. However, certain delivery enhancers combined with specific APIs can lead to systemic absorption and produce unintended systemic effects (e.g., in the central nervous system) and side effects that occur with other systemic delivery systems.

There is little to no publicly available information on the various formulations and compounding protocols used by different compounding pharmacists or compounding physicians across the country. Compounded topical pain creams frequently combine more than one API—and sometimes up to four to six APIs—which creates potential for combined toxicity and drug–drug interactions. In addition, owing to inadequate labeling requirements for compounded preparations, health care providers and patients may not be aware of all potential interactions or side effects of the components in a given topical pain cream. Furthermore, patients may not know that compounded preparations are not subject to the same level of

extensive testing and stringent regulatory oversight as FDA-approved products. Therefore, this is potential cause for concern regarding the safety and effectiveness of the preparations prescribed and dispensed for patient use.

A specific concern is that the safety of topical drug formulations depends on the rate and extent of the drug's absorption into the skin and beyond. This is determined by the drug's physiochemical properties, dose, and mechanism(s) of action, as well as activity of the vehicle used to support drug delivery. Formulating a compounded topical pain cream requires selecting an appropriate vehicle for the API from the wide range of available excipients.[2] Although excipients are frequently called "inactive" ingredients, they ultimately affect the quality, safety, and potential effectiveness of a compounded preparation by affecting solubility, stability, release of the active ingredient, and skin penetration. Excipients also have the potential to interact with other ingredients or with APIs in ways that are difficult to predict.

Several cream bases are now commercially available, some of which contain proprietary ingredients including skin penetration enhancers and other chemicals. In this context, even the compounding pharmacist may not know all of the ingredients present in the proprietary compound and how they may affect API effectiveness. Furthermore, there is currently little publicly available evidence regarding the quality and safety of the range of excipients used in compounded preparations, particularly with respect to how they influence absorption of a specific API, meaning how they facilitate the travel of the API from topical (local) to transdermal (regional and systemic) action. Thus, lack of transparency about ingredients in the cream base is an important safety issue.

Reports of patients who have experienced adverse events related to topical pain cream drug toxicity from systemic absorption underscore the importance of better understanding the safety of these preparations. The skin is a formidable barrier to active ingredients in topical pain therapies and, consequently, compounded pain creams may contain much higher concentrations of APIs than oral formulations. This is not generally a concern when topical pain therapies are used on a restricted local area by adults with healthy intact skin, and the excipient included in the formulation does not result in toxic levels of systemic absorption. However, it is a major concern that can create life-threatening situations in cases where those therapies are topically applied to large areas relative to body size, to skin that is unhealthy or injured (e.g., diaper rash, other skin rashes, burns), or to skin that is thin or otherwise delicate, as in young children or older adults.

[2] Excipients are vehicles, bases, or solvents that influence the quality attributes, physicochemical characteristics, and/or sensory characteristics of a formulation.

SAFETY AND EFFICACY OF INGREDIENTS IN COMPOUNDED TOPICAL PAIN CREAMS

Given substantial recent growth in the use of compounded topical pain creams, FDA asked the National Academies of Sciences, Engineering, and Medicine to convene a committee to review the safety and effectiveness of ingredients commonly used in these preparations. FDA identified 10 high-priority APIs of interest, and the committee agreed these were appropriate to include for evaluation. Categories considered to be adequately represented from the priority list include muscle relaxant drugs with different mechanisms of action (baclofen, cyclobenzaprine, orphenadrine); opioid agonists (tramadol); NMDA receptor antagonists (memantine); alpha-2-adrenergic receptor agonists (clonidine); antiepileptics (gabapentin, topiramate); NSAIDs (meloxicam); and antidepressants (amitriptyline).

To support comprehensiveness across potential pain mechanisms, the committee expanded the scope of its study by including an additional 10 ingredients that are commonly used in compounded topical pain creams: anesthetics (ketamine, bupivacaine, lidocaine), antiepileptic (carbamezepine), NSAID (naproxen), cannabinoid (cannabidiol), steroid (dexamethasone), calcium channel antagonist (nifedipine), antidepressant (doxepin), and phosphodiesterase inhibitor (pentoxifylline).

These APIs were selected based on (1) mechanism of action or drug class, (2) representation between and within relevant drug classes, (3) widespread use or relevance in clinical pain management, and (4) safety concerns or reported adverse events. *The final list of reviewed APIs is not comprehensive for all APIs used in compounded topical pain creams. Therefore, it is important to note that omission of a category or mechanism does not imply safety or efficacy of drugs in that category when used in compounded topical pain creams*. For example, certain categories may have been excluded from consideration if the mechanism was not related to FDA-approved treatments for pain indications, such as antihistamines and antibiotics.

In coordination with one of the National Academies' senior research librarians, the committee constructed a literature search strategy that would identify a broad body of research evidence that could inform its work. Based on the committee's research questions, the scope of the literature was limited to topical application of any of the 20 ingredients to treat pain when applied to intact skin.

After articles relevant to the committee's task were identified, systematic reviews and all studies with a comparator group were reviewed for evidence regarding safety and effectiveness of the drug applied topically to treat pain. For ingredients lacking in this level of evidence, case reports, case series, or preclinical studies are discussed where relevant. Additionally,

because study design is not the only measure of quality evidence, the committee's review also considered evidence of overall methodological rigor detailed in the publications. Using the 2019 Cochrane Risk of Bias Assessment Tool, the committee assessed the risk of bias for all randomized controlled trials identified relevant to the committee's charge.

From its review of the literature, the committee made several determinations related to the available evidence on the effectiveness and safety risks of the 20 studied ingredients, including (1) out of the 20 APIs reviewed, 3 individual APIs (doxepin, lidocaine, and naproxen) and 1 two-drug combination (pentoxifylline/clonidine) demonstrate potential clinical effectiveness in compounded topical pain creams, and (2) a substantial amount of high-quality research is still needed to identify effectiveness as well as 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 areas of concern and potential opportunities to help mitigate 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.

Inadequate Regulation and Oversight

Owing in part to the historical nature of small-scale compounding and to the patient-specific, ad hoc processes it involves, compounding has not traditionally been subject to rigorous oversight at the federal or state level. 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, thereby widening the potential patient population receiving compounded topical pain creams.[3]

Of note, within the current regulatory landscape, FDA does not routinely inspect 503A compounding pharmacies nor does FDA assess the quality, safety, or efficacy of the drugs they compound. In addition,

[3] U.S. federal law has established two categories of compounding, referred to as "503A pharmacy compounding" and "503B outsourcing facilities." 503A compounding pharmacies are allowed to produce compounded preparations upon receipt of a valid patient-specific prescription, or in limited quantities in anticipation of future prescriptions. 503B outsourcing facilities are permitted to compound without patient-specific prescriptions and ship prescriptions to clinicians and patients across the United States.

state-level oversight of compounding is limited and widely variable. After the tragic death of 64 chronic pain patients who received compounded injectable steroids contaminated with fungus in 2012, Congress added provisions for FDA oversight of compounding without a patient-specific prescription (503B outsourcing facilities). However, because 503B outsourcing facilities must volunteer to be overseen by FDA, and must adhere to stricter requirements than 503A compounding pharmacies, whether this option to self-identify is commonly used remains unknown. As a potential consequence, an increasing fraction of drugs used in the United States may be created without FDA oversight for quality.

In addition, compounded drugs are not dispensed with *standardized* product inserts that describe instructions for use, known side effects, or safety warnings related to use, even if such warnings are required for similar FDA-approved products. In certain cases, compounding facilities may market their compounded drugs—implicitly or explicitly—as safe and effective, incorrectly implying that the drugs meet FDA-approval standards. Many of the adverse events related to compounded topical pain creams reported to FDA can be attributed to patients misusing the cream through overapplication or application on nonintact skin. This points to the need for more specific patient education and labeling of compounded pain creams.

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. Coupled with limited regulatory oversight, this lack of data poses challenges for accurate risk–benefit assessments and for changes to public health policy related to compounded drugs. Additionally, certain stakeholders have taken advantage of the lack of regulations around marketing of compounded formulations. In a number of high-profile fraud cases, the U.S. Department of Justice implicated pharmacies and medical professionals for prescribing unnecessary compounded medications, many of which included ingredients that would provide maximal reimbursement to prescribers and pharmacies. As a result of fraud and kickback controversies, many insurance companies have become reluctant to cover compounded topical pain creams in recent years, placing patients potentially at financial risk as well. Other risks may be faced by patients who are prescribed and dispensed compounded preparations without evidence of their safety or efficacy.

Data Collection and Surveillance

Barriers to surveillance and data collection around the safety and use of compounded medications include the following:

- Fragmented and inconsistent federal and state regulation;
- Lack of centralized data collection;
- Unwillingness on the part of compounding pharmacies and outsourcing facilities to share information on unique formulations or quantity of compounded preparations sold;
- Lack of insurance coverage that would typically provide important data sources; and
- Unstandardized practices and procedures between and within pharmacies.

Potential data on use that could be collected in a standardized format include number, weight, or volume of units prepared; commonly compounded formulations of topical pain cream; number of prescriptions compounded; cost or value of each unit; and number of patients who receive prescriptions. Because reporting of adverse events for compounded preparations dispensed by compounding pharmacies is not legally mandated for 503A pharmacies, there are no standardized surveillance procedures or established protocols for ensuring the appropriate reporting of adverse events related to patient use.

Education, Training, and Procedural Protocols

Pharmacists and other health care providers who perform compounding require theoretical knowledge and practical, hands-on training to ensure the quality, safety, effectiveness, and batch-to-batch reproducibility of compounded formulations. They also require knowledge of the components within the cream base used, because this can be a particularly important driver of drug absorption and drug delivery. A single compounded preparation may require selection of a large number of components, including APIs and excipients. However, these decisions appear to be made without sound scientific evidence for either (1) safety and efficacy of these agents applied topically, or (2) use of the agents in combination with each other and with "inactive" pharmaceutical ingredients, such as excipients or fillers. All of the components in a preparation carry potential risks individually and in each permutation of interaction among them, so it is critical to consider the potential risks associated with polypharmacy and drug–drug interactions. Poor compounding practices, such as inadequate quality control testing, incomplete adherence to standards in United States Pharmacopeia (USP) <795> or <797>, or lack of standardized formulations, can also compromise a drug's potency and purity.[4]

[4] USP <795> Pharmaceutical Compounding–Nonsterile Preparation contains standards for compounding nonsterile drugs. USP <797> Pharmaceutical Compounding–Sterile Preparations describes requirements for sterile compounding.

As the focus of the practice of pharmacy has shifted over time from compounding to dispensing commercially made FDA-approved medications, education about compounding practices in pharmacy schools has declined. Today, compounding instruction in pharmacy schools is highly variable and often minimal, particularly with respect to training or guidance about which formulations may be most effective to treat specific types of conditions and which populations of patients may benefit most from use of particular formulations. Topical pain creams are a public health risk if they are compounded by personnel lacking requisite knowledge and training to assess potency, purity, quality, and bioavailability.

The process of compounding varies by pharmacist and pharmacy, making compounded formulations more susceptible to modifications in process variables than manufactured drugs. For multi-ingredient topical pain formulations, a sound evidence base is needed to assess

- the degree to which each component contributes (if at all) to effectiveness of the compounded product,
- appropriate dosage and dosing interval for each component, and
- potential interactions among each of the components.

The safety and effectiveness of individual ingredients, ingredient interactions, and absorption by the body should be regulated by setting standardized thresholds or guidelines, while retaining a pharmacist's ability to customize compounds for patients with specific clinical needs.

Furthermore, there is a lack of clinical guidelines and best practices for clinicians who prescribe compounding preparations or compound themselves. Ultimately, it is the prescribing clinician who bears responsibility for specific types and quantities of ingredients used in a compounded prescription. Providers who prescribe a compounded preparation that causes adverse effects can be exposed to liability, especially if an appropriate FDA-approved alternative is available. State boards of medicine regulate the practice of medicine and all compounding performed by physicians; however, recent national surveys from the U.S. Government Accountability Office and The Pew Charitable Trusts suggest that many state boards of medicine are not actively overseeing the compounding practices of prescribing clinicians. These findings raise significant concerns about best practices when prescribing compounded topical pain creams.

CONCLUDING STATEMENTS

Compounded topical pain creams may have a potential therapeutic role in integrative pain management plans for patients with specific clinical needs. However, three critical areas of concern related to safety and

effectiveness of such compounded topical pain creams need to be addressed by stakeholders:

- Limited evidence to describe safety and effectiveness of APIs commonly used in these preparations;
- Inadequate training, procedural protocols, and evidence-based guidance for pharmacists who formulate and dispense these preparations as well as for prescribing clinicians; and
- Significant gaps in federal and state-level regulation, oversight, and surveillance of medications not approved by FDA.

In its review of available scientific evidence, the committee determined that the vast majority of APIs commonly used in compounded topical pain creams have little to no scientific evidence to support their claims of effectiveness in treatment of various pain conditions. Furthermore, potential for systemic absorption and toxicity of many of the APIs reviewed remains largely unknown. These findings give rise to substantial concerns related to the excessive application of compounded topical preparations, as well as the use of preparations that contain excipients with enhancers that increase absorption of an ingredient beyond the intended site of action.

The committee also determined that selection of active and inactive ingredients used in many compounded topical preparations does not seem to incorporate the full spectrum of complexities related to skin absorption and dose. In many cases, there is no clear clinical rationale for specific combinations of APIs and dosages used. As a result, the committee concluded that lack of publicly disclosed rationales for formulation development, inadequate labeling requirements, and (for 503A compounding pharmacies in particular) the nonstandardized surveillance procedures and protocols for ensuring appropriate reporting of adverse events underpin a substantial public health concern related to the use of these preparations.

From its research findings, the committee drew three overarching conclusions:

> *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.*[5]

[5] This text has changed since the prepublication release of this report to clarify the available FDA-approved topical NSAID 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.

RECOMMENDATION REGARDING TREATMENT

Recommendation 1: Caution should be used when prescribing or dispensing compounded topical pain cream preparations.

Prescribing clinicians, compounding pharmacists, and nonpharmacists who compound should exercise caution when considering inclusion of compounded topical pain creams in pain management plans, given the lack of scientific evidence to support their safety or effectiveness beyond a few limited ingredients.

RECOMMENDATIONS TO ADDRESS PUBLIC HEALTH CONCERNS

Given the public health concerns related to the use of compounded topical pain creams, the committee recommends additional research, education, and oversight to support safety, effectiveness, and use of these 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.

Pain researchers, public and private funding agencies, and relevant patient advocacy organizations should prioritize research efforts to examine the safety and effectiveness of compounded topical pain creams, including but not limited to:

- Randomized, double-blind, placebo-controlled clinical trials with sufficient numbers of patients to study, both in isolation and in combinations, APIs and inactive ingredients commonly used in compounded topical pain cream formulations

- Clinical research on APIs with demonstrated effectiveness to treat pain in preclinical animal models, which may indicate a potential therapeutic effect in humans (e.g., cannabidiol)
- Obtaining high-quality evidence to inform the safety profile for all APIs that act systemically
- Research on potential new topical or transdermal therapeutic agents to treat pain

Funding agencies that could drive these efforts include the Agency for Healthcare Research and Quality, National Center for Complementary and Integrative Health, other relevant institutes or centers of the National Institutes of Health, and Patient-Centered Outcomes Research Institute.

Patient advocacy organizations that could drive these efforts include the American Academy of Hospice and Palliative Medicine, American Academy of Pain Medicine, American Cancer Society, American Chronic Pain Association, American Society for Pain Management Nursing, Oncology Nursing Society, and U.S. Pain Foundation.

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.

Interprofessional organizations representing pharmacy, nursing, medical sectors, and other professions with prescriber authority to treat pain conditions should advocate for state-level certification of individuals who seek to begin or continue to prescribe compounded topical pain creams. Formal clinical education should be offered in parallel to continuing medical education courses for clinicians who prescribe topical pain creams.

Interprofessional organizations that could drive these efforts include the American Academy of Hospice and Palliative Medicine, American Academy of Physician Assistants, American Association of Nurse Practitioners, American Cancer Society, American Medical Association, American Society of Anesthesiologists, and American Society of Interventional Pain Physicians.

State boards of pharmacy, local and regional schools of pharmacy, and nonprofit professional societies and organizations within the medical and pharmaceutical sectors should support and incentivize more in-depth training on compounding delivered by schools of medicine and pharmacy, as well as relevant nonprofit professional societies and organizations. These courses should:

- Review the compounding process, including the complexities of formulation science, which aim to ensure that all formulations are optimized when multiple APIs are combined.

- Examine current peer-reviewed, evidence-based conclusions on the safety and effectiveness of commonly used APIs and excipients in topical applications.
- Review the potential risks and reported adverse effects associated with the use of compounded topical pain creams.

Additional continuing medical education courses hosted by for-profit organizations should not substitute for this more in-depth training, owing to potential conflicts of interest.

Recommendation 4: Additional state-level oversight of compounded topical pain creams is needed to improve safety and effectiveness.

The National Association of Boards of Pharmacy should convene the state boards of pharmacy to unify and increase their oversight of 503A compounding pharmacies. The charge to increase oversight should also require all 503A compounding pharmacies to do the following:

- Provide a standardized insert for all dispensed compounded pain cream preparations with (1) a detailed description of the formulation, including all APIs and excipient components; (2) clear guidance for use, including how much (cream surface area and volume) and under which conditions to apply; and (3) caution for potential adverse effects.
- Report adverse events to the state boards of pharmacy and FDA through an established mechanism, such as FDA's Adverse Event Reporting System or MedWatch.
- Monitor, record, and annually report the types, formulations, payers, and dispensing rates of compounded pain cream preparations.
- Uniformly adopt standards in USP <795> to ensure the quality of dispensed nonsterile compounded preparations.

FDA and global standards-setting organizations (e.g., USP) should collaboratively develop standard processes for testing APIs (in solitude and combinations) and excipients commonly used in compounded topical pain creams. These testing standards should include protocols to examine the mechanisms by which APIs are absorbed and released from compounded preparations, with a prioritized focus on APIs in formulations with transdermal properties that allow drugs to travel through the skin to act regionally or systemically.

1

Introduction

Pain is a diverse, complex medical condition that is often difficult to measure and effectively treat (IASP, 2017; NASEM, 2017). Estimates suggest that millions of Americans suffer from clinical pain conditions (Croft et al., 2010; Dahlhamer et al., 2018; IOM, 2011; Johannes et al., 2010; Nahin, 2015; Portenoy et al., 2004). However, prevalence estimates for pain conditions can vary quite dramatically across pain type (e.g., nociceptive, neuropathic, nociplastic, mixed), pain duration (i.e., acute, chronic), and pain severity. Multiple coexisting conditions and comorbidities are associated with pain—particularly chronic pain—which make it difficult to accurately estimate the overall effect on an individual's health, function, and quality of life (Dahan et al., 2014; Fine, 2011; IOM, 2011; NASEM, 2017). These complexities of pain contribute to the challenge of determining the true burden of pain in America (IOM, 2011).

To help address the pressing public health issue of pain in the midst of a national opioid epidemic, increasing numbers of health care professionals, patients, and patient advocates are exploring integrative strategies for treating pain, including both pharmaceutical and nonpharmaceutical approaches. Alternate pharmacological pain management options, such as the use of topical pain cream products, have shown some evidence of success (Kopsky and Hesselink, 2012). For many years, topical pain creams have served a role in pain management by providing a level of versatility not available via oral alternatives. Indeed, compared to many oral pain medications, topical dosage forms of medication applied to the skin are often lauded as having fewer side effects, lower likelihood for abuse, and greater convenience (Leppert et al., 2018; Pickering et al., 2017). Given

this background, and to provide alternatives to pain medications approved by the U.S. Food and Drug Administration (FDA), some health care clinicians and patients have begun to turn to *compounded* topical pain cream preparations.

Compounding is an age-old pharmaceutical practice of combining, mixing, or adjusting ingredients to create a tailored medication to meet the needs of a patient (FDA, 2017). The aim of compounding, historically, has been to provide patients with access to therapeutic alternatives that are safe and effective, especially for people with clinical needs that cannot otherwise be met by FDA-approved drugs (e.g., liquid formulations when patients cannot swallow pills) (FDA, 2017; Glassgold, 2013; Gudeman et al., 2013; IACP, 2019; USP, 2017). In 2019, the American College of Clinical Pharmacy (AACP) released a report that questions the more current rationales for compounding and provides guidance to assist pharmacists and prescribing clinicians in evaluating the appropriateness of prescribing and dispensing compounded formulations. The authors of the AACP report identify key factors that should be considered in specific situations in which compounding may be needed. These factors include drug cost and availability, dosage and formulation, and allergies and intolerances to excipients (i.e., other active or nonactive ingredients in the medication's formulation) (McBane et al., 2019).

A key lesson of the report is that any determination of whether the use of a compounded preparation is justified should be made on a patient-by-patient basis. This requires prescribing clinicians and pharmacists to weigh the potential benefits compounding may provide to an individual patient with the risks of using a formulation that does not have rigorous safety and effectiveness data (McBane et al., 2019). See Chapter 3 for an additional discussion on the fundamentals of compounding. Although there may be some advantages to using compounded topical pain creams in pain treatment, it is important to consider key differences that exist between the regulation of compounded preparations and FDA-approved medications. Under current U.S. drug regulatory law, compounded preparations—including topical pain creams that meet certain conditions—are exempt from federal requirements that FDA review and approve their safety, quality, and effectiveness before they are marketed and dispensed to patients.

Although many of the most common ingredients used in compounded pain creams have been FDA approved for pain indications, most have not been FDA approved for *topical* use. As a result, the drug profiles for many of the ingredients in compounded topical pain creams have not been reviewed or optimized for topical application. This increases the risk of applying too little medication—less than needed to effectively treat pain—or too much medication, which can result in overdose and consequent side effects. In addition, compounded creams may contain

other ingredients that have not been FDA approved to treat pain and, as such, their profiles of safety and effectiveness in compounded preparations are unknown. For example, those ingredients may interact with the active drug to lessen or enhance its action. Furthermore, many compounded pain cream preparations contain multiple active ingredients, many of which are compounded in novel, untested combinations not found in current commercial products.

Finally, based on current federal law, there is no specific requirements for 503A compounding pharmacies or 503B outsourcing facilities to include safety information or drug warnings on their labels or package inserts. As a result, labeling for compounded topical pain creams is often insufficient to educate patients and clinicians about their use and potential risks. Together, these issues are a cause for public health concern, especially given the more recent evolution toward precision medicine and personalized care and resultant resurgence of compounding in recent years (McPherson et al., 2019).[1]

Importantly, certain compounding pharmacies have taken advantage of regulatory loopholes in the current environment of limited federal and state regulations, giving rise to questionable practices and procedures for the development and marketing of compounded formulations. In a number of high-profile fraud cases, the U.S. Department of Justice has implicated pharmacies and medical professionals for pushing unnecessary compounded prescriptions on patients. These compounds often included ingredients that would provide maximal reimbursement to prescribing clinicians and pharmacies but provide questionable benefit to the patient (DOJ, 2017, 2018a,b,c). At the other extreme, many compounded pain creams are not reimbursed by insurers, burdening patients with the costs and creating potential disparities in access as a result.

In 2016, the Office of Inspector General for the U.S. Department of Health and Human Services released a report expressing concern over the rapidly rising cost of compounded preparations for Medicare (HHS, 2016). In this report, researchers found that between 2006 and 2015, Part D annual spending for compounded preparations climbed from $70.2 million to $508.7 million—an increase of 625 percent. And although there was growth in spending across all forms of compounding, the largest area of growth was for compounded topical preparations. This growth may have been driven by an increase in the average cost of prescriptions as well as an increase in the number of beneficiaries receiving the medications. For example, the average cost for compounded topical preparations rose from

[1] Several private marketing reports predict the global market for compounded medications will continue to see a robust growth over the next few years (e.g., Ugalmugale and Mupid, 2018; Zion Market Research, 2018).

$40 in 2006 to $331 in 2015, an increase of 727 percent. From 2006 to 2015, the number of beneficiaries receiving compounded topical preparations grew 281 percent (from 73,368 to 279,873).[2] This substantial increase in the development and dispensing of compounded preparations to patients is both striking and disconcerting, given the lack of regulatory oversight regarding these medications' quality, safety, and effectiveness.

Although many compounded pharmacies are not required to report adverse events to FDA, a number of adverse events related to compounded preparations—including topical pain creams—have been reported over the past several years. These issues range from accidental exposures to local irritation of skin to unintended overdoses that sometimes resulted in coma and even death.[3] These diverse and complex safety and effectiveness issues related to development, marketing, and use of compounded topical pain creams create a public health concern for a multitude of stakeholders including medical practitioners, patients, health advocacy organizations, and federal and state public health agencies.

CHARGE TO THE COMMITTEE

To explore issues regarding the safety and effectiveness of the ingredients used in compounded topical pain creams, FDA requested that the National Academies of Sciences, Engineering, and Medicine appoint an ad hoc committee to conduct a study of the ingredients used in compounded topical pain creams. The resulting Committee on the Assessment of the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain Creams was charged with conducting a study adhering to the Statement of Task in Box 1-1.

REPORT SCOPE

Given the broad charge to evaluate the safety and effectiveness of ingredients used in compounded topical pain creams, the committee first identified strategies to define and limit the scope of its work. In the committee's first open-session meeting, the study sponsor, FDA, introduced a list of 37 active pharmaceutical ingredients (APIs) that have been identified

[2] As a comparison, a National Academies report (2018) determined that since the early 1980s prescription drug spending had increased at almost 4 percent annually, even after adjusting for inflation and population growth. In addition, Joyce et al. (2018) described that although generic drug prices declined in aggregate between 2007 and 2013, a small but growing fraction of generic drugs doubled in price over the course of 1 year.

[3] A discussion of adverse event reporting and examples of adverse events related to the use of compounded topical pain creams are located in Chapter 7 and Appendix F.

BOX 1-1
Statement of Task

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will conduct a study of the ingredients used in compounded topical pain creams. The committee will identify and analyze the available scientific data relating to the ingredients used in compounded topical pain creams and evaluate how that data translates to the safety and effectiveness of compounded topical pain creams with various combinations of those ingredients. Based on this assessment, the committee will develop a report that summarizes its findings, including addressing the following specific items:

- Identify the ingredients that the available scientific data suggest may not be safe and effective to treat pain topically,
- Describe the concentrations and combinations of ingredients that may raise significant safety issues, and
- Comment on the level of benefit expected for the various ingredients given their likelihood of absorption through the skin.

Based on these findings, the report will offer recommendations regarding the treatment of patients with compounded topical pain creams.

in common formulations of compounded topical pain creams.[4] Of these 37 APIs, FDA identified 10 to be of high-priority interest, which the committee elected to include for evaluation. Categories considered to be adequately represented from the priority list include the following:

- Muscle relaxant drugs with different mechanisms of action (baclofen, cyclobenzaprine, orphenadrine)
- Opioid agonists (tramadol)
- NMDA receptor antagonists (memantine)
- Alpha-2-adrenergic receptor agonists (clonidine)
- Antiepileptics (gabapentin, topiramate)
- Nonsteroidal anti-inflammatory drugs (NSAIDs) (meloxicam)
- Antidepressants (amitriptyline)

[4] It is the committee's understanding that the FDA-presented ingredients were identified from examples of commonly compounded topical pain medication formulas and that the list was generated through online research efforts, as well as through personal communications with other government agencies (e.g., Centers for Medicare & Medicaid Services, U.S. Department of Defense, and U.S. Department of Veterans Affairs).

Recognizing that this priority list was not a comprehensive list of ingredients used in compounded topical pain cream preparations, the committee elected to expand the scope of its review in an attempt to produce a more comprehensive report. Upon deliberation, the committee ultimately identified the following 10 additional ingredients to examine in its research efforts:

- Anesthetics (ketamine, bupivacaine, lidocaine)
- Antiepileptic (carbamazepine)
- NSAIDs (naproxen)
- Cannabinoid (cannabidiol)
- Steroid (dexamethasone)
- Calcium channel antagonist (nifedipine)
- Antidepressant (doxepin)
- Phosphodiesterase inhibitor (pentoxifylline)

Each of these additional drugs uses a mechanism relevant to the treatment of pain and is used currently in some compounded pain topical creams, but none of them are represented on the original FDA priority list. A complete list of the 20 ingredients the committee chose to investigate can be found in Box 1-2. Factors considered by the committee for choosing these ingredients included, but were not limited to

- mechanism of action or drug class,
- representation between and within relevant drug classes,
- widespread use or relevance in clinical pain management, and
- safety concerns or reported adverse events.

A local anesthetic was not included in the original FDA priority list because several of these drugs are already FDA-approved for topical use. However, the committee chose to evaluate bupivacaine, because of its known cardiotoxicity, and lidocaine, because it is commonly mixed with other priority ingredients. Uniquely, lidocaine can be considered a positive control for other topical ingredients because there is an FDA-approved lidocaine gel patch.

It is important to note that the omission of a category, or mechanism, does not imply safety or effectiveness, or potential usefulness of drugs in that category used in compounded topical pain creams. For example, certain categories may not have been considered if the mechanism was not related to FDA-approved treatments for pain indications (e.g., antihistamines, antibiotics).

BOX 1-2
Classification of Committee-Selected Ingredients of Interest

Ingredients of high priority to the U.S. Food and Drug Administration (FDA) and their associated chemical class:

- Amitriptyline—antidepressant
- Baclofen—muscle relaxant
- Clonidine—alpha-2-adrenergic receptor agonist
- Cyclobenzaprine—muscle relaxant
- Gabapentin—antiepileptic
- Meloxicam—nonsteroidal anti-inflammatory drug (NSAID)
- Memantine—NMDA receptor antagonist
- Orphenadrine—antispasm
- Topiramate—antiepileptic
- Tramadol—opioid agonist

Committee-selected ingredients, associated drug class, and reason for inclusion:

- Bupivacaine—long-acting local anesthetic; significant potential toxicity if absorbed
- Cannabidiol—commonly available cannabinoid with rapid growth in use
- Carbamazepine—sodium channel antiepileptic; toxicity profile from oral use
- Dexamethasone—potent steroid widely used for treatment of pain and itch; significant toxicity with systemic absorption over long periods of time
- Doxepin—antidepressant, chosen to expand this class beyond amitriptyline; also used as an antihistamine to treat itch
- Ketamine—anesthetic agent used to treat pain and high potential toxicity when absorbed
- Lidocaine—short-acting local anesthetic with FDA-approved products but also used in compounded topical creams; may account for significant degree of effectiveness in multidrug compounded creams
- Naproxen—short-acting commonly used predominately COX-1 nonsteroidal, chosen to expand NSAID group beyond meloxicam, which is predominately COX-2 and long acting
- Nifedipine—calcium channel blocking agent; known vascular side effects with oral use
- Pentoxifylline—improves local blood flow; may enhance absorption of other agents, which could increase local effectiveness and systemic blood levels

KEY DEFINITIONS

Definition of *Topical*

The term *topical* generally encompasses all of the preparations and products that are intended for application on the skin, mucous membranes, or cavities. Topical products are typically developed as semisolid preparations or transdermal patches and are most commonly applied to elicit local effects in or on the skin (e.g., treatment of burns). Importantly, certain topical medications have the capability to also permeate (travel) through the skin to act regionally (e.g., for the treatment of muscle or join pain) or systemically (e.g., for the treatment of migraines) at sites a distance away from the topical application site (Leppert et al., 2018). Such distal responses may be intended or unintended actions of the topical product, but they are critically important features in the consideration of a medication's safety profile. An illustrative example comes from the recent article by Matta et al. (2019), where systemic absorption levels of topical sunscreens' active ingredients were found to exceed the threshold established by FDA for potentially waiving certain nonclinical toxicology studies for sunscreens.

For the purpose of this report, the term *cream* will be used to designate any semisolid preparations (e.g., cream, ointment, gel, lotion) intended for external application to the skin. Creams have relatively soft, spreadable consistency and are rubbed at the site of application. A transdermal patch is a more complex topical delivery system that is designed to deliver drugs intended for systemic absorption; however, for the purpose of this report, such systems are outside of the study's scope.

Compounded Preparations Versus Commercial Products

To ensure consistency with the terminology and guidelines issued by the United States Pharmacopeia and other national compounding and pharmaceutical standard-setting organizations, the committee elected to refer to compounded medications as *preparations*, rather than *products*. This decision attempts to reinforce the distinction that compounded preparations are not required to complete the federal-level testing and standards for drug quality, safety, or effectiveness that are required of FDA-approved commercial products. This important distinction will continue to be noted throughout the report.

Focus on Intact Skin

Furthermore, in the committee's review of the literature on the safety and effectiveness of ingredients in compounded topical pain creams, the

committee maintained an explicit focus on the use of topical creams on *intact* skin. The committee limited its attention to external skin, *excluding* mucosal membranes and cavities such as the mouth, eyes, vulva, vagina, anus, and nose. There remains a substantial literature base that reviews the safety, effectiveness, and use of topical pain creams on membrane or mucosal surfaces; however, this evidence was not explicitly reviewed or discussed in this report.

Focus on Human Populations

The committee did not examine the use, safety, or effectiveness of compounded topical pain creams that were explicitly formulated to address health indications relevant to the fields of veterinary science or animal care. Although the animal population is estimated to be one of the largest consumers of compounded medications (Persistence Market Research, 2019), this area of focus was determined to be outside of the scope of the report based on the Statement of Task.

A Focus on Nonsterile Preparations

Compounded products can be sterile or nonsterile. In sterile compounding, medications are prepared in a clean-room environment using aseptic techniques to ensure solutions are free of microorganisms. Sterile compounding is primarily used for injectable, parenteral (i.e., nonoral and nonrectal administration), and ophthalmic preparations. In nonsterile compounding, medications are prepared in a clean environment without sterile techniques required. This type of compounding is mainly used for oral and topical preparations, such as capsules, solutions, suspensions, ointments, creams, and suppositories. Because the focus of this report is on topical applications, not injectable dosage forms, the committee evaluated no sterile preparations. An overview of key definitions is provided in Box 1-3. See Appendix D for a full glossary of terms.

Use of the Terms *Effectiveness* and *Efficacy*

The current research study has a charge to evaluate the effectiveness, rather than the efficacy, of compounded topical pain creams. While similar, the terms are not synonymous. Efficacy refers to the therapeutic effect of a treatment under controlled conditions, while effectiveness refers to the therapeutic effect in "real-world" situations in which certain contextual measures (e.g., placebo effect) may not be strictly controlled and broad outcome measures (e.g., health-related quality of life) are considered. Effectiveness data alone may not be sufficient to inform conclusions regarding a treatment's therapeutic effect (Ernst and Pittler, 2006; Kim, 2013).

BOX 1-3
Key Definitions for the Report

Creams: A semisolid oil-in-water emulsion for application to the skin. Creams are spreadable and easily rub into the skin without a greasy residue, and can be washed off with water.

Excipient: A pharmacologically inactive ingredient used in the formulation of a drug that lends various functional properties to the drug formulation (i.e., dosage form, drug release, etc.). They are also sometimes referred to as diluents, bases, or carriers and can sometimes increase absorption of active ingredients.

Gels: Also referred to as jellies, gels are a semisolid dosage form that appears transparent or translucent and employs either a hydrophobic or hydrophilic base.

Lotions: While similar to a cream, this dosage form has a more liquid consistency. The lower viscosity may provide a cooling effect to the area where applied as solvents in the lotion evaporate.

Ointments: A semisolid preparation with four general classes ranging from occlusive, hard to remove hydrocarbon bases, to easily washable water-soluble bases.

Patch: A patch (not preferred terminology, but it is commonly used) or transdermal delivery system is a preparation of drug substances in a carrier device that is applied topically. The drug substance is designed to be released in a controlled manner over a specified time. The carrier device is removed after use.

Penetration enhancer: An excipient or vehicle that aids in absorption of ingredients through the skin.

Vehicles: A component that is used as a carrier or diluent in which liquids, semisolids, or solids are dissolved or suspended.

For the purposes of this report, the committee evaluated all relevant data produced by randomized controlled trials (RCTs), nonrandomized clinical studies, case reports, and where applicable, preclinical studies to help address the study's charge. As a result, many of the research findings discussed throughout the report assess outcomes related to the potential effectiveness or efficacy of compounded topical pain creams. Given its broader application to the body of research reviewed, the term *effectiveness* is used more generally across the report.

STUDY APPROACH

The National Academies appointed an 11-member committee of experts to address objectives in the Statement of Task. The committee included experts in a variety of disciplines and fields, including drug research and development, pharmacology, toxicology, pain management and care, drug evaluation, epidemiology, and pharmaceutical compounding and manufacturing. See Appendix I for biographical sketches of the committee members.

The committee met in person for four closed-session meetings and held two half-day virtual meetings to discuss its research, review, and report drafting efforts. In addition to closed-session meetings, three public information-gathering sessions were held to gather additional testimony and data to inform the committee's charge. See Appendix A for public meeting agendas. Participants in these supplemental information-gathering processes included a range of subject matter experts, including compounding pharmacists, clinicians, researchers, policy experts, and officials representing various stakeholder organizations. Members of the general public were invited to provide comments at all public meetings. The committee used the gathered evidence to formulate findings, conclusions, and actionable recommendations.

In addition to the evidence collected at its public meetings, the committee also conducted reviews of the peer-reviewed literature and gray literature (e.g., research reports, online publications, books for a lay audience) on topic areas relevant to the study's Statement of Task. In coordination with one of the National Academies' senior research librarians, the committee constructed a literature search strategy that would identify a broad body of research evidence that could inform its work. Based on the committee's research questions, the scope of the literature was limited to the topical application of any of the 20 ingredients to intact skin.

For each of the selected ingredients, the committee evaluated all systematic reviews and all studies with control groups for evidence regarding the safety and effectiveness of the drug applied topically to treat pain. For ingredients lacking this level of evidence, case series, case reports, or preclinical studies were discussed when relevant.[5] Additionally, because study design is not the only measure of quality evidence, the committee also considered methodological rigor in its review of the evidence. Using the 2019 Cochrane risk of bias assessment tool (Sterne et al., 2019), the committee evaluated the risk of bias in all RCTs identified as relevant to the committee's charge. See Chapter 6 and Appendix B for additional details on the committee's literature review.

[5] Of note, the committee identified several other published studies with tangential relevance to the committee's charge (e.g., use of compounded topical pain creams to treat itch); however, only the studies with the most direct relevance were reviewed in this report.

Over the course of the study, the committee's research efforts uncovered gaps in knowledge about the dermal drug delivery process and the permeability of select ingredients used in topical pain treatment. As a result, the committee commissioned Dr. S. Narasimha Murthy, Professor of Pharmaceutics and Drug Delivery at the University of Mississippi, to develop a review paper on these topics (see Appendix C for the commissioned paper).

Finally, in recognition of the limited peer-reviewed evidence to describe the use, safety, and effectiveness of compounded topical pain creams from a consumer's perspective, the committee made concerted efforts to collect relevant anecdotal, survey, and (when possible) quantitative data from national stakeholders to supplement its research efforts. The collected data included, but were not limited to:

- Survey data from the American Chronic Pain Association on consumer use of topical pain creams;
- Oral testimony on the clinical need for topical pain creams from a palliative care clinician;
- Submitted literature reviews from the Professional Compounding Centers of America (PCCA) on the safety, effectiveness, and use of compound topical pain creams;
- Additional survey data from PCCA on the quality, safety, and median costs of compounded topical pain creams;
- Data from FDA on reported adverse events related to the use of compounded topical pain creams;
- Data from the National Association of Boards of Pharmacy related to the use of APIs in compounded topical pain creams; and
- Data from the American Association of Poison Control Centers on adverse event cases related to the use of the 20 ingredients in topical pain creams examined by the committee.

ORGANIZATION OF THE REPORT

The report is organized into eight chapters. Chapter 2 provides a brief overview of the role of compounded topical pain creams in pain management, complexity of pain, and pain treatments. In that chapter, the committee describes the complexity of pain and pain management, reviews standards of care and pharmacological approaches related to pain treatment, and highlights the advantages of using topical pain creams in pain management plans. Chapter 3 explores the fundamentals, use, and common ingredients in compounded topical pain creams. It also provides an overview of the use and demand for compounded preparations as well as pain conditions associated with their use. It concludes with a description of the active pharmaceutical ingredients commonly used in those preparations.

Chapter 4 describes the current federal and state-level regulation and oversight of compounded preparations.

Chapter 5 examines the science behind compounded topical pain creams. This includes reviewing pharmacokinetic properties of the committee's ingredients of interest and examining the important role of excipients in compounded formulations. Chapter 6 features a review of the key findings from the committee's literature review efforts for the 20 ingredients of interest commonly used in compounded topical pain creams. The ingredients reviewed are organized by their primary drug class. Chapter 7 describes a selection of concerns associated with the use of compounded topical pain creams that are faced by individuals who compound, clinicians who prescribe compounded preparations, and patients. Chapter 8 is the final chapter of this report and serves as the report's overall summary chapter. This chapter synthesizes the report's research conclusions and issues important recommendations to a diverse set of stakeholders, including medical practitioners, patients, health advocacy organizations, and federal and state public health agencies.

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2

Role of Topical Pain Creams in Pain Management

Pain is a global problem affecting approximately 1 in 5 adults across the world, with nearly 1 in 10 adults newly diagnosed with chronic pain each year (Goldberg and McGee, 2011). The effective treatment of pain has therefore been viewed with increasing importance in clinical practice, leading to the consideration of pain as the "fifth vital sign" (Baker, 2017). General consensus among pain researchers and clinicians holds that optimal pain management plans require patient-centered care involving clinicians from multiple disciplines, including application of integrative treatments to enhance patient outcomes, relieve suffering, and restore function (AAPM, 2020; Gordon et al., 2005; Hsu et al., 2019; Koele et al., 2014; Scascighini et al., 2008). An increasingly aging and diversifying American population is bringing limits of current pain management therapies to the forefront of consciousness, with patients and clinicians eager for better pain management strategies.

This chapter examines the complexities inherent in both the individual experience of pain and in its effective management. It also situates topical pain creams within the spectrum of integrative approaches to treating pain, with particular attention paid to special populations that may benefit from alternatives to FDA-approved pain treatments.

COMPLEXITY OF PAIN

Categories of Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential bodily damage or injury (IASP, 2019a). The experience

of pain is subjective, complex, and multifactorial (IASP, 2019a). Pain is commonly categorized broadly into three major categories: nociceptive, neuropathic, or nociplastic pain.[1] Nociceptive pain arises from actual or threatened damage to nonneural tissue (IASP, 2019a). Visceral and non-visceral nociceptive pain is commonly associated with noxious stimuli to internal organs, the musculoskeletal system, soft tissues, or skin (Leppert et al., 2018).[2] Neuropathic pain—which is commonly associated with damage or disease of the somatosensory nervous system—is often described as sharp, burning, or shooting pain (Colloca et al., 2017) and may occur even in the absence of an identified condition or disease.[3] Nociplastic pain may arise without any clear evidence of actual or threatened tissue damage (Trouvin and Perrot, 2019).[4] In certain instances, there is overlap in the experience of these different pain types, as seen in people with chronic low back pain and cancer patients with bone metastases (Leppert et al., 2018).

The major categories of pain are often further delineated by etiology and time duration (IASP, 2019b). Examples of pain defined in terms of etiology or cause includes cancer pain (attributable to cancer or its treatment), diabetic neuropathy, postherpetic neuralgia, regional pain syndrome, erythromelalgia, and site pain. In contrast, referred pain is perceived at a site other than where the pain originates, because of interconnecting sensory nerves (Murray, 2009). As both a symptom and a disease, pain is further categorized with respect to time duration. Acute pain is generally confined to a given period of time and severity, typically lasting no more than 3 months. Chronic pain is defined by a duration persisting longer than 3 months or beyond the time for normal tissue healing (IASP, 2019b). Acute pain is often the progenitor of chronic pain, although little is known about this relationship (Gerbershagen et al., 2014). Some studies suggest that inadequate management of acute pain may increase risks for development of chronic pain (Clarke et al., 2012; Sinatra, 2010); current research efforts are examining potential strategies to decrease such risks (McGreevy et al., 2011) and help mitigate pain's negative effect on overall health and well-being.

[1] Additional pain types, including central types of pain phenomena, such as fibromyalgia syndrome, also exist.

[2] Nociceptive pain is associated with conditions such as pancreatitis (visceral pain), postoperative surgery on nonneural tissue (visceral pain), fractures (nonvisceral pain), or muscle sprains (nonvisceral pain), and is generally described as aching or dull pain (Reeves and Swenson, 2008).

[3] Peripheral neuropathic pain conditions include painful diabetic peripheral neuropathy and complex regional pain syndrome; central neuropathic pain conditions include pain resulting from spinal injury or stroke (Nicholson, 2006).

[4] Nociplastic pain conditions include central sensitization symptoms, such as those symptoms associated with fibromyalgia syndrome.

Prevalence of Chronic Pain

A 2016 U.S. Department of Health and Human Services (HHS) survey estimated that 50 million U.S. adults are living with chronic pain, making it one of the most common reasons adults seek medical care (Dahlhamer et al., 2018). Causes of chronic nociceptive pain include musculoskeletal pain conditions including neck, back, and knee pain (Pitcher et al., 2019). Chronic neuropathic pain includes neuralgia, diabetic neuropathy, HIV infection, amputation, peripheral nerve injury pain, and stroke (Colloca et al., 2017). Conditions associated with nociplastic pain, include fibromyalgia and complex regional pain syndrome type 1 (Trouvin and Perrot, 2019). A recent survey of pain characteristics found the most common locations for chronic pain are headache/migraine, leg, low back, joints, neck, and jaw (Pitcher et al., 2019). Importantly, people living with chronic pain may experience overlapping pain conditions such as fibromyalgia, low back pain, headache, neck ache, and complex regional pain syndrome (Peppin et al., 2015). It has been proposed that chronic pain may itself be considered a disease syndrome because it leads to changes in the nervous system over time (IOM, 2011).

Chronic pain has reached epidemic portions and has become a national public health problem (NCCIH, 2018) (see Box 2-1). It is receiving a great

BOX 2-1
National and Global Impact of Pain

Pain is a global problem affecting approximately 20 percent of adults worldwide, with 1 in 10 adults diagnosed with chronic pain each year (Goldberg and McGee, 2011; Gureje et al., 1998). The Institute of Medicine report *Relieving Pain in America* estimated that 100 million Americans live with chronic pain (IOM, 2011). More recently, the Centers for Disease Control and Prevention estimated that 50 million adults live with chronic pain and 19.6 million adults live with high-impact chronic pain (Dahlhamer et al., 2018). Estimates suggest that Americans spend more than $40 billion per year out of pocket on chronic pain management and treatment (Gaskin and Richard, 2012). In the United States, pain complaints are the most frequent cause of disability. They result in approximately 300 million lost workdays annually and are the leading reason for all physician visits (when combining joint disorders and back problems), costing approximately $300 billion in annual health care expenditures (Gaskin and Richard, 2012; IOM, 2011; St Sauver et al., 2013). Chronic pain is also the leading cause of long-term disability, costing more than $635 billion annually in health care payments, worker's compensation, and lost productivity in the United States (Gaskin and Richard, 2012). The costs associated with absenteeism in and outside the workplace remain unknown.

deal of attention owing to its cost and myriad accompanying symptoms and comorbidities, including impaired memory, cognition, and attention; sleep disturbances; reduced physical functioning; and reduced overall quality of life. Pain can interfere with all aspects of life—physical functioning, psychological functioning, economic productivity, and family and social roles—thereby impairing an individual's overall health and well-being, while also negatively affecting the individual's caregivers, family, and community (Dahan et al., 2014; Fine, 2011; IOM, 2011).

Conclusion 2-1

Pain is a complex global public health problem with individual and societal impacts.

PHARMACOLOGICAL APPROACHES TO TREATING PAIN

A wide range of pharmacological therapies are available to treat acute and chronic pain conditions (Turk et al., 2011). The most common U.S. Food and Drug Administration (FDA)-approved medications include nonopioid analgesic medications (e.g., acetaminophen; nonsteroidal anti-inflammatory drugs [NSAIDs], including COX-2 inhibitors; ibuprofen; aspirin), opioid agonists, and adjuvant analgesic drugs (IOM, 2011). Other classes of medications, some of which are not FDA approved to treat pain indications, have limited evidence to suggest effectiveness in off-label use to alleviate pain. These therapies include but are not limited to medications within the classes of antidepressants, anticonvulsants, glucocorticoids, muscle relaxants, and cannabinoids.

Topical Pain Creams

Although there are multiple routes of administration for analgesics,[5] the committee focused on topical pain creams in this report. For many years, topical pain creams have augmented pain management. In theory, topical pain creams provide clinicians with the ability to treat pain through multiple mechanisms of action and offer a level of versatility potentially greater than that of oral dosage forms. For example, topical creams can be

[5] Routes of administration include oral, sublingual, buccal, intranasal, inhaled, subcutaneous, intravenous, intramuscular, rectal, intramedullary, intrathecal, transdermal, and topical (Leppert et al., 2018).

formulated to support the penetration of drugs into the skin's subcutaneous skin tissue to produce intended local, regional, and/or systemic effects to alleviate pain symptoms.[6] Local effects occur when the drug is applied and absorbed into the skin at the site of pain (Leppert et al., 2018). Systemic effects occur when a drug is absorbed through the skin and accesses the blood stream for distribution throughout the body by the systemic circulation. In this circumstance, the drug does not have to be applied on the skin at the site of pain. Regional effects are experienced when a drug is applied to the skin near the intended site of action. In this setting, a small concentration of the drug may enter into the systemic circulation, even though this may not be the intended action of the drug.

Because topical medications provide a noninvasive method to administer pain medication, this may support patient compliance (Pickering et al., 2017). Topical application of pain medications for local or regional pain may also potentially avoid adverse side effects that occur when analgesics are administered by other routes that result in higher systemic levels (e.g., oral) (Leppert et al., 2018). The complexity of pain management and the many proposed advantages of topical pain creams have fueled increased interest in personalized pain treatment options, including compounded topical preparations created to address a patient's specific needs.

Potential Role of the Placebo Effect in Topical Pain Creams

The placebo effect is an important consideration that pertains to pain treatments, including topical modalities. A placebo is an inactive treatment or sham procedure. The placebo effect occurs when the therapeutic benefit reported by a control group (i.e., a group that received a treatment with no active ingredients) was the same or greater than groups that received the experimental drug or treatment (NASEM, 2017; NIA, 2020). This difference is attributable to more than just the sham treatment, medicine, or procedure. It can be influenced by any of the various factors that contribute to the overall therapeutic context of the situation, such as the patient–physician relationship and emotional factors (IOM, 2011). Placebo effects are a known element of pain treatments in particular because it has been shown in research and clinical settings that the expectation of pain relief can induce an analgesic effect. The extent of a placebo effect is highly variable and is influenced by prior experiences and verbal suggestions. In fact, the effect of any pain

[6] Drugs intended for systemic absorption are placed in more complex transdermal delivery systems to better control their release. Such systems are not the focus of this study. In addition, there are a number of critical clinical factors that attribute to the penetration and absorption of drugs through skin and are recognized as a highly complex phenomenon (see Law et al., 2020, and Chapter 5 for additional details).

treatment may be a combination of the therapeutic agent and the placebo effect (IOM, 2011). Given this background, pharmacological treatments must show an effect over and above the placebo effect in randomized controlled trials (RCTs) to be approved by FDA for human use (Vase and Wartolowska, 2019). Meta-analyses of RCTs for FDA-approved chronic pain treatments report small, but significant, improvements in pain and physical functioning when compared with placebo (Busse et al., 2018; IOM, 2011).

The placebo effect has further complicated the search for effectiveness and mechanisms of action in compounded topical pain creams, owing to a long-held belief that the majority of pain relief from topical applications comes from cutaneous stimulation or rubbing of the painful area. While many RCT studies have disproved this by having the control group rub a placebo (Creamer, 2000; Derry et al., 2017), it remains true that rubbing an area often relieves pain (Field et al., 2014; Lee et al., 2015; Satran and Goldstein, 1973). Placebo effect also indicates that elements of care other than the drug can also have beneficial effects on alleviating pain.

Conclusion 2-2

FDA-approved topical pain creams are available to help manage painful conditions.

COMPLEXITY OF PAIN MANAGEMENT

General consensus across research efforts and medical professional guidelines holds that optimal pain management plans require early access to high-quality patient-centered care involving clinicians from multiple disciplines (e.g., dentistry, medicine, nursing, occupational therapy, physical therapy, psychology, social work) and the application of integrative treatments (e.g., cognitive-behavioral, physical/rehabilitation, interventional strategies, and pharmaceutical strategies) to enhance patient outcomes, relieve suffering, and restore function (AAPM, 2020; Gordon et al., 2005; Hsu et al., 2019; Koele et al., 2014; Scascighini et al., 2008). A 2019 report from the HHS Pain Management Best Practices Inter-Agency Task Force also promotes the use of multiple approaches to pain management in order to act synergistically on different aspects of an individual's pain (HHS, 2019). Figure 2-1 provides illustrative examples of how different patients may interact with health services to arrive at an individualized (personalized) pain management plan, as well as depicting the wide variety of treatment options in a clinician's toolbox.

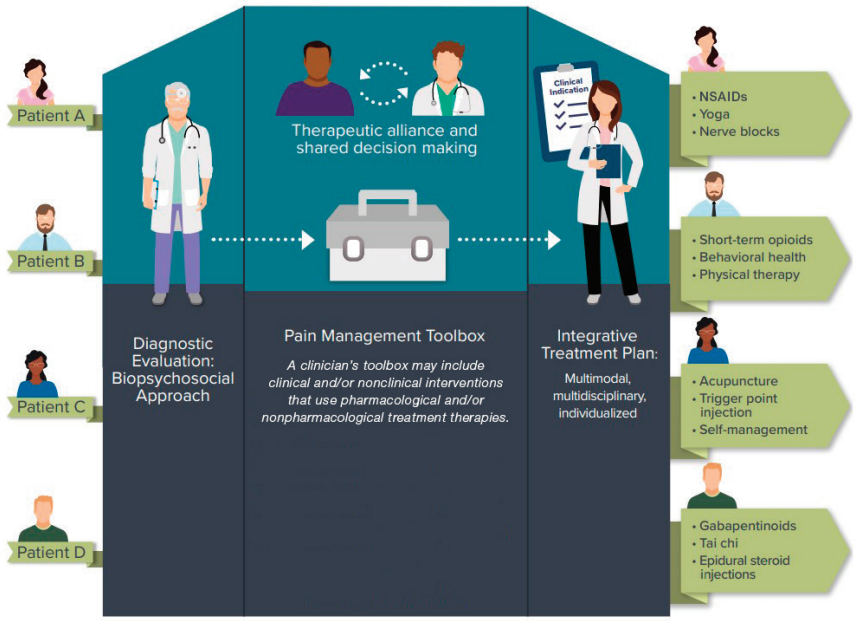

FIGURE 2-1 Process of developing an integrative pain treatment plan.
SOURCE: Adapted from HHS, 2019.

Pain treatments range from simple and inexpensive (e.g., massage) to complicated and expensive (e.g., surgical interventions, nerve blocks); pain treatment also incorporates shared decision making (Tick et al., 2018). An overview of nonpharmacological approaches to treating pain is provided in Box 2-2. Although progress has been made, additional clinical studies are needed to help clinicians determine the optimal sequence of therapies for each patient (Colloca et al., 2017). Given the broad spectrum of available pain therapies and treatment approaches, certain considerations need to be made prior to implementing an integrative pain treatment plan. These considerations include the clinical status of the patient, comorbidities, age, socioeconomic status, gender, race, and ethnicity (McCleane, 2008). In addition, the development of a pain management plan should consider patient adherence—meaning, whether they will reliably take the medicines as prescribed—and the need to minimize potential adverse side effects of treatment (e.g., caused by the route of analgesic administration and drug dose) (Leppert et al., 2018). In certain situations, prescribing clinicians may consider including compounded topical pain creams in the treatment plans of patients whose needs cannot be fully addressed by FDA-approved topical pain products.

BOX 2-2
Nonpharmacological Approaches to Treating Pain

Complementary and integrative medicine has gained popularity as more prescribing clinicians and patients become aware of the effectiveness of these modalities. Such therapies include acupuncture, massage, osteopathic manual medicine, chiropractic, exercise and physical therapy, and psychological therapies. While the mechanism of action for these disciplines and therapies is less established than many pharmacological interventions, and systematic reviews evaluating their effectiveness have been mixed, there is enough evidence to warrant further research (NASEM, 2017). Additionally, some evidence supports the use of self-engaged movement and meditative therapies like yoga and tai chi, and lifestyle or behavioral treatments such as stress management and cognitive-behavioral therapy. A large benefit of these therapies is encouraging the patient to be less passive in their care regimen, as they require more patient participation and commitment than taking pills (Tick et al., 2018).

Drug–Drug Interactions

Populations who are more likely to use pharmacological pain treatments (e.g., geriatrics, cancer patients) are also more likely to be using other medications concurrently. It is therefore important to consider the potential risks and adverse events associated with polypharmacy and drug–drug interactions. Such interactions occur when a drug, supplement, or food affects a medication's effectiveness, often through enzyme induction or inhibition. For example, if an individual is taking two drugs that are both metabolized by the same enzyme pathway, the drugs could initially be limited in their effectiveness because they are in competition for limited enzymes. However, if the medications are taken for a long period of time, they could cause the body to overproduce those enzymes, thus increasing the body's capacity to metabolize those drugs and reduce the medications' potential effectiveness. One study found that each additional prescription dispensed increases the potential risk of a drug–drug interaction by 138 percent (Taylor et al., 2013). Little is known about the full gamut of potential drug–drug interactions, and even less about the potential interactions that arise from exposure to topical medications. See Chapter 6 for an additional discussion on the dearth of information available on the safety and effectiveness of ingredients commonly used in compounded topical pain creams containing multiple active pharmaceutical ingredients, and see Chapter 7 for additional discussion on risk of potential drug–drug interactions to patients.

Special Populations to Consider in Pain and Pain Management

The individual experience of pain and response to painful stimuli is highly variable. A key factor in this variability may be the way the pain message is modulated in an individual's central nervous system (Ossipov et al., 2010), suggesting that clinicians' ability to diagnose and treat pain depends on their understanding of the various processes involved in experiencing pain (Sluka et al., 2009). Mechanisms underlying individual differences in pain response include the following:

- Biological factors: genetics, developmental stage, gonadal (sex) hormones, endogenous pain inhibition and modulation[7]
- Psychological factors: pain coping, anxiety, depression, cognitive factors, behavioral factors[8]
- Sociocultural factors: social determinants of health, culture, discrimination, gender roles, family history, work roles[9] (Sluka et al., 2009)

Accordingly, there is great variability in patients' response to specific pharmacological and nonpharmacological pain treatments (Skelly et al., 2018; Twycross et al., 2015). Pain management decision making is also variable and complicated by disparities in access to care driven by sociodemographic and economic factors. Many patients report that their pain complaints are often unheard (or dismissed) and therefore undertreated[10] (Baratta et al., 2014; Sinatra, 2010). Pain care is further complicated by insufficient clinician and patient education, misinformation, poor communication between clinicians and patients, and variability in clinician attitudes.[11]

Complexities of pain and its management are further intensified in special populations. The confluence of biological, psychosocial, and sociodemographic factors that drive wide variability in individual-level responses

[7] Twin studies have demonstrated that genetic influences account for approximately 50 percent of the variance in chronic pain (Fillingim et al., 2008).

[8] There is a high prevalence of psychiatric illnesses in chronic pain patients, which are associated with increased pain perception, as well as impairment in activity and function (Rajmohan and Kumar, 2013).

[9] Differences in pain sensitivity between women and men are partly attributable to social conditioning and to psychosocial factors (Wiesenfeld-Hallin, 2005).

[10] Undertreatment of pain can lead to decreased physical activities, diminished mental health, weakened social interactions, missed workdays, and lower quality of life while also placing an increased financial burden on the patient and health care system as a whole.

[11] Physicians report lesser goals for treating chronic pain and less satisfaction with their care when compared to other conditions, including acute and cancer pain, but they report greater goals for pain management in the palliative care arena (Green et al., 2003).

to pain also contribute to substantial between-group differences (Coghill, 2010; Fillingim et al., 2008). Social determinants of health—including age, race, ethnicity, gender, place of residence, and socioeconomic status—profoundly influence pain measurement, coping, response, and overall disability (Green et al., 2003). Factors that mediate treatment differences among special populations remain poorly understood, affecting the quality of pain care received by those groups (Green et al., 2003). Furthermore, the safety and efficacy of FDA-approved pain treatments typically are not studied in representative populations stratified by age, race, gender, or other sociodemographic factors (Green et al., 2003; McBane et al., 2019). As a result, there is much to learn regarding the potential clinical usefulness of topical pain creams and other alternative modalities such as compounded topical pain creams to address the complexities of pain management in these special populations. See Appendix H for an additional discussion on the understudied populations highlighted above.

Conclusion 2-3

There is a need for additional research and improvements to ensure high-quality pain management, particularly for special populations, including those stratified by age, race, gender, or other sociodemographic factors.

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3

Fundamentals, Use, and Common Ingredients in Compounded Topical Pain Creams

This chapter opens with brief descriptions of the fundamentals of the practice of compounding in the United States. It then provides an overview of the market and demand for compounded preparations in general, as well as patient use and pain conditions generally associated with compounded topical pain creams. The chapter concludes by identifying a set of active pharmaceutical ingredients (APIs) that are commonly used in formulations of compounded topical pain creams.

FUNDAMENTALS OF COMPOUNDING

In general, compounding can be defined as "the process of combining, mixing, or altering ingredients to create a sterile or nonsterile medication tailored to the needs of a patient" (FDA, 2017).[1] Compounded preparations represent therapeutic alternatives for patients with clinical needs that cannot be met by drugs approved by the U.S. Food and Drug Administration (FDA) (FDA, 2017; Glassgold, 2013; Gudeman et al., 2013; IACP, 2019). Customized formulations can be compounded to (1) create alternate dosage strengths or forms, or (2) omit components of FDA-approved drugs that a patient cannot tolerate (Glassgold, 2013; USP, 2017). Patient populations that have

[1] In an effort to provide additional guidance, the United States Pharmacopeia (USP) offers a more detailed definition of compounding: "the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice" (USP, 2017).

traditionally benefited from customized compounded preparations include pediatric patients, people living with chronic pain, people at end of life, and people with rare medical or physical conditions (e.g., patients who cannot swallow pills might be provided with a liquid version of their medication) (Kochanowska-Karamyan, 2016; USP, 2017).

The process of compounding can produce sterile or nonsterile preparations and is conducted within a wide range of pharmaceutical and medical settings.[2] For example, compounding commonly occurs in community pharmacies, physicians' offices,[3] mail-order compounding pharmacies, hospital pharmacies, and specialty compounding facilities. United States Pharmacopeia (USP) standards suggest that compounded preparations should be developed in designated areas that are adequately designed to support the sterile or nonsterile processes; this includes providing proper storage for those preparations under the appropriate conditions, such as designated temperature, light, moisture, and ventilation (USP, 2018).[4,5]

Compounding remains an important component of pharmacy practice, particularly in smaller, independent community pharmacies (McPherson et al., 2006). Studies have found that compounding preparations at community pharmacies may strengthen the patient–pharmacist relationship, improve pharmacists' professional satisfaction and perceived quality of patient care, and imbue pharmacists with a greater responsibility to provide patient-centered care (McPherson and Fontane, 2010; Yancey et al., 2008).

Due in part to the historical nature of patient-specific small-scale compounding and the ad hoc processes it involves, compounded preparations have not been subject to stringent federal and state-level regulatory policies to inform and enforce good compounding practices or procedures to ensure the safety, effectiveness, or quality of the preparations prior to their being marketed to patients (Takaoka et al., 2018). As a critical comparison, FDA maintains a rigorous, multistep drug development, approval, and postmarketing surveillance process for FDA-approved drug products in order to inform medical practice and to protect the patient. Efforts have been made over recent decades to regulate compounding more rigorously in an attempt to

[2] In sterile compounding, medications are prepared in a clean-room environment using aseptic techniques to ensure solutions are free of microorganisms. Sterile compounding is primarily used for injectable, parenteral, and ophthalmic preparations. In nonsterile compounding, medications are prepared in a clean environment without sterile techniques required, mainly for oral and topical (skin) formulations: capsules, solutions, suspensions, ointments, creams, and suppositories.

[3] The frequency of compounding performed in a physician's office tends to vary by specialty.

[4] The United States Pharmacopeial Convention is a nonprofit organization that works to ensure the quality of compounded medicines by setting public standards for identity, strength, quality, and purity. USP has developed three types of standards for compounding: United States Pharmacopeia-National Formulary (USP-NF) monographs for bulk drug substances, USP-compounded preparation monographs, and essential General Chapters.

[5] USP does not have regulatory or enforcement authority, but its standards are enforceable by state law.

ensure patient safety while preserving patients' access to compounded preparations (FDA, 2017). See Chapter 4 for a discussion on the current federal and state-level oversight of compounding practices.

OVERVIEW OF THE USE AND DEMAND FOR COMPOUNDED PREPARATIONS

In recent years, the increasing demand for personalized medical care—coupled with the lack of regulations and oversight for the development of compounded preparations—has catalyzed a resurgence in compounding for treating a much broader patient population than traditionally intended (Burch, 2017; Glassgold, 2013). More specifically, the increased supply and demand for compounded preparations is driven by a host of factors that include

- Frequent shortages of commercially produced drugs (particularly sterile generic injectables);
- Preferences among patients and prescribing clinicians for personalized formulations;
- The growing aging population; and
- Evolving business strategies in the pharmaceutical sector toward marketing compounded preparations for specific indications, rather than case-by-case clinical needs (Glassgold, 2013).

The growing demand for compounded preparations is reflected in their use to treat a wide spectrum of conditions across a range of therapeutic areas, including pain management, hormone therapy, sports medicine, weight loss, dental care, veterinary care, pediatrics, and hospice care (Glassgold, 2013; McPherson et al., 2016). Indeed, the use of compounded preparations has become common in the fields of allergy, dermatology, immunology, otolaryngology, oncology, ophthalmology, neurology, and rheumatology specialties (NABP, 2017).

Conclusion 3-1

Compounded preparations may offer potential therapeutic alternatives, or adjunctive therapy, to FDA-approved drug products, particularly when an FDA-approved product is unable to meet the specific clinical needs of a patient.[6]

[6] This text has changed since the prepublication release of this report. Here and in other instances throughout the report, "commercially available product(s)" was replaced with "FDA-approved drug product(s)."

The Compounding Market

There are no federal reporting requirements for compounding pharmacists or pharmacies to disclose data on use or demand of compounding preparations, and as a result, it is difficult to secure an accurate estimate of the compounding market (Glassgold, 2013). However, available data, largely produced by surveys, suggest that the compounding industry has expanded quite considerably over the past few decades and has become increasingly lucrative (HHS OIG, 2016; McPherson et al., 2016). Several private marketing reports have estimated the global market revenue for compounded preparations to fall between $2 and $9 billion. Those analyses all predict growth in the next few years, ranging from 3 to 7 percent.

A caveat is that these estimates come from private marketing reports and are based on data sources that are publicly unverifiable (Bourne Partners, 2018; Global Market Insights, 2018; Market Research Engine, 2018; ReportsnReports, 2018; Zion Market Research, 2018). Private marketing reports have also analyzed the pain management segment of the compounding market. They estimate that the pain management market held the greatest revenue share of the U.S. compounding market in 2017 ($1.6 billion) and predict steady growth and consumer demand in that market through 2025 (Global Market Insights, 2018).[7]

Data on compounded preparations are also available from national data on workers' compensation claims. Compounding is a growing trend in workers' compensation programs; prescriptions for compounded preparations increased almost 5-fold between 2007 and 2012, from 6,416 to 30,669 (Walls et al., 2014). Several surveys of pharmacists and prescribing clinicians have sought to elicit information about the use of compounded preparations, but the information obtained has been limited owing to low response rates (McPherson et al., 2019; Ness et al., 2002; Warner and Tuder, 2014).

Looking at insurance claims data, the number of beneficiaries receiving compounded preparations also increased substantially by 281 percent, from 73,368 in 2006 to 279,873 in 2015 (HHS OIG, 2016). A retrospective analysis of prescription claims data found that the prevalence of eligible members using compounded preparations increased by around 27 percent between 2012 and 2013, with 1.4 percent of eligible members using compounded preparations in 2013. The number of claims for compounded preparations also increased by around 34 percent (from 486,886 to 653,360) during the same period (McPherson et al., 2016). Given the evidence for the substantial use of compounded preparations and the current

[7] Given the limited resources of the committee, it was unable to access the private reports to verify whether the market segment for topical pain creams was reviewed.

gaps in federal and state oversight protections for patients, the committee is concerned that an increasing fraction of drugs used in the United States is consumed without assurance for quality, safety, and effectiveness.[8]

THE USE OF COMPOUNDED TOPICAL PAIN CREAMS

As described in the previous sections, there is a substantial market for compounded preparations for pain management. However, there is little empirical evidence to describe the individuals who use compounded preparations, the number of preparations that are compounded, the common formulations dispensed, or the conditions they are intended to treat (Glassgold, 2013). The growing supply and demand for compounded preparations provides a compelling rationale to learn more about the clinical use of compounded topical pain creams, as the lack of data poses challenges for risk–benefit assessment of these preparations and for the development of evidence-based public health policy to govern their use.

Data on Patient Use

Clear data are unavailable to describe the use of compounded topical pain creams and patients' overall experience with those preparations. This is attributable in part to a constantly evolving compounding landscape, which has seen the emergence of large, mail-order compounding pharmacies as well as changes in insurance coverage (McPherson et al., 2019). In recent years, payers have drastically reduced their coverage of compounded preparations (Chavez-Valdez, 2018; DoD, 2017; Silverman, 2014). If insurance companies are tracking compounded preparation prescriptions, these data have not been widely published or analyzed by researchers. Furthermore, no database exists to capture the use of those preparations by customers who pay out of pocket. In the context of tracking patient use, another caveat is that many patients may not be aware that their medication is compounded.

Because both FDA-approved products and compounded preparations are prescribed by their doctors, consumers may not be effectively educated by their prescribing clinicians or pharmacists about the difference between the compounded preparations and FDA-approved medications (Cowan, 2019). This lack of education affects patients' knowledge about the risks and benefits of the compounded preparations they are taking. They may also be unaware of the potential risks reported by patient health surveys or of adverse events that have been reported.

[8] In Chapter 6 of this report, the committee reviews the scientific evidence to support claims related to the safety and effectiveness of common active pharmaceutical ingredients used in compounded topical pain creams.

Although data sources paint an incomplete picture of the use of compounded topical pain creams, the increasing numbers of prescriptions being written appear to reflect substantial interest in prescribing these preparations (HHS OIG, 2016). To expand the evidence base, much more robust epidemiological data are needed in order to identify

- the demographics of the patients;
- the frequency with which the preparations are being used;
- the conditions for which the preparations are used; and
- any adverse events that have taken place as a result of use of these preparations.

This type of research and surveillance is needed to understand the prevalence of use of compounded preparations as well as to appropriately inform evidence-based decisions on rationale for use, targeted populations for use, and minimum labeling requirements to help educate patients about the preparations they are consuming.

PAIN CONDITIONS FOR WHICH COMPOUNDED TOPICAL PAIN CREAMS ARE COMMONLY USED

The committee reviewed numerous medical position statements, recommendations, and clinical guidance in an attempt to identify the clinical specialties, pain conditions, and types of compounded topical pain cream formulations that are recommended for use. The few professional organizations that explicitly mentioned the clinical use of compounded topical pain creams often cautioned that there was a lack of evidence to support the effectiveness or reliable safety of these treatments (ACPA, 2019; Paterson and Yuen, 2015; Tavares, 2015). Of note, compounded preparations were mentioned as potential treatment options for chronic and neuropathic pain, including chronic cancer pain (Paice et al., 2016); chemotherapy-induced peripheral neuropathy (ACPA, 2019); and peripheral neuropathic pain (Paterson and Yuen, 2015). However, one organization, the International Association for Hospice and Palliative Care, recommended against the use of multidrug compounded preparations to treat chronic pain and instead promoted the administration of different drugs independently (IAHPC, 2013).

Rationale for Patient Use

Although there is a dearth of clinical guidance for use, the medical literature has a number of articles that mention the use of compounded topical pain creams in treatment plans for pain-related medical conditions. The conditions highlighted in Table 3-1 were identified during the committee's

literature review on the safety and effectiveness of selected ingredients commonly used in compounded topical pain creams (see Chapters 1 and 6 for more information on the committee's literature review efforts).

To add to the body of knowledge related to the rationale for use, a small survey was recently conducted of patients of compounded topical pain creams (McPherson et al., 2019). The 107 respondents ranged in age from 35 to 96 years, with about 80 percent between 48 and 83 years of age and an average age of 67 years; 77 percent of respondents were female. The most common reasons cited for using the compounded pain creams were arthritis pain (29 percent) and general pain in the feet, knee, hip, shoulder, back, or neck (26 percent); 12 percent said they used the medications for neuropathic pain. Around half of respondents reported using compounded topical pain cream in addition to other medications (McPherson, 2019; McPherson et al., 2019).

Based on the committee's review of the literature, compounded topical pain creams appear to be used for a variety of different reasons. For example, clinicians and compounding pharmacists commonly associate compounded topical pain cream use with a range of perceived benefits, including

- selectively delivering drugs to peripheral sites of action;
- improving tolerability, owing to less contact with the gastrointestinal system;
- combining multiple drugs with different mechanisms of action at varying dosages to meet individual patient needs; and

TABLE 3-1
Sample of Reported Pain Conditions Treated with Compounded Topical Pain Creams

Type of Pain	Pain Conditions for Which Compounded Topical Pain Creams Were Used
Neuropathic pain	• Peripheral neuropathy (diabetic, chemotherapy-induced) • Postherpetic neuralgia • Neuropathic pain from spinal cord injury • Neuropathic pain from multiple sclerosis • Chronic idiopathic axonal polyneuropathy • Radicular pain
Nociceptive pain	• Musculoskeletal pain • Rheumatoid arthritis • Osteoarthritis • Back and neck pain • Visceral pain, muscle spasms • Abdominal pain • Idiopathic proctodynia
Nociplastic pain (mixed pain)	• Fibromyalgia • Trigeminal neuralgia

- having less systemic absorption, fewer side effects, lower abuse potential, and greater convenience compared to oral pain medications (Branvold and Carvalho, 2014; Brutcher et al., 2019).

Although the reported benefits of compounded topical pain creams are intriguing, in general, many of these claims, particularly those related to the safety and effectiveness of the preparations, are not yet supported by a strong body of empirical research.

ACTIVE PHARMACEUTICAL INGREDIENTS COMMONLY USED IN COMPOUNDED TOPICAL PAIN CREAMS

The ad hoc nature of compounding creates a situation in which the formulations of various compounded topical pain creams are not standardized across different compounding pharmacists, compounding pharmacies, or between states. In addition, as discussed in Chapter 7 of this report, there are no central repositories to collect formulations for specific pain conditions or special populations of patients. Much of these data lie in the hands of the individual compounding pharmacies and outsourcing facilities. For example, in an effort to better understand the types of APIs used in the development of compounded topical pain formulations, the committee submitted a research request to FDA. From data provided by outsourcing facilities during required product reporting in 2017 and 2018, FDA supplied the committee with aggregated data for five APIs that were the most commonly used in multidrug combination creams.[9,10] The submitted data show that during 2017 and 2018, baclofen and gabapentin were each used in more than 5,200 formulations, cyclobenzaprine in just less than 5,000, clonidine in just more than 1,000, and amitriptyline in 416 formulations.[11,12]

In June 2019, the committee submitted a data request to the National Association of Boards of Pharmacy (NABP) to gather information on the most common formulations of compounded topical pain creams. From its 2016–2018 collection of pharmacy inspection application requests, NABP submitted a compiled list of the five most dispensed formulations from both

[9] This text has changed since the prepublication release of this report to clarify the data source.

[10] Data were aggregated across all outsourcing facilities in order to keep each outsourcing facility's production volume confidential.

[11] FDA. 2019. Email from G. Cosel to National Academies staff regarding aggregated volume output of products containing ingredients of interest to compounded topical pain medication study. August 30. Available through the National Academies' Public Access File.

[12] Additional outsourcing facility preparation reports can be found at https://www.fda.gov/drugs/human-drug-compounding/information-outsourcing-facilities (accessed April 13, 2020).

503A compounding pharmacies and 503B outsourcing facilities.[13] Given the limitations in the data-reporting process, the committee was not able to confidently distinguish between APIs that were used in compounded preparations from those that were dispensed as a manufactured product (NABP, 2019), which prohibited the analysis of these data for this report.

From its research efforts, the committee has found that many APIs formulated in compounded topical pain creams include those found in FDA-approved topical pain products, FDA-approved nontopical pain products, or products approved by FDA for nonpain indications. Moreover, many compounding pharmacies develop compounded topical pain creams formulations that contain four, five, or even more APIs. Using the Micromedex database as a resource, Table 3-2 provides details on APIs selected for the committee's review and includes information about FDA-approved pain indications, off-label use, and associated major adverse effects.[14,15]

Again—owing to a lack of a central database and clinical guidance—it is not possible to draw clear, specific conclusions on when and why these multi-ingredient preparations are prescribed to treat specific health indications and the potential adverse effects that may occur. Therefore, because of the limited regulation and oversight for compounding, pharmacists and prescribing clinicians hold enormous privilege and responsibility in determining the appropriate medical formulation and dose to treat the patient.

Conclusion 3-2

There is a paucity of reproducible data or evidence-based guidance on compounded topical pain creams to describe consumers' therapeutic need, inform prescribing practices, or identify the appropriate formulations for treating specific pain conditions.

[13] The majority of these reports came from pharmacies that voluntarily came to NABP requesting an inspection, though some inspections were mandated owing to state disciplinary action.

[14] Micromedex is an evidence-based, multidatabase drug search engine that provides comprehensive information on pharmaceutical drugs. See https://www.micromedexsolutions.com/home/dispatch (accessed December 10, 2019).

[15] For the purposes of this report a drug is considered off-label when an approved drug product is prescribed for a condition, or in a dose, other than that for which it received its approval.

TABLE 3-2
FDA-Approved and Off-Label Indications Limited to Pain Indications for Which Topical Pain Creams Are Often Used

Drug Product	Formulation(s)	Drug Class	FDA-Approved Pain Indications
Amitriptyline	Oral	Tricyclic antidepressants	None
Baclofen	Oral, intrathecal	Skeletal muscle relaxant	Muscle spasms
Bupivacaine	Injection	Local anesthetic	None
Cannabidiol	Oral	Cannabinoid	None
Carbamezapine	Oral	Anticonvulsants	Trigeminal neuralgia
Clonidine	Transdermal	Alpha-2 adrenergic agonist	None
Clonidine HCl	Epidural, oral	Alpha-2 adrenergic agonist	None
Cyclobenzaprine	Oral	Skeletal muscle relaxant	Skeletal muscle spasm

	Off-Label/Non-FDA Uses for Pain	Example Adverse Effects from FDA-Approved Label	Example Serious Adverse Effects from Micromedex (2019)
	Fibromyalgia, postherpertic neuralgia	Cardiovascular, CNS and neuromuscular, anticholinergic, allergic, hematologic, gastrointestinal, and endocrine adverse reactions (Sandoz, 2014)	Black box warning for increased suicidal thoughts; cardiac arrhythmias
	Trigeminal neuralgia, peripheral neuropathy	Drowsiness, dizziness, and weakness (Metacel Pharmaceuticals, LLC, 2019)	Gastrointestinal bleeding
	Pain	Excitation and/or depression of the CNS system as well as cardiovascular adverse reactions (Pfizer, 2012)	Cardiac arrest, respiratory depression
	None	Somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, malaise, asthenia, rash, sleep disorders, and infections (GW Pharmaceuticals, 2018)	Increased suicidal thoughts; increased liver enzymes
	None	Dizziness, drowsiness, unsteadiness, nausea, and vomiting adverse reactions. The most severe reactions observed have been in the hemopoietic system, skin, liver, and cardiovascular system (Novartis, 2009)	Stevens-Johnson syndrome, toxic epidermal necrolysis, atrioventricular block, syncope, liver failure
	None	Dry mouth, drowsiness, fatigue, headache, lethargy, and sedation (Boehringer Ingelheim Pharmaceuticals, Inc., 2011)	Atrioventricular block
	Muscle spasms	Dry mouth, drowsiness, dizziness, constipation, and sedation (Boehringer Ingelheim Pharmaceuticals, 2009)	Atrioventricular block
	Fibromyalgia	Drowsiness, dry mouth, fatigue, and headache (McNeil Consumer Healthcare, 2013)	Cardiac dysrhythmia, heart block, myocardial infarction, syncope

TABLE 3-2
Continued

Drug Product	Formulation(s)	Drug Class	FDA-Approved Pain Indications	
Dexamethasone	Oral, ophthalmic, injection	Adrenal corticosteroid	None	
Doxepin	Oral, topical	Tricyclic antidepressants	None	
Gabapentin	Oral, topical	Anticonvulsants	Postherpetic neuralgia	
Ketamine	IV, IM	Local anesthesia	None	
Lidocaine	Rectal, topical	Local anesthetic	Postherpetic neuralgia	
Meloxicam	Oral	NSAID	Osteoarthritis, rheumatoid arthritis	
Memantine	Oral	NMDA receptor antagonist	None	
Naproxen	Oral	NSAID	Rheumatoid arthritis, osteoarthritis	
Nifedipine	Oral	Calcium channel blocker	None	

	Off-Label/Non-FDA Uses for Pain	Example Adverse Effects from FDA-Approved Label	Example Serious Adverse Effects from Micromedex (2019)
	None	Allergic reactions, cardiovascular, dermatologic, endocrine, fluid and electrolyte disturbances, gastrointestinal, metabolic, musculoskeletal, neurological/psychiatric, and ophthalmic adverse reactions (Fera Pharmaceuticals, 2004)	Cardiomyopathy, hyperglycemia, pancreatitis
	Chronic pain	Burning/stinging at the site of application, drowsiness, dry mouth, pruritus, and fatigue (Bioglan Pharma, Inc., 2002)	Ventricular arrhythmia, thrombocytopenia, suicidal thoughts, kidney damage
	Fibromyalgia, Diabetic peripheral neuropathy	Dizziness, somnolence, and peripheral edema (Pfizer, 2010a)	Stevens-Johnson syndrome
	Acute pain	Cardiovascular, respiratory, ocular, genitourinary, psychological, neurological, and gastrointestinal adverse reactions (JHP Pharmaceuticals, 2012)	Bradyarrhythmia, cardiac dysrhythmia, respiratory depression
	Diabetic neuropathy, acute pain	Application site reactions such as irritation, erythema, and pruritus (Scilex Pharmaceuticals, Inc., 2018)	—
	None	Diarrhea, upper respiratory tract infections, dyspepsia, and influenza-like symptoms (Boehringer Ingelheim Pharmaceuticals, 2012)	Black box warning for increased risk of cardiovascular events, gastrointestinal bleeding and ulceration
	None	Dizziness, headaches, confusion, and gastrointestinal adverse effects (Forest Pharmaceuticals, 2013)	Cerebrovascular accident, seizures, kidney failure
	None	Gastrointestinal, CNS, dermatologic, cardiovascular and special senses disturbances (visual and hearing) adverse reactions (Roche, 2007)	Black box warning for increased risk of cardiovascular events, gastrointestinal bleeding and ulceration
	None	Peripheral edema, headache, dizziness, fatigue, nausea, and constipation adverse reactions (Bayer Healthcare, 2011; Pfizer, 2010b)	Myocardial infarction, ventricular arrhythmia, suicidal thoughts, kidney damage

TABLE 3-2
Continued

Drug Product	Formulation(s)	Drug Class	FDA-Approved Pain Indications	
Orphenadrine	Injection, oral	Skeletal muscle relaxant	Musculoskeletal pain	
Pentoxyifyline	Oral	Vasoactive phosphodiesterase inhibitor	None	
Topiramate	Oral	Anticonvulsants	Migraine prophylaxis	
Tramadol	Oral	Opioid agonist	Chronic pain	

NOTE: CNS = central nervous system; FDA = U.S. Food and Drug Administration; HCl = hydrochloride; IM = intramuscular injection; IV = intravenous injection; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug; REMS = Risk Evaluation and Mitigation Strategy.

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	Off-Label/Non-FDA Uses for Pain	Example Adverse Effects from FDA-Approved Label	Example Serious Adverse Effects from Micromedex (2019)
	None	Dry mouth, tachycardia, palpitation, urinary hesitancy or retention, and blurred vision (3M Pharmaceuticals, 2006)	Palpitations, tachyarrhythmia
	None	Cardiovascular, digestive, and nervous system adverse reactions (Validus Pharmaceuticals, LLC, 2016)	Thrombocytopenia
	None	Paresthesia, anorexia, and weight loss (Janssen Pharmaceuticals, Inc., 2017)	Dermatologic: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
	Cancer pain	Constipation, nausea, dizziness, and headache (Johnson & Johnson, 2009)	Black box warning for addiction, abuse, misuse. Required REMS by FDA. Respiratory depression, accidental ingestion, sedation, coma, and death if used with benzos or alcohol

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4

Gaps in Regulation, Oversight, and Surveillance

CURRENT REGULATION AND LEGISLATION

Compounded drugs have long been part of the medical armamentarium for serving patients with unique clinical needs that otherwise cannot be addressed with drugs approved by the U.S. Food and Drug Administration (FDA). However, FDA does not have the regulatory authority to verify the safety or effectiveness of compounded drugs before they are marketed and dispensed to consumers (FDA, 2017a). While FDA's role in overseeing compounding has expanded in recent decades, state entities such as state boards of pharmacy are currently the primary regulators of drug compounding practices (The Pew Charitable Trusts and NABP, 2018). In contrast, FDA exercises substantial oversight over other types of prescription products and commercial over-the-counter drugs under the auspices of the Federal Food, Drug, and Cosmetic Act (FDCA), which grants FDA the authority to oversee the safety of food, drugs, medical devices, and cosmetics. Since the 1962 Kefauver-Harris Amendments to the FDCA, manufacturers have been required to demonstrate efficacy as well as safety of new drugs before they can be sold in the United States, thereby protecting the public from ineffective or potentially dangerous products (Kim, 2017).[1]

Evidence suggests that the use of compounded preparations is substantial and is expected to increase (Ugalmugale, 2018). The minimal federal and state oversight protection for consumers is cause for marked concern

[1] Drug Amendments Act of 1962, Public Law 87-781, 87th Cong., 2nd sess. (October 10, 1962):S 1522.

that an increasing fraction of drugs used in the United States are consumed without assurance of their quality, safety, or effectiveness. Gaps in federal and state-level regulation and oversight need to be addressed to provide confidence in the safe and appropriate use of compounded topical pain creams. Throughout this chapter, the committee will provide a brief overview of current regulations for compounded medication compared to FDA-approved medications, as well as highlighting opportunities to address current gaps in the system.

FDA Drug Approval Process for Human Prescription and Human Over-the-Counter Drug Products

FDA's drug development and approval processes are intended to ensure patients receive safe and effective medications. However, the path from the lab bench to the patient bedside is inherently complex and costly. FDA's Center for Drug Evaluation and Research regulates human prescription and human over-the-counter drugs, and it is responsible for helping to ensure drugs are safe and effective for their intended use in patients (FDA, 2019c). See Figure 4-1 for a visual description of select steps within the drug approval process. The FDCA requires that pharmaceutical companies demonstrate basic safety and efficacy of new drugs before they can be sold in the United States, but most candidate drugs are unable to meet those standards and do not receive approval (Wong et al., 2018). FDA approves a new drug only after careful review of the information on its effects to determine whether the benefits outweigh known and potential risks (FDA, 2019c). The next section provides an overview of the process by which FDA regulates and oversees drug development, approval, and postmarketing surveillance for a typical new drug. FDA also has guidance specific to the approval of products with multiple active ingredients. In these cases, each ingredient's benefit is typically established with clinical data from studies that compare the fixed-combination drug product to individual component treatment arms (with and without placebo) over multiple doses.[2,3]

[2] Fixed-combination prescription drugs for humans. 21 CFR § 300.50 (January 5, 1999).

[3] FDA regulation for fixed-combination drug products allows for two or more drugs to be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (including amount, frequency, and duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the drug labeling.

U.S. Food and Drug Administration Oversight of Drug Development, Approval, and Postmarketing Surveillance

FDA's direct involvement begins when the drug sponsor has gathered sufficient preclinical information to warrant clinical testing in humans. The drug sponsor must submit the results of its preclinical testing in an investigational new drug application, which FDA reviews to ensure that research participants will not be exposed to undue risk (FDA, 2016a). FDA regulations describe a multistage process of human clinical testing:

- Phase 1 trials are designed to assess drug metabolism and excretion, and identify the most frequent, acute safety issues (usually tested in a small number of healthy volunteers).
- Phase 2 trials are typically conducted via randomized controlled trials (RCTs) to gather initial data about drug activity and clinical effects in a larger number of individuals who have the condition or disease the product is intended to treat. These trials often evaluate a range of doses to determine the optimal dose for both efficacy and safety.
- Phase 3 trials are intended to provide the primary clinical evidence of safety and efficacy of the drug, typically through RCTs that compare the drug with a placebo or another product approved for the sought indication. These trials may also study different populations, different drug dosages, or the drug in combination with other drugs that are already approved (FDA, 2016a).

Depending on the results of these clinical trials, the drug sponsor—typically a pharmaceutical company—may file a new drug application proposing that FDA approve a new product for sale and marketing in the United States. FDA reviews the information to determine (1) whether the studies demonstrate the drug has substantial evidence of efficacy for the proposed indication, sufficient safety, and benefits that outweigh the risks; (2) appropriateness and content of the proposed package label; and (3) adequacy of the methods used in manufacturing and controls used to maintain the drug's quality (FDA, 2019d).

Further safety monitoring after FDA approves a drug is critical, because the clinical trials that support approval cannot predict all effects when the drug is used more broadly. Broad use of the drug in patients with other concomitant diseases or patients who are using other medications may lead to adverse events that were not observed in clinical studies. Manufacturers of approved drugs are required to submit regular safety updates to FDA, including results of further studies and individual reports of adverse events from clinicians and the public. FDA's postmarket surveillance programs also

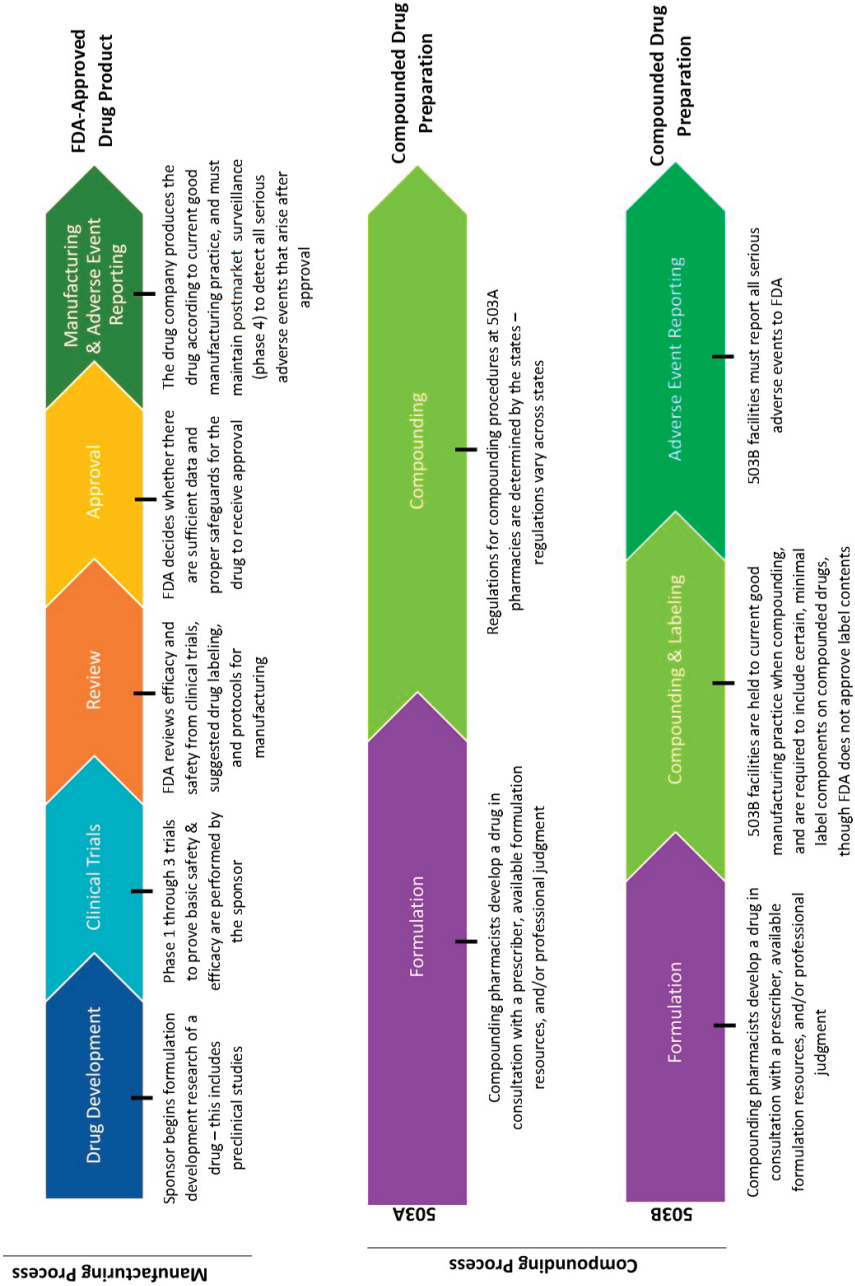

FIGURE 4-1 Comparison of select steps within the statutory and regulatory processes for FDA-approved drug products and compounded drug preparations.
NOTES: The figure is intended to provide a general overview of the statutory and regulatory processes required of FDA-approved drug products and compounded drug preparations. The figure does not offer a complete summary of the complex regulatory framework for all drug products or compounded preparations. Compounding preparations can be made from either bulk drug substances or FDA-approved products that are subsequently modified. 503B outsourcing facilities can make compounded drugs without a patient-specific prescription.
SOURCE: Original image. Information sources include FDA, 2016a; Federal Food, Drug, and Cosmetic Act § 503A and § 503B.

collect reports submitted voluntarily to FDA by health professionals and consumers. FDA also maintains the Sentinel Initiative, a large electronic database of health outcomes derived largely from administrative and claims data from health insurers that can be used to follow up on safety signals identified through postmarket safety reports (FDA, 2016c). Additionally, FDA may require that sponsors monitor the risks and benefits of a drug in phase 4 trials or postmarket surveillance studies and, for certain drug products that carry serious risks, a risk evaluation and mitigation strategy may be required to reduce occurrence or severity of particular serious adverse events (FDA, 2019g).

Regulation and Oversight for Compounded Preparations

Compounded preparations are not subject to the same FDA oversight and approval processes as manufactured prescription drugs or commercial over-the-counter products. However, Congress has clarified the role FDA plays in regulating compounding in recent decades, under provisions of the FDCA.[4] Federal law in the United States establishes two categories of compounding, referred to as "503A pharmacy compounding" and "503B outsourcing facilities." These two categories were created by the Food and Drug Administration Modernization Act of 1997 and the Drug Quality and Security Act of 2013, which added Sections 503A and 503B of the FDCA, respectively. (See Figure 4-1 for a visual description comparing select steps within the statutory and regulatory processes for FDA-approved drugs and compounded preparations.)

503A Compounding Pharmacies and 503B Outsourcing Facilities

The specifics of federal and state regulatory authority over compounding are different for 503A compounding pharmacies versus 503B outsourcing facilities.

503A compounding pharmacies Compounding pharmacies that qualify for Section 503A exemptions are not required to register with FDA. These pharmacies are allowed to produce compounded preparations upon receipt of a valid patient-specific prescription, or in limited quantities in anticipation of future prescriptions. Compounded preparations made under 503A are exempt from FDA's requirements for new drug approval, labeling with adequate directions for use, and current good manufacturing practice requirements. To qualify, they are required to meet certain requirements described in Section 503A of the FDCA, including but not limited

[4] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

to (1) being compounded by a licensed pharmacist or licensed physician, (2) being compounded in a state that has entered into a Memorandum of Understanding with FDA or within a licensed pharmacy (or by a licensed physician) where the compounded preparations distributed out of state do not exceed 5 percent of total prescriptions dispensed or distributed by that particular pharmacy or physician,[5] (3) not using components of drugs removed from the market for being unsafe or ineffective,[6] and (4) complying with the prescription requirement mentioned above. Additionally, 503A compounding pharmacies are still required to comply with other applicable requirements in the FDCA, such as the prohibition of insanitary conditions. (See Box 4-1 for an additional discussion on regulations for allowable compounding practices under the FDCA.)

503B outsourcing facilities These facilities are subject to different requirements than 503A compounding pharmacies, and similarly qualify for different exemptions. If a compounding facility decides it would like to qualify for the exemptions permitted under Section 503B, it must first voluntarily register with FDA as an outsourcing facility. In addition to registering with FDA, outsourcing facilities must comply with all other 503B requirements, including but not limited to (1) producing drugs compounded by or under the direct supervision of a licensed pharmacist, (2) not using components of drugs removed from the market after being found to be unsafe or ineffective, and (3) minimal labeling requirements. Outsourcing facilities are *not* exempt from current good manufacturing practice requirements. Unlike 503A compounding pharmacies, 503B outsourcing facilities must report adverse events to FDA and are subject to routine FDA inspections on a risk-based schedule. (See Box 4-3 for an additional discussion on adverse event reporting.) Facilities that comply with all of 503B's requirements qualify for exemption from FDA's requirements for new drug approval, drug supply-chain security, and labeling with adequate directions for use.[7] Importantly, 503B outsourcing facilities are permitted to compound without patient-specific prescriptions and ship prescriptions to clinicians and patients across the United States. Therefore, they tend to be

[5] A standard Memorandum of Understanding has not yet been finalized. A draft form of the agreement, published in 2018, can be found at https://www.fda.gov/media/91085/download (accessed April 13, 2020).

[6] A list of drugs that have been removed from the market for reasons of safety or effectiveness can be found online. See Drug products withdrawn or removed from the market for reasons of safety or effectiveness. 21 CFR 216.24 (December 11, 2018).

[7] 503B facilities must include labeling information such as drug name, dosage form, and strength, and a statement that the drug is compounded; however, these requirements do not meet the current labeling standards for FDA-approved products. In addition, FDA does not review the contents of compounded drug labels (The Pew Charitable Trusts, 2016b).

BOX 4-1
Allowable Compounding Under the FDCA

Compounding After Receipt of a Valid Prescription

A prescribing clinician may write a prescription for an identified individual patient who needs a compounded preparation. As a common next step, either the prescribing clinician or the patient then brings or sends the prescription to the 503A pharmacy, where the pharmacist creates the compounded preparation for the patient according to the prescription. In other cases, a prescribing clinician may place an order in a patient's health record for a compounded preparation, which in most cases is provided by the health care facility's pharmacy.

Compounding Before Receipt of a Valid Prescription Order

In certain situations, a pharmacist or physician may compound a batch of drugs in anticipation of receiving a patient-specific prescription. This is allowed in cases where there is a history of receiving prescriptions for a particular preparation to be compounded for an identified individual patient and/or in the context of an established relationship with a particular prescribing clinician or patient. Having limited quantities of anticipated compounded preparations on hand may reduce the time it would take for a compounded preparation to be made available to a patient upon receipt of a valid prescription order for that patient.

Compounding for Office Stock

Hospitals, clinics, and health care practitioners can obtain compounded preparations that are not patient specific to be kept as office stock from outsourcing facilities registered under Section 503B. This office stock can increase efficiency and reduce the likelihood of human error that is associated with compounding many small batches of a preparation after the receipt of individual prescriptions for the same drug. On the other hand, there are also greater risks associated with the formulation of large batches of drugs—such as contamination and subpotent/superpotent preparations—that would affect a much larger group of patients.

SOURCES: The Pew Charitable Trusts, 2016a; The Pew Charitable Trusts and NABP, 2018; Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

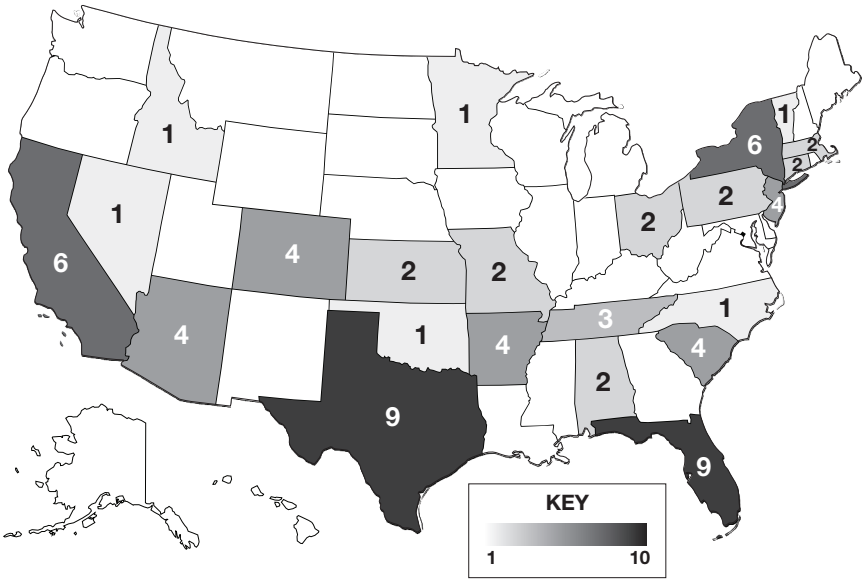

FIGURE 4-2 Geographic distribution of 503B outsourcing facilities throughout the United States.
NOTES: Darker shading reflects a greater number of 503B outsourcing facilities in the state. See Appendix E for additional data on 503A compounding pharmacies and 503B outsourcing facilities.
SOURCE: FDA, 2019e.

larger operations that produce sizable quantities of compounded preparations (The Pew Charitable Trusts, 2016b). Figure 4-2 depicts the geographic distribution of 503B outsourcing facilities across the nation.[8]

Sections 503A and 503B also place limits on the bulk drug substances (i.e., active pharmaceutical ingredients) that these pharmacies can use in compounding drug preparations (FDA, 2019a,b). Section 503A pharmacies may only use bulk drug substances that (1) comply with an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph and the USP chapter on pharmacy compounding, (2) are components of FDA-approved drug products if an applicable USP or NF monograph does not exist, or (3) appear on FDA's list of bulk drug substances that can be used in compounding. By contrast, 503B facilities may only use bulk drug substances that (1) are used to compound drug products that appear on FDA's drug shortage

[8] Values of 503A pharmacies are difficult to estimate due to a lack of standardized reporting, wide-ranging scopes of compounding between pharmacies, and frequent changes in the number of 503A compounding pharmacies.

list at the time of compounding, distribution, and dispensing, or (2) appear on FDA's list of bulk drug substances for which there is a clinical need.

As stated above, both 503A and 503B permit the use of bulk drug substances that appear on lists developed by FDA, but these lists are just one of the potential sources from which individuals who compound may select bulk drug substances. FDA is in the process of compiling 503A and 503B "bulk lists" of allowable bulk drug substances for compounding. Anyone with sufficient information can nominate bulk drug substances to the lists and anyone may challenge the nomination of a bulk drug substance to either list during a notice-and-comment period. However, until the lists are finalized, FDA's interim policy authorizes facilities to compound *any* bulk drug substance that has been nominated to the lists with sufficient information for FDA to evaluate the substance in the future, except when FDA has identified significant safety risks related to the use of the substance in compounding (FDA, 2017b,c).[9]

United States Pharmacopeia Standards

The U.S. Pharmacopeial Convention is a nonprofit organization committed to ensuring the quality of compounded medicines by setting public standards for identity, strength, quality, and purity, including those used in compounded preparations. Specifically, there are three types of standards for compounding[10]:

1. USP-NF monographs for bulk drug substances and other ingredients that may be used in compounded preparations set standards for identity, quality, purity, strength, packaging, and labeling.[11]
2. USP-compounded preparation monographs provide guidance and set quality standards for preparing a limited number of compounded formulations.[12] These monographs include formulas, directions for compounding, beyond-use dates, packaging and storage information, acceptable pH ranges, and stability-indicating assays.

[9] This text has changed since the prepublication release of this report to clarify that compounders cannot use bulk substances nominated to the lists if FDA is aware of significant safety risks.

[10] Although drugs in the USP-NF must adhere to USP standards, this requirement does not differentiate between commercially manufactured products and compounded prescription medicines.

[11] The FDCA describes which bulk drug substances may be used in compounding. It states that compounders may use bulk drug substances that have a USP-NF monograph, and that these bulk drug substances must comply with the standards set forth in the corresponding USP-NF monograph and the USP chapter on pharmacy compounding. See Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[12] At the time of this report, USP currently provides more than 175 compounded preparation monographs.

3. Eight essential General Chapters provide overviews of relevant information, procedures, and analytical methods for compounding (see Box 4-2).

USP itself does not have regulatory or enforcement authority, but USP standards are enforceable under federal law in the FDCA, and some state regulations have also incorporated references to USP standards. USP standards for compounding were first included in the federal law in Section 503A of the FDCA.

State-Level Regulation and Oversight

As described in this chapter, while FDA provides some regulations for compounding preparations, state boards of pharmacy retain primary responsibility for the regulation and oversight of 503A compounding pharmacies. Both the frequency and content of state board of pharmacy inspections vary greatly by state. State-level oversight usually involves a site inspection, which may include a review of compounding procedures, facilities, equipment, staff training, quality assurance, and documentation, among other aspects (Dowell, 2019). Important to the document review are standard operating procedures that detail facility activities and maintenance, personnel, compounding equipment and preparation, and tests to be performed on finished preparations (Allen, 2012; USP, 2017). Violations may result in warning letters, product seizures, injunctions, or prosecution by state authorities, and violators may be referred to FDA.

Voluntary Accreditation

Compounding pharmacies can undergo a voluntary accreditation process to gain third-party validation and (potentially) a competitive edge in the marketplace. For instance, the Accreditation Commission for Health Care's Pharmacy Compounding Accreditation Board has developed national standards for compounding pharmacies based on the consensus of industry experts (Springer, 2013). This accreditation evaluates compliance with the nonsterile and sterile pharmacy compounding processes defined by USP <795> and USP <797> for improved quality and safety. Similarly, the Joint Commission Medication Compounding certification program assesses a pharmacy's compliance with specific standards for preparation and dispensing of sterile and unsterile products in accordance with USP <795> and <797> (Joint Commission, 2019). Starting in fall 2019, the Board of Specialty Pharmacies began offering an exam for pharmacists to become accredited in compounded sterile preparations, though the specialty has yet to receive accreditation from the National Commission for Certifying Agencies (Board of Pharmacy Specialties, 2020).

BOX 4-2
United States Pharmacopeia General Chapters Essential to Compounding

<795> Pharmaceutical Compounding—Nonsterile Preparation contains standards for compounding nonsterile drugs—including process, facilities, equipment, components, documentation, quality controls, and training—to help ensure that medications are safe and effective while reducing the risk of contamination, infection, or incorrect dosing.

<797> Pharmaceutical Compounding—Sterile Preparations describes requirements for sterile compounding, such as training and responsibilities for compounding personnel, facilities, environmental monitoring, storage, and testing of finished preparations.

<800> Hazardous Drugs—Handling in Healthcare Settings provides standards and requirements for all health care personnel who come into any contact with hazardous drugs or the environments in which hazardous drugs are handled.

<825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging describes the standards and procedures for preparing manufactured radiopharmaceuticals and compounding patient-specific radiopharmaceuticals.

<1160> Pharmaceutical Calculations in Pharmacy Practice describes how to appropriately perform calculations required for compounding and dispensing medications, including quantities of ingredients, dosages, infusion rates, endotoxin load, stability, and expiration dates.

<1163> Quality Assurance in Pharmaceutical Compounding explicates the responsibilities and practices of a robust quality assurance system for compounded preparations.

<1168> Compounding for Phase 1 Investigational Studies provides guidance on compounding investigational drugs for use in phase 1 clinical trials.

<1176> Prescription Balances and Volumetric Apparatus Used in Compounding describes the balances and volumetric apparatuses for measuring drugs and other substances used in compounding.

NOTES: At the time of this report, revised versions of select USP chapters have been published. A discussion of proposed revisions to the published chapters can be found at https://www.usp.org/compounding/compounding-appeals (accessed April 16, 2020).
SOURCE: USP, n.d.

GAPS IN FEDERAL AND STATE REGULATION AND OVERSIGHT FOR COMPOUNDED PREPARATIONS

As the compounding market adjusts to its continuously evolving regulatory ecosystem, new sets of gaps and challenges are emerging at the federal and state levels. Gaps in the regulation and oversight of compounding pharmacies and outsourcing facilities need to be addressed to mitigate the potential safety risks and concerns related to the effectiveness of the compounded preparations. These gaps include

- Variable inspections of compounding pharmacies and outsourcing facilities,
- State-level variability in the oversight of compounding,
- Insufficient labeling requirements, and
- Insufficient data collection and surveillance of dispensed compounded preparations (The Pew Charitable Trusts, 2016b).

Insufficient Regulation and Oversight of Compounding Pharmacies and Outsourcing Facilities

Insufficient Inspections of Pharmacies and Facilities

FDA neither routinely inspects compounding pharmacies nor assesses the quality of the compounded preparations produced by those pharmacies (Gudeman et al., 2013). Therefore, unlike FDA-approved products, compounded preparations are not necessarily produced using validated processes or properly calibrated and cleaned equipment (Gudeman et al., 2013). The shelf life of a sterile compounded preparation may not have been verified by stability testing to ensure that it retains its original strength and purity over time (Gudeman et al., 2013). Insanitary conditions have been reported in a number of compounding pharmacies, which can lead to drug contamination with bacteria, fungus, or virus (USP, 2017). Even if a certificate of analysis for a drug substance is provided, there may be questions regarding whether follow-up testing was carried out. For example, a study conducted in 2001 by FDA found that up to one-third of a small sample of compounded preparations failed quality testing (FDA, 2018). Between 2006 and 2009, the Missouri Board of Pharmacy found quality failures in 11–25 percent of the compounded preparations it evaluated; drug potency ranged from 0 percent to 450 percent (Missouri Board of Pharmacy, 2009).

In general, the evidence suggests that certain compounded preparations may not be prepared in accordance with safe and appropriate compounding practices, and quality assurance of those compounds may not be sufficient. Patient safety issues associated with poor drug quality include inadequate

therapy, adverse events, antimicrobial resistance, and health care–associated infections (USP, 2017).

State-to-State Variability in State-Level Regulation and Oversight

Although most compounding is patient specific and under state jurisdiction, regulation and oversight of compounding practices are widely variable state by state (GAO, 2016). For example, recent data from the National Association of Boards of Pharmacy[13] suggest that greater than 30 percent of states do not require full compliance with compounding standards issued by USP for either nonsterile or sterile compounding (NABP, 2018). See Figure 4-3 to review state-by-state variation in required compliance with USP standards.

Furthermore, compounding performed in licensed physicians' offices is not regulated in the same way as 503A compounding pharmacies—in most states, there is no oversight of this practice by state boards of medicine or pharmacy (NABP, 2017; The Pew Charitable Trusts, 2016a). Moreover, the scope of physician compounding is poorly understood and not well quantified (NABP, 2017). Similarly, the extent to which hospitals carry out large-scale in-house compounding is not sufficiently quantified or regulated (Myers, 2013).

Oversight mechanisms may be unclear to state regulators (GAO, 2016), and the resources for appropriately rigorous state-level oversight are often unavailable (Glassgold, 2013). In 2014, The Pew Charitable Trusts convened an advisory committee to establish best practices to support state oversight, which recommended eight best practices (The Pew Charitable Trusts, 2016a). A few years later it published an update on states' progress that targeted these three best practices:

1. Applying USP quality standards for sterile compounding,
2. Harmonizing with federal law on compounding without prescriptions, and
3. Carrying out annual inspections of sterile compounding facilities (The Pew Charitable Trusts and NABP, 2018).

A 2018 Pew review found that most states conform with the first two best practices, but that state inspections of 503A sterile compounding have declined, which is likely caused by a lack of resources and capacity (The Pew Charitable Trusts and NABP, 2018).[14]

[13] The National Association of Boards of Pharmacy is a nonprofit professional membership association for state boards of pharmacy.

[14] In an attempt to promote consistency in pharmacy inspections across states, NAPB has recently developed a Multistate Pharmacy Inspection Blueprint Program (NABP, 2019).

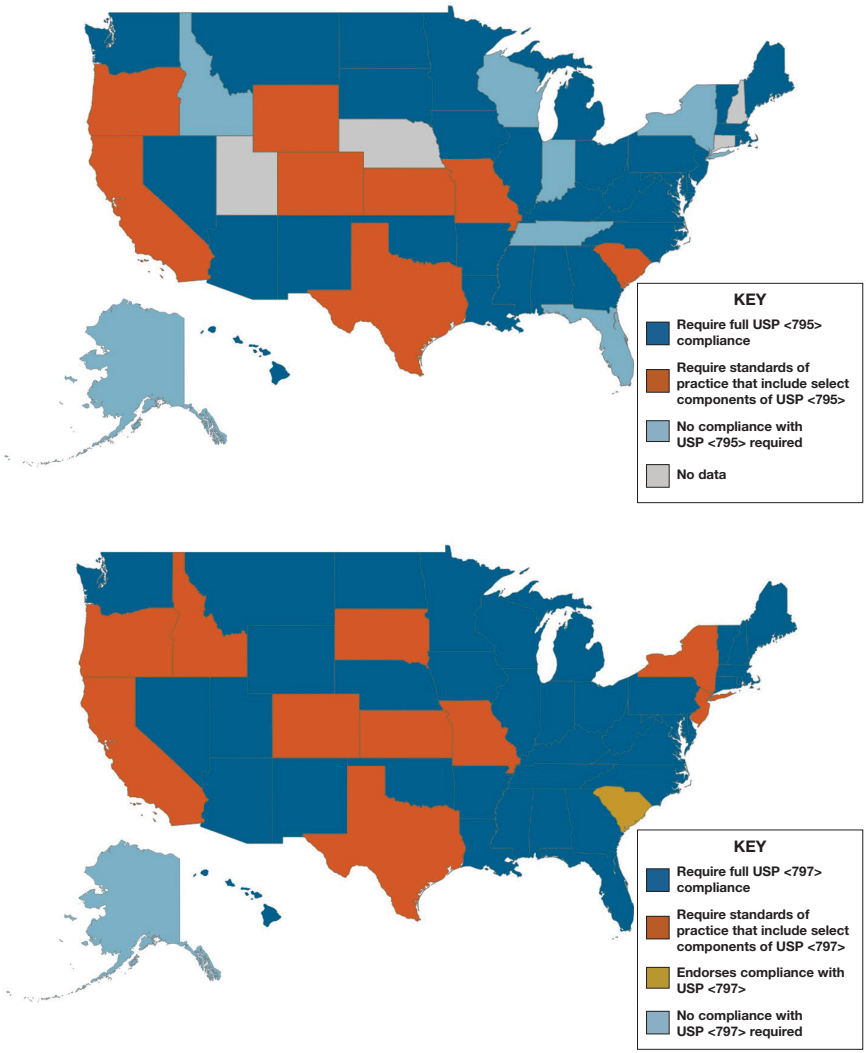

FIGURE 4-3 Variability in state requirements for 503A compounding pharmacy compliance with USP <795> (top) and <797> (bottom) standards.
NOTES: Maps are based on survey data reported by state boards of pharmacy and collected by the National Association of Boards of Pharmacy, as well as updates from state boards that had pending legislation at the time of data collection (Idaho Administrative Code, Section 27.01.05.100.05; Illinois Administrative Code, Section 1330.640; Code of Maryland Regulations, Section 10.34.19.02; Pennsylvania Code, Section 49.27.601).
SOURCE: The Pew Charitable Trusts and NABP, 2018.

Variability in compounding quality standards enforced from state to state is only one piece of the puzzle. States also differ in the quality standards they apply to out-of-state pharmacies that ship drugs into their state. Some states require that out-of-state pharmacies follow the regulations of the state into which the compounded preparations are shipped, while others enforce those of the state where the drug is compounded. A consequence is that compounded formulations made in states with less rigorous quality standards can find their way into the hands of a patient that lives in a state that enforces the compounding quality standards outlined in USP <795> and <797> (The Pew Charitable Trusts and NABP, 2018).

Insufficient Labeling Requirements

Federal requirements for 503A compounding pharmacies are relatively lax compared with 503B outsourcing facilities. For example, compounded preparations from 503A compounding pharmacies are not dispensed with standardized product inserts that outline instructions for use, known side effects, or safety warnings, even if such warnings are required for similar FDA-approved manufactured drug products. Although certain compounding pharmacies may dispense written information with compounded preparations, there is no regulation to require standardization of this practice between pharmacies or even within states. As such, patients are likely receiving variable information regarding what is in their preparation (i.e., active ingredients, inactive ingredients), how to use the preparation, or potential adverse reactions. See Chapter 7 for an additional discussion on the effect of insufficient labeling on patients' misuse of compounded topical pain creams.

Conclusion 4-1

Regulations and oversight currently in place are inadequate to address the potential risks associated with compounded preparations.

Insufficient Data Collection and Surveillance

The committee encountered difficulty in securing publicly available, accurate data on the use, safety, and effectiveness of compounded preparations in general, and of compounded topical pain creams in particular. It is likely that multiple barriers to data collection contribute to this dearth of evidence (Glassgold, 2013; McPherson et al., 2019), including

- Lack of a locus for centralized data collection;
- Lack of federal reporting requirements; and
- Variable insurance coverage for a broad range of compounded medications.

Additional complicating factors are the amount of variance in state-level oversight and in the procedures used between and within compounding pharmacies across the nation (The Pew Charitable Trusts and NABP, 2018). Even if records of formulations, prescribing practices, and patient use are kept, they are generally not standardized and therefore are not conducive to drawing specific research conclusions. Potential data on the use of compounded topical pain creams that could be collected in a standardized format include

- the number, weight, or volume of units prepared;
- commonly compounded formulations of topical pain creams;
- the number of prescriptions compounded;
- the cost or value of each unit; and
- the number of patients who receive prescriptions.

Although the concept of the length of treatment per single prescription may be nebulous across pharmacies, how it is defined in practice—for example, as a week or month(s) supply—is also a critical data point to collect.

In addition, as discussed in sections above, it is often difficult to assess potential adverse effects or events related to the use or misuse of compounded preparations because they are not subject to postmarketing surveillance as required of FDA-approved products. 503A compounding pharmacies are not required to collect or share adverse event data with FDA; without these data, it is difficult to accurately characterize the public health aspects of compounded medications. See Box 4-3 for an additional discussion on adverse event reporting. Owing to the substantial growth in demand for compounded preparations, regulatory gaps remain a high-priority concern.

Conclusion 4-2

Surveillance, data collection, and adverse event reporting for compounded topical pain creams are not mandatory in most cases and lack standardization. As a result, safety concerns may be underestimated.[15]

[15] This text has changed since the prepublication release of this report. As described in the chapter, 503B compounding facilities are required to submit serious adverse events to FDA.

BOX 4-3
Adverse Event Reporting

Adverse drug events are defined by the U.S. Food and Drug Administration (FDA) as "any unanticipated experience or side effect associated with the use of a drug or therapeutic biologic in humans, whether or not it is considered related to the product." Instances of adverse events may range from minor symptoms to permanent disability and death, but all adverse event reporting is important to advance knowledge about drug safety.

Clinical trials assessing drug efficacy are a required component of FDA's drug approval process and help to provide insight into the drug's safety as well. Adverse events identified during preapproval clinical trials are described in the approved product's labeling. The critical information listed in an approved drug's labeling is intended to inform prescribing clinicians' benefit–risk analysis when making prescribing decisions in concert with their patients. Based on current federal law, there is no specific requirements for 503A compounding pharmacies or 503B outsourcing facilities to include safety information or drug warnings on their labels or package inserts.

Manufactureres, individuals who compound, and clinicians can report adverse events to FDA via FDA's Adverse Events Reporting System, which can be publicly searched and is subject to analysis. As outlined in the Federal Food, Drug, and Cosmetic Act, 503B facilities are required to submit adverse events reports to FDA. In addition, those subject to mandatory reporting regulations must maintain records of all adverse events for 10 years. However, these requirements do not apply to 503A compounding pharmacies, which therefore are not required to submit reports to FDA for any known or suspected adverse events. Clinicians and consumers can also report adverse events or other problems to FDA via the Medwatch Program, and health insurers can submit administrative and claims data to FDA's Sentinel Initiative. In addition, in the wake of recommendations by the Institute of Medicine in 2000 to expand adverse event reporting systems, some states created their own systems to work in parallel with the FDA reporting requirements. However, a 2015 report revealed that only 28 states had systems for reporting adverse events.

Underreporting of adverse events related to the use of prescribed drugs is not uncommon. Many clinicians and patients may not know that an adverse outcome is caused by a drug, and when they do, they often do not think to report that outcome to FDA or the manufacturer. In light of this, and given the lack of stringent labeling requirements for compounded preparations, the underreporting of adverse events related to compounded drugs may be greater than for FDA-approved drugs. The failure to report these events hinders the ability of researchers to identify data patterns that could signal specific safety issues for certain compounded preparations.

BOX 4-3 Continued

Although those required to comply with adverse event reporting regulations may consider them to be burdensome, the data they provide are part of the system that can help inform patients about drug safety. In recent decades, advances in technology have opened new pathways to begin to search for such safety signals through other data sources such as claims databases, clinical trial databases, and social media. As data collection efforts move forward, it is critical for 503B outsourcing facilities, 503A compounding pharmacies, and other health professionals strive to commit to reporting all known and suspected adverse drug events.

SOURCES: FDA, 2013, 2015, 2020; IOM, 2000; Kesselheim, 2019; Pappa and Stergioulas, 2019; Ventola, 2018.

Need for a Balanced Approach to Regulatory Expansion

Owing in part to the lack of stringent regulatory oversight, poor-quality compounded drugs have been associated with multiple outbreaks of infections and deaths over the past decades, although the number of people who have been harmed by compounded drugs remains unknown (Glassgold, 2013). In the aftermath of the New England Compounding Center meningitis outbreak of 2012, 753 people became ill and 64 people died after receiving contaminated steroid injections (CDC, 2015). That disaster was highly publicized, but there have been other adverse events in recent years that resulted in patient injuries and deaths (Staes et al., 2013) (see Chapter 7 and Appendix F for a discussion of adverse events associated with the use of compounded topical pain creams). These events have prompted Congress to clarify FDA's regulatory authority over compounding with the passage of the Drug Quality and Security Act in 2013 (Woodcock and Dohm, 2017). Since 2013, FDA has issued multiple guidances pursuant to compounding as well as compounding priorities that describe FDA's plans to further reduce the risks of compounded preparations (FDA, 2019f; Gottlieb, 2018; Gottlieb and Abram, 2019) (see Box 4-4 for a brief summary of FDA's Compounding Priorities).

Although there are concerns that the practice of compounding has "effectively outgrown the laws designed to regulate it" (Shepherd, 2018), regulatory efforts can continue to strive to balance safety and effectiveness for the clinical populations that need access to compounded therapies. These two strands are not in opposition to each other; rather, efforts can

BOX 4-4
Overview of the U.S. Food and Drug Administration's (FDA's) Compounding Priorities

- To develop a more flexible, risk-based approach to current good manufacturing practice requirements for outsourcing facilities, including the establishment of a Center of Excellence on Compounding for Outsourcing Facilities and finalized guidance to help individuals who compound identify insanitary conditions;
- To restrict compounding of drugs that are essentially copies of FDA-approved drugs;
- To advance policies related to compounding from bulk drug substances by 503A compounding facilities and 503B outsourcing facilities, and to develop lists of bulk drug substances;
- To solidify FDA's partnership with state regulatory authorities in compounding oversight and regulating interstate distribution of compounded products, with FDA to focus on outsourcing facilities and on the 503A facilities that present the greatest risks;
- To finalize biological products guidance and clarify other policies on activities that individuals who compound undertake; and
- To monitor compliance and take enforcement action when needed.

SOURCES: Gottlieb, 2018; Gottlieb and Abram, 2019.

be made to accomplish them in tandem. FDA has stated that it seeks to strike such a balance between preserving access to lawfully marketed compounded drugs for patients who have a clinical need for them while protecting patients from the risks associated with compounded drugs that are not produced in accordance with the applicable requirements of federal law (FDA, 2017a). The safety of the individual ingredients, ingredient interactions, and absorption by the body need to be regulated by evidence-based guidelines. This would help to ensure that the components of compounded medications are safe and effective, while still maintaining pharmacists' abilities to customize the compounds.

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5

Science of Compounded Topical Pain Creams

As discussed in Chapter 2, there are potential advantages for the use of topical medications to treat pain indications, including provision of local, regional, and systemic therapeutic effects, as well as the potential for better safety profiles than oral medications.[1] Owing in part to their clinical potential, topical medications are one of the most commonly compounded preparations in the United States (HHS OIG, 2016; McPherson et al., 2016). The term *topical* refers to all preparations and products that are intended for application on the skin, mucous membranes, or external body cavities (e.g., mouth, nose, vagina).[2] The term *cream* is used to designate any semisolid preparation (e.g., cream, ointment, gel, lotion), typically with a relatively soft and spreadable consistency, that is intended for external application to the skin.

To explore how the science of compounded topical pain creams affects their safety and effectiveness, this chapter begins with an overview of the art and science of compounding, which highlights the overall complexity involved in formulating safe and effective compounded preparations. This section is followed by a description of the dermal absorption of drugs, including the basic structure and properties of the skin that affect absorption and potential variation in skin absorption among individuals. Subsequent sections describe factors affecting drug delivery and dose, including

[1] For a more detailed discussion on the use of topical creams in pain management, see Chapter 2.

[2] Transdermal patches use a more complex topical delivery system that is designed to deliver drugs intended for systemic absorption; however, such systems are outside of the study's scope.

BOX 5-1
Key Definitions

Cream: A semisolid oil-in-water emulsion for application to the skin. Creams are spreadable and easily rub into the skin without a greasy residue, and can be washed off with water.

Excipient: A pharmacologically inactive ingredient used in the formulation of a drug that lends various functional properties to the drug formulation, such as dosage form, drug release, etc. They are also sometimes referred to as diluents, bases, or carriers and can sometimes increase absorption of active ingredients.

Gel: Also referred to as jellies, a semisolid dosage form that appears transparent or translucent, and employs either a hydrophobic or hydrophilic base.

Lotion: While similar to a cream, this dosage form has a more liquid consistency. The lower viscosity may provide a cooling effect to the area where applied as solvents in the lotion evaporate.

Ointment: A greasy semisolid dosage form that exerts occlusive properties over the outer layer of the skin, thereby increasing drug transfer across the skin.

Patch: A patch (not preferred terminology, but it is commonly used) or transdermal delivery system is a preparation of a drug substance in a carrier device that is applied topically. The drug substance is designed to be released in a controlled manner over a specified period of time. The carrier device is removed after use.

Penetration enhancer: An excipient or vehicle that aids in absorption through the skin.

Vehicle: A component of excipients that is used as a carrier or diluent in which liquids, semisolids, or solids are dissolved or suspended.

properties of active ingredients, excipients, and penetration enhancers. Box 5-1 provides key definitions for this chapter.[3] See Appendix D for a full glossary of terms.

[3] This chapter draws on a paper commissioned by the Committee on the Assessment of the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain Creams titled "Topical Dosage Form Development and Evaluation," by S. Narasimha Murthy (see Appendix C).

THE ART AND SCIENCE OF COMPOUNDING

Formulation science is critical in the development, manufacturing, and testing of chemical—including pharmaceutical—products and preparations. Individuals experienced in this area of expertise are able to make difficult determinations regarding the proper combination of active and inactive ingredients, in consideration of the quality, stability, and effectiveness of compounded preparations, including topical pain creams (American Chemical Society, 2020). It is important to note that compounding pharmacists often follow formulations provided by compounding supply companies or published in journals or textbooks (Birnie, 2004; Dooms and Carvalho, 2018); however, they are still individually responsible for assessing the quality, stability, and effectiveness of every compounded preparation they dispense. *Of critical importance, a compounding pharmacist often does not have the same training or experience as a formulation scientist, nor access to the same data for evaluation and determination of quality, stability, and effectiveness.* See Box 5-2 for an overview of selected considerations for formulation scientists.

Finally, given that compounding is an extemporaneous process, compounded topical pain creams are formulated based on unique prescriptions filled by individual pharmacies. As a result, compounded topical pain creams are more susceptible to modifications in process variables than manufactured drug products that are made by a single drug maker with detailed, U.S. Food and Drug Administration (FDA)-approved manufacturing protocols (Gudeman et al., 2013). Furthermore, the process by which a preparation is compounded is subject to interpharmacist and interpharmacy variations, so a patient may receive a compounded topical pain cream that

BOX 5-2
Selected Considerations for Formulation Scientists

- Ingredient selection
  - Clinical needs to address health indications
  - Physicochemical and physiologic properties
  - Quality
  - Cost
- Drug delivery and dosage form selection
  - Optimized drug delivery
  - Cost
- Product formulation
  - Pharmaceutical calculations for function and stability
  - Preparation of dosage form

has distinct skin permeation and bioavailability profiles depending on who fills the prescription or where it is filled.

At the committee's public meeting in May 2019, invited speaker Dr. S. Narasimha Murthy discussed how the process by which a formulation is compounded is critical to the attributes and performance of any drug. He concluded that changing even one variable in the compounding process—such as amount of time homogenizing the mixture, or the sequence in which drugs are added—will change the formulation microstructure, even if identical quantities of the same ingredients are used (Murthy, 2019). These changes in microstructure lead to notable differences in the characteristics and performance of the formulation and, ultimately, to differences in the absorption and bioavailability of the drug (Chang et al., 2013).

DERMAL ABSORPTION

Dermal absorption is a critical consideration in the science of compounded topical pain creams. The clinical benefits and potential harms of topically applied medications relate to the rate and extent of a drug's absorption into the skin and beyond. Topically absorbed drugs first penetrate the outer barrier of dead skin cells (stratum corneum), then move through the viable layers of the epidermis to reach the vascularized dermis layer of the skin (see Figure 5-1). Skin cells (keratinocytes) are produced in the lower basal layer of the epidermis and then migrate upward, forming the epidermal skin. Specialized cells (melanocytes) in the epidermis produce melanin, which is taken up by keratinocytes to protect the skin from ultraviolet (UV) radiation; other cells have immunological functions (e.g., Langerhans cells, dendritic cells, memory T cells) (Richmond and Harris, 2014). Nerve endings extend from the dermis toward the epidermis like root fibers (Sewell et al., 2018).

In addition to having blood vessels, the dermis is primarily composed of extracellular matrix proteins that provide structure and elasticity, while also allowing free movement of immune cells (Richmond and Harris, 2014). The skin thus maintains high immunological surveillance and activity to ward off pathogenic and foreign substances. However, this process may also contribute to allergenic reactions to active ingredients or excipients.

Local, Regional, and Systemic Effects

Once a drug ingredient has crossed the outer layer of skin (stratum corneum), topical preparations such as pain creams can have local, regional, and/or systemic effects. Local effects of a drug ingredient occur primarily in the viable layers of skin, including the nerve endings in the epidermis and dermis (Ruela et al., 2016). Regional-area effects in muscles or joints occur

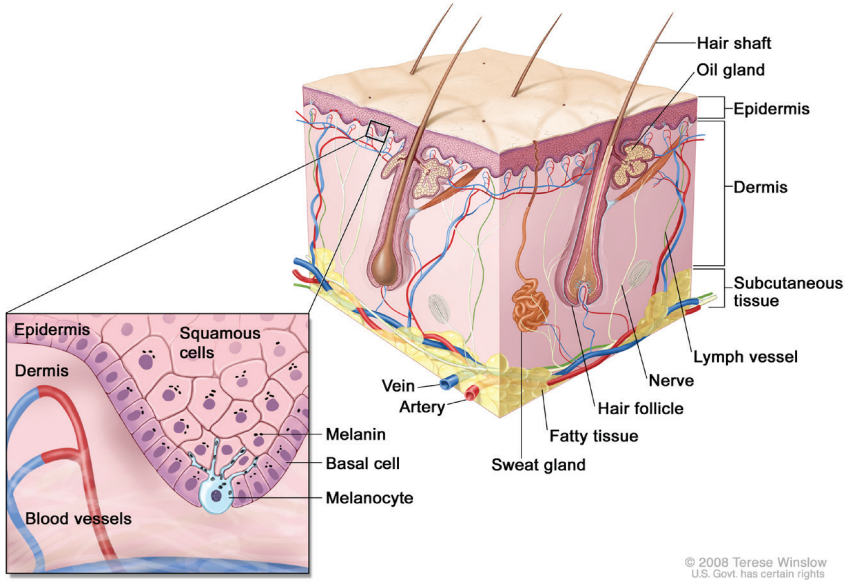

FIGURE 5-1 Anatomy of skin.
NOTES: The product or preparation must be formulated so the active drug is released from the cream or the patch into the skin. Additionally, the active drug must penetrate the outer protective barrier of the skin (stratum corneum) and reach the viable lower layers of the epidermis and dermis to effectively treat pain. Transdermal patches use a more complex topical delivery system to deliver drugs intended for systemic absorption; such systems are outside of the study's scope.
SOURCE: Adapted from Winslow, 2008.

through subsequent diffusion of the drug ingredient through the skin and fatty layer—which also has nerve endings (Richmond and Harris, 2014)—to nearby tissues. Systemic effects occur throughout the body caused by uptake of the drug ingredient by blood or lymphatic vessels in the dermis; the ingredient ultimately travels to the central circulation (Ruela et al., 2016).

In theory, pharmaceuticals intended to treat local or regional pain act on nerves in the skin or in underlying muscles or joints by blocking nerve signals, reducing inflammation, relaxing muscle spasms, or potentiating the effects of other substances (Cline and Turrentine, 2016; Leppert et al., 2018). Distal responses to topical applications can also occur that, whether intended or not, can affect a medication's safety and effectiveness profile. Systemic action is also an important consideration in reviewing potential drug–drug interactions. As an example, consider a patient who is prescribed the maximum oral amount of a nonsteroidal anti-inflammatory drug (NSAID) and then uses a topical gel formulated with another NSAID.

If the systemic contribution of the topically applied NSAID is sufficient, it will contribute to an excess of NSAIDs in the blood stream and create the potential for severe adverse reactions.

Today, most commercially manufactured FDA-approved creams are intended for local action, while patches are intended for systemic activity. However, there are exceptions in both cases. For example, nitroglycerin cream has long been used for its systemic effect (Fougera Pharmaceuticals, 2019), while lidocaine patches are generally used for regional analgesic effect in muscle tissue (Leppert et al., 2018). Of note, many compounded pain creams are marketed as transdermal (Swidan and Mohamed, 2016) and are intended to deliver the drug to tissues below the skin or into systemic circulation. For systemic activity, the transdermal patches or cream formulations deliver the drug into the systemic circulation through uptake in blood vessels in the dermis (Benson, 2005). (See Figure 5-2 for an illustrative example of the systemic absorption of a topical active ingredient.)

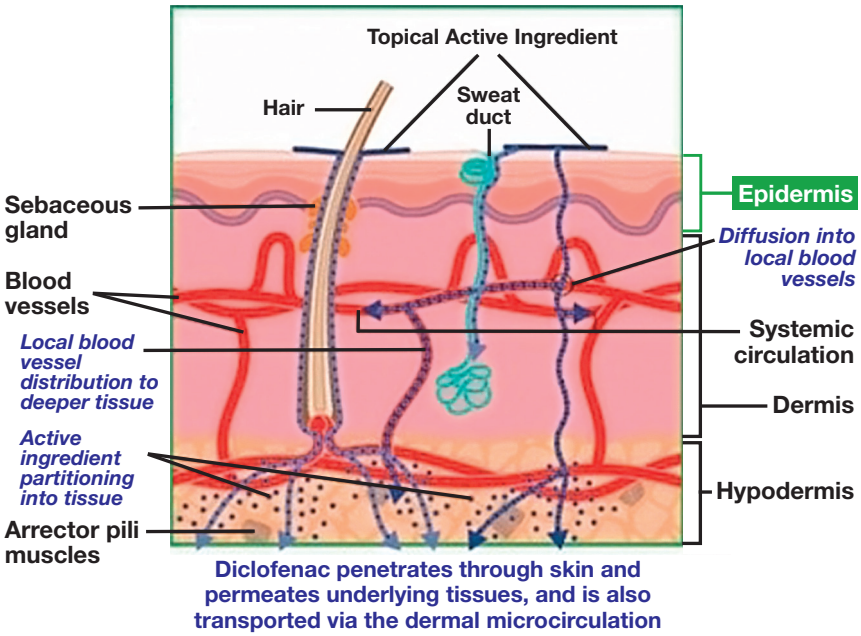

FIGURE 5-2 Routes of systemic absorption after topical application of a drug.
NOTES: Drugs that are applied topically can reach systemic circulation if the drug is able to penetrate to the blood vessels in the dermis. The figure was adapted from an illustration for topical diclofenac; for other active pharmaceutical ingredients, additionally absorption pathways may exist.
SOURCE: Adapted from Hagen and Baker, 2017.

FACTORS AFFECTING DERMAL ABSORPTION

The physical and chemical properties of skin are modified by factors relating to age, gender, and ethnicity, and these factors affect the dermal absorption of topical drugs. Physiochemical properties of active pharmaceutical ingredients (APIs) and features of the drug's delivery mechanisms also contribute to the success of absorption through the skin (for more details, see Law et al., 2020). These considerations are discussed in greater detail in the sections below.

The Properties of Skin

When topical formulations are applied, the drug (e.g., the API) is released from the formulation and crosses several skin barriers—each with different physical and chemical properties that affect drug diffusion—to reach deeper sites for its pharmacological activity (Chang et al., 2013). The stratum corneum is the main barrier to external agents (Law et al., 2020). This layer is made up of tightly packed dead cells (corneocytes) in a lipid (fat) matrix, resulting in a relatively impermeable, mostly lipophilic layer (van Logtestijn et al., 2015) (see Figure 5-3). Moderately lipophilic (i.e., fat- or oil-soluble) drugs are able to pass the stratum corneum more readily than those that are hydrophilic (i.e., water soluble) or highly lipophilic. Skin also typically contains 10–20 percent water by weight, much of which is associated with hydrated corneocytes (Forslind, 1994; Singh and Morris, 2011). The lipid layer between corneocytes is composed of approximately equal molar amounts of free fatty acids, ceramide (waxy lipids), and cholesterol organized in a bilayer lamellar pattern, with more polar groups on the outer layers and long-chain fatty acids (waxlike) and cholesterol in the interior (Boncheva, 2014) (see Figure 5-3).

Pathways of Substances Through the Outer Barrier of Skin

Pathways of substances through the stratum corneum include diffusion through the lipid layer around skin cells (paracellular or intercellular), passage through the skin cells (transcellular), and entry through sweat or sebaceous glands or hair follicles (transappendageal) (Dabrowska et al., 2018) (see Figure 5-4). Substances that are soluble in oil or fats are able to penetrate the outer layer of skin though the lipid matrix around skin cells. Hydrating the skin, however, can increase the moisture content by 20-fold and may enhance the passage of substances that are more water soluble (Singh and Morris, 2011). Transcellular passage through skin cells is a more selective route that requires lipophilic and hydrophilic properties to cross the lipophilic cell membrane and the hydrophilic cellular contents.

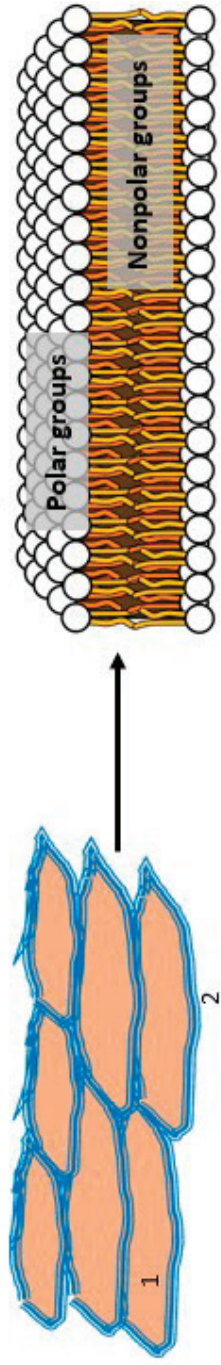

FIGURE 5-3 Structure of stratum corneum.
NOTE: (Left) Top view of the stratum corneum showing tightly packed skin cells (corneocytes in light brown) with intercellular space filled with lipids (blue). (Right) The intercellular lipids arranged in a bilayer lamellar pattern.
SOURCE: Phospholipids aqueous solution structures by Mariana Ruiz Villarreal, LadyofHats is licensed under Creative Commons CC0.

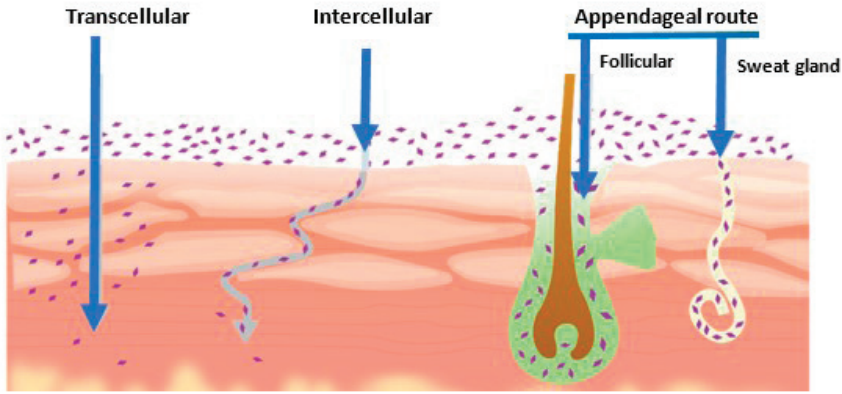

FIGURE 5-4 Transport of drugs through the layers of the skin.
NOTE: Intracellular or transcellular transport through skin cells is seen on the left. Intercellular or paracellular transport around the cells is presented in the middle. Appendageal transport through hair follicles and pores is seen on the right.
SOURCE: Shaker et al., 2019.

Compared to the stratum corneum, the underlying viable epidermis and the dermis below that layer are more hydrophilic (i.e., more soluble in water) (Perrie et al., 2012), thereby favoring diffusion of hydrophilic substances. However, the lower fatty layer below the dermis favors diffusion of more lipophilic substances to adjacent tissues (see Figure 5-4).

The transappendageal pathway through skin pores and hair follicles is a means of entry for large or hydrophilic substances (Ruela et al., 2016). This could be considered a less important pathway, because pores represent only 0.1 percent of the surface area of the body (Dabrowska et al., 2018). In addition, although these pores extend below the skin layers into the dermis, substances must then penetrate the cellular barrier lining the pores. It has been reported that hair on the faces of men increases the permeability of the facial skin of men compared to women (Dabrowska et al., 2018).

Regional Differences in Skin Absorption on the Body

Regional differences in skin absorption on the body occur as a function of thickness of the outer stratum corneum layer, differences in skin lipid content (including those attributable to variation in sebaceous glands), hydration state, and amount of physical contact (Guzzo et al., 1996). Skin penetration is thus greater on the face, in the genital area, and in skin areas that contact or rub against each other; less penetration occurs on the trunk,

forearms, palms, and soles (Guzzo et al., 1996; Law et al., 2020; Prausnitz et al., 2012).[4]

Individual Differences in Metabolic Enzyme Activity

Individual differences in metabolic enzyme activity also play a role. Unlike the oral administration of drugs, the dermal route of exposure avoids the gastrointestinal tract and the first-pass metabolism process in the liver. Still, the skin is estimated to have about 10 percent of the capacity of the liver to metabolize drugs to either inactive or active forms, depending on the drug and enzymes (Singh and Morris, 2011). Therefore, individual differences in metabolic enzyme activity may also have an effect on topical dosing.[5]

Integrity of the Skin

Integrity of the skin is another important factor. Dermal penetration is increased in skin that is denuded or compromised (e.g., skin that is burned, abraded, or dry). Therefore, dermal penetration is affected by diseases that disrupt the skin—such as psoriasis or atopic dermatitis—or by health conditions such as hypothyroidism (Dabrowska et al., 2018).[6] In general, enhancement of absorption through damaged or diseased skin is greater for substances that are more water soluble than for substances that are fat soluble (Law et al., 2020). Increased absorption through compromised skin could increase the effectiveness of topical treatments, but it may also enhance potential *systemic* absorption and increased the risk of toxicity (Law et al., 2020).

Effect of Age

Age can have effects on the skin that may alter dermal absorption.[7] Preterm infants have a thinner epidermis and stratum corneum than adults,

[4] For additional resources on the regional differences in skin absorption, see Bronaugh and Maibach, 1991; Feldmann and Maibach, 1967; and Rougier et al., 1986.

[5] For drugs that reach viable layers and systemic circulation, elimination from the body occurs through urinary or biliary excretion routes, either metabolized or unmetabolized (Feldmann and Maibach, 1969). For more information on the metabolism of drugs in skin, see Bronaugh et al., 2005.

[6] Note that for the purposes of this report, the committee maintained an explicit focus on the use of topical creams on intact skin. There remains a substantial literature base that reviews the safety, effectiveness, and use of topical pain creams on membrane and mucosal surfaces. However, this evidence was not explicitly reviewed or discussed in this report.

[7] For an in-depth review of the effects of age on skin absorption, refer to Roskos et al., 1989.

thus higher permeability is expected (Oranges et al., 2015). Before 30 weeks of gestation, infants have 100- to 1,000-fold greater skin permeability than term infants (Barker et al., 1987), while full-term infants have skin permeability that is 3-fold to 4-fold greater than adults (Fernandez et al., 2011). Higher permeability in neonates is thought to be related to incomplete maturation of the skin barrier (Singh and Morris, 2011). Full-term neonates have similar epidermal thickness and lipid composition as adults. However, in the first few months of life, surface pH decreases while sloughing of the outer layer of skin cells (desquamation) increases. In the first week after birth, sebum (lipid) secretion increases, and in the first 14–17 weeks after birth, capillary loops and cutaneous blood flow develop in the dermis (Ramos-e-Silva et al., 2012).

In adults, skin changes that occur with aging result in increasing dryness of the stratum corneum (Ramos-e-Silva et al., 2012) as well as thinning of the epidermis and dermis (Singh and Morris, 2011). Evidence suggests that drying of the stratum corneum with age is associated with less active sebaceous glands and lower surface lipid content—along with atrophy of the cutaneous capillaries—thereby reducing drug delivery through viable layers (Perrie et al., 2012; Ramos-e-Silva et al., 2012). Skin penetration by more hydrophilic drugs has been reported to decrease with age, whereas lipophilic drugs were not similarly affected (Perrie et al., 2012; Singh and Morris, 2011).

Compared to men, infants, children, and many women have larger surface areas relative to their body size and relatively larger volumes of drug distribution. As a result, they absorb a larger internal dose from an application to a proportionally similar skin area. For example, a study using stable isotopes of nanosized zinc oxide particles (19 nm) in sunscreen measured higher zinc isotope blood levels in women than in men, even though a smaller amount of sunscreen per area (g/cm^2) was applied to the backs of women than to the backs of men (Gulson et al., 2010). The study was unable to distinguish the form of zinc absorbed, but it may have been soluble ionic zinc.

Difference Among Genders

Compared to women, men have longer keratinocytes, larger pores, more active sebaceous and sweat glands, and lower skin pH (Singh and Morris, 2011). However, the few studies that have examined gender differences in dermal absorption have found little difference in dermal absorption between men and women (Singh and Morris, 2011).

Racial and Ethnic Differences

Ethnic differences in skin properties that may potentially affect dermal absorption have been described in the literature, with some conflicting reports. Several studies report that compared to Caucasians, African Americans or Afro-Caribbeans have higher transepidermal water loss (see Muizzuddin et al., 2010), a thicker and more cohesive stratum corneum with more cell layers, and lower dermal penetration (Dabrowska et al., 2018; Muizzuddin et al., 2010; Singh and Morris, 2011). Higher levels of natural moisturizing factors in the stratum corneum have been reported in Chinese compared to Caucasians or African Americans; however, other studies report no significant differences in skin hydration among ethnic groups (Dabrowska et al., 2018).

A small experimental study compared dermal penetration of radiolabeled benzoic acid, caffeine, or acetyl-salicylic acid in Asian, African American, and Caucasian volunteers (6–9 per group). The vehicles (i.e., carrier substances) used for each of the three compounds to form the topical cream or gel were optimized for the compound's properties; absorption was measured analyzing urine and skin tape strips. The study found no statistically significant differences among the three racial groups (Lotte et al., 1993). Another study measured percutaneous absorption using methyl nicotinate in four lipophilic vehicles in four ethnic groups (12 subjects per group; subjects aged 20–60 years). The study reported the order of increasing rate of absorption among the groups as Blacks < Asians < Caucasians < Hispanics (Leopold and Maibach, 1996). Considerable individual variation was observed within these groups, but the only statistically significant difference was lower skin absorption in Blacks compared to Hispanics (Leopold and Maibach, 1996). Absorption rates were more similar among racial groups than among vehicles, with vehicles showing consistent rank order of absorption rate for all four racial groups.

A larger study involving 73 African Americans, 119 Caucasians, and 149 East Asians reported the following racial differences in stratum corneum properties, in order of lowest to highest (Muizzuddin et al., 2010):

- Transepidermal water loss: African Americans < East Asians < Caucasians
- Skin barrier strength: East Asians < Caucasians < African Americans
- Stratum corneum cohesion (protein content): East Asians and Caucasians < African Americans
- Ceramides (lipid lamellae in the stratum corneum): African Americans < East Asians and Caucasians
- Maturation index: East Asians < Caucasians < African Americans

- Proteolytic enzymes[8]: African Americans < East Asians and Caucasians

Overall, the understanding of racial differences in skin properties and penetration of drugs is limited by the small number of studies, small numbers of study participants in most of those studies, and high levels of individual variation (Dabrowska et al., 2018). This work is further limited by the likelihood of great individual-level variability, which may be affected by diet and nutrition, health and diseases, genetic and environmental factors, socioeconomic status, and age. Furthermore, comparisons among skin types with different amounts of pigmentation may be confounded by greater UV damage in those with less pigmentation, particularly in older adults (Singh and Morris, 2011).

Physiochemical Properties of the Active Pharmaceutical Ingredient

Complex Considerations

The physiochemical properties of a drug's active ingredients play a substantial role in the drug's absorption. For example, a drug's ability to be absorbed into the skin is affected by whether its substances are lipophilic (soluble in oil) or hydrophilic (soluble in water), as well as whether its substances are acidic or basic (i.e., pH). The surface of the skin is acidic in nature, while the inner layers have a more neutral physiological pH (Ohman and Vahlquist, 1994). The pH gradient across the different layers prevents microorganisms from penetrating into deeper layers of skin (Schmid-Wendtner and Korting, 2006), but it also poses challenges for drug absorption. In addition, the skin tissue contains enzymes to break down substances, which constitute a metabolic barrier (Pyo and Maibach, 2019). Therefore, drug properties that increase dermal absorption include

- low molecular weight, generally less than 400–500 Daltons;
- moderately lipophilic properties;
- a melting point below 200°C;
- both lipophilic and hydrophilic properties; and
- a high partition coefficient, so the drug will partition from the vehicle to the skin.

In addition to the above properties, a drug's acid dissociation constant or acid ionization constant (pKa) is another important factor determining

[8] Enzymes that help in the breakdown of skin protein as part of the turnover (sloughing) of the outer layer of skin.

dermal absorption. At an ambient pH that is equal to a drug's pKa, half of the drug will be in the ionized form and half will be in the un-ionized form. At pH levels greater than the pKa, more of the drug will be in the ionized form. Therefore, a drug with a lower pKa will be in a more un-ionized state at skin pH (4–5) or neutral to basic pH. As noted in Appendix C, un-ionized forms are more extensively absorbed through nonpolar transdermal pathways through the skin than ionized forms are absorbed by polar pathways through the skin. In addition, oppositely charged drugs may form neutral ion pairs that, in turn, enhances their skin absorption (Hadgraft and Valenta, 2000). This complexity is critical to consider in selecting the appropriate APIs to compound together within a given formulation.

As an example of the considerations to be made, Table 5-1 provides a summary of select physiochemical properties of APIs commonly used in compounded topical pain creams. As outlined in the table, each ingredient, regardless of drug class, has unique considerations for the formulation process. Additional layers of complexity need to be considered in cases where multiple APIs (each with different pKAs) are combined with multiple ingredients within an excipient into a single formulation. See Box 5-3 for an illustrative example of considerations related to the absorption of compounded topical formulations with multiple APIs. For an additional discussion of these complex considerations, see Naik et al. (2000), Ng (2018), Prausnitz et al. (2012), Sewell et al. (2018), and Appendix C in this report.

Evidence to Evaluate Topical Absorption

There is limited clinical evidence available to evaluate the extent of topical absorption or potential transdermal penetration of ingredients commonly used in compounded topical pain creams. In vitro skin permeation testing using Franz diffusion cells is one method used by researchers to examine a drug's potential permeability through animal or human skin (see Appendix C for an additional description of the assay). Research using these types of in vitro studies to examine the permeability of topical analgesics indicate that out of the reviewed drugs, ketamine has the highest flux, or rate of permeation over a specified area of human cadaver skin. In addition, there is a relatively high percent of drug absorbed for ketamine, diclofenac, and pentoxifylline with lower absorption for baclofen, bupivacaine, orphenadrine, clonidine, and gabapentin (Bassani and Banov, 2016; Wang and Black, 2013) (see Tables 5-2 and 5-3). However, these studies did not report the mass balance of applied and recovered drugs, an important quality-control measure for testing of percutaneous absorption (Kluxen et al., 2019). Therefore, it is not possible to thoroughly evaluate the methodological procedures used in the studies, nor is it possible to make conclusive statements about the drugs' absorption.

TABLE 5-1
Summary of the Physiochemical Properties Affecting Skin Absorption of Select Active Ingredients Commonly Used in Compounded Topical Pain Creams

Drug	Molecular Weight (g/mol)	Log P (oct-water)	Melting Point (°C)	pKa
Amitriptyline	277.40	4.92	197	9.4
Baclofen*	213.66	1.3	207	9.62 and 3.67
Bupivacaine	288.43	2.59	107	8.2
Cannabidiol	314.46	—	66	5.79
Carbamazepine	236.27	2.45	191	7
Clonidine	230.09	1.59	130	8.12
Cyclobenzaprine*	275.39	5.2	218	8.47
Dexamethasone	392.46	1.93	262	12.42
Doxepin	273.38	−0.548	184	8.96
Gabapentin	171.24	−1.1	166	3.68 and 10.70
Ketamine	237.73	3.12	92.5	7.5
Lidocaine hydrochloride	270.80	< 0	77	7.9
Meloxicam	351.40	3.43	254	4.08
Memantine	179.31	3.28	258	10.27
Naproxen	230.26	2.79	153	4.15
Nifedipine	346.30	2.50	173	4.3
Orphenadrine	269.39	3.77	156	8.91
Pentoxifylline	278.31	0.38	105	—
Topiramate	339.36	−0.5	125	8.6
Tramadol	263.38	1.34	181	9.4

NOTES: To add an additional layer of complexity of physiochemical properties that affect dermal absorption, certain drugs have chemical functional groups on the drug molecule with different pKa values, such as baclofen (pKa of 9.62 for the amino group and 3.67 for the carboxyl group) and gabapentin (pKa of 10.70 for the primary amine and 3.68 for carboxylic acid group). oct-water = octanol-water partition coefficient; pKa = acid ionization constant.

* Zwitterionic in nature.

SOURCES: DrugBank, 2020; Expert Committee on Drug Dependence, 2017; Plumley et al., 2009; PubChem, 2020.

Given the limitations of in vitro data for many topical drugs, mathematical models are often used for predicting skin permeability. Skin permeability resulting in an absorbed dose can be modeled as a flux rate—a function of partition and diffusion coefficients over a length of the path to the target site, and the applied concentration—resulting in an amount of

BOX 5-3
Considerations for the Absorption of Compounded Formulations with Multiple APIs

The unknown effect of combining multiple active and inactive ingredients in one formulation becomes readily apparent when considering (1) the complexity of the physiochemical properties of each active ingredient, and (2) the functionality of the various excipients used in compounded cream formulations. This creates potential not only for physical incompatibilities and chemical reactions between the components within the formulation, but also the potential for these interactions to be magnified as the number of components increases. A formulation that has been optimized to deliver one active ingredient may not release another active ingredient or may cause it to be absorbed at a much higher rate. In one such example, which considers only pKa—just one component of the physiochemical properties that affect drug absorption—it would be challenging to adjust the pH to favor the permeation of a topical pain product containing amitriptyline (pKa 9.4) and ketamine (pKa 7.5). At a formulation pH of 9, most of the ketamine (96.93 percent) would exist in un-ionized form. But at the same pH, only 39.81 percent of amitriptyline would exist in un-ionized form. In this case, ketamine would likely be much more readily absorbed by the skin than would amitriptyline. Any further increase in the formulation pH may not be acceptable, because extreme basic pH could potentially cause skin irritation. If meloxicam or nifedipine were formulated in combination with the above drugs, they would exist in an almost completely ionized state at pH 9, which could hamper their penetration significantly. In summary, optimizing a formulation to properly deliver multiple active ingredients with differing physiochemical properties in a reproducible manner is a difficult balance of both art and science. The quality, safety, and efficacy assurances required of compounded preparations are likely to be inadequate without sufficient compatibility and performance testing.

SOURCES: Murthy, 2019; see Appendix C in this report.

drug reaching this site per time (Keurentjes and Maibach, 2019; Prausnitz et al., 2012) (see also Appendix C for additional discussion). Models of flux rate based on a compound's octanol-water partition coefficient and size (molecular weight) have been reported to more accurately predict in vivo skin permeability than more complex models involving more parameters (Lian et al., 2008).

Nevertheless, a study recently evaluated three such simple models used to calculate fluxes of 17 drugs used in FDA-approved transdermal delivery systems. For more than two-thirds of these drugs, researchers found

TABLE 5-2
The Amount of Drug Absorbed Across the Human Cadaver Skin from Topical Pain Creams (n = 6; mean ± SD)

Active Pharmaceutical Ingredient	Percent of Applied Drug Dose Absorbed Across the Cadaver Skin	
	Reference Cream	Versatile Cream
Bupivacaine	0.277 ± 0.108	0.441 ± 0.175
Diclofenac	0.846 ± 0.223	1.96 ± 0.896
Gabapentin	0.381 ± 0.429	0.30 ± 0.237
Ketamine	1.03 ± 0.317	1.45 ± 0.591
Orphenadrine	0.130 ± 0.0495	0.191 ± 0.0613
Pentoxifylline	1.51 ± 0.451	3.63 ± 1.78

NOTE: Versatile cream is a base commonly used in formulations for compounded topical creams.

SOURCE: Wang and Black, 2013.

TABLE 5-3
The Amount of Drug Absorbed Across the Human Cadaver Skin from Topical Pain Creams with Lipoderm and Lipoderm ActiveMax (n = 3; mean ± SD)

Active Pharmaceutical Ingredient	Percent of Applied Drug Dose Absorbed Across the Cadaver Skin	
	Lipoderm	Lipoderm ActiveMax
Baclofen	0.27 ± 0.27	0.10 ± 0.08
Clonidine	3.955 ± 2.60	4.38 ± 0.95
Gabapentin	0.41 ± 0.34	0.19 ± 0.08
Ketamine	35.48 ± 9.03	45.52 ± 2.42

NOTE: Lipoderm and Lipoderm ActiveMax are two bases commonly used in formulations for compounded topical creams.

SOURCE: Bassani and Banov, 2016.

overestimation or underestimation by 10 to 100 times compared to experimental in vivo data. Although the model predictions were correlated with the in vivo results, the models underpredicted the rate flux for more than half of the drugs. There were several major limitations of the models: the models had uncertainties in their parameter databases, and the in vivo data were based on studies in the literature that used different study designs, sample sizes, and analytical methods (Keurentjes and Maibach, 2019). Overall, many factors limit the ability to predict skin absorption for many topically applied drugs.

CRITICAL FACTORS AFFECTING DRUG DELIVERY: ACTIVE INGREDIENTS AND EXCIPIENTS

Considerations for Active Ingredients

Not all drugs are absorbed in the skin to the same degree or at the same rate. In fact, some drugs may not be absorbed by the skin at all. Compounding pharmacists and other individuals who compound must consider not only physiochemical properties of active ingredients, but also how dose affects drug absorption, mechanisms of action of APIs, and selection of excipients. The sections below provide a brief overview of select critical factors that affect drug delivery through the skin.

Applied and Absorbed Dose of the Active Pharmaceutical Ingredient

Dose can refer the amount of drug administered to the individual (applied dose) or taken into the body (absorbed dose). For topical pain cream ingredients, the relevant dose for efficacy is the mass of drug delivered to the site of action. Key determinants of dose for a topical formulation involve (1) the concentration of the drug in the cream formulation, (2) the amount of cream applied, (3) the surface area of application on the body relative to body weight, and (4) the frequency of application (Law et al., 2020). Based on simple diffusion, the magnitude of the applied dose represents the driving force for dermal absorption (Prausnitz et al., 2012). Although the amount of drug applied to the skin is easily determined, the amount of absorption and the effective internal dose may vary depending on factors related to the drug or formulation, the application (including the vehicle), and properties of the skin and underlying tissues (Guzzo et al., 1996).

Furthermore, absorption through the skin is not necessarily constant for a given applied dose. For example, a large amount of cream applied to a smaller area versus a smaller amount of cream applied to a larger area may have the same applied dose. However, an excessive amount of cream over a small area may not allow all of the drug in the cream to contact the skin for absorption before it is rubbed off, adsorbed to clothing, or washed off.[9]

Similarly, the amount of drug that is solubilized in the vehicle is the available concentration for absorption, meaning that increasing the concentration of a drug in a cream will only increase the dose being delivered if the drug is solubilized (Prausnitz et al., 2012). Depending on drug properties and the vehicle, drugs may also penetrate the stratum corneum and either reside as a reservoir in skin layers or more readily reach systemic circulation

[9] Of note, drug removal from the stratum corneum may also occur either by exfoliation (Law et al., 2020) or by washing, which is dependent on the nature of the drug and the solvent (Chan et al., 2013).

(Guzzo et al., 1996; Prausnitz et al., 2012). Another important consideration affecting the dose of a drug that penetrates the skin is frequency of application. Though data are sparse, multiple doses of topically applied drug have been shown to deliver more drug through the skin than single doses (Wester and Maibach, 2005). For example, 1 gram of cream applied twice daily may deliver more drug than 2 grams of cream applied once daily.

Insufficient dermal penetration for some drugs may reduce the internal dose to below the therapeutic range (Yamamoto et al., 2017). On the other hand, a slower rate of entry via skin absorption may achieve a more constant systemic dose rather than the peaks—which could result in toxicity for more sensitive individuals—and valleys that might occur by intravenous injection or oral ingestion (Brown et al., 2006; Prausnitz et al., 2012). For some substances that have low absorption by the oral route (e.g., CBD oil), dermal application with or without skin penetration enhancers has been reported to be an effective means of systemic drug delivery (Lodzki et al., 2003; Paudel et al., 2010a). This is particularly the case for substances that are greatly metabolized by the first-pass effect of the liver from the oral route of administration (Paudel et al., 2010b).

Mechanisms of Action of Active Ingredients

The local, regional, or systemic location where a drug is intended to exert its pharmacological effect is informed largely by the mechanism of action of that drug (Schenone et al., 2013). For example, a drug that blocks sodium channels would need to reach nerve cells, which contain sodium channels that mediate stimuli such as pain (Bhattacharya et al., 2009). Details on the mechanisms of actions for the drugs reviewed within this report can be found in Chapter 6.

Excipients ("Inactive" Ingredients)

A wide range of bases, vehicles, and solvents are used to formulate topical pain creams. These would generally be classified as excipients, which constitute a wide range of materials that influence the quality attributes of topical products, physicochemical characteristics of the drug, and sensorial characteristics (i.e., taste, smell, texture) of the formulation. Excipients are frequently called "inactive" ingredients. However, it is important to note that excipients will ultimately affect the final performance of the compounded preparation by affecting properties such as solubility, stability, release of the active ingredient, and skin penetration. In some cases, patients are allergic to certain excipients; this requires preparations to be specially compounded without these allergens. Specific bases, vehicles, and solvents may be used in compounding to avoid certain allergenic excipients used in

commercial products (e.g., peanut oil) or to support patient compliance by adding flavoring to a medication for a young child (McBane et al., 2019). Excipients are critical components of a topical pain cream formulation and play a number of roles, including

- enhancing the solubility of the active drug,
- modifying the viscosity of the cream,
- emulsifying the formulation,
- enhancing drug penetration,
- stabilizing the formulation,
- extending the shelf life of a cream, and
- modifying the sensorial properties of the cream.

The United States Pharmacopeia (USP) provides a list of excipients as well as instructions to verify their identity and purity. USP <795> advises that all excipients in compounded preparations should meet compendial standards or otherwise be evaluated for safety and purity (USP, 2018). Table 5-4 contains a partial list of excipients found within published monographs from the USP-National Formulary, which outline quality standards for each listing. A second list of more than 1,700 unique excipients are published online in FDA's inactive ingredient database, which also describes the maximum potencies of excipients in FDA-approved products (FDA, 2019). These lists were developed over years of study to identify inactive ingredients that have been shown to be generally safe for inclusion in compounded preparations and commercial drug products. As such, they serve

TABLE 5-4
Compendial Excipients from USP-National Formulary 19

Functional Categories of Excipients (number)	Listing of Excipients
Emollient (35)	Alkyl (c12-15) benzoate; almond oil; aluminum monostearate; canola oil; castor oil; cetostearyl alcohol; cholesterol; coconut oil; cyclomethicone dimethicone; ethylene glycol stearates; glycerin; glyceryl monooleate; glyceryl monostearate; hydrogenated lanolin; isopropyl isostearate; isopropyl myristate; isopropyl palmitate; isostearyl isostearate; lecithin; mineral oil; mineral oil, light; myristyl alcohol; octyldodecanol; oleyl alcohol; oleyl oleate; petrolatum; polydecene, hydrogenated; propylene glycol dilaurate; propylene glycol monolaurate; safflower oil; soybean oil, hydrogenated; sunflower oil; wax, cetyl esters; xylitol; zinc acetate

TABLE 5-4
Continued

Functional Categories of Excipients (number)	Listing of Excipients
Ointment base (24)	Caprylocaproyl polyoxylglycerides; coconut oil; diethylene glycol monoethyl ether; lanolin; lanolin, hydrogenated; lanolin alcohols; lauroyl polyoxylglycerides; linoleoyl polyoxylglycerides; ointment, hydrophilic; ointment, white; ointment, yellow; oleoyl polyoxylglycerides; paraffin; petrolatum; petrolatum, hydrophilic; petrolatum, white; polydecene, hydrogenated; polyethylene glycol; polyethylene glycol 3350; polyethylene glycol monomethyl ether; polyglyceryl 3 diisostearate; rose water ointment; squalane; stearoyl polyoxylglycerides; vegetable oil, hydrogenated, type II; vitamin E polyethylene glycol succinate
Stiffening agent (18)	Alpha-lactalbumin; castor oil, hydrogenated; cetostearyl alcohol; cetyl alcohol; cetyl palmitate; dextrin; hard fat; paraffin; paraffin, synthetic; rapeseed oil, fully hydrogenated; rapeseed oil, superglycerinated fully hydrogenated; sodium stearate; stearyl alcohol; wax, cetyl esters; wax, emulsifying; wax, microcrystalline; wax, white; wax, yellow
Suppository base (6)	Agar; cocoa butter; hard fat; palm kernel oil; polyethylene glycol; polyethylene glycol 3350
Suspending and/or viscosity-increasing agent (89)	Acacia; agar; alamic acid; alginic acid; alpha-lactalbumin; aluminum monostearate; attapulgite, activated; attapulgite, colloidal activated; bentonite; bentonite, purified; bentonite magma; carbomer 910; carbomer 934; carbomer 934p; carbomer 940; carbomer 941; carbomer 1342; carbomer copolymer; carbomer homopolymer; carbomer interpolymer; carboxymethylcellulose calcium; carboxymethylcellulose sodium; carboxymethylcellulose sodium 12; carboxymethylcellulose sodium, enzymatically hydrolyzed; carmellose; carrageenan; cellulose, microcrystalline; cellulose, microcrystalline, and carboxymethylcellulose sodium; cellulose, powdered; cetostearyl alcohol; chitosan; corn starch, pregelatinized hydroxypropyl corn; corn syrup; corn syrup solids; cyclomethicone; dextrin; egg phospholipids; ethylcellulose; gelatin; gellan gum; glyceryl behenate; glyceryl dibehenate; guar gum; hydroxyethyl cellulose; hydroxypropyl cellulose; hypromellose; isomalt; kaolin; magnesium aluminum silicate; maltitol solution; maltodextrin; medium-chain triglycerides methylcellulose; pectin; polycarbophil polydextrose; polydextrose, hydrogenated; polyethylene oxide; polysorbate 20; polysorbate 40; polysorbate 60; polysorbate 80; polyvinyl alcohol; potassium alginate; povidone; propylene glycol alginate; pullulan; silica, dental-type; silica, hydrophobic colloidal; silicon dioxide; silicon dioxide, colloidal; sodium alginate; sorbitan monolaurate; sorbitan monooleate; sorbitan monopalmitate; sorbitan monostearate; sorbitan sesquioleate; sorbitan trioleate starch, corn; starch, hydroxypropyl; starch, hydroxypropyl pea; starch, hydroxypropyl potato; starch, pea; starch, potato; starch, pregelatinized hydroxypropyl pea; starch, pregelatinized hydroxypropyl potato; starch, tapioca; starch, wheat; sucrose; sucrose palmitatel tragacanth; vitamin E polyethylene glycol succinate; xanthan gum

SOURCE: USP, 1999.

as important resources to support the selection and use of excipients in compounded preparations (Osterberg et al., 2011).[10]

Of particular concern for compounded topical formulations is the marketing and use of excipients that do not have quality standards established by USP or have not been evaluated by FDA. Consequently, those excipients have limited (if any) available evidence of quality, safety, and functionality for their use in compounded preparations. Even in the case of excipients that have been reviewed for use in one commercial topical product, their effect on dermal delivery and absorption may not be the same when the excipients are used for another formulation. Understanding the effects of individual ingredients is further confounded when multiple inactive and active ingredients are incorporated into formulations.

Composition and Safety Profiles of Ingredients Used in Excipients

A review of topical formulations in the *Journal of Pharmaceutical Sciences* explains that individuals who compound should consider "intended dosage form, route of administration, safety profile, manufacturing process, and regulatory aspects" when selecting excipients (Simoes et al., 2018). Of course, excipients that cause degradation of the API are undesirable, thus part of the formulation development process involves verifying that excipients do not cause API degradation. Changing ratios of components or substituting excipients can dramatically affect product quality or alter product performance.

Additionally, when designing a formulation, it is important to understand which excipients have the potential to interact with each other by way of synergistic or opposing excipient–excipient interactions (Beraldo-de-Araújo et al., 2019; Karande and Mitragotri, 2009). For example, an excipient used to decrease viscosity may affect the performance of a permeation enhancer, thus inadvertently increasing the absorbed dose of drug delivered to the tissues below (Osborne and Musakhanian, 2018). On the other hand, if inappropriately formulated, the effects of excipients may have actions that oppose one another (Karande and Mitragotri, 2009). For example, the inclusion of certain preservatives may decrease the effect of an emulsifying agent. *As an important consequence, the use of proprietary bases that do not disclose the composition makes it difficult for even the most experienced formulation scientist to evaluate how the ingredients may affect product quality and performance.*

In a search for publically available formulations of compounded topical pain creams, the committee identified three examples that listed excipients

[10] Additional reference lists are available in international pharmacopeia, such as the European Pharmacopeia (see https://www.edqm.eu/en/databases [accessed March 2, 2020]).

TABLE 5-5
Listed Excipients in Select Compounded Topical Pain Cream Formulations Described on Public Websites

Select Excipients	Active Pharmaceutical Ingredients in Select Compounded Topical Pain Creams	Listed Excipients
Sample 1	Amitriptyline HCl 2% Baclofen 2% Ketamine HCl 5% Ketoprofen 10%	Ethyl alcohol
		Ethoxy diglycol reagent
		Emulsifix
		Lipoderm
Sample 2	Baclofen 2% Clonidine HCl 0.2% Gabapentin 10% Ketamine HCl 5%	Propylene glycol
		Lipoderm
Sample 3	Amitriptyline HCl 2%, Clonidine HCl 0.01%	Glycerine USP
		Lipoderm

SOURCE: FDA, 2018.

(see Table 5-5). It is important to note that after reviewing these excipients, the committee determined the following:

- The rationale for the selection of the chemicals in the formulations is unclear.
- It is unclear whether the excipients selected for these pain creams were selected based on guidance from the FDA and USP lists.
- It is unclear whether any of the ingredients that are not on the FDA or USP lists could be unsafe individually or in combination.
- No information is available about whether these ingredients cause instability in the API or interact unfavorably with each other.

Among the listed excipients in Table 5-5, Lipoderm is listed twice and Emulsifix is listed once. Unfortunately, neither Emulsifix nor Lipoderm provide a publicly available list of excipients to inform the decision-making process of the pharmacists, prescribing clinician, or patient. This is also the case with several other proprietary bases used in compounded preparations.

One exception is Lipoderm ActiveMax, a patented base that is similar to Lipoderm and Emulsifix in that it contains preformulated excipients for topical application. The composition of Lipoderm ActiveMax is available on a publicly available patent (Ray and Hodge, 2013) and is detailed below in Table 5-6. In reviewing the composition of this base, half of the listed excipients are not included either in the USP-National Formulary 19 compendium or in the FDA inactive ingredient database. In addition, given the long list of excipients included, it is difficult to evaluate the potential

TABLE 5-6
Listed Components in Lipoderm ActiveMax from Patent US2013/0085171

Excipient	Listed on FDA-Approved Inactive Ingredient Database (Y/N)	Listed on USP List of Excipients	Listed on the Homœopathic Pharmacopœia of the United States
Water	n/a	Y	n/a
Cetearyl alcohol	Y	N	N
Piukenetia volubilis seed oil	N	N	N
Isopropyl myristate	Y	Y	N
Propylheptyl caprylate	N	N	N
Sodium stearoyl glutamate	N	N	N
PEG-8/SMDI copolymer	N	N	N
PEG-100 stearate	N	N (includes other forms of PEGs)	N
Glyceryl stearate	Y	Y	N
Glycerin	Y	Y	N
Tocopheryl acetate	N	Y (in other forms)	N
Lecithin	Y	Y	N
Hydrogenated lecithin	N	N	N
Populus tremuloides bark extract	N	N	Y
Lonicera japonica (honeysuckle) flower extract	N	N	N
Lonicera caprifolium (honeysuckle) flower extract	N	N	N
Leuconostoc radish root ferment filtrate	N	N	N
Pentaclethra macroioba seed oil	N	N	N
Butyrospermum parkii (shea butter)	N	N	N
Carthamus tinctorius (safflower) seed oil	N	Y	N
Cocos nucifera (coconut) oil	Y	Y	N
Tocopherol	Y	Y	N

TABLE 5-6
Continued

Excipient	Listed on FDA-Approved Inactive Ingredient Database (Y/N)	Listed on USP List of Excipients	Listed on the Homœopathic Pharmacopœia of the United States
Ascorbyl palmitate	Y	N (includes other forms of palmitate)	N
Squalane	Y	Y	N
Ceramide 3	N	N	N
Alcohol	Y	Y (in other forms)	N
Caprylic capric triglyceride	N	Y (medium chain)	N
Xanthan gum	Y	Y	N
Gluconolactone	Y	N	N
Sodium dehydroacetate	N	N	N
Disodium edetate (EDTA)	Y	Y	N
Butylated hydroxytoluene	Y	N	N

NOTE: EDTA = ethylenediaminetetraacetic acid; FDA = U.S. Food and Drug Administration; PEG = polyethylene glycol; SMDI = saturated methylenediphenyldiisocyanate; USP = United States Pharmacopeia.

SOURCES: FDA, 2019; HPUS, 2020; Ray and Hodge, 2013; USP-NF, 2019.

interactions of these excipients with each other or with APIs included in the pain cream; the patent provides minimal information to this regard.[11] Furthermore, it is doubtful that each of those 30 or more ingredients actually contribute a unique advantage to the formulation, because formulations should be designed to be as simple as possible (Chang et al., 2013). This casts a cloud of doubt on the necessity of all the listed excipients in optimizing the safety and the effectiveness of the preparation.

[11] The available patent information generally describes how these excipients enhance penetration. For example, paragraph 0060 states "In particular, the absorption profiles indicate a rapid penetration to a peak flux for gabapentin and baclofen occurring approximately 1 hour after dose application, and between approximately 4 to approximately 10 hours after dose application for ketamine" (Ray and Hodge, 2013).

Classes of Excipients: Penetration Enhancers

Penetration enhancers are a class of excipients of additional importance. This type of excipient enhances penetration of a drug into the inner tissues and ultimately into the blood stream (Prausnitz and Langer, 2008).[12] Many chemicals can enhance penetration through the outer skin barrier by disrupting the highly ordered structure of lipid bilayers. However, this increased transdermal penetration is also associated with increased potential for irritation (Prausnitz and Langer, 2008). Many preformulated bases sold by such companies as the Professional Compounding Centers of America and Medisca are marketed as transdermal bases and touted for their ability to penetrate deeper below the skin (Medisca, 2020; PCCA, 2013). In addition, even products intended to act near the skin surface, such as sunscreen agents, are actually absorbed into the systemic circulation (Matta et al., 2019). Clearly, safety is an issue if large doses of a topically applied drug are absorbed systemically, especially if it is assumed that the drug is limited to local action or a drug has a narrow therapeutic window.

The 11 commonly accepted categories of permeation enhancers, classified by chemical structure, are water; hydrocarbons; alcohols; acids; amines; amides; esters; surfactants; terpenes, terpenoids, and essential oils; sulfoxides; and lipids (Karande and Mitragotri, 2009). Between and within these classes are numerous chemicals with different properties that affect their effectiveness as enhancers. A recent analysis of skin permeation studied more than 40 different enhancers in hairless mouse skin or human epidermal membrane. The analysis found that molecules within the same class and those with similar structures can have drastically different enhancer potencies. For example, 2-nonanol exhibited an enhancer potency parameter over four times greater than 2-octanol (Li and Chantasart, 2019). Obviously, factors such as potency and concentration need to be considered by individuals who compound when they choose to add permeation enhancers to their compounded preparations.

Dimethyl sulfoxide (DMSO) is a penetration enhancer used in compounded topical pain creams that has repeatedly occasioned concern among the committee. DMSO appears to be used in compounded topical pain creams as both a penetration enhancer and as an active ingredient (Kopsky and Keppel Hesselink, 2011; Russo and Santarelli, 2016). While the evidence is far from conclusive, some studies suggest that DMSO may help treat osteoarthritis pain and complex regional pain syndrome (Brien et al., 2008; NHS, 2020). In fact, DMSO is the primary inactive ingredient in PENNSAID, an FDA-approved topical solution for osteoarthritis pain

[12] For additional information on penetration enhancers and their various effects, see Dragičević and Maibach, 2017.

(Nuvo Research, 2016). However, the primary concern surrounding DMSO is its effect as a potent penetration enhancer.

The material safety data sheet for DMSO states "DMSO readily penetrates skin and may significantly enhance the absorption of numerous chemicals. Increased absorption of these other chemicals could lead to their increased toxicity" (Fisher Scientific, 2007). The instructions for use for PENNSAID caution patients to apply the medication to clean skin and to avoid the application of other drugs or cosmetics to the area (Nuvo Research, 2016). There is concern that the addition of DMSO to other ingredients in topical pain creams may affect toxicity and safety of the preparation. Furthermore, patients using compounded DMSO preparations may not be provided with adequate instructions and warnings to ensure safe use.

Given the potential complexity of compounding, the Federal Food, Drug, and Cosmetic Act (FDCA) requires that to qualify for exemptions from new drug approval and other, drugs compounded at 503A or 503B facilities must not "present demonstrable difficulties for compounding" and directed FDA to provide guidance on this matter.[13] Accordingly, in 2016, FDA developed a "Difficult to Compound" list that will preclude the use of listed drugs in compounded preparations. Many examples of drug preparations and categories have been nominated to the Difficult to Compound List. However, no final determinations on which drugs will be included have been made to date.[14] See Box 5-4 for FDA's criteria for a drug that is difficult to compound.

[13] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[14] See Section 503A Bulks List Final Rule Questions and Answers; Guidance for Industry; Small Entity Compliance Guide; Availability. 84 FR 24027 (May 24, 2019) (FDA announces development of criteria to evaluate drugs as demonstrably difficult to compound under 503A and 503B).

BOX 5-4
Criteria for Determining Whether a Drug Is Difficult to Compound

In 2016, an internal U.S. Food and Drug Administration (FDA) working group proposed six criteria to evaluate whether drug products or categories of drug products should be included on the list. After review by FDA's Pharmacy Compounding Advisory Committee, the following criteria were published in a July 28, 2017, *Federal Register* notice.

1. Complexity of the formulation
2. Complexity of the drug delivery mechanism
3. Complexity of the dosage form
4. Complexity of the bioavailability issues
5. Complexity of the compounding process
6. Physicochemical or analytical testing complexity

FDA stated that it will consider these criteria individually and collectively when evaluating whether a drug product or a category of drug products is demonstrably difficult to compound.

SOURCE: Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket. 82 FR 35214 (July 28, 2017).

Conclusions 5-1 to 5-4

Compounding topical pain creams is an extemporaneous process that raises significant concern that the selection of active and inactive ingredients may not incorporate the full spectrum of complexities related to skin absorption and dose (e.g., variability, permeability, efficacy, drug–drug interactions).

Dermal penetration and absorption are influenced by the complexity of formulations, including active and inactive ingredient selection, principles and procedures for compounding preparations, quality, and stability. To address this complexity and to minimize potential variability in performance, there is a need for optimal consistency in formulations of compounded topical pain creams—with standardized methods for disclosing formulation procedures—to ensure acceptable and consistent performance of the compounded preparation.

There is insufficient evidence to evaluate the extent of topical absorption or potential transdermal penetration of active and inactive ingredients (used alone or in combination) in compounded topical pain creams.

There is insufficient evidence regarding compatibility and stability for specific combinations of active pharmaceutical ingredients and inactive ingredients in compounded topical pain creams.

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6

A Review of the Safety and Effectiveness of Select Ingredients in Compounded Topical Pain Creams

The safety and effectiveness of each active pharmaceutical ingredient (API) in a compounded topical pain cream depends on two factors. First, the API should have a mechanism of action to treat pain, and second, the topical formulation must deliver the API to the site of action in an amount that is sufficient to achieve an effect but is also appropriate to be safe. In theory, topical APIs intended to treat local or regional pain act on nerves in the skin or in underlying muscles or joints by blocking nerve signals, reducing inflammation, relaxing muscle spasms, or increasing the effects of other substances (Cline and Turrentine, 2016; Leppert et al., 2018). However, distal responses to topical applications may also occur (Glinn et al., 2017; Leppert et al., 2018). Whether these systemic actions are intended or not, they are critically important considerations in the review of a compounded topical preparation's safety and effectiveness profile.

Despite their many benefits, all pain medications—including U.S. Food and Drug Administration (FDA)-approved pain medications—have some potential for adverse effects or intolerance among certain populations of patients. For example, chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen may cause gastrointestinal effects (e.g., ulcers, bleeding) as well as be linked to kidney and liver damage. Based on clinical studies and the product's label, pharmacists and prescribing clinicians know to exercise certain cautions when treating certain populations with NSAIDs, including older populations, patients on anticoagulants or steroid drugs, and women in early pregnancy. The ongoing opioid epidemic in the United States serves as another cautionary example of the potential risks of pain medication. Inappropriate use of opioids in pain management plans

has contributed to a substantial increase in the rates of opioid addiction and consequential deaths from overdose (Solomon et al., 2010; Wehrwein, 2010).

Given this context, clear, evidence-based conclusions on the safety and effectiveness of pain medications helps to inform clinical guidelines for the use of pain medications and to mitigate risks of adverse effects in specific patients. Currently, little is known about the safety and effectiveness of compounded topical pain creams. In the context of the somewhat recent rise in the supply and demand of compounded preparations, this gap in knowledge creates a substantial public health concern.

This chapter addresses the committee's charge to identify and analyze available scientific data relating to the ingredients used in compounded topical pain creams. There are several sections in this chapter. A total of 20 ingredients were selected using a process described in the next section, followed by a summary of the search strategy employed to identify relevant data. Following this introductory overview of the committee's research approach, overall conclusions and the data on which they are based are tabularized in the subsequent section. Next, each of the 20 ingredients is separately discussed, with ingredients grouped by category. Of note, some published reports also include data on compounded preparations containing multiple active ingredients. The committee summarized these research findings in the final section of this chapter.

Primary data reviewed by the committee included safety, efficacy, and/or effectiveness studies in humans.[1] When available, the committee prioritized findings of randomized controlled trials (RCTs), followed by quasi-experimental designs and cohort studies. Select case reports are briefly summarized to inform the overall database for each ingredient. Effectiveness data are followed by pharmacokinetic and safety data for each ingredient, where available. Additionally, preclinical animal pharmacokinetic data are discussed for ingredients that lacked such evidence in humans.

[1] The current research study has a charge to evaluate the effectiveness, rather than the efficacy, of compounded topical pain creams. While similar, the terms are not synonymous. Efficacy refers to the therapeutic effect of a treatment under controlled conditions, while effectiveness refers to the therapeutic effect in "real-world" situations in which certain contextual measures (e.g., placebo effect) may not be strictly controlled and broad outcome measures (e.g., health-related quality of life) are considered. Effectiveness data alone may not be sufficient to inform conclusions regarding a treatment's therapeutic effect (Ernst and Pittler, 2006; Kim, 2013). For the purposes of this report, the committee evaluated all relevant data produced by randomized controlled trials, nonrandomized clinical studies, case reports, and where applicable, preclinical studies to help address the study's charge. As a result, many of the research findings discussed throughout the report assess outcomes related to the potential effectiveness and/or efficacy of compounded topical pain creams. Given its broader application to the body of research reviewed, the term effectiveness is used more generally across the report.

It is important to note that the committee's review of the literature primarily focused on the application of nonsterile compounded topical creams to treat pain when applied to intact external skin.[2] The committee largely excludes discussions on wound care and mucosal membranes and cavities (e.g., mouth, eyes, vulva, vagina, anus, and nose); however, in select circumstances these findings are included where there is insufficient evidence to comment on outcomes of topical application on intact skin. In addition, evidence on oral administration is occasionally discussed to highlight potential side effects if the data show evidence of systemic absorption.[3]

RESEARCH APPROACH

Selection of Active Pharmaceutical Ingredients for Review

APIs evaluated by the committee are listed in Box 6-1; these APIs were chosen using a process described in Chapter 1. FDA introduced a list of 37 APIs that have been identified in common formulations of compounded topical pain creams, 10 of which were determined to be of high-priority interest and were selected for evaluation by the committee. Recognizing that this high-priority list was not a comprehensive list of ingredients used in compounded topical pain cream products, the committee chose 10 additional chemicals to ensure examples from various possible pain pathways in humans were represented. Specific choices were made to expand the groups of substances (e.g., inclusion of drugs with potential local and systemic anesthetic actions) and to include additional drugs from important groups (e.g., NSAIDs). *It is important to note that the omission of a category, or mechanism, does not imply safety or effectiveness of drugs in that category when used in compounded topical pain creams.*

Search Strategy Summary

The study committee conducted a literature search to identify a comprehensive body of evidence to inform its work. In coordination with one of the National Academies' senior research librarians, the committee constructed a literature search strategy to identify a broad body of research evidence. An initial search queried six databases—Medline, Embase, PubMed, Scopus, ClinicalTrials.gov, and Toxnet—for content

[2] There is a growing literature on the overlap of signaling pathways between sensations related to itch and pain (Schmelz, 2019). As such, there are several APIs with indications for itch that may be also used to treat pain and vice versa. However, for the purposes of this report, the focus is on the effectiveness of the API to treat pain.

[3] See Appendix G for an overview of the potential systemic side effects related to the use of the 20 APIs reviewed.

BOX 6-1
Classification of APIs Chosen for Review of Safety and Effectiveness

- Alpha-2-adrenergic receptor agonist: clonidine (page 135)
- Anticonvulsants: carbamazepine, gabapentin, topiramate (page 139)
- Antispasmodics (muscle relaxants): baclofen, cyclobenzaprine, orphenadrine (page 147)
- Calcium channel blocking agent: nifedipine (page 154)
- Cannabinoid: cannabidiol (page 156)
- Dissociative anesthetic and NMDA receptor antagonist: ketamine (page 160)
- Local anesthetics: bupivacaine, lidocaine (page 165)
- NMDA receptor antagonist: memantine (page 171)
- Nonsteroidal anti-inflammatory drugs (NSAIDs): meloxicam, naproxen (page 172)
- Opioid agonist: tramadol (page 177)
- Steroid: dexamethasone (page 179)
- Tricyclic antidepressants: amitriptyline, doxepin (page 179)
- Vasodilator: pentoxifylline (page 186)

related to the safety and effectiveness of the 20 APIs used in topical products. This literature search included human, animal, and in vitro studies, but it was limited to peer-reviewed articles published in the English language. The search was not limited by date of publication, but editorials, commentaries, letters, and notes were excluded. A complete description of the search syntax used can be found in Appendix B. The search yielded 1,716 articles for the 10 APIs prioritized by FDA and 7,306 articles on the additional 10 APIs added by the committee with potential relevance to the committee's charge.

An initial screen of the 9,022 articles was performed by National Academies staff to eliminate articles not relevant to the study's scope. A total of 7,230 articles were removed for either (1) discussing only topical application to the eye, or (2) not discussing the treatment of pain in the title, keywords, or abstract of the article. After this first screen, the remaining 1,792 articles were assigned a type of evidence rating by National Academies staff based on study design, using a modified Cochrane scale to expand the nonrandomized trial categories (Harris et al., 2001; University of Oxford, 2009). Given the committee's research questions, the scope of the literature search was limited to the topical application of any of the 20 ingredients to skin with the intent to treat pain. Committee members then screened all articles for content relevance, which resulted in a total of 169

articles.[4] See Figure B-1 in Appendix B for a depiction of the flow of articles through the search and selection process. See also the Search Strategies section in Appendix B for the full list of specific terms used in the literature search efforts.[5]

After articles relevant to the committee's task were identified, all systematic reviews, RCTs, and all clinical studies with a control group were reviewed for evidence regarding the safety and effectiveness of the drug applied topically to treat pain. Case reports, case series, and preclinical studies were discussed (where relevant) for APIs lacking the level of evidence provided by systematic reviews and controlled clinical studies.[6] Because study design is not the only measure of quality evidence, the committee also considered evidence of methodological rigor detailed in the publications in its review of the evidence. Using the 2019 Cochrane Risk of Bias Assessment Tool (Sterne et al., 2019), the committee evaluated the risk of bias in all RCTs identified as relevant to the committee's charge.[7] In summary, out of the 22 RCTs that reviewed the effectiveness of *individual* APIs, 7 were determined to have a high risk of bias, 13 have a low risk of bias, and 2 were noted as having some concerns. Notably, out of the 11 RCTs that reviewed the effectiveness of *multiple* ingredients in compounded topical pain creams, 7 were determined to have a high risk of bias, 3 have a low risk of bias, and 1 was noted as having some concerns. The level of bias attributed to each RCT is included in footnotes within the summaries below.

[4] Of note, these calculations represent the true number of articles resulting from the 20-ingredient literature search. There are a number of articles with relevance to multiple APIs that are represented more than once in the total. In addition, the committee identified many other published studies that have tangential relevance to the committee's charge; however, only the studies with the most direct relevance were reviewed in this report. As such, the references for this chapter represent the most relevant data and are not an inclusive list of all of the articles reviewed.

[5] In recognition of the limited peer-reviewed evidence to describe the safety and effectiveness of compounded topical pain creams, the committee also reviewed submitted resources from national stakeholders, such as the Professional Compounding Centers of America, to support its research efforts. These are available in the study's Public Access Folder; see https://www8.nationalacademies.org/pa/managerequest.aspx?key=HMD-HSP-18-18 (accessed April 9, 2020).

[6] Case series, case reports, and preclinical studies were considered to be low-tier evidence for informing the clinical effectiveness of APIs in topical compounded topical creams (Harris et al., 2001; University of Oxford, 2009).

[7] A few additional RCTs are referenced within the summaries, but their research focus was considered to be out of scope.

SUMMARY OF RESEARCH FINDINGS

Topical Application of Single-Ingredient Compounded Topical Pain Creams

From its review of the evidence, the committee determined several key findings related to the safety and effectiveness of topical application of single-ingredient compounded pain cream preparations, including the following:

- There are very few well-designed, randomized, placebo-controlled research trials that have investigated the bioavailability, effectiveness, or safety of active pharmaceutical ingredients in compounded topical pain creams used to treat pain.
- There is preclinical data (for a limited number of ingredients) that suggest a potential for effectiveness to treat pain in humans.
- Based on the available evidence, the 20 ingredients reviewed demonstrated wide variability in their potential for skin absorption, which was found to be dependent on the drug characteristics, skin condition, and excipient(s) used.[8]
- If topical dosing is sufficient to provide centralized pain relief, adverse effects and drug interactions for systemic exposure are a concern.
- For many specific combinations of drugs and excipients, evidence is inadequate to determine whether the ingredients are absorbed at the local, regional, or systemic level, and there is very little data on the relative risk of adverse effects in any of those three categories.
- When used appropriately, little conclusive data support high risk of safety concerns for any of the 20 studied ingredients beyond local skin irritation; however, high levels of systemic absorption can have potentially life-threatening consequences particularly for preparations including ketamine, clonidine, and bupivacaine.

The committee details its review of the literature below; however, to provide clarity, the committee organized its major research findings into a table (see Table 6-1). This table includes short, descriptive summaries related to the research findings on the safety and effectiveness of the 20 APIs reviewed in this report. It is critical to note that in an effort to create such a table, a substantial amount of context and detail was sacrificed. To obtain a comprehensive appreciation of the body of evidence reviewed in

[8] A significant limitation in a large portion of the body of evidence reviewed is the failure of studies to disclose the excipients or enhancers used in the compounded topical formulations. The absence of this information hinders a complete interpretation of the research results.

this report—including the pain conditions, measurements, and assessments, as well as the quality of the studies reviewed—it is critical that the reader reviews the detailed narrative text in the remainder of the chapter.

Topical Application of Multiple-Ingredient Compounded Topical Pain Creams

Given their popularity and use (see Chapter 2), the committee also reviewed evidence on the safety and effectiveness of compounded topical pain creams that contain combinations of multiple APIs. In summary, little information was found to inform the committee's charge. Several RCTs, clinical trials, and case reports were identified, but overall there was a dearth of information on the performance of individual agents compared to combined agents, which limited the interpretability of the results. In addition, many of the articles lacked appropriate controls to address potential placebo effects. As discussed in Chapter 2, the placebo effect is a well-recognized experience in the health care field (IOM, 2011; NIA, 2020). Rubbing a cream on skin can be comforting, and the action itself can be therapeutic, an important confounder that can be addressed in well-designed, placebo-controlled trials.

An additional confounding factor in several of the multiagent studies is the presence of lidocaine in the compounded formulation. Lidocaine is already FDA approved clinically to induce topical anesthesia, and data were insufficient to determine whether effectiveness improved in combination with other ingredients. Importantly, no conclusions can be made on the committee's review of the creams containing five to seven ingredients because of the consistent presence of lidocaine, the inclusion of APIs not evaluated individually by the committee, or the lack of appropriate controls. In regard to findings related to safety, the adverse effects were determined to be similar to those reported for the individual ingredients. A more detailed review of the committee's findings on the safety and effectiveness of multiple-ingredient compounded topical pain creams can be found in the later sections of this chapter.

TABLE 6-1
Available Clinical Evidence for the Topical Application of Single-Ingredient Compounded Pain Preparations

Active Pharmaceutical Ingredient (API)	Does the Available Evidence Suggest Effectiveness When Used on Intact Skin?	Is There Evidence of Systemic Absorption?	Is There Evidence to Conclude That the API Is Safe?	What Were the Demographics of the Populations Studied?	
Amitriptyline	No, based on limited and inconsistent data	Yes, based on limited evidence	No; data are extremely limited	Adult; Caucasian and Asian	
Baclofen	Insufficient data	Insufficient data (no studies)	Insufficient data (no studies)	Adult; majority Caucasian and female	
Bupivacaine	Insufficient data (no studies)	Insufficient data (no studies)	Insufficient data (no studies)	Adult; pediatric	
Cannabidiol	Insufficient data	Yes, based on limited preclinical data	Insufficient data	Adult; pediatric	
Carbamazepine	Insufficient data (no studies)	Insufficient data	Insufficient data	Adults only	

	What Adverse Effects Have Been Described?	Comments
	• At 10% concentration: rash, skin irritation, and drowsiness • Single case report of overdose from excessive use of compounded cream with multiple APIs (amitriptyline 360 mg)	—
	• No data • Single case report of overdose from excessive use of compounded cream with multiple APIs (baclofen 900 mg)	• Preclinical studies suggest antinociception activity when given systemically • In a combination cream containing baclofen, amitriptyline, and ketamine, serum concentrations of baclofen have been detected at low therapeutic levels in the blood
	Not described	• Evidence of effectiveness and safety as a liquid in open wounds • Via other routes of administration, there is potential for cardiac and central nervous system collapse if absorbed at ≥ 4μg/mL
	Not described	• Potential effectiveness indicated in a few clinical studies with dermal lesions and limited preclinical studies • Evidence of systemic absorption in preclinical studies • Via other routes of administration, there is potential for depressive effects, liver dysfunction, rash, insomnia, infections, suicidal thoughts or actions
	• Only with systemic doses	• Poor-quality data for all topical uses; relevant data on oral use including pain efficacy and side effects were found

Active Pharmaceutical Ingredient (API)	Does the Available Evidence Suggest Effectiveness When Used on Intact Skin?	Is There Evidence of Systemic Absorption?	Is There Evidence to Conclude That the API Is Safe?	What Were the Demographics of the Populations Studied?	
Clonidine	Insufficient data	Yes, based on limited data	Yes	Adults; geriatric, pediatric, non-Hispanic White, Native American, Black, Hispanic/ Latino, Asian	
Cyclobenzaprine	Insufficient data	Yes, based on limited data	Insufficient data	Adults; Romanian men and women	
Dexamethasone	Insufficient data (no studies)	Insufficient data (no studies)	Insufficient data (no studies)	n/a	
Doxepin	Yes, based on limited data	Yes, based on limited data (one study)	Yes, based on limited data (one study)	Adult; men, women	
Gabapentin	Insufficient data	Insufficient data (one study)	Insufficient data	Adults only	
Ketamine	No	Yes, based on preclinical data	No, based on limited data	Adult; Black, Hispanic/ Latino, Asian, Caucasians	
Lidocaine	Yes, based on limited data	Yes, based on limited data	Yes	Adults only	

	What Adverse Effects Have Been Described?	Comments
	• Minimal effects (e.g., skin reactions) • Two adverse events in children who developed toxicity from inappropriate exposure to compounded cream containing clonidine	• Evidence of serious complications with systemic absorption
	• Minimal effects (e.g., rash)	• Clinical studies of effectiveness have significant limitations • Central mode of action indicates topical application would need considerable systemic absorption to be effective
	n/a	• No data available on dexamethasone as a single ingredient in compounded topical pain creams
	• Limited data insufficient to describe rates	• Effectiveness: randomized controlled trial comparing active arms (capsaicin cream) only, showing equivalence • Side effects: in comparison to capsaicin cream only • 3.3% doxepin penetration through human skin resulted in measured serum concentrations of 0–47 ng/mL (reported therapeutic range: 30–150 ng/mL)
	• Insufficient data on topical but oral safety suggest low level of concern	—
	• Minimal effects (e.g., adverse skin reactions) • Case reports of toxicity from excessive use	• There is evidence that topical ketamine is not superior to placebo for a variety of conditions including postherpetic neuralgia, complex regional pain syndrome (types I and II), painful diabetic neuropathy, and other types of neuropathic pain
	• Minimal effects (e.g., skin reactions) • Single case report of overdose from excessive use of a compounded cream with multiple APIs (lidocaine 900 mg)	• In other routes of administration, it is a potent antiarrhythmic drug and high doses can precipitate CNS disturbances, such as psychosis and seizures. Limit to application amount and area based on the risk of absorption

Active Pharmaceutical Ingredient (API)	Does the Available Evidence Suggest Effectiveness When Used on Intact Skin?	Is There Evidence of Systemic Absorption?	Is There Evidence to Conclude That the API Is Safe?	What Were the Demographics of the Populations Studied?	
Meloxicam	Insufficient data	Yes, based on preclinical data	Insufficient data	n/a	
Memantine	Insufficient data (no studies)	Insufficient data (no studies)	Insufficient data (no studies)	n/a	
Naproxen	Yes, based on limited and inconsistent data	Yes, based on limited data	Yes, based on limited data	Adult; men, women	
Nifedipine	Insufficient data	Insufficient data (no studies)	Insufficient data	n/a	
Orphenadrine	Insufficient data (no studies)	Insufficient data	Insufficient data	n/a	
Pentoxifylline	No, based on limited data	Insufficient data	No, based on limited data (one study)	Adult, predominantly White; both sexes	
Topiramate	Insufficient data (no studies)	Insufficient data (no studies)	Insufficient data (no studies)	n/a	
Tramadol	Insufficient data (no studies)	Insufficient data (no studies)	Insufficient data (no studies)	n/a	

	What Adverse Effects Have Been Described?	Comments
	Not described	—
	n/a	—
	• Minimal effects (e.g., skin irritation, itching)	—
	n/a	• No studies of nifedipine for use on the skin; all data on effectiveness and safety are from studies on application to anal fissures
	n/a	—
	• Concern about lowering blood pressure but not significant problem in healthy subject in an experimental randomized controlled trial	• Well-done animal and human experimental data from a single lab; randomized controlled trial in patients with pain pending
	n/a	—
	n/a	Insufficient data available on tramadol as a single ingredient in topical pain creams

Conclusions 6-1 to 6-5

Out of the 20 active APIs reviewed, 3 individual APIs and 1 two-drug combination demonstrate potential clinical effectiveness in compounded topical pain creams. Of these, doxepin (tricyclic antidepressant) and lidocaine (local anesthetic) alone show evidence of effectiveness. Naproxen (nonsteroidal) alone has inconsistent evidence, but demonstrates potential effectiveness to treat certain types of pain. A high dose of pentoxifylline/clonidine combination (vasodilator/nerve receptor agonist) has limited evidence of effectiveness in one pain model, possibly due to systemic absorption of its APIs, but additional studies are needed. Additional research and further justification are needed to determine the effectiveness of all 20 APIs to treat specific pain conditions through their use in compounded topical pain creams.

Data are inadequate to support conclusions regarding safety and risks related to the use of compounded topical pain creams. Importantly, however, the absence of data does not prove safety or indicate that adverse events have not occurred. This is of particular concern where there is evidence of systemic absorption.

Data are inadequate to quantify the extent to which APIs reviewed in this report are absorbed and present at local, regional, or systemic levels.

As reflected in adverse event reports, high levels of systemic absorption 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.

A REVIEW OF THE SAFETY AND EFFECTIVENESS OF SELECT ACTIVE PHARMACEUTICAL INGREDIENTS IN COMPOUNDED TOPICAL PAIN CREAMS

Alpha-2-Adrenergic Receptor Agonist: Clonidine

Summary

Clonidine, an alpha-2 and imidazoline receptor agonist, is typically used to treat hypertension, but it is also used to treat attention deficit hyperactivity disorder in children, and it is used as adjunct epidural therapy for severe cancer-related pain (Yasaei and Saadabadi, 2019). Although it does not have an FDA-approved indication for pain, studies related to the use of topical clonidine to treat pain largely focus on its efficacy for peripheral neuropathy.

Based on a small systematic review, RCTs, and observational studies there is some suggestive evidence for the efficacy of topical clonidine cream (0.1 percent to 0.2 percent concentration) to alleviate pain for diabetic neuropathy; however, the data are conflicting. No significant safety concerns are reported, but the area of application and serum levels have limited discussion in the studies. See Box 6-2 for a summary of research findings.

Overall, the committee reviewed four RCTs: two studies were assessed as having a low risk of bias (Campbell et al., 2012; Kiani et al., 2015a), and two studies raised some concerns of bias (BioDelivery Sciences International, 2017a,c; see Appendix B for more details). In addition to reviewing studies where clonidine alone was analyzed, the committee also included studies of clonidine used in combination with other APIs. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

Effectiveness

Systematic review A systematic review conducted by Wrzosek et al. (2015) assessed the efficacy of clonidine (alone) in topical creams to treat chronic neuropathic pain in adults and the frequency of adverse events related to use. The systematic review examined the outcomes of two studies, Campbell et al. (2009, 2012),[9] determined by the authors to be of moderate to low quality. In these studies, the authors conducted a double-blind, randomized, placebo-controlled parallel study to evaluate the efficacy of topical clonidine 0.1 percent gel in diabetic patients (type 1 or 2) with painful peripheral neuropathy defined as an average numeric pain rating

[9] Risk-of-bias assessment by committee (Campbell et al., 2012): Low (see Appendix B for more details). Note that, given its publication as an abstract, a risk-of-bias assessment was not conducted for Campbell et al. (2009).

BOX 6-2
Summary of Research Findings on Clonidine in Compounded Topical Pain Creams

Effectiveness: There is insufficient evidence to suggest effectiveness of topical clonidine to treat neuropathic pain conditions when applied to intact skin.

Dermal penetration/bioavailability: There is limited evidence to suggest that topical clonidine may result in detectable serum concentrations in certain subjects.

Safety and adverse effects: Evidence suggests that topical clonidine is associated with minimal adverse effects. However, if systemic absorption to therapeutic levels is achieved through topical application, there is potential for side effects similar to other routes of administration (e.g., oral). Two case reports describe toxicity in pediatric populations and supratherapeutic levels of ingredients.

scale (NPRS) ≥ 4 during the 7 days prior to treatment. Participants were randomized in blocks in order to stratify baseline pain severity. Participants applied a metered dose (0.65 mg clonidine) to each foot three times per day for 12 weeks. One hundred seventy-nine patients completed the study. No significant difference was noted in reduction in pain intensity between clonidine and placebo groups.

The authors also tested a pain response to capsaicin in a subset of participants. In the participants who experienced a pain response ≥ 2, the clonidine group experienced a mean decrease in NPRS of 2.6 compared to a reduction of 1.4 in the placebo group. Serum concentrations were obtained at regular visits. Specific pharmacokinetic results are not provided. However, the authors state that only two patients had serum clonidine concentrations greater than 200 pg/ml (therapeutic is > 1,000 pg/ml) and that these participants did not experience adverse effects attributable to clonidine. However, no details are provided. The gel used in these studies appears to be a proprietary compound from Arcion Therapeutics (2009).

Randomized controlled trials A double-blind, randomized, placebo-controlled parallel study conducted by BioDelivery Sciences International evaluated the efficacy of topical clonidine 0.1 percent gel in diabetic patients (type 1 or 2) with painful peripheral neuropathy defined as an average NPRS of ≥ 4 during the 24 hours prior to treatment (BioDelivery Sciences

International, 2017a).[10] A total of 130 subjects were enrolled in each group, and 117 completed the study in the clonidine group and 114 completed the study in the placebo group. The clonidine group applied a total dose of 3.9 mg clonidine to each foot each day for 12 weeks with an option to enroll in an open-label study following the treatment phase. The primary endpoint was reduction in NPRS. Clonidine was not superior to placebo in change in NPRS from baseline. In addition, there was no difference between the two groups in mean daily NPRS scores for worst pain intensity.

A double-blind, randomized, comparator-controlled parallel study evaluated the efficacy of topical clonidine 0.1 percent gel in diabetic patients (type 1 or 2) with painful peripheral neuropathy defined as an NPRS of ≥ 4 during the 24 hours prior to treatment (BioDelivery Sciences International, 2017c).[11] Gel is described as an aqueous gel formulation for topical use. Gel was applied to both feet three times per day, but the total amount of drug applied to each foot was not mentioned. A total of 138 patients were enrolled and evenly divided between the two groups; 58 in the clonidine group completed the study compared to 67 in the comparator group. Clonidine gel was not superior to the comparator. No significant difference occurred in mean reduction in NPRS or mean daily worst pain intensity NPRS scores between the two groups.

A randomized, double-blind study was conducted to evaluate the efficacy and safety of clonidine versus capsaicin in the treatment of painful diabetic neuropathy in patients with type 2 diabetes pain assessed using a visual analog scale (VAS) of ≥ 4 (Kiani et al., 2015a).[12] Clonidine was administered as a 0.1 percent gel with details about the preparation of the gel provided. Capsaicin was supplied as a 0.75 percent cream. Drugs were applied below the ankle to the feet three times per day for a period of 12 weeks. Participants were assessed at 4-week intervals. There was no difference between the groups in reduction in pain as assessed by the VAS. A total of 70 patients were allocated to the capsaicin group and 69 to the clonidine group; 30 participants dropped out of the capsaicin group and 16 from the clonidine group. No significant changes in blood pressure were noted in the clonidine group, of which 53 patients completed.

Clinical studies An open-label study to assess the long-term use of clonidine 0.1 percent gel was conducted after the completion of the 12-week study noted above (BioDelivery Sciences International, 2017b). A total of 197 subjects were enrolled in the open-label study. It is not clear how many of the 197 subjects came from the previously mentioned study. Clonidine was

[10] Risk-of-bias assessment by committee: Some concerns (see Appendix B for more details).
[11] Risk-of-bias assessment by committee: Some concerns (see Appendix B for more details).
[12] Risk-of-bias assessment by committee: Low (see Appendix B for more details).

applied in the same manner as the double-blind, placebo-controlled study. Only 47 subjects completed the study. The primary outcome was the summary of neuropathic pain symptom inventory documented at the last visit. The mean score was 34.4, which, based on supportive clinical guidance, is categorized as high pain symptom severity (Wong et al., 2019).

A pilot study was conducted in 17 patients with chronic orofacial pain who were diagnosed with neuralgia or neuropathy (Epstein et al., 1997) and given clonidine 0.2 mg/g in a cream base manufactured by Glaxo. Participants were instructed to apply the cream with their finger to the site of pain four times per day for 4 weeks. A VAS was used to determine level of pain. Out of 17 patients, 7 individuals reported improvement of 75 percent or greater, 8 reported no improvement, 1 reported 40 percent improvement, and 1 reported 10 percent improvement. In patients with neuralgia, 4 out of 7 reported improvement, and 6 out of 12 patients with neuropathic pain reported improvement.

Case report Kopsky and Keppel Hesselink (2017) describe a 54-year-old woman with neuropathic pain in both feet reported as 8 out of 10 on the Numerical Rating Scale (NRS) following chemotherapy treatment despite being prescribed oral gabapentin 2,000 mg daily and oxycodone 20 to 30 mg daily. Pain was reduced to 3 by a test application of compounded topical baclofen 5 percent cream, which was said to be a greater reduction than with compounded clonidine 0.2 percent cream or compounded lidocaine 3 percent combined with isosorbide dinitrate 0.4 percent cream. Allodynia was still present but eliminated with ketamine 10 percent cream. Pain level increased over time from 3 to 7 on the NRS, which led to further treatment.

Dermal Penetration/Bioavailability

Randomized controlled trials Campbell et al. (2009) reported that subjects with detectable clonidine concentrations after topical application of clonidine 0.1 percent or 0.2 percent gel achieved more pain relief than subjects who did not have detectable serum concentrations. Clonidine has an elimination half-life of 6–20 hours (PubChem, 2020a).

Campbell et al. (2012) did not provide specific pharmacokinetic results; however, the authors reported that participants' serum levels of clonidine at 2 weeks were similar to those at 12 weeks. They also noted that generally, serum levels were below the level of detection (10 pg/mL) but that two outliers produced levels at 796 pg/mL and 315 pg/mL. For context, they note that the average plasma level of clonidine for treating hypertension is more than 1,000 pg/mL.

Safety and Adverse Effects

Randomized controlled trials In Campbell et al. (2012) discussed above, no serious adverse events were noted in the clonidine group, but skin reactions were noted in the placebo group. In BioDelivery Sciences International (2017a), discussed above, more serious adverse events, which include cardiac, gastrointestinal, musculoskeletal, nervous system, respiratory, and vascular disorders, were noted in the clonidine group (12 versus 7 in the control group) while other nonserious adverse events, including peripheral edema, back pain, headache, and skin disorders were in the placebo group (58 versus 38). In BioDelivery Sciences International (2017c), a small number of serious adverse events were documented (clonidine group—2; comparator group—6) as well as other adverse effects (clonidine—4; comparator—2). Finally, in BioDelivery Sciences International (2017b), discussed above, serious adverse events were reported in 23 patients and other adverse events in 79 patients.[13]

From the FDA-approved label, serious adverse effects from oral administration of this API include increased suicidal thoughts and cardiac arrhythmias. See Table G-1 in Appendix G.

Anticonvulsant: Carbamazepine

Summary

Carbamazepine is an anticonvulsant drug that exerts its effect by blocking voltage-gated sodium channels, which results in neural membrane stabilization and decreased ectopic nerve discharges. In the United States, oral carbamazepine is FDA approved for the treatment of patients with focal onset seizures and generalized onset seizures. For neuropathic pain, it is FDA approved for the treatment of trigeminal neuralgia and glossopharyngeal neuralgia. It also has an FDA-approved indication for bipolar disorder (acute treatment of hypomania and mild moderate manic or mixed episodes). Some studies, mostly performed prior to gabapentin becoming available, suggest effectiveness in patients with painful diabetic neuropathy and possibly other neuropathic pain conditions.

Systemic carbamazepine has many side effects that include dose-dependent toxic effects that more commonly occur with rapid dosage increase, such as dizziness, drowsiness, nausea, ataxia, and blurred vision. Other potential side effects are impaired liver function and hyponatremia that require routine monitoring during therapy. Treatment with oral carbamazepine has also been associated with serious side effects: blood dyscrasias (bone marrow depression, including aplastic anemia, agranulocytosis,

[13] One confirmed death during the course of the study, but cause of death was not disclosed.

leukopenia thrombocytopenia), lymphadenopathy, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and others. Other dermatological side effects include pruritus and skin rash. Systemic carbamazepine also has many drug–drug interactions and is a strong CYP3A4 inducer that reduces the serum levels of many other medications.

Related to the topical application of carbamazepine, well-designed clinical studies that address the committee's specific research interests are not available. The literature includes a few case studies either as single-ingredient compounded topical drug or in combination with other medications. The quality of the data does not allow any conclusion regarding effectiveness or safety. Information on the safety of topical carbamazepine is limited. The quality of the data does not allow any conclusion regarding effectiveness or safety. As described above, as an oral medication it has many systemic side effects including potentially severe drug reactions that affect the bone marrow, skin, and liver. There is a suggestion in preclinical and in vitro studies that topical carbamazepine is toxic to epidermal keratinocytes when applied in high concentration and with a long exposure. See Box 6-3 for a summary of research findings.

BOX 6-3
Summary of Research Findings on Carbamazepine in Compounded Topical Pain Creams

Effectiveness: There is no evidence to determine the effectiveness of topical carbamazepine in the treatment of pain when applied to intact skin.

Dermal penetration/bioavailability: There is insufficient evidence on the dermal penetration and bioavailability of topical carbamazepine. A single in vitro study suggests poor absorption through human skin owing to the highly lipophilic structure of carbamazepine. Modifications to the ingredient or excipient may increase aqueous solubility and increase absorption.

Safety and adverse effects: There is insufficient evidence on the safety of topical carbamazepine. A single in vitro study suggests cytotoxic properties at high concentrations and long exposures to the drug. However, if systemic absorption to therapeutic levels is achieved through topical application, there is potential for side effects similar to other routes of administration (e.g., oral).

Effectiveness

There are no relevant clinical studies that examine the single-drug use of carbamazepine in compounded topical creams to treat pain when applied to intact skin.

Dermal Penetration/Bioavailability

In vitro studies A study by Fourie et al. (2004) in Franz diffusion cells using human abdominal skin showed that modifications to the (very lipophilic) carbamazepine molecule can enhance skin permeation by increasing the aqueous solubility, in particular as N-methyl- and as N-(2-hydroxyethyl)-carbamazepine. Of note, the excipients vary according to author, with no clear information about the effect on skin penetration or absorption (see Anonymous, 2008; Zhou et al., 2015). See Chapter 5 for a discussion on the critical role of excipients in drug delivery and absorption.

Safety and Adverse Events

In vitro studies Al-Musawi et al. (2017) conducted a toxicity analysis of topical drugs (i.e., amitriptyline, carbamazepine, gabapentin) commonly used for the treatment of neuropathic orofacial pain. After examining the effects on keratinocytes in cell culture, the authors reported that carbamazepine was cytotoxic to skin and oral keratinocytes, demonstrating significant decrease in cellular viability and cell counts, at high concentrations (1.7 mM) and with long exposure (2 hours). The authors also reported that topical gabapentin was only minimally cytotoxic to skin or oral keratinocytes at high concentrations (5.54 mM) and long exposure (24 hours). Importantly, topical amitriptyline was reported as cytotoxic to skin and oral keratinocytes at both short (30 minutes) and long (24 hours) exposure times and at low (200 µM) and high concentrations (1.8 mM).

From the FDA-approved label, serious adverse effects from oral administration of this API include Stevens-Johnson syndrome, toxic epidermal necrolysis, atrioventricular block, syncope, and liver failure. See Table G-1 in Appendix G.

Anticonvulsant: Gabapentin

Summary

Gabapentin, while structurally related to gamma aminobutyric acid (GABA), is believed to exert its effect by binding to the α_2ò subunit of voltage-gated calcium channels on primary afferent neurons with the central nervous system (CNS). Gabapentin and the structurally similar medication

pregabalin are often labeled as "gabapentinoids," with pregabalin binding to the same receptors as gabapentin, but with higher binding affinity. Both are believed to bind presynaptically to modulate calcium influx at the nerve terminals, thus inhibiting the release of excitatory neurotransmitters. Gabapentin is entirely excreted through the kidney and pregabalin predominately this way with almost no direct drug–drug interactions (PubChem, 2020b,d).

Oral gabapentin is an FDA-approved anticonvulsant. Gabapentin is commonly used orally, in part because it is relatively safe with few clinically relevant drug interactions. Most common side effects are somnolence, dizziness, and peripheral edema. Occasionally significant peripheral edema can lead to discontinuation, with complete reversal of symptoms with cessation of the medication (PubChem, 2020b).

In the United States, gabapentin is labeled as an adjunctive therapy in the treatment of focal seizures (with or without generalization), and it is FDA approved for the management of postherpetic neuralgia. Pregabalin has also labeled indications for fibromyalgia, painful diabetic neuropathy, and neuropathic pain associated with spinal cord injury (PubChem, 2020d). Studies and guidelines support the use of gabapentin in these conditions; for example, it is used as a first- or second-line therapy to treat painful diabetic neuropathy (Attal, 2010; Bril, 2011; Finnerup, 2013; NICE, 2013).

As outlined in the section below, well-designed clinical studies focusing on the safety and effectiveness on topical gabapentin are not available; therefore, definitive conclusions on its safety and effectiveness in this dosage form are not possible. The best single-drug studies are available for vulvodynia where case series suggested benefit, but a recent blinded and placebo-controlled crossover study failed to show benefit for gabapentin.[14] Studies of urine concentration in patients exposed to topical gabapentin suggest very low to undetectable absorption rates. In vitro studies using Franz diffusion cells document absorption rates that vary greatly by excipient used. Information on safety is limited. Major adverse effects were only reported for single cases, where topical compounded creams also included other drugs, with toxicity not likely caused by gabapentin. Gabapentin in oral preparation is considered fairly safe, thus the risk of side effects from topical gabapentin appears low, even if there is some degree of systemic absorption. See Box 6-4 for a summary of research findings. (See the Multiagent Compounded Topical Pain Creams section of this chapter for further discussion of creams with gabapentin in combination with other APIs.)

[14] Vulvodynia is outside the scope of this review as the vulva is not representative of normal skin. However, several studies have shown benefit of gabapentin in treating vulvodynia (e.g., Boardman et al., 2008; University of Rochester and Mae Stone Goode Foundation, 2015).

BOX 6-4
Summary of Research Findings on Gabapentin in Compounded Topical Pain Creams

Effectiveness: There is insufficient evidence to determine the effectiveness of gabapentin to treat pain when applied to intact skin.

Dermal penetration/bioavailability: Evidence suggests topical gabapentin can be detected at low concentrations in urine specimens of patients. In vitro evidence suggests that topical gabapentin penetrates through human skin and that the absorption varies greatly with the excipient used.

Safety and adverse effects: There is insufficient evidence to determine the safety of topical gabapentin. However, if systemic absorption to therapeutic levels is achieved through topical application, there is potential for side effects similar to other routes of administration (e.g., oral).

Effectiveness

Randomized controlled trials There are no relevant RCTs that examine the single-drug use of gabapentin in compounded topical creams to treat pain when applied to intact skin. The best evidence for single-drug topical gabapentin is from studies in vulvodynia, which was outside the scope of the committee's research focus.

Case reports and case series Hiom et al. (2014) published a case series in patients with mixed neuropathic pain and reported benefit in 20 of 23 patients when treated with gabapentin 6 percent topically applied three times per day. Eleven of 23 patients reported at least 30 percent pain reduction, and 2 of 3 patients with postherpetic neuralgia reported reduction in pain by 60 percent and 57 percent.

Vadaurri (2008) provides a narrative review about topical medication in palliative care that includes two patients treated with a topical gabapentin cream, with gabapentin 5 percent compounded in pluronic lecithin organogel. Two patients described received gabapentin 5 percent in pluronic lecithin organogel with benefit reported with marked reduction in numeric pain scores within days. One patient had severe right leg pain (with no clear diagnosis provided) and used the cream as 2 mL twice daily. The other patient had painful neuropathy following chemotherapy and was started on 1 mL to each hand and foot twice daily.

Many case reports and case series include gabapentin as part of multidrug topical preparations that are summarized in the Multiagent Compounded Topical Pain Creams section of this chapter.

Preclinical studies Animal studies evaluating the peripheral action of gabapentin include Ortega-Varela et al. (2007), who studied subcutaneous injection in the rat model to treat formalin-induced injury.

Dermal Penetration/Bioavailability

Clinical studies Glinn et al. (2017) reported on urine drug concentrations in a large number of patients receiving gabapentin as oral and/or topical medication. Glinn et al. analyzed 29,139 urine specimens with gabapentin prescribed in an oral formulation with urine detection positive in 34 percent (9,948) positive. In 85 percent of positive results from patients prescribed oral gabapentin the concentration was above 10,000 ng/mL. In the 187 patients with gabapentin prescribed in the form of a cream, gabapentin was detected in 22 (12 percent). Of the positive cases, all but two had gabapentin present below 1,500 ng/mL. Two specimens showed gabapentin present greater than 10,000 ng/mL, likely owing to receiving gabapentin orally as well as topically, but that information was not included in the patient demographic information. Glinn et al. concluded that gabapentin topically results in very low detection in urine compared to oral administration. For the positive oral specimens, the mean urine concentration level was greater than 10,000 ng/mL. In contrast, for the positive topical specimens, the mean concentration was reported as 261 ng/mL.

The authors also analyzed amitriptyline, ketamine, and cyclobenzaprine urine drug concentration levels. They noted that in contrast to gabapentin and amitriptyline, ketamine and cyclobenzaprine were more readily detectable and with higher concentrations (as percentage of levels with oral dosing). Excipients varied across studies and absorption rates varied greatly between excipients.

Preclinical studies Wang et al. (2013) reported on the percutaneous absorption of gabapentin in Franz diffusion cells with human trunk skin, as well as other model drugs. They compounded their preparations in two different bases, the "Versatile" cream and a reference base. They reported on the pharmacokinetic profile for each drug for up to 48 hours. For gabapentin, the peak absorption (flux rate) peaked at 4 hours and was sustained at a lower and gradually diminishing rate thereafter. As with the other drugs, the Versatile base formulation provided enhanced absorption compared to the reference.

Martin et al. (2017) reported on a variety of topical gabapentin preparations that included commercially available proprietary bases and enhancers. They report that topical gabapentin delivery varies greatly. They showed that gabapentin 6 percent with Carbopol hydrogels containing dimethyl sulfoxide (DMSO) or 70 percent ethanol, and a compounded gabapentin 10 percent in Lipoderm formulation, were able to facilitate permeation of the gabapentin molecule across human skin.

Bassani and Banov (2016) studied the skin absorption of two mixed compounded topical creams using cadaver skin by the Franz Finite Dose Model. The transdermal creams contained ketamine 5 percent, gabapentin 10 percent, clonidine 0.2 percent, and baclofen 2 percent. One cream was compounded using Lipoderm and the second was compounded using Lipoderm ActiveMax. All drugs were shown to penetrate into and through human cadaver trunk skin.

Bryson et al. (2014) reported an in vitro study of the transdermal penetration of gabapentin in Franz diffusion cells and an in vivo preclinical rodent study. The penetration of gabapentin was studied in Franz diffusion cells using porcine skin, with gabapentin compounded as 5 percent in two commonly used commercial bases (Lipobase, Lipoderm) and a standard poloxamer lecithin organogel. The penetration and retention of gabapentin was dependent on base and overall poor, with only microgram levels of gabapentin penetrating into the porcine skin over a 24-hour period. With the poloxamer lecithin organogel base, three to four times as much gabapentin was retained in the skin compared to Lipobase and Lipoderm bases.

For the in vitro study, the authors used gabapentin 5 percent and 1 percent that were compounded using Lipoderm as the base and tested in an in vivo preclinical rodent formalin pain model (hind paw). They documented reduced nociceptive behavior of paw flinches with subcutaneous injection of gabapentin and with 5 percent topical gabapentin gel applied to the ipsilateral hind paw prior to formalin administration. The authors noted evidence of systemic effect of gabapentin applied topically, as well as the local effect, as was shown by reduced formalin-induced behavior with gabapentin applied ipsilateral versus no effect when applied to the contralateral limb. (Note that studies by Bryson et al. had pharmaceutical industry support.)

Le Uyen et al. (2018) reported in vitro analysis of penetration across porcine skin for different gabapentin preparations. In their study, they compared gabapentin encapsulated elastic liposomes with compounded gabapentin-based pluronic lecithin organogel regarding their efficiency in transdermal delivery of gabapentin. Gabapentin released slowly from liposomes over 12 hours while it was rapidly released from pluronic lecithin organogel within 4 hours. After 24 hours, liposomes significantly accelerated the percutaneous penetration of gabapentin through the porcine skin leading to

higher cumulative drug concentrations (~98 percent of drug permeated) as compared to pluronic lecithin organogel (~55 percent of drug permeated).

Safety and Adverse Events

Studies listed for gabapentin as a single-drug compounded cream do not report side effects from the topical medication.

Case reports and case series Pomerleau et al. (2014) describes a 23-year-old man with accidental overdose after rubbing a compounded topical with multiple drugs over his entire body. In this single case, safety concerns owing to high absorption were likely caused by the clonidine component of the compounded drug (documented by very high serum levels), rather than gabapentin.

In vitro studies Al-Musawi et al. (2017), as discussed in the carbamazepine section above, conducted a toxicity analysis of commonly used topical drugs (i.e., amitriptyline, carbamazepine, gabapentin) commonly used for the treatment of neuropathic orofacial pain. After examining the effects on keratinocytes in cell culture, the authors reported that carbamazepine was cytotoxic to skin and oral keratinocytes, demonstrating significant decrease in cellular viability and cell counts, at high concentrations (1.7 mM) and with long exposure (2 hours). The authors also reported that topical gabapentin was only minimally cytotoxic to skin or oral keratinocytes at high concentrations (5.54 mM) and long exposure (24 hours). Importantly, topical amitriptyline was reported as cytotoxic to skin and oral keratinocytes at both short (30 minutes) and long (24 hours) exposure times and at low (200 µM) and high concentrations (1.8 mM).

From the FDA-approved label, serious adverse effects from oral administration of this API include Stevens-Johnson syndrome. See Table G-1 in Appendix G.

Anticonvulsants: Topiramate

Summary

Oral topiramate is FDA approved as an anticonvulsant, though it is not structurally related to existing anticonvulsants (Privitera, 1997). Topiramate has multiple pharmacological mechanisms of action, which led to its approval to treat migraine prophylaxis. The most notable mechanisms of action thought to be responsible for its reported effectiveness treating these conditions are its role as a sodium channel blocker, GABA-A receptor enhancer, and calcium channel inhibitor (Wiffen et al., 2013). Common

BOX 6-5
Summary of Research Findings on Topiramate in Compounded Topical Pain Creams

Effectiveness: There is no evidence on the effectiveness of topical topiramate to treat pain when applied to intact skin.

Dermal penetration/bioavailability: There is no evidence on the dermal penetration and bioavailability of topical topiramate.

Safety and adverse effects: There is no evidence on the safety of topical topiramate. However, if systemic absorption to therapeutic levels is achieved through topical application there is potential for side effects similar to other routes of administration (e.g., oral).

adverse drug reactions to oral dosage of topiramate include dizziness, cognitive disturbance, weight loss, and nausea (Sommer and Fenn, 2010).

No relevant clinical studies regarding the use of compounded topical topiramate were found, so no conclusions regarding its safety or effectiveness can be formed. From the FDA-approved label, serious adverse effects from oral administration of this API include erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. See Table G-1 in Appendix G. Studies are needed as there are no data to support its use. See Box 6-5 for a summary of research findings.

Antispasmodic: Baclofen

Summary

Oral and topical baclofen is FDA approved to treat reversible spasticity. Baclofen is thought to be primarily a centrally acting drug, is a structural analogue of GABA, and an agonist of $GABA_B$ receptors in the CNS with the greatest density in the dorsal horn of the spinal cord. By binding to these receptors, monosynaptic and polysynaptic spinal reflexes are inhibited, thus, reducing muscle tone and especially flexor spasms. Presynaptic binding reduces calcium influx while postsynaptic binding increases potassium efflux from the Ia afferent terminal, resulting in hyperpolarization and interruption of the action potential transmission (Elovic, 2001).

Evidence from animal studies suggests that a peripheral antinociceptive effect of baclofen may occur by a mechanism related to specific types of potassium channels (Reis and Durarte, 2006). See Box 6-6 for a summary of research findings.

BOX 6-6
Summary of Research Findings on Baclofen in Compounded Topical Pain Creams

Effectiveness: There is insufficient evidence on the effectiveness of topical baclofen to treat pain when applied to intact skin.

Dermal penetration/bioavailability: There is no evidence on the dermal penetration and bioavailability of topical baclofen.

Safety and adverse effects: There is no evidence on the safety of topical baclofen. However, if systemic absorption to therapeutic levels is achieved through topical application there is potential for side effects similar to other routes of administration (e.g., oral).

In addition to reviewing studies where baclofen alone was analyzed, the committee also included studies of baclofen used in combination with other APIs. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

Effectiveness

Randomized controlled trials There are no relevant RCTs that examine the single-drug use of baclofen in compounded topical creams to treat pain when applied to intact skin.

Case reports Hesselink and Kopsky (2013) describe a 65-year-old woman with acromegaly and neuropathic pain in her legs. The patient reported pain as 9 on a 0–10 NRS and was initially treated with a compounded analgesic cream, based on baclofen 5 percent and told to apply 1 gram maximally three times per day. After 2 weeks, she reported reduction of her pain by more than 95 percent based on one application daily, but she complained of numbness in her legs. The dose was reduced to baclofen 2 percent, and she reported benefits with use only 1–3 times per week for 6 months without side effects.

Kopsky and Hesselink (2017) describe a 54-year-old woman with neuropathic pain in both feet reported as 8 out of 10 on the NRS following chemotherapy treatment despite being prescribed oral gabapentin 2,000 mg daily and oxycodone 20 to 30 mg daily. Pain was reduced to 3 by a test application of compounded topical baclofen 5 percent cream, which was said to be a greater reduction than with compounded clonidine 0.2 percent

cream or compounded lidocaine 3 percent combined with isosorbide dinitrate 0.4 percent cream. Allodynia was still present but eliminated with ketamine 10 percent cream. Pain level increased over time from 3 to 7 on the NRS, which led to further treatment.

Preclinical studies Preclinical studies using animal pain models suggest that baclofen (2.5–10 mg kg^{-1} doses) has antinociception activity in mice and rats when given systemically for a formalin test (Shafizadeh et al., 1997) and tail-flick test (Sabetkasai et al., 1999) or intrathecally for tail-flick and hot plate tests (Aran and Hammon, 1991), but there are no studies of topical application.

Dermal Penetration/Bioavailability

No relevant studies with baclofen alone were found in the literature; however, the committee included studies of baclofen used in combination with other APIs. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

Safety and Adverse Effects

No relevant studies with topical baclofen alone were found in the literature. From the FDA-approved label, serious adverse effects from oral administration of this API include gastrointestinal bleeding. See Table G-1 in Appendix G.

Antispasmodic: Cyclobenzaprine

Summary

Cyclobenzaprine is a tricyclic amine salt with structural similarities to the tricyclic antidepressants such as amitriptyline. Although it has sedative effects and has been investigated as an antidepressant, when taken orally its central action also relaxes skeletal muscle and is FDA approved for relief of musculoskeletal pain and muscle spasms (Kroenke et al., 2009; McNeil Consumer Healthcare, 2013). Off-label use has also included chronic pain states such as fibromyalgia (Bryson et al., 2015). Cyclobenzaprine depresses noradrenergic and serotonergic descending pathways from the brain, thereby inhibiting alpha and gamma motor neurons in the ventral horn of the spinal cord (Bryson et al., 2015; McNeil, 2013). Its action is therefore primarily within the CNS at the brain stem, although some effect at the spinal cord level may contribute to muscle relaxation (McNeil Consumer Healthcare, 2013). Cyclobenzaprine is highly bound to blood proteins, metabolized by

the liver to glucuronides, and eliminated primarily via urinary excretion, with an effective half-life after oral ingestion of 18 hours (8 to 37 hours measured in 18 subjects) and a plasma clearance of 0.7 L/min (McNeil Consumer Healthcare, 2013; Pesko, 1998). Cyclobenzaprine is also excreted in bile and undergoes enterohepatic circulation (McNeil Consumer Healthcare, 2013).

Cyclobenzaprine relieves muscular spasms of local origin through its centrally inhibition action, but it is ineffective for spasm resulting from CNS disease. No clear evidence supports a peripheral mechanism of action. The available literature is unclear on whether topical treatment will result in absorption of a sufficient systemic dose to result in pain relief. See Box 6-7 for a summary of research findings.

In addition to reviewing studies where cyclobenzaprine alone was analyzed, the committee also included studies of cyclobenzaprine used in combination with other APIs. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

Effectiveness

Randomized controlled trials There are no relevant RCTs that examine the single-drug use of cyclobenzaprine in compounded topical creams to treat pain when applied to intact skin.

Clinical studies A retrospective cohort study indicated that cyclobenzaprine as part of a compounded topical pain cream with four other drugs was more effective than Volatren gel; however, as with the clinical trials, the individual effect of cyclobenzaprine cannot be assessed (Somberg and Molnar, 2015a).

BOX 6-7
Summary of Research Findings on Cyclobenzaprine in Compounded Topical Pain Creams

Effectiveness: There is insufficient evidence on the effectiveness of topical cyclobenzaprine to treat pain when applied to intact skin.

Dermal penetration/bioavailability: Limited evidence (in humans and animal studies) suggests dermal penetration of topically applied cyclobenzaprine.

Safety and adverse effects: Insufficient evidence suggests topical application of cyclobenzaprine may cause allergic contact dermatitis.

Preclinical studies The effect of topical cyclobenzaprine formulations (1 or 5 percent in Lipoderm base) on nociception was studied using male hamsters (six animals per group) injected in the hind paw with formalin to produce pain (Bryson et al., 2015). In addition to the two cyclobenzaprine topical treatment groups, a control group received topical Lipoderm base and another group received a subcutaneous injection of 10 µg/kg cyclobenzaprine. Animals were treated with 0.5 mL of topical cream to the ventral and dorsal hind paw or subcutaneous injection 30 minute before receiving the injection of formalin. Pain reaction was scored as the number of paw flicks or holding the paw up. Topical application of cyclobenzaprine at either concentration did not reduce pain-related behaviors compared to the vehicle control. Subcutaneous injection (location not specifically stated) did reduce pain-related behaviors compared to the vehicle control and topical pain cream groups. The mechanism of action for oral administration of cyclobenzaprine in treating musculoskeletal pain or spasms involves a primary action at the brain stem level and not locally. It appears to be unknown whether local targets exist for pain relief by this compound. Thus, the available literature is unclear on whether topical treatment will result in sufficient systemic dose to result in pain relief.

Dermal Penetration/Bioavailability

Clinical studies Urinary samples were analyzed for drug constituents (including cyclobenzaprine) in patients prescribed a compounded topical cream or oral medications with the same compounds (Glinn et al., 2017). Patients were adults with the largest fraction (26 percent) for the oral group being ages 51–60 years, and the largest fraction for the topical pain cream group (26 percent) was ages 31–40 years old. Pain creams tested typically contained one or more of 6 percent gabapentin, 2 percent cyclobenzaprine, 5 percent ketamine, or 5 percent amitriptyline by weight, and also frequently contained ketoprofen, baclofen, clonidine, or lidocaine, which were not analyzed. Of the 74 subjects in the topical application group tested for cyclobenzaprine and its major metabolite, norcyclobenzaprine, in urine, only 7 were positive for the former and 6 for the latter. Higher percentages tested positive for the group prescribed oral cyclobenzaprine (884 positive for cyclobenzaprine and 867 for norcyclobenzaprine with n = 9,036), and the urinary concentrations were much higher. Detected mean urinary concentrations in the topical group were 54 ng/mL and 57 ng/mL for cyclobenzaprine and norcyclobenzaprine, respectively, compared to mean detected urinary concentrations in the oral group of 383 ng/mL and 272 ng/mL, respectively. Glinn et al. (2017) noted that the low percentages of detections may be the result of patients taking their pain medication

only when needed and not frequently enough to result in more detectable urinary concentrations.

Preclinical studies Dermal penetration of cyclobenzaprine was studied in vitro using a Franz diffusion cell model with 5 percent cyclobenzaprine in three different bases: Lipoderm, Lipobase, and standard poloxamer lecithin organogel. Cyclobenzaprine in each of the three bases showed dermal penetration. For formulations 1 and 2, penetration was rapid within the first 30 minutes to 1 hour, reaching approximately 76 to 84 percent of maximum levels (30 to 40 $\mu g/cm^2$) within 1 hour. For formulation 3, penetration was initially slower but reached a maximum of 600 $\mu g/cm^3$ after 25 hours. "Modest levels" were retained in the skin (formulation 1: 28.94; formulation 2: 55.07; formulation 3: 42.70 µg/g skin).

In animal model studies, Bryson et al. (2015) postulated that topical cyclobenzaprine (at 1 percent and 5 percent concentration) was ineffective in relieving local pain unlike subcutaneous injection (10 mcg/kg) because topical application did not result in a sufficiently high systemic concentration.

Safety and Adverse Events

Case studies Cyclobenzaprine was reported to have caused an allergic skin reaction in a 39-year-old White male with degenerative disc disease and cervical radiculopathy who experienced substantial pain relief from application (Turrentine et al., 2015). The topical pain cream contained 10 percent ketamine, 5 percent diclofenac, 2 percent baclofen, 1 percent bupivacaine, 2 percent cyclobenzaprine, 6 percent gabapentin, 3 percent ibuprofen, and 3 percent pentoxifylline in Lipoderm ActiveMax cream base. However, after several weeks of use, a pruritic rash occurred at the site of application. Discontinuation of the cream cleared the rash with return of the pain. Subsequent patch testing of the individual components and the mixture implicated cyclobenzaprine. Removal of cyclobenzaprine from the original mixture resolved the allergic reaction.

From the FDA-approved label, serious adverse effects from oral administration of this API include cardiac dysrhythmia, heart block, myocardial infarction, and syncope. See Table G-1 in Appendix G.

Antispasmodic: Orphenadrine

Summary

Orphenadrine is an FDA-approved (oral, injection) skeletal muscle relaxant that is often used to relieve pain caused by muscle injuries (e.g.,

sprains). Orphenadrine binds and inhibits both histamine H1 receptors and NMDA receptors. It exhibits anticholinergic effects and may have a relaxing effect on skeletal muscle spasms (by central antimuscarinic action). The most common side effects of oral dosages include drowsiness, dry mouth, confusion, and visual disturbances. Orphenadrine also has potential for abuse, and fatal overdoses have been reported (NIDDK, 2017). No data were found on the effectiveness or safety of orphenadrine used topically. See Box 6-8 for a summary of research findings.

Effectiveness

There are no relevant clinical studies that examine the single-drug use of orphenadrine in compounded topical creams to treat pain when applied to intact skin.

Dermal Penetration/Bioavailability

In vitro studies Diffusion of orphenadrine across human cadaver skin was evaluated using the Franz diffusion cell (Wang and Black, 2013). A 10 percent cream was formulated in Versatile cream base and compared to a reference cream (not defined). After 48 hours, a total of 0.00477 mg (0.191 percent) in the Versatile cream and 0.00326 mg (0.130 percent) in the reference cream were measured in the receiver compartment.

BOX 6-8
Summary of Research Findings on Orphenadrine in Compounded Topical Pain Creams

Effectiveness: There is no evidence on the effectiveness of topical orphenadrine to treat pain when applied to intact skin.

Dermal absorption/bioavailability: Insufficient evidence suggests that topical orphenadrine may penetrate through human skin in in vitro assays. Modifications to the ingredient or excipient may increase aqueous solubility and increase absorption.

Safety and adverse effects: There is no clinical evidence on the safety of topical orphenadrine. However, if systemic absorption to therapeutic levels is achieved through topical application there is potential for side effects similar to other routes of administration (e.g., oral).

Safety and Adverse Effects

No data were found on the safety of orphenadrine alone in topical pain creams. From the FDA-approved label, serious adverse effects from oral administration of this API include palpitations and tachyarrhythmia. See Table G-1 in Appendix G.

Calcium Channel Antagonist: Nifedipine

Summary

Nifedipine is a dihydropyridine calcium channel blocking agent. It works by inhibiting the influx of extracellular calcium into myocardial cells and into vascular smooth muscle cells. Its pharmacologic actions include vasodilation, and it is used primarily as an antihypertensive and for angina. The most common adverse events reported in clinical trials include peripheral edema, headache, dizziness, constipation, and flushing (Snider et al., 2008). Nifedipine does not have an FDA-approved indication to treat pain.

Topical nifedipine has been used in the treatment of anal fissures and has demonstrated evidence of relative safety and effectiveness (see Golfam et al., 2010; Khaledifar et al., 2015; Perrotti et al., 2002; Salem et al., 2018); however, for this report, the committee largely excludes discussions on wound care and mucosal membranes and cavities (e.g., mouth, eyes, vulva, vagina, anus, and nose). Related to the report's focus, there is insufficient evidence on the effectiveness or safety of nifedipine used topically on intact skin for the relief of pain. In fact, the committee's search identified only a single retrospective study, which demonstrated no difference between compounded topical formulations (with or without nifedipine) in predicting efficacy in treating pain. See Box 6-9 for a summary of research findings.

In addition to reviewing studies on nifedipine alone, the committee also included studies of nifedipine used in combination with other APIs. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

Effectiveness

Randomized controlled trials There are no relevant RCTs that examine the single-drug use of nifedipine in compounded topical creams to treat pain when applied to intact skin.

Retrospective clinical studies A retrospective review of data from patient charts examined the influence of 2 percent nifedipine in treating inflammatory disorders (Somberg and Holnar, 2015b). In this study, the authors

BOX 6-9
Summary of Research Findings on Nifedipine in Compounded Topical Pain Creams

Effectiveness: There is insufficient evidence on the effectiveness of topical nifedipine to treat pain when applied to intact skin.

Dermal penetration/bioavailability: There is no evidence on the dermal penetration and bioavailability of topical nifedipine.

Safety and adverse effects: There is insufficient evidence on the safety of topical nifedipine. However, if systemic absorption to therapeutic levels is achieved through topical application there is potential for side effects similar to other routes of administration (e.g., oral).

applied two formulations both containing ketamine 10 percent, baclofen 2 percent, gabapentin 6 percent, amitriptyline 4 percent, bupivacaine 2 percent, and clonidine 0.2 percent, but one cream also contained 2 percent nifedipine (n = 205) and the other cream did not (n = 78). Both creams contained inactive ingredients of pentoxifylline and Tranilast (listed as an antiallergic agent used for treatment of inflammatory disorders). The authors determined no differences between formulations (with or without nifedipine) in predicting efficacy. The location of patient charts were not specified, and the authors had no affiliation with a medical institution.

Dermal Penetration/Bioavailability

No data were found on the dermal penetration and bioavailability of nifedipine alone in topical pain creams.

Safety and Adverse Effects

In Somberg and Molnar (2015b), the formulation with 2 percent nifedipine produced an adverse effect rate of 3.8 percent, as compared to a rate of 5.7 percent for the other cream. Adverse effects were minor to moderate and included skin irritation, burning, rash, flushing, and three cases of unspecified minor adverse effects. However, the authors did not differentiate between the two treatment groups with respect to the adverse effects.

From the FDA-approved label, serious adverse effects from oral administration of this API include myocardial infarction, ventricular arrhythmia, suicidal thoughts, and kidney damage. See Table G-1 in Appendix G.

Cannabinoid: Cannabidiol

Summary

Medicinal use of marijuana (*Cannabis sativa*) can be traced back 5,000 years for treatment of cramps and pain in China (Zou and Kumar, 2018). Of the more than 100 phytocannabinoids in *Cannabis*, cannabidiol (CBD) has attracted recent medicinal attention because of its antiepileptic,[15] antinociceptive, anti-inflammatory, and antifibrotic drug properties, as well as its low intoxicating effects, unlike Δ^9-tetrahydrocannabinol (THC)[16] (Bruni et al., 2018; NASEM, 2017; VanDolah et al., 2019). Based on a few case and experimental animal studies, topically applied CBD oil appears to be absorbed locally, regionally, and systemically to reduce pain, inflammation, and fibrosis. Possible safety concerns from systemic absorption by other routes include CNS depression, liver enzyme elevation, and suicidal thoughts and actions. RCTs are needed to establish efficacy and safety for topical use of CBD in humans. Variable concentrations of THC in CBD oil is concerning (VanDolah et al., 2019). See Box 6-10 for a summary of research findings.

Effectiveness

Randomized controlled trials There are no relevant clinical studies that examine the single-drug use of CBD in compounded topical creams to treat pain when applied to intact skin.[17]

A transdermal gel for regional and systemic delivery of CBD (Zynerba Pharmaceuticals) is in clinical development for treatment of epilepsy, developmental and epileptic encephalopathy, fragile-X syndrome, and osteoarthritis (Bruni et al., 2018).[18] The manufacturer's website notes that this product is currently experimental and not yet approved by FDA.

Case reports Chelliah et al. (2018) reported on a case series of three children (6 months old, 3 years old, and 10 years old) using topical CBD alone

[15] CBD has been approved by FDA as the active ingredient in an oral solution (EPIDIOLEX) for the treatment of rare forms of severe epilepsy, along with other medications (FDA, 2018; GW Biosciences, 2018). The mechanism of action for seizure reduction, however, is unknown and does not appear to involve the cannabinoid receptors (GW Biosciences, 2018). Currently, CBD is not FDA approved to treat pain.

[16] THC is present at variable low levels in CBD, typically < 0.3 percent (VanDolah et al., 2019).

[17] Preclinical and pilot studies using CBD and hemp oils have been conducted for treatment of inflammation and pain (VanDolah et al., 2019).

[18] Compounded drugs prepared for investigational new drug trials are subject to current good manufacturing practice requirements under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

BOX 6-10
Summary of Research Findings on Cannabidiol in Compounded Topical Pain Creams

Effectiveness: There is insufficient evidence on the effectiveness of topical cannabidiol to treat pain when applied to intact skin. Evidence from animal studies suggests that topically applied cannabidiol in a gel may be superior to placebo for treatment of pain, inflammation, and fibrosis.

Dermal penetration/bioavailability: There is limited preclinical evidence to suggest that cannabidiol penetrates animal skin. Modifications to the ingredient or excipient may increase aqueous solubility and increase absorption.

Safety and adverse effects: There is insufficient evidence on the safety of topical application of cannabidiol. However, if systemic absorption to therapeutic levels is achieved through topical application, there is potential for side effects similar to other routes of administration (e.g., oral).

or in combination with emu oil to treat painful lesions from epidermolysis bullosa (authors from the Stanford University Medical Center). Information on treatment and outcome appears to have been collected from parents with little specifics on amount or frequency applied. The topical CBD oil was reported to promote faster wound healing, less blistering, and reduction in pain for all three children, and one was weaned off oral opioid analgesics.

In a case series in the Netherlands, one case included topical CBD application in addition to sublingual CBD oil (20 mg/mL) with THC (13 mg/mL) to treat epidermolysis bullosa (Schraeder et al., 2019). A 64-year-old woman was started at sublingual doses of 0.5 mg CBD and 0.325 THC four times daily, which was increased stepwise to 2.5 mg CBD and 1.625 mg THC four times daily. By 3 months, she was able to wean off oxycodone except for dressing changes, and for the next 2 years she replaced topical morphine with 1 mg topical CBD and 0.65 mg THC applied daily to her painful heel and was weaned off amitriptyline. The CBD/THC oil applications also resulted in a moderate reduction in pruritus, with increased appetite as the only side effect.

Preclinical studies Del Rio et al. (2018) administered the CBD aminoquinone derivative (VCE-004.3) by intraperitoneal injection or topically in a mouse model of fibrotic disease. After induction of subcutaneous fibrosis, CBD derivative was administered topically (250 μM; formulated with 7:3 polypropylene glycol:ethanol) and by injection (20 mg/kg) for 3 weeks

(location of fibrosis of topical application not specified). CBD reduced expression of fibrotic genes to below vehicle control levels, and was as effective as injected CBD in reducing skin fibrosis, although neither completely restored the decrease in the adipose tissue layer.

Hammell et al. (2016) applied CBD hydroalcoholic gel (1 or 10 percent CBD) to the shaved backs of rats after inducing arthritis of the knee by injections of Freund's adjuvant. Of the applied CBD doses (0.6, 3.1, 6.2, or 62.3 mg/day for 4 days), the two higher doses equally reduced swelling (including immune markers of inflammation) and pain indicators in the knee by about 50 percent of vehicle control.

Lodzki et al. (2003) examined the anti-inflammatory effect of 100 mg CBD gel (3 percent weight concentration [w/w] CBD and 40 percent ethanol in a carbomer gel) applied to the abdomen and hip area of mice (abdomen and hip area) under an occluded patch for 19 hours before carrageenan injection in a paw. Paw thickness after this injection was about 0.1 mm in CBD treated mice compared to about 0.3 mm in injected controls without CBD.

Dermal Penetration/Bioavailability

Preclinical studies Reported advantages of topically administered CBD are the potential for greater systemic absorption of this highly lipophilic drug with poor bioavailability by the oral route, while also avoiding extensive first-pass metabolism of ingested CBD (Bruni et al., 2018).[19] CBD in a polyethylene gel was reported to readily cross the stratum corneum in rats, with some accumulation likely in the skin because this lipophilic compound cannot as readily cross the more aqueous dermis layer (Paudel et al., 2010). Lipophilic properties are also expected to result in dermal penetration through skin follicles with accumulation in sebaceous glands (Bruni et al., 2018).

Animal studies indicate the ability of topical CBD to reach systemic circulation. Hammell et al. (2016) reported CBD plasma concentrations after 4 days of topical application to the shaved backs of rats at doses of 0.62, 3.1, 6.2, and 62.3 mg/day were 3.8 ± 1.4, 17.5 ± 4.4, 33.3 ± 9.7, and 1,629.9 ± 379 ng/mL, respectively. Application of 100 mg of CBD to the abdomen and hip area of mice resulted in plasma concentrations of 0.68 to 1.07 µg/mL in the first 24 hours that afterward stabilized to 0.67 µg/mL for the duration of the study (72 hours) (Lodzki et al., 2003). After 24 hours, a reservoir of CBD was measured in abdominal (110 µg/cm^2) and hip (37 µg/cm^2) skin and in abdominal muscle (11.5 µg/g). Topical application of

[19] Ingested CBD is metabolized mainly by the cytochrome P450 (CYP) 2C19 and CYP3A4, and UGT1A7, UGT1A9, and UGT2B7 isoenzymes primarily by the liver (GW Biosciences, 2018; Ujvary and Hanus, 2016).

CBD to the backs of guinea pigs under occluded patch resulted in a steady-state plasma concentration of 6.3 ng/mL beginning at 15.5 hours (Paudel et al., 2010). Plasma concentrations began to decline 6 hours after the patch was removed after 48 hours of application. Addition of a penetration enhancer increased plasma concentrations by 3.7 times.

Safety and Adverse Events

Preclinical studies Hammell et al. (2016) reported that none of the CBD systemic doses in rats (up to 1629.9 ± 379 ng/mL in plasma from topical application of 62.3 mg/day for 4 days) affected their behavior using the open-field exploratory behavior test.

Based on individual clinical response and tolerability, the maximum recommended maintenance dosage of oral administration of CBD is 10 mg/kg twice daily (20 mg/kg/day) (GW Biosciences, 2018). The most common side effects noted in clinical trials of this oral drug were sleepiness, decreased appetite, diarrhea, increased liver transaminase levels, tiredness and weakness, rash (hypersensitivity), insomnia, and infections (GW Biosciences, 2018). The approved drug label also notes nausea, vomiting, and fever and warns of suicidal thoughts or actions (about 1 in 500 people); and that adjustments of doses are necessary in patients with moderate or severe hepatic impairment because of an increase in exposure to CBD (2.5 to 5.2 times higher area under the curve) (GW Biosciences, 2018). Effects related to the gastrointestinal tract are likely not relevant for topical administration. However, variable amounts of THC (with psychogenic effects) in unregulated CBD oils is concerning for patient safety (VanDolah et al., 2019).

In terms of potential drug–drug interactions, according to the clinical trials of oral CBD, the effects of CBD on sleepiness may be increased by other drugs (e.g., clobazam) or alcohol (GW Biosciences, 2018). Coadministration of CBD with drugs or substances that affect key metabolic enzymes (CYP3A4 or CYP2C19, and possibly UGT1A7, UGT1A9, and UGT2B7) may affect its efficacy or potential for adverse effects. Moderate to strong inhibitors of these enzymes (e.g., valproate, keloconazole) will increase CBD plasma concentrations and increase the risk of adverse effects (e.g., liver transaminase elevations) (GW Biosciences, 2018). Alternatively, effectiveness may be reduced by coadministration of certain antiepilepsy drugs (e.g., carbamazepine, topiramate, phenytoin) or the antibiotic rifampin, which induces these enzymes and increases CBD metabolism (Alsherbiny and Li, 2019; GW Biosciences, 2018).

CBD can also alter the toxicity or efficacy of other drugs through inhibition of certain enzymes. For example, increases in the plasma concentration of diazepam and the active metabolite of clobazam have been reported

with coadministration of EPIDIOLEX (GW Biosciences, 2018). Studies of patients with treatment-resistant epilepsy have reported that coadministration of CBD altered serum levels of topiramate, rufinamide, clobazam, eslicarbazepine, and zonisamide (Alsherbiny and Li, 2019).

In general, however, topically administered CBD, which would be associated with less first-pass metabolism and lower peak plasma levels than by the oral route, may be less likely to have such metabolic enzyme interactions with other drugs. From the FDA-approved label, serious adverse effects from oral administration of this API include increased suicidal thoughts and increased liver enzymes. See Table G-1 in Appendix G.

Dissociative Anesthetic and NMDA Receptor Antagonist: Ketamine

Summary

Ketamine is an FDA-approved anesthetic agent (intravenous, intramuscular) that has dissociative properties. In addition to anesthetic properties it also has analgesic, anti-inflammatory, and antidepressant properties. It works by blocking the NMDA receptor and reducing release of the excitatory neurotransmitter glutamine. Ketamine has a complicated pharmacologic profile and also has actions on AMPA, $GABA_A$, muscarinic, nicotinic, mu and kappa opiate, dopamine, and various ion channels, among others (Jonkman et al., 2017; Vadivelu et al., 2016).

While its systemic effects are well demonstrated, there is no evidence that topical ketamine is superior to placebo for various neuropathic pain conditions in concentrations from 1 to 10 percent, or that it reduces allodynia or hyperalgesia. There are also no data about the pharmacokinetic properties of ketamine following dermal application.

The majority of pharmaceutical preparations of ketamine are a racemic mixture. The S(+) isomer (esketamine) is available as a nasal spray to treat depression. S(+) ketamine is the active enantiomer. Ketamine is metabolized in the liver. The primary active metabolite is norketamine, which has approximately 20–30 percent of the analgesic activity of parent ketamine (Mion et al., 2013). Ketamine has a half-life of approximately 2–3 hours, but it has an active metabolite, norketamine, that has a half-life up to 12 hours (Quibell et al., 2015). Ketamine is primarily excreted in the urine; however, less than 5 percent is excreted unchanged (Zanos et al., 2018). See Box 6-11 for a summary of research findings.

Overall, the committee reviewed six RCTs: two were assessed as a low risk of bias (Finch et al., 2009; Lynch et al., 2003) and four were assessed as a high risk of bias (de Barros et al., 2012; Lynch et al., 2005b; Mahoney et al., 2012; Pöyhiä and Vainio, 2006). (See Appendix B for more details.) In addition to reviewing studies where ketamine alone was analyzed, the

BOX 6-11
Summary of Research Findings on Ketamine in Compounded Topical Pain Creams

Effectiveness: There is evidence that topical ketamine is not superior to placebo for a variety of conditions including postherpetic neuralgia, complex regional pain syndrome (types I and II), painful diabetic neuropathy, and other types of neuropathic pain. One randomized controlled trial suggests that topical ketamine in a 10 percent gel may reduce allodynia in certain subjects with complex regional pain syndrome.

Dermal penetration/bioavailability: There is in vitro evidence to suggest that topical ketamine can penetrate human skin. Serum concentrations of ketamine and its metabolite norketamine have been detected following topical use, although far below therapeutic concentrations. Modifications to the ingredient or excipient may increase aqueous solubility and increase absorption.

Safety and adverse effects: Limited evidence suggests that topical ketamine is associated with minimal adverse effects after therapeutic application. Application of excessive amounts of ketamine containing topical products has led to significant altered mental status and seizures.

committee also included studies of ketamine used in combination with other APIs. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

Effectiveness

Randomized clinical trials Six RCTs evaluated ketamine topically for neuropathic pain including postherpetic neuralgia, complex regional pain syndrome (CRPS) and diabetic peripheral neuropathy. Ketamine did not reduce pain any better than the comparator or placebo treatment. In Finch (2009), 20 consecutive patients with CRPS (type I or type II) who attended a small private pain center in Perth, Australia, were studied to determine whether ketamine had any sensory effect, particularly on allodynia.[20] Ketamine 10 percent in pluronic lecithin organogel (referred to as ketamine cream by the Professional Compounding Centers of America) was studied compared to the vehicle alone. Patient and investigators were blinded to the products. An investigator applied 0.5 mL cream to the most hyperalgesic

[20] Risk-of-bias assessment by the committee: Low (see Appendix B for more details).

dorsal aspect of the symptomatic limb (hand or foot) with 0.5 mL of the other applied to the healthy limb; sensory testing was conducted on each side of the forehead. This process was repeated with a reversal of the cream applied with at least 1 week between assessments.

The investigators conducted sensory testing before and 30 minutes after application of cream that included threshold to light touch, pressure–pain, punctate stimulation, light brushing, and thermal stimuli. Venous blood was obtained 1 hour after application in the first 10 patients and analyzed for ketamine and norketamine by high-performance liquid chromatography. Pain or touch threshold did not change after treatment with ketamine. However, ketamine did reduce allodynia in the symptomatic limb as well as pain invoked by pricking the skin in both the symptomatic and healthy limb. Allodynia and hyperanalgesia to various experimental stimuli was reported in the ipsilateral forehead, which in some cases was lessened with ketamine treatment of the symptomatic limb. Ketamine and its metabolite were not detected at a threshold of 0.7 mcg/L ketamine and 0.5 mcg/L norketamine.

In Mahoney (2012), ketamine 5 percent cream versus placebo (vehicle composed of primarily Aquaphor gel) was studied in 27 patients for the treatment of painful diabetic neuropathy in patients with either type 1 or type 2 diabetes.[21] Methods were poorly described. Patients were included if they had at least a score of 8 on the Michigan Neuropathy Screening Instrument or a score of 3 on the physical examination instrument. The physical examination instrument was not described. Patients were randomly divided into the treatment or placebo arm, although the exact randomization process was not described. A compounding pharmacy prepared the ketamine cream and placebo and blinded the products to the investigators and patients. Participants applied 1 mL of cream three times per day to the entire foot distal to the ankle for a 1-month period of time. Seven pain characteristics (intensity, sharpness, hot, cold, dull, sensitive, and itchy) were assessed prior to study and after the study was completed using an 11-point Likert scale. Twenty-seven patients were enrolled, but 10 (37.0 percent) dropped out at what appears to be prior to the start of treatment and no reasons were stated for the withdrawal. Pain scores for all seven pain characteristics were reduced in both the ketamine and placebo group.

de Barros (2012) provides a short communication that describes a randomized, double-blind, placebo-controlled crossover study in 12 patients that investigated the role of s-ketamine 1 percent ointment in the treatment of postherpetic neuralgia.[22] Details about the methods were limited. Twelve patients were enrolled in the study and applied the ointment to the site of

[21] Risk-of-bias assessment by the committee: High (see Appendix B for more details).
[22] Risk-of-bias assessment by the committee: High (see Appendix B for more details).

pain four times per day for 15 days, followed by a 7-day washout and then a second treatment exactly as the first treatment. Patients reported Numerical Verbal Scale pain scores (0–10). There was a significant reduction in pain scores for both groups over time. However, there was no difference between s-ketamine and placebo at reducing pain scores. Several patients experienced adverse skin reactions.

Pöyhiä and Vainio (2006) evaluated the ability of ketamine applied topically to reduce capsaicin-evoked hyperalgesia in healthy volunteers.[23] In one study nine healthy volunteers were assigned ketamine 5 percent versus placebo gel 1 mL 10 minutes prior to injection of capsaicin intradermally to the left forearm. Treatments were applied in a randomized, double-blind, and crossover manner with three test periods conducted with a 1-week interval between each. The testing included ketamine gel on the left forearm and placebo on the right; placebo on the left and ketamine on the right; or placebo on both sides assigned in a randomized fashion. Ketamine did not affect spontaneous burning pain but the intensity of the hyperalgesia was significantly reduced when ketamine was applied to the either forearm, suggesting a systemic effect.

Lynch et al. (2003, 2005b) evaluated the effects of topical ketamine, amitriptyline, or a combination of the two in the treatment of neuropathic pain. To minimize redundancy within the chapter, a review of these studies is described in the Multiagent Compounded Topical Pain Creams section below.

Clinical studies In Rabi et al. (2016), ketamine 10 percent in Lipoderm was studied in five subjects with a spinal cord injury and neuropathic pain at an outpatient rehabilitation hospital. Subjects applied up to 4 grams to the site of maximum pain every 8 hours for 2 weeks. The patients' reduction in pain scores from baseline was as follows: 63 percent, 43 percent, 25 percent, 14 percent, and 60 percent. No subject was able to reduce oral pain medications. No adverse effects were noted. Patients were noted to be very satisfied (n = 1), somewhat satisfied (n = 2), indifferent (n = 1), and somewhat unsatisfied (n = 1).

Retrospective clinical studies Durham (2018) provided a retrospective chart review of 16 patients 18 years of age and older with complex regional pain syndrome who were treated with topical ketamine between May 2006 and April 2013 at an academic medical center specialty pain clinic. The authors state that nine different compounds were used by the patients, although the manuscript only lists eight including one product with just ketamine 6 percent alone. The other seven compounds used in the study

[23] Risk-of-bias assessment by the committee: High (see Appendix B for more details).

included ketamine 10 percent with 1–4 additional ingredients that included gabapentin (6–10 percent), ketoprofen 10 percent, lidocaine (3–5 percent), clonidine 0.2 percent, and baclofen 1 percent. Improvement was noted by eight subjects; seven subjects reported worsening of pain.

Quan (2003) provided a short communication where authors report on 23 patients with postherpetic neuralgia that were treated with a topical ketamine gel preparation of 0.5 percent between 1994 and 2002. There was some improvement: from severe to mild, $n = 8$; severe to moderate, $n = 7$; and no improvement, $n = 8$.

Case reports Ushida et al. (2002) described the effectiveness of topical ketamine in five patients with complex regional pain syndrome type I (CRPS I) and in two patients with type II (CRPS II). With a concentration of ketamine of 0.5 percent to 0.85 percent applied three times per day, a decrease in allodynia and hyperalgesia was noted (measured by the VAS in four patients with acute early dystrophic stage of CRPS I). No pain relief was observed in the one patient with chronic atrophic stage CRPS I and in both patients with CRPS II.

Skavinski (2019) reported the use of ketamine gel to treat severe pain associated with decubitus ulcers on the heels of a 54-year-old woman with a complicated medical history and course of therapy, admitted to a palliative care service. Ketamine 5 percent gel did not work, but increasing the ketamine concentration to 10 percent and adding lidocaine (2 percent gel) resulted in a decrease in opioid requirement. Ultimately the patient was switched to a topical product with ketamine 15 percent alone with limited data on success.

In Hesselink and Kopsky (2013), the authors describe a case of a 72-year-old woman with severe pain, swelling, and a poor quality of life, diagnosed with CRPS I. She was treated with ketamine 10 percent cream and palmitoylethanolamide capsules. The swelling improved, and the patient was more mobile at 1 month and continued to improve at 2 months. It is not clear which of the two treatments contributed to her improvement.

In Gammaitoni et al. (2000), the authors describe five patients that applied doses ranging from 0.13 to 0.37 mg/kg of ketamine gel for neuropathic pain. Of the three patients with regional sympathetic dystrophy, two had no response and one patient noted a reduction in pain of 55 to 60 percent. One patient with postherpetic neuralgia reported a 63 percent reduction in pain, and one patient with a postlaminectomy syndrome radiculopathy described between 53 and 100 percent reduction in pain depending on the site.

Dermal Penetration/Bioavailability

In vitro studies Percutaneous absorption of ketamine in Lipoderm and Lipoderm ActiveMax (Bassani and Banov, 2016) and Versatile compared to a reference gel (Wang and Black, 2013) was studied using human cadaver skin in Franz diffusion cell chambers. Ketamine penetrated into and through human cadaver skin in all cases. A few of the RCTs described above were able to detect ketamine and metabolite in some participants.

Safety and Adverse Events

Ketamine, when administered systemically, has the potential to cause adverse effects because of its actions on numerous receptors. Potential adverse effects include cognitive impairment, emergence reactions, elevated heart rate and blood pressure, hypertonic muscle movements, and nausea and vomiting.

Case reports In a case report, a 35-year-old man who applied excessive amounts of a topical pain cream containing ketamine, baclofen, amitriptyline, lidocaine, and ketoprofen presented to the hospital unresponsive after a presumed seizure. He required endotracheal intubation and mechanical ventilation for 2.5 days. Ketamine was detected in his central spinal fluid by gas chromatography-mass spectrometry (Sigillito et al., 2003). In a second case (Cardis and Pasieca, 2016), a man in his 80s with Parkinson's disease presented with altered mental status after applying a topical pain cream containing ketamine 10 percent, amitriptyline 5 percent, and lidocaine 5 percent to most of his upper body the day prior to presentation. A stroke was ruled out, and after persistent delirium and altered levels of consciousness, the history of the topical pain cream use was elicited. Amitriptyline, lidocaine, and ketamine and metabolites were detected in urine by mass spectroscopy. Amitriptyline, lidocaine, and ketamine concentration was 2,360 ng/mL (normal level, 0 ng/mL) (Cardis and Pasieca, 2016).

From the FDA-approved label, serious adverse effects from oral administration of this API include bradyarrhythmia, cardiac dysrhythmia, and respiratory depression. See Table G-1 in Appendix G.

Local Anesthetic: Bupivacaine

Summary

Bupivacaine hydrochloride is an FDA-approved amide local anesthetic (injection). Local anesthetics block the generation and propagation or conduction of action potentials in axons by reversible inhibition of ion flux through the voltage-dependent sodium channel (Berde, 1993; Hospira,

2011). Amide local anesthetics such as bupivacaine are metabolized to inactive byproducts in the liver via conjugation with glucuronic acid, so diseases that result in decreased liver blood flow or enzyme dysfunction decrease clearance of bupivacaine. Generally, bupivacaine is considered a long-acting local anesthetic. It has high protein binding capacity (95 percent) and low fetal/maternal ratio (0.2 to 0.4). Bupivacaine's half-life in adults is 2.7 hours and in neonates 8.1 hours (Fresenius Kabi, 2018).

Although outside the scope of the current report, RCTs indicate liquid bupivacaine is effective in providing local anesthesia for suturing of superficial skin lacerations. In addition, low levels have been shown to be absorbed after topical application to damaged skin, but no data were found on dermal penetration through intact skin (Alvi et al., 1998; Jellish et al., 2018). See Box 6-12 for a summary of research findings.

In addition to reviewing studies where bupivacaine alone was analyzed, the committee also included studies of bupivacaine used in combination with other APIs. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

Effectiveness

Randomized controlled trials There are no relevant clinical studies that examine the single-drug use of bupivacaine in compounded topical creams to treat pain when applied to intact skin. However, although outside the scope of the current report, there are several randomized clinical trials that demonstrated potential effectiveness of compounded topical bupivacaine in treating pain in patients after receiving skin grafts for a variety of surgical

BOX 6-12
Summary of Research Findings on Bupivacaine in Compounded Topical Pain Creams

Effectiveness: There is no evidence to suggest the effectiveness of topical bupivacaine to treat pain when applied to intact skin.

Dermal penetration/bioavailability: There is no evidence on the dermal penetration and bioavailability of topical bupivacaine when applied to intact skin.

Safety and adverse effects: No evidence was found on the safety of topical bupivacaine. However, if systemic absorption to therapeutic levels is achieved through topical application, there is potential for serious side effects similar to other routes of administration (e.g., oral).

conditions (Butler et al., 1993) and in suturing skin lacerations (Eidelman et al., 2005; Keyes et al., 1998; Kuhn et al., 1996; Smith et al., 1996).

Dermal Penetration/Bioavailability

Randomized controlled trials No clinical studies were found on the dermal absorption or bioavailability of topical bupivacaine through intact skin. However, although outside of the committee's research scope, the committee identified two RCTs that examined the pharmacokinetic properties of topical bupivacaine in damaged skin (i.e., burn patients). These studies, Alvi et al. (1998) and Jellish et al. (2018), determined that low levels of buvipicaine are absorbed and present in serum concentrations after topical application to damaged skin.

Safety and Adverse Effects

Clinical and preclinical studies The systemic toxic effects of local anesthetics such as bupivacaine primarily affect the cardiovascular system and the CNS. As described in Alvi et al. (1998), local anesthetics at low dose have beneficial cardiac antidysrhythmic effects. However, higher bupivacaine concentrations are associated with CNS toxicity (e.g., seizures), myocardial depression, and vasodilation. The intravenous dose in monkeys causing toxicity is 4.3 mg/kg, and seizures occur in humans after large doses of bupivacaine at serum levels greater than 4 mcg/mL. Toxic levels of bupivacaine particularly affect the cardiac conduction system, depressing cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, which is sometimes fatal (Pfizer, 2012). A recent clinical report suggests that cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine, so incremental dosing and ultrasound guidance for precise drug delivery are recommended to minimize, or lipid emulsion to treat, such complications (Waldinger et al., 2020).

Given the half-life of bupivacaine in adults is 2.7 hours and in neonates 8.1 hours, it is not surprising that cardiac arrest in patients receiving bupivacaine requires resuscitation for several hours to give enough time for the drug to ultimately decrease in the heart so the conduction system can return to normal. Cardiac and CNS collapse, and even death, have been reported in otherwise healthy individuals receiving the highest concentration of bupivacaine (0.75 percent) given by injection, hence the FDA black box warning that lower doses be used for obstetrical anesthesia and precautions (e.g., divided doses) taken for any nerve blocks with bupivacaine where systemic absorption is possible (Pfizer, 2012). Topical administration of bupivacaine on mucous membranes or nonintact skin could enhance systemic absorption and potentially result in significant toxicity.

From the FDA-approved label, serious adverse effects from oral administration of this API include cardiac arrest and respiratory depression. See Table G-1 in Appendix G.

Local Anesthetic (Short-Acting): Lidocaine

Summary

Lidocaine is an FDA-approved local anesthetic for topical or rectal treatment of postherpetic neuralgia. It is also used off-label to treat diabetic neuropathy and acute pain. Lidocaine is a nonselective, voltage-gated sodium channel inhibitor, affecting both the generation and conduction of nerve impulses. It stabilizes nerve membranes, reducing ectopic activity in damaged afferent pain receptors. Other effects on keratinocytes and immune cells, or activation of irritant receptors (TRPV1 and TRPA1), may also contribute to the analgesic effect of topical lidocaine (Sawynok and Liu, 2014).

FDA-approved creams, gels, foam sprays, and solutions containing lidocaine are most often used for short-term analgesia, such as before painful medical procedures or to treat cuts, burns, and insect bites, but it may also be used as a patch in chronic conditions. The concentration of lidocaine in these formulations is usually around 2 percent to 5 percent w/w (FDA, 2019a). Its usual use is for injection for dental analgesia and minor surgery, or infiltration into wounds, but it can also provide surface anesthesia when applied topically, such as a medicated plaster, gel, or spray. Lidocaine is readily absorbed from mucous membranes and through damaged skin, and from injection sites, but absorption through intact skin is poor. To be clinically useful as a topical agent, lidocaine must be formulated with a carrier to facilitate transfer across the skin. These products contain high concentrations of lidocaine because it crosses intact skin poorly.

The committee elected to review the effectiveness, absorption, and safety of topical lidocaine because it is commonly mixed with other priority ingredients. Uniquely, the committee determined that lidocaine can be considered a positive control for other topical ingredients because there is an FDA-approved lidocaine ointment (5 percent). The committee was unable to obtain the original full FDA review of the product. As such, the committee relied on data from FDA-submitted resources and approval documents for the FDA-approved lidocaine patch. In addition to reviewing studies where lidocaine alone was analyzed, the committee also included studies of lidocaine used in combination with other APIs. See Box 6-13 for a summary of research findings. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

BOX 6-13
Summary of Research Findings on Lidocaine in Compounded Topical Pain Creams

Effectiveness: Limited evidence suggests effectiveness of topical lidocaine gel (5 percent) to treat pain when applied to intact skin.

Dermal penetration/bioavailability: There is limited evidence on the dermal penetration and bioavailability of topical lidocaine gel (5 percent). Although as a reference, the absorption of lidocaine from a lidocaine patch (5 percent) is minimal (less than 3 percent). Modifications to the ingredient or excipient may increase aqueous solubility and increase absorption.

Safety and adverse effects: There is evidence to suggest safety of topical lidocaine gel (5 percent). However, with extensive systemic absorption, there is potential for adverse effects, including precipitating CNS disturbances, such as psychosis and seizures.

Effectiveness

FDA-approval of lidocaine gel Submitted resources provided by FDA (2019b) informed the committee that 5 percent lidocaine ointment was first FDA approved under NDA 008048 on May 17, 1951. According to the *Federal Register* Notice (Vol. 35, No. 172, p. 14020-1) published on September 3, 1970, 5 percent Xylocaine (lidocaine) ointment (NDA 008048), marketed by AstraZeneca Pharmaceutical Products, Inc., was determined to be effective under the Drug Efficacy Study Implementation (DESI) program.[24] Specifically, 5 percent topical Xylocaine ointment was found to be effective "for production of anesthesia of accessible mucous membranes of the oro-pharynx" and possibly effective for the "control of itching, burning, and other unpleasant symptoms due to abrasions, herpes zoster, eczema, and similar conditions; hemorrhoids, fissures, postoperative anorectal conditions, nipple soreness and for anesthesia of unbroken skin." In a follow-up *Federal Register* Notice (Vol. 43, No. 206, p. 49570-2), published on October 24, 1978, 5 percent Xylocaine ointment (RX; NDA 008048), marketed by AstraZeneca Pharmaceutical Products, Inc., was found to be effective for two additional indications "for use as an anesthetic lubricant for endotracheal intubation" and "for the temporary relief of pain and itching associated with minor burns and abrasions of the skin."

[24] For more information on FDA's DESI program, see https://www.fda.gov/drugs/enforcement-activities-fda/drug-efficacy-study-implementation-desi (accessed March 8, 2020).

Other clinical studies In a Cochrane evaluation, a total of 12 small studies (508 patients) of modest quality that tested topical lidocaine against topical placebo for a number of weeks were evaluated (Derry et al., 2014). One study also tested a cream containing amitriptyline, which is an antidepressant. The 508 patients in the studies had different types of neuropathic pain, with pain after herpes zoster infection the most common. Six studies enrolled participants with moderate or severe postherpetic neuralgia, and the remaining studies enrolled different, or mixed neuropathic pain conditions, including trigeminal neuralgia and postsurgical or posttraumatic neuralgia. Four different formulations were used: 5 percent medicated patch, 5 percent cream, 5 percent gel, and 8 percent spray. Most studies used a crossover design, and two used a parallel-group design.

All studies reviewed in this evaluation were categorized as third-tier, very low-quality evidence. Specifically, the authors stated that these studies contained a small number of participants who were considered very likely to be biased or used outcomes of limited clinical usefulness, or both. From this group, all but one study indicated that topical lidocaine was more effective than placebo at providing some measure of pain relief. From the group of studies, only one multiple-dose study reported primary outcome of participants with ≥ 50 percent or ≥ 30 percent pain intensity reduction (Meier et al., 2003).

Dermal Penetration/Bioavailability

Clinical and preclinical studies There is insufficient evidence on dermal penetration/bioavailability of FDA-approved topical lidocaine gel (5 percent). Based on resources provided by FDA (2019a), it is unlikely that in vivo or in vitro penetration studies were performed when this drug was brought for approval in the 1950s.[25]

In the topical application of Lidoderm (lidocaine patch, 5 percent), the systemic exposure of lidocaine is minimal. In healthy volunteers, the absorption of lidocaine after 12 hours of topical application of three lidocaine patches, which contain 2,100 mg of lidocaine, was 3 ± 2 percent of applied dose (Endo Pharmaceuticals, 2015). Lidocaine does not cross intact skin well, and when applied as a patch, with steady controlled release of the drug, the amount of lidocaine that penetrates is enough to cause analgesia, but not anesthesia (Hong et al., 2016). In an in vitro lidocaine patch permeation study through excised rat skin, the results exhibited large unequal, within lot, variation in the amount of permeation (FDA, 1998).

[25] It was difficult for FDA to obtain and appropriately review the original approval information from the early 1950s (FDA, 2019a).

Likewise, a clinical study that examined the release of lidocaine from the patch applied to the chest area of volunteers, resulted in significant variability within subject; variation occurred between subject, within lot, and between lots (FDA, 1998).

Safety and Adverse Events

Clinical studies Systemic adverse reactions following appropriate use of a lidocaine patch is unlikely, owing to the small dose absorbed; however, in circumstances of systemic administration, lidocaine is a potent antiarrhythmic drug, and at high doses it can cause CNS disturbances, such as psychosis, seizures, and at high concentration even death. The amount of lidocaine reaching the systemic circulation when the patch is used is low (of the order of 3 percent), which is well below therapeutic antiarrhythmic concentrations or toxic concentrations in patients with normal cardiac, renal, and hepatic function. However, toxicity could be reached if patients inappropriately use several lidocaine patches at once. Lidocaine is metabolized in the liver and excreted by the kidneys, so caution is also required when an individual has severe cardiac, renal, or hepatic impairment.

In the Cochrane evaluation of 12 small studies (508 patients) there was no clear evidence of an effect of topical lidocaine on the incidence of adverse events or withdrawals; however, localized skin reactions to the patch or carrier in the formulation have occurred (Derry et al., 2014).

NMDA Receptor Antagonist: Memantine

Summary

Oral memantine is an FDA-approved NMDA receptor antagonist and is used orally to treat dementia associated with Alzheimer's disease. It is not approved to treat pain, but it has been suggested to reduce peripheral nociceptive activity when administered systemically or intrathecally (Davidson and Carlton, 1998). Adverse effects occurring in patients receiving memantine in these clinical studies include dizziness, confusion, agitation, vertigo, vomiting, and hypertension (PubChem, 2020c). From the FDA-approved label, serious adverse effects from oral administration of this API include cerebrovascular accident, seizures, and kidney failure. See Table G-1 in Appendix G. No clinical evidence was found on the effectiveness or safety of memantine use in compounded topical pain creams. See Box 6-14 for a summary of research findings.

BOX 6-14
Summary of Research Findings on Memantine in Compounded Topical Pain Creams

Effectiveness: There is no evidence on the effectiveness of topical memantine to treat pain when applied to intact skin.

Dermal penetration/bioavailability: There is no evidence on the dermal penetration and bioavailability of topical memantine.

Safety and adverse effects: There is no evidence on the safety of topical memantine.

Nonsteroidal Anti-Inflammatory Drug (NSAID): Meloxicam

Summary

Oral meloxicam is an FDA-approved NSAID that is a potent inhibitor of cyclo-oxygenase-2 (COX-2) and prostaglandin synthesis, used to treat arthritis-related pain. In vitro evaluation of NSAIDs (meloxicam) on cell signaling pathways in cultured synovial fluid indicates these agents may interfere with a natural regulatory signal that limits inflammation (Largo et al., 2004). The physiochemical properties of meloxicam indicate that this NSAID is not an ideal drug for delivery through the skin. Meloxicam is zwitterionic, and it is lipophilic with a high melting point and low solubility, which make it unsuitable for transdermal delivery (Ah et al., 2010). However, a variety of approaches have been investigated to enhance the topical delivery of meloxicam with promising outcomes in animal studies (Chen and Gao, 2016). Numerous in vitro and in vivo animal studies have demonstrated that meloxicam can be delivered into the skin and underlying tissues. No human clinical trials have been conducted to confirm the safety or effectiveness of meloxicam administrated in a compounded topical cream. See Box 6-15 for a summary of research findings.

Effectiveness

Randomized controlled trials A review of randomized clinical trials provided insufficient evidence to compare topical NSAID therapies with oral delivery of the same agent, other topical treatments, or other treatments (Glass, 2006).

Preclinical Meloxicam gel (1 percent w/w gel) showed lower analgesic effectiveness than piroxicam (0.5 percent w/w) and diclofenac (1 percent

BOX 6-15
Summary of Research Findings on Meloxicam in Compounded Topical Pain Creams

Effectiveness: There is insufficient evidence on the effectiveness of topical meloxicam to treat pain in intact skin.

Dermal penetration/bioavailability: Limited preclinical evidence suggests topical meloxicam is absorbed through the skin only under certain circumstances. One study demonstrates a 1 percent gel (containing the penetration enhancer, transcutol) penetrates into dog synovial fluid at higher levels than detected in plasma. Other in vitro diffusion cell studies indicate therapeutically relevant amounts of meloxicam can penetrate human skin in vitro with the addition of penetration enhancers.

Safety and adverse effects: There is insufficient evidence on the safety of topical meloxicam. Preclinical studies have examined the potential for skin irritation after topical application. However, if systemic absorption to therapeutic levels is achieved through topical application there is potential for side effects similar to other routes of administration (e.g., oral).

w/w) gels in the rat writhing test and in formalin-induced phase 1 pain. Meloxicam gel provided greater protection than the comparator gels in formalin-induced phase 2 pain (Gupta et al., 2002).

Dermal Penetration/Bioavailability

Preclinical studies Permeation through human cadaver skin in Franz diffusion cell chambers was reported as having a flux of 2.43 ± 0.47 mcg/cm^2/h following application of 0.5 g meloxicam 0.3 percent gel formulation containing 2.5 percent hydroxypropylcellulose in 1:1:1 propylene glycol, ethanol, and water with the addition of 5 percent menthol as a penetration enhancer (Jantharaprapap and Stagni, 2007).

A comparison of oral and transdermal plasma and synovial fluid levels was conducted in six beagle dogs using liquid chromatography-tandem mass spectrometry. The oral dose given was 0.31 mg/kg. The meloxicam gel (1 percent meloxicam in carbopol 940) was formulated with the penetration enhancer, transcutol. The meloxicam gel was administered transdermally at 1.25 mg/kg. Relative bioavailability of the topical gel was 1.05 percent of the oral plasma concentration. The ratio of meloxicam in synovial fluid compared to the plasma concentration was higher for topical

administration than oral delivery. This result was attributed to direct penetration into the target tissue following topical administration (Yuan et al., 2009).

Other preclinical studies have examined the pharmacokinetics of meloxicam following topical delivery in rats (Chang et al., 2007; Gupta et al., 2002; Jain et al., 2008). Some of these studies, and others, have used advanced drug delivery formulations to improve penetration rates and systemic absorption of the meloxicam (Chang et al., 2007; Duangjit et al., 2014a,b; Huang et al., 2011; Jain et al., 2008; Machado et al., 2018; Ngawhirunpat et al., 2009; Zhang et al., 2009).

Safety and Adverse Effects

No human clinical data have been reported; however, several studies have evaluated the potential for skin irritation with meloxicam following topical (transdermal) delivery in animal models (Bachhav and Patravale, 2010; Jiang et al., 2018; Khurana et al., 2013a,b,c).

From the FDA-approved label, serious adverse effects from oral administration of this API include increased risk of cardiovascular events, gastrointestinal bleeding, and ulceration. See Table G-1 in Appendix G.

Nonsteroidal Anti-Inflammatory Drug (NSAID): Naproxen

Summary

Oral naproxen is an FDA-approved NSAID with analgesic, anti-inflammatory, and antipyretic activities. The mechanism of action is unknown but involves inhibition of cyclo-oxygenase (COX-1 and COX-2), which leads to reduced prostaglandin synthesis. Well-designed clinical studies focusing on the effectiveness of topical naproxen are limited and often provide inconsistent results. For example, some studies indicate topical naproxen (1 percent to 10 percent gel) is more effective than placebo, while in others, naproxen was determined to be no more effective than placebo in acute conditions (Moore et al., 1998). Several studies lack strong methodological rigor. Studies reported very few adverse effects, with the exception of self-reported skin irritation or itching, and there is clinical evidence that naproxen exhibits dermal penetration when applied topically. Overall, the committee reviewed six RCTs: one study was assessed as having a high risk of bias (Cokmez et al., 2003), and five were assessed as having a low risk of bias (Baixauli et al., 1990; Eslamian et al., 2017; Montagna et al., 1990; Nadal et al., 1990; Thorling et al., 1990). See Box 6-16 for a summary of research findings. (See Appendix B for more details.)

BOX 6-16
Summary of Research Findings on Naproxen in Compounded Topical Pain Creams

Effectiveness: There is limited and inconsistent evidence to suggest that naproxen (1–10 percent gel) is effective to treat pain related to soft tissue injuries.

Dermal penetration/bioavailability: There is limited evidence to suggest that topical naproxen sodium gel (1 percent) penetrates through human skin in vivo.

Safety and adverse effects: There is limited evidence to suggest that topical naproxen is associated with skin irritation and itching adverse effects.

Effectiveness

Systematic review A systematic review by Moore et al. (1998, p. 333) examined "the effectiveness and safety of topical non-steroidal anti-inflammatory drugs in acute and chronic pain conditions." In a review of five placebo-controlled trials, the authors determined that topically applied naproxen did not show significant efficacy in acute pain conditions (e.g., soft tissue trauma, strains, and sprains). The efficacy of topically applied naproxen in chronic pain conditions was not described in the review.

Randomized controlled trials In a nonblinded RCT by Cokmez et al. (2003) to prevent infusion phlebitis in Turkey, Naprosyn gel was applied to patients' skin over the course of the vein proximal to the cannulas (n = 127).[26] This was compared to 10 mg/day transdermal glyceryl trinitrate (GTN) patches (n = 136) and controls (n = 123). The study found patients who received the Naprosyn gel developed less phlebitis compared to no treatment control and the GTN group ($p < .05$).

In a double-blind RCT by Eslamian et al. (2017) in Iran, the analgesic efficacy of 5 percent naproxen gel was tested for pain associated with orthodontic separator placement.[27] Thirty-four patients (11 males and 23 females) between the ages of 14 to 20 (mean: 16.88 years) were put in a split mouth design study. The 5 percent naproxen gel and placebo gel were applied immediately after spacer placement and every 8 hours after

[26] Risk-of-bias assessment by committee: High (see Appendix B for more details).
[27] Risk-of-bias assessment by committee: Low (see Appendix B for more details).

for 3 days. Pain was rated using a VAS (0–100 in increments of 10) at 2 and 6 hours after placement, as well as at 10 am and 6 pm of the second, third, and seventh days after application of the gel. The gel was comprised of carbomer P934 gel-forming substance (50 g), preservatives (5 g methylparaben and 1 g propylaparaben), glycerin as humectant (400 ml), pH regulator (NaOH), and 10 g naproxen powder. Findings show the naproxen gel side had lower pain scores at all times compared with placebo ($p < .001$).

Montagna et al. (1990) conducted a single-blind study comparing 5 percent meclofenamic acid gel to 10 percent naproxen gel in patients ($n = 40$, 20 each group) with musculoskeletal disorders.[28] Evaluation was on pain, tenderness, swelling, and restriction of movement. Patients applied cream for 15 days (the amount and frequency are unclear). Meclofenamic acid gel outperformed naproxen gel by alleviating symptoms faster, although both were effective in controlling the symptoms and showed similarly good tolerance.

Nadal et al. (1990) performed a similar study comparing 10 percent naproxen gel to piketoprofen cream (ketoprofen).[29] Fifty patients (25 in each group) were treated for soft tissue lesions, and cream was applied every 12 hours, as and when required. The naproxen gel was considered more effective and more rapid in onset than piketoprofen cream. Both were tolerated well.

Baixauli et al. (1990) also did a comparative study between 10 percent naproxen gel and 10 percent ketoprofen gel in 30 patients with moderate to severe pain caused by acute soft tissue lesions.[30] There were 15 patients in the naproxen group (8 male, 7 female; mean age: 72.2 years) and 14 in the ketoprofen group (8 male, 6 female; mean age: 33.3 years). Three to 5 cm of gel was applied once every 12 hours as needed for 7 days. Naproxen gel and ketoprofen gel efficacy and tolerability were deemed comparable, except on deep palpation where naproxen gel had a significantly greater reduction in pain by the third day of treatment.

In a narrative review by Heyneman (1995), she discussed a double-blinded, randomized, and parallel study by Thorling et al. (1990) that compared 10 percent naproxen gel and a placebo in 120 patients with soft tissue injuries (mostly synovitis and tendinitis).[31] There were several limitations to the study (dosage was not standardized, no adherence measure, some took acetaminophen 500 mg tablets, and measurement error), but the study did find the naproxen gel significantly reduced pain compared to placebo.

[28] Risk-of-bias assessment by committee: Low (see Appendix B for more details).
[29] Risk-of-bias assessment by committee: Low (see Appendix B for more details).
[30] Risk-of-bias assessment by committee: Low (see Appendix B for more details).
[31] Risk-of-bias assessment by committee: Low (see Appendix B for more details).

Dermal Penetration/Bioavailability

Clinical studies In the study by Attia (2009), transdermal administration of 1 percent naproxen sodium gel prepared without penetration enhancers, when compared with oral administration of sodium naproxen tablets, was significantly different on maximum blood concentration (lower), time to reach the peak blood concentration (the same), terminal elimination half-life (1 hour sooner), and area under the curve (higher).

There were no studies that evaluated the blood levels of naproxen resulting from topical versus oral administration of the drug. Only Attia (2009) discussed serum concentrations, which peaked at 1.3 μg/mL after approximately 8 hours after application of a 1 percent naproxen gel.

Safety and Adverse Effects

No severe adverse events were reported (Cokmez et al., 2003; Eslamian et al., 2017; Nadal et al., 1990; Thorling et al., 1990).

From the FDA-approved label, serious adverse effects from oral administration of this API include increased risk of cardiovascular events, gastrointestinal bleeding, and ulceration. See Table G-1 in Appendix G.

Opioid Agonists: Tramadol

Summary

Oral tramadol is an FDA-approved analgesic that is a weak agonist at the mu opioid receptor and also inhibits the uptake of norepinephrine and serotonin. It is considered a treatment for mild to moderate chronic pain, but not severe pain. Tramadol is available orally alone or in combination with acetaminophen in immediate release and extended release preparations. Onset of effects is within 1 hour with peak analgesic effects within 2 hours after immediate release preparation. Time to peak concentrations are 1–3 hours with immediate release preparations and 12 hours with extended-release preparations. Tramadol undergoes extensive metabolism by the liver and has an active metabolite, *O*-desmethyl-tramadol. Approximately 30 percent is excreted unchanged in the urine. The half-life of tramadol is approximately 6 hours, and the half-life of the active metabolite is approximately 7 hours (Ardakani and Rouini, 2007; Skinner et al., 2009). No data were found on the safety and effectiveness of topically applied tramadol. See Box 6-17 for a summary of research findings.

In addition to reviewing studies where tramadol alone was analyzed, the committee also included studies of tramadol used in combination with other APIs. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

BOX 6-17
Summary of Research Findings on the Use of Tramadol in Compounded Topical Pain Creams

Effectiveness: There is no evidence on the effectiveness of topical tramadol to treat pain in intact skin.

Dermal penetration/bioavailability: There is no evidence on the dermal penetration and bioavailability of topical tramadol.

Safety and adverse effects: There is no evidence on the safety of topical tramadol. However, if systemic absorption to therapeutic levels is achieved through topical application there is potential for side effects similar to other routes of administration (e.g., oral).

Effectiveness

Randomized controlled trials There are no relevant clinical studies that examine the single-drug use of tramadol in compounded topical creams to treat pain when applied to intact skin.

Dermal Penetration/Bioavailability

There is no evidence on the ability of tramadol to penetrate the skin or enter the blood stream.

Safety and Adverse Effects

There is no relevant evidence on the safety or adverse effects of compounded topical tramadol. If a formulation were developed that produced a systemic level after topical application, then systemic side effects should be considered. After oral administration side effects would be expected to be similar to other opioid analgesics, for which the most common adverse effects are skin (flushing and pruritus), gastrointestinal (constipation, nausea, vomiting), and neurologic (dizziness, drowsiness) (Khansari et al., 2013).

From the FDA-approved label, serious adverse effects from oral administration of this API include potential addiction, abuse, and misuse; respiratory depression; accidental ingestion; and sedation, coma, and death if used with benzodiazepines or alcohol. See Table G-1 in Appendix G.

BOX 6-18
Summary of Research Findings on Dexamethasone in Compounded Topical Pain Creams

Effectiveness: There is no evidence on the effectiveness of topical dexamethasone to treat pain when applied to intact skin.

Dermal penetration/bioavailability: There is no evidence on the dermal penetration and bioavailability of topical dexamethasone.

Safety and adverse effects: There is no evidence on the safety of topical dexamethasone. However, if systemic absorption to therapeutic levels is achieved through topical application there is potential for side effects similar to other routes of administration (e.g., oral).

Steroid: Dexamethasone

Summary

Dexamethasone is a potent glucocorticoid that has anti-inflammatory properties. It is FDA approved to be used topically in ophthalmic and otic preparations. It has been studied for application in the mouth and treatment of recurrent aphthous ulcers, but it has no approved indications to treat pain. No relevant evidence exists regarding effectiveness, absorption, or safety of dexamethasone alone or in combination with other active ingredients in compounded topical pain creams. From the FDA-approved label, serious adverse effects from oral administration of this API include cardiomyopathy, hyperglycemia, or pancreatitis. See Box 6-18 for a summary of research findings. See Table G-1 in Appendix G.

Tricyclic Antidepressant: Amitriptyline

Summary

Oral amitriptyline is an FDA-approved tricyclic antidepressant that was originally developed as a mood-regulating agent. It is thought to work by inhibiting the reuptake of norepinephrine and serotonin by presynaptic neuronal membranes in the CNS. At the spinal cord, amitriptyline exhibits ion-channel blocking effects on sodium, potassium, and NMDA channels. Norepinephrine, and sodium and NMDA channels, are involved in maintenance of some types of neuropathic pain. Off-label use of the oral formulation has been found to consistently reduce neuropathic forms of pain to a greater degree than comparison placebo groups (Moore et al.,

BOX 6-19
Summary of Research Findings on Amitriptyline in Compounded Topical Pain Creams

Effectiveness: There is limited and inconsistent evidence to suggest that topical amitriptyline is not effective to treat neuropathic pain when applied to intact skin.

Dermal penetration/bioavailability: Limited evidence suggests that a minimal amount of topically applied amitriptyline penetrates through human skin. Serum concentrations of topical amitriptyline have been detected at very low levels following topical use.

Safety and adverse effects: Limited evidence suggests that topical amitriptyline is associated with minimal adverse effects such as skin irritation, dryness, itching and redness, and drowsiness.

2015). However, there is very little evidence for its effectiveness when applied as a topical agent. Very low doses were detected in the blood stream after topical application. Adverse clinical effects included skin irritation, dryness, itching, and redness. One patient reported drowsiness as a side effect with use of 10 percent amitriptyline cream. See Box 6-19 for a summary of research findings.

Overall the committee reviewed six RCTs. Three were assessed as having a low risk of bias (Dualé et al., 2008; Kiani et al., 2015b; Lynch et al., 2003), and three were assessed as having a high risk of bias (Gerner et al., 2003; Ho et al., 2008; Lynch et al., 2005b). (See Appendix B for more details.) In addition to reviewing studies where amitriptyline alone was analyzed, the committee also included studies of amitriptyline used in combination with other APIs. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

Effectiveness

Randomized controlled trials A double-blind, randomized, placebo-controlled crossover study evaluated the efficacy of topical 5 percent amitriptyline, 5 percent lidocaine, or placebo (compounded in pluronic lecithin organogel) in treating patients with neuropathic pain (Ho et al., 2008).[32] Thirty-five patients (16 males, 19 females; mean age 57.4 years)

[32] Risk-of-bias assessment by committee: High (see Appendix B for more details).

with postsurgical neuropathic pain, postherpetic neuralgia, or diabetic neuropathy with allodynia or hyperalgesia were assigned in random sequence to apply 3–5 mL of a cream twice daily for 1 week. The primary outcome measure was change in pain intensity (baseline versus posttreatment average pain) using a 0 to 100 mm VAS. No significant change in pain intensity was found with amitriptyline. Both lidocaine and placebo resulted in significantly ($p < .05$) reduced scores compared to amitriptyline.

The effectiveness of 2 percent amitriptyline in treating peripheral diabetic neuropathy was evaluated in 51 patients (17 males, 34 females; mean age 57.5 years) (Kiani et al., 2015b).[33] A matched group of 51 patients given 0.75 percent capsaicin served as controls. Patients applied the cream three times daily to their feet for 12 weeks. Pain was measured by the VAS with a 50 percent reduction considered a positive response. After 12 weeks, 43.1 percent of patients given amitriptyline and 37.3 percent of patients given capsaicin were considered responders, which was not statistically significant.

The sensory effects of amitriptyline diluted in water/isopropanol/glycerin solution were examined in 15 healthy young male volunteers given randomized treatments of 0 (vehicle), 25, 50, or 100 mM on different areas of the skin of the back (Dualé et al., 2008).[34] Total dose for the session was 82.4 mg. Saline and lidocaine–prilocaine cream served as negative and positive controls, respectively. Mechanical thresholds for touch and nociception, and thermal thresholds for cold, warm, and heat sensation were recorded for each area. Amitriptyline induced a mild increase ($p \leq .01$) of the tactile and mechanical nociceptive thresholds at ≥ 50 mM, and all concentrations significantly decreased ($p \leq .01$) cold and heat thresholds compared to controls. These effects were no longer significant after 4 hours.

Analgesic effects of amitriptyline were evaluated in 14 healthy volunteers (sex not stated) by application of 0.3 mL of 0, 10, 50, or 100 mmol/L solutions to the upper arm (Gerner et al., 2003).[35] The vehicle was water/isopropanol/glycerin, and pain was measured by poking with a blunt needle. The VAS was significantly reduced at concentrations ≥ 50 mmol/L for up to 4 hours after removal of the gauze.

Lynch et al. (2003, 2005b) evaluated the effects of topical ketamine, amitriptyline, or a combination of the two in the treatment of neuropathic pain. To minimize redundancy within the chapter, a review of these studies is described in the Multiagent Compounded Topical Pain Creams section below.

[33] Risk-of-bias assessment by committee: Low (see Appendix B for more details).
[34] Risk-of-bias assessment by committee: Low (see Appendix B for more details).
[35] Risk-of-bias assessment by committee: High (see Appendix B for more details).

Case reports Three patients with neuropathic pain in the hands and feet were treated with 3 mL of 5 and 10 percent amitriptyline (Kopsky et al., 2012). All patients noted partial relief with the 5 percent cream and almost complete relief with the 10 percent cream. Two patients reported tiredness/drowsiness with 10 percent cream.

Another patient (42 years, male) was prescribed 5 percent amitriptyline, three times daily, for chronic severe pain in the ankle after a fall. After 1 month, his pain score decreased by 30 percent (Kopsky and Keppel Hesselink, 2011).

A 42-year-old male was given amitriptyline cream (150 mg/2 mL) for abdominal pain caused by Crohn's disease (Scott et al., 1999). The cream was applied to the chest at bedtime, and the patient monitored for 6 weeks. The abdominal pain remained unchanged with treatment, although the patient reported his mood improved.

A 62-year-old woman with pain in the upper arms and left foot attributable to multiple sclerosis was prescribed 5 percent amitriptyline (Kopsky and Keppel Hesselink, 2012; Kopsky et al., 2012). Application of the cream to the upper forearms resulted in decreased pain in the foot and upper arms after several minutes delay. Blood levels were not measured.

Preclinical studies Animal studies have also demonstrated a potential cutaneous effect. Two studies tested cutaneous nociception in male Sprague-Dawley rats (n = 6–8) before and after application of 0.3 mL containing amitriptyline to the shaved back for 3 hours under a patch. Test solutions were formulated in isopropyl alcohol/water or saline/glycerin. The cutaneous trunci muscle reflex response was measured via pinprick. A 2.5 percent solution resulted in complete block to the pinprick for 4.5 hours with complete recovery at 96 hours (Colvin et al., 2011). Concentration-related analgesic effect was observed with almost 100 percent at 500 mM, 90 percent at 100 mM, and 50 percent at 50 mM; no effects were seen after several days, 25 hours, and 10 hours, respectively. Rats given 500 mM developed redness and skin induration at the application site, which disappeared after several hours (Haderer et al., 2003).

Dermal Penetration/Bioavailability

Clinical studies Five urine samples were collected to evaluate drug levels resulting from topical amitriptyline application (Glinn et al., 2017). Dosing and formulation information were not available. Amitriptyline was detected in two samples, both at < 25 ng/mL, while nortriptyline was not detected. The therapeutic level of amitriptyline is typically defined as between 70 and 220 ng/mL (Ulrich et al., 2001).

Amitriptyline was not detected (Limit of Detection = 2 ng/mL) in plasma samples from 15 healthy young male volunteers following application of 82.4 mg to the skin of the back (Dualé et al., 2008).

A 42-year-old male was given amitriptyline gel (150 mg/2 mL) for application to the chest once daily to treat abdominal pain caused by Crohn's disease (Scott et al., 1999). After 9 days of treatment, blood levels were measured over 24 hours. The patient had previously been given amitriptyline 80 mg/day by intramuscular injection for 19 days resulting in a steady state level of 201 ng/mL. With application of the amitriptyline gel, blood levels ranged from 196.2 to 263.3 ng/mL.

Preclinical studies Dermal penetration and deposition were measured using excised skin from the backs of female nude mice and pigs (Liu et al., 2016). A 15 mM amitriptyline solution in 20 percent propylene glycol was placed on the donor side of the skin for 24 hours. The amount deposited in the skin, the flux, and the total percent absorbed (skin + receptor) were 28.25 nmol/mg, 10.22 nmol/cm^2/h, and 21 percent, respectively, for nude mouse skin and 11.76 nmol/mg, 22.53 nmol/cm^2/h, and 14 percent, respectively, for pig skin. Using a 6.5 mM solution, the total absorbed was 33 percent and 19 percent for nude mouse and pig, respectively.

Safety and Adverse Effects

Clinical studies One study reported in patients with peripheral diabetic neuropathy treated with 2 percent amitriptyline, 8.8 percent reported dryness and 4.4 percent had itching (Kiani et al., 2015b). Another clinical study reported redness was observed at the application site (upper arm) up to 6 hours after application in 10 out of 14 volunteers (50 mmol/L treatment) and 12 out of 14 volunteers (100 mmol/L treatment) (Gerner et al., 2003).

Drowsiness was reported in a patient treated with 10 percent cream for neuropathic pain in the feet (Kopsky et al., 2012).

From the FDA-approved label, serious adverse effects from oral administration of this API include increased suicidal thoughts or cardiac arrhythmias. See Table G-1 in Appendix G.

Tricyclic Antidepressant: Doxepin

Summary

Doxepin is an FDA-approved psychotherapeutic agent (oral, topical) from the class of dibenzoxepin tricyclic compounds. The mechanism of action of doxepin has not been confirmed. The current understanding is that doxepin prevents reuptake of norepinephrine into nerve terminals by

influencing activity in the synapse; this allows neurotransmitter activity to be prolonged. Norepinephrine is thought to be involved in the maintenance of some types of neuropathic pain, and this provides a rationale for off-label use of doxepin to treat certain types of pain.

Evidence from a few clinical studies and case reports suggest topical doxepin at 3.3 percent concentration as aqueous cream may be potentially effective for treating pain, including neuropathic pain and complex regional pain syndrome. Safety data indicate the potential for centrally mediated side effects when systemic absorption occurs, including drowsiness, rash, and headache. Topical applications also demonstrated occasional drowsiness and headache, as well as local effects such as itching and burning. The one relevant RCT reviewed by the committee was assessed as having a low risk of bias (McCleane, 2000). See Box 6-20 for a summary of research findings. (See Appendix B for more details.)

Effectiveness

Randomized controlled trials One randomized, double-blind, placebo-controlled human study was conducted to assess the analgesic efficacy of topical administration of 3.3 percent doxepin HCl cream compared to 0.025 percent capsaicin cream and a combination cream of 3.3 percent doxepin and 0.025 percent capsaicin for treating chronic neuropathic pain

BOX 6-20
Summary of Research Findings on Doxepin in Compounded Topical Pain Creams

Effectiveness: There is limited evidence to suggest that topical doxepin may be effective to treat chronic human neuropathic pain when administered at 3.3 percent concentration as an aqueous cream on intact skin.

Dermal penetration/bioavailability: There is limited evidence to suggest that topical doxepin penetrates through human skin. One preclinical study detected serum concentrations (0–47 ng/mL, $n = 19$) overlap with therapeutic concentrations (reported as 30–150 ng/mL).

Safety and adverse effects: Limited evidence suggests that topical doxepin is associated with minimal adverse effects. One clinical study determined potential effects include local stinging or burning, drowsiness, headache, rash, and itching/allergic contact dermatitis. Drowsiness may be caused by systemic absorption.

(McCleane, 2000).[36] Patients across the three comparative treatment groups (n = 95) produced similar analgesic effects with the combination treatment having fastest onset. Overall pain was unchanged in the placebo group.

No relevant clinical trials are listed in ClinicalTrials.gov; two trials are disclosed—one is for treating oral mucositis and the other is for treating pruritus.

Case reports and case series A case report describes a 17-year-old female leukemia patient with mucormycosis infection that developed severe refractory peripheral neuropathy believed to be a side effect from treatment. The patient responded "dramatically and consistently" to topical treatment with 5 percent doxepin cream three times daily (Dworsky et al., 2017).

Another case report exists of a 32-year-old female patient with complex regional pain syndrome type 1 resulting from a wrist injury. Symptoms were reduced significantly after 2 weeks of twice-daily topical application of doxepin cream (McCleane, 2002).

Preclinical studies Topical doxepin was significantly more effective than control ($p < .05$) in rat nociceptive pain (Gerner et al., 2006).

Dermal Penetration/Bioavailability

Preclinical studies Permeation through human cadaver skin was reported as having a flux of 2.74 ± 0.14 μg/h cm^2 following application of doxepin formulated in a 3 percent (weight/volume) nanoemulsion (Sandig et al., 2013).

Safety and Adverse Events

Clinical trials In one clinical trial, side effects were indicated as minor. Drowsiness occurred in four patients (9.7 percent) in the doxepin and two patients (5.5 percent) in the doxepin/capsaicin group, skin rash was reported in one patient (2.4 percent) with doxepin, headache was reported in one patient (2.8 percent) with doxepin/capsaicin, and itching was reported by two patients (4.9 percent) with doxepin. Twenty-seven patients (81 percent) in the capsaicin group, 22 patients (61 percent) in the doxepin/capsaicin group, and 4 patients (17 percent) in the doxepin group reported burning discomfort after application of cream (McCleane et al., 2000).

From the FDA-approved label, serious adverse effects from oral administration of this API include ventricular arrhythmia, thrombocytopenia, suicidal thoughts, or kidney damage. See Table G-1 in Appendix G.

[36] Risk-of-bias assessment by committee: Low (see Appendix B for more details).

Vasodilator: Pentoxifylline

Summary

Pentoxifylline is a methylxanthine derivative that is used in microcirculatory disorders as a vasoactive drug promoting blood flow via oral route of administration. In the United States, oral pentoxifylline is FDA approved for symptomatic treatment of patients with chronic occlusive peripheral vascular disorders of the extremities. In such patients pentoxifylline may give relief of signs and symptoms of impaired blood flow, such as intermittent claudication or trophic ulcers. It is nearly completely absorbed by oral administration with relatively few reported side effects. The primary side effects of oral administration have been malaise (1–3 percent), flushing (1–3 percent), dizziness/light-headedness (9.4 percent), headache (4.9 percent), nausea (14 percent), vomiting (3.4 percent), and abdominal discomfort, bloating, diarrhea, or dyspepsia (1–3 percent) (Cunha, 2016).

There is a well-designed clinical crossover randomized study demonstrating efficacy of compounded pentoxifylline on experimentally induced allodynia and pain induced by the injection of dermal capsaicin in humans (Ragavendran et al., 2016). There is also one carefully designed and conducted crossover study in rats demonstrating efficacy in experimentally induced neuropathic pain symptoms (Ragavendran et al., 2013). Finally, there is one ongoing randomized clinical trial of topical pentoxifylline with clonidine in patients with neuropathic pain by the same research group, but recruitment has been slow and results are not expected to available until the end of 2020 (Coderre et al., 2017). Other literature includes few case studies either as single-drug compounded topical drug or in combination with others (Carr et al., 1994; Paulis et al., 2015; Safaeian et al., 2016). The quality of the remaining studies does not allow any additional conclusions regarding effectiveness or safety. See Box 6-21 for a summary of research findings.

The one RCT reviewed by the committee was assessed as having a low risk of bias (Ragavendran et al., 2016). (See Appendix B for more details.) In addition to reviewing studies where pentoxifylline alone was analyzed, the committee also included studies of pentoxifylline used in combination with other APIs. (See the Multiagent Compounded Topical Pain Creams section of this chapter.)

Effectiveness

Randomized controlled trials A randomized crossover study (Ragavendran et al., 2016) was conducted in 69 patients exposed to intradermal injection of capsaicin to induce allodynia and pain.[37] The evaluation of

[37] Risk-of-bias assessment by committee: Low (see Appendix B for more details).

BOX 6-21
Summary of Research Findings on Pentoxifylline in Compounded Topical Pain Creams

Effectiveness: There is limited evidence to suggest topical pentoxifylline is not effective to treat pain when applied to intact skin.

Dermal penetration/bioavailability: There is insufficient evidence to suggest that topical pentoxifylline penetrates through human skin. Based on a single in vitro study, the absorption varies greatly with the excipient used.

Safety and adverse effects: There is limited evidence on the safety of topical pentoxifylline. However, if systemic absorption to therapeutic levels is achieved through topical application, there is potential for side effects similar to other routes of administration (e.g., oral).

pentoxifylline alone involved application of pentoxifylline 5 percent in a vehicle of anhydrous ethanol (6.5 percent), polyethylene glycol 400 (20 percent), propylene glycol (53.5 percent), and oleyl alcohol (20 percent) topically to intact skin in the area of capsaicin-induced allodynia. The control was the vehicle alone. Dosing was controlled by a pump equipped with an actuator, which when pressed once was calibrated to deliver 0.5 ± 0.04 mL of solution used to cover approximately 1,200 mm^2 of the skin overlapping the area of capsaicin-induced hypersensitivity. The effect of pentoxifylline on VAS scores, dynamic mechanical allodynia, or punctate mechanical allodynia was no different from that of the inactive vehicle.

A forthcoming study by the same research group will examine clinical outcomes from a randomized clinical trial of topical pentoxifylline with clonidine in patients with neuropathic pain.

Preclinical studies In rats with induced neuropathic pain via (1) chronic postischemia pain, (2) chronic constriction injury of the sciatic nerve, (3) diabetic neuropathy, or (4) chemotherapy-induced painful neuropathy, topical application of pentoxifylline and its active metabolite lisofylline were tested across a variety of concentrations (Ragavendran et al., 2013). An amount of 150 mg ± 2.7 mg of the ointment was used for all rat hind paw applications and compared to ointment base application to the ipsilateral paw. Pentoxifylline alone was tested at 0.6, 1.2, 2.5, and 5 percent w/w ($n = 6$), and lisofylline alone was tested at 0.063, 0.09, 0.125, and 0.25 percent w/w ($n = 10$). All of the rats underwent initial baseline paw

withdrawal threshold (PWT) assessment before application of the ointment followed by testing at 45–90 minutes postapplication. When tested alone, pentoxifylline only significantly elevated PWT at the highest dose tested (5 percent). Lisofylline alone significantly increased PWT at 0.09, 0.125, and 0.25 percent w/w.

In a separate study of rats (Laferriere et al., 2014) with induced hind paw chronic postischemia pain and allodynia, a topical application of lisofylline (an analogue of pentoxyfilline) and apraclonidine produced significant dose-dependent antiallodynic effects when compared with the vehicle/base in rats with chronic postischemia pain (n = 30), a finding not reproduced with control treatment of the nonpainful paw. Topical combination produced antiallodynic effects lasting up to 6 hours (n = 15).

Dermal Penetration/Bioavailability

In vitro studies One study (Wang and Black, 2013) examined the dermal penetration of multiple products including pentoxifylline, showing better transdermal absorption with a novel proprietary product showing 2–3 times the penetration with the novel excipient. There is no clear interpretation of the values in a clinical sense.

Safety and Adverse Effects

Randomized controlled trials Ragavendran et al. (2016) determined that at a dose of pentoxifylline 5 percent, no subject exhibited a drop in blood pressure greater than 15 percent to 30 percent. Additionally, no subjects reported any adverse events associated with the administration of active treatments or vehicle.

From the FDA-approved label, serious adverse effects from oral administration of this API include thrombocytopenia. See Table G-1 in Appendix G.

MULTIAGENT COMPOUNDED TOPICAL PAIN CREAMS

As summarized in the introduction of this chapter, with one exception (i.e., a clinical study of clonidine and pentoxifylline), little information was found to inform the effectiveness and safety of topical pain creams containing multiple chemicals. In addition, adverse events were similar to those reported for the individual ingredients. An important confounding factor identified in several of the studies described below is the presence of lidocaine in the compounded formulation. Lidocaine is used clinically, and is FDA approved, to induce topical analgesia. The methodological controls and outcome data in many of the articles reviewed below were insufficient to determine whether efficacy improved in combination with

other ingredients. As a result, no conclusions can be made on the committee's review of the creams containing five to seven ingredients owing to the consistent presence of lidocaine, the inclusion of chemicals not evaluated individually by the committee, or the lack of appropriate controls.

Relevant data within the categories of effectiveness, dermal absorption/bioavailability, and safety and adverse effects are summarized where possible.

Two-Drug Combinations: Amitriptyline and Ketamine

Effectiveness

Randomized controlled trials and other clinical trials Lynch et al. (2003) conducted a double-blind, placebo-controlled, four-way crossover pilot study in 20 patients to evaluate the safety, efficacy, and tolerability of ketamine, amitriptyline, or a combination of the two in the treatment of neuropathic pain.[38] Patients with postherpetic neuralgia, diabetic neuropathy, or postsurgical or posttraumatic neuropathic pain who had moderate to severe pain for 3 months or greater duration with allodynia and hyperalgesia were included in the study. Treatment included four different topical creams: amitriptyline 1 percent; ketamine 0.5 percent; amitriptyline 1 percent + ketamine 0.5 percent; or placebo (vehicle only). Subjects applied 5 mL of cream to the site of maximum pain four times daily for 2-day treatment periods. Pain was measured using the McGill Pain Questionnaire and a Likert scale measuring pain intensity "now" and "past 24 hours" and a VAS indicating pain relief (no relief to complete relief). Plasma concentrations of amitriptyline and ketamine and norketamine were measured. It is not clear whether there was a washout period between the four arms. All 20 patients completed the study, and analysis was conducted on 18 subjects who had complete data. There was no significant difference in the McGill Pain Questionnaire by drug type. There was a reduction over time of pain regardless of the treatment. Ketamine and norketamine concentrations were low overall and below detectable limits in 8 out of 11 subjects, with norketamine below limit of detection in 5 of those 8 patients.

Lynch et al. (2005b) conducted a randomized placebo-controlled study in 92 subjects to evaluate the efficacy of topical amitriptyline 2 percent versus ketamine 1 percent versus a combination of amitriptyline 2 percent/ketamine 1 percent for the treatment of neuropathic pain over a 3-week period in patients with mixed neuropathic pain.[39] The excipient was described as a moisturizing creamlike base. Patients with a diagnosis of

[38] Risk-of-assessment by the committee: Low (see Appendix B for more details).
[39] Risk-of-bias assessment by the committee: High (see Appendix B for more details).

postherpetic neuralgia, diabetic neuropathy, or postsurgical/posttraumatic neuropathic pain that was moderate to severe in nature and persisted for 3 months or more were eligible to participate. Subjects applied 4 mL of cream to site of maximum pain three times per day for 3 weeks. Average pain levels were assessed at baseline and at weeks 2 and 3. Outcome measures included measures of spontaneous pain using the numeric rating scale for pain intensity, the McGill Pain Questionnaire, and a measure of spontaneous pain that assesses sensory and affective dimensions of pain; perceived disability; and patient satisfaction. Plasma concentrations of amitriptyline, ketamine, and norketamine were measured after 2 weeks and 3 weeks of treatment. A total of 92 subjects were randomized to the four treatment arms, and 80 subjects completed the study. Reason for withdrawal was adverse events in five patients. All groups experienced a reduction in pain over time, but there was no difference between treatment groups with respect to pain measures, sensory measures, or perceived disability. All groups identified a moderate level of satisfaction. Detectable but low ketamine concentrations were found in three subjects. One patient using 2 percent amitriptyline cream for 3 weeks had blood levels of amitriptyline and nortriptyline of 92 ng/mL and 24 ng/mL, respectively; the study noted two other patients not given amitriptyline also had detectable blood levels (Lynch et al., 2005b). Blood levels in patients using the 1 percent cream were below the limit of detection, < 15.7 ng/mL (Lynch et al., 2005b). With longer treatment, pain scores after 2 to 12 months were 3.83–4.42 compared to a pretreatment score of 6.57 resulting in a 34–46 percent reduction in pain (Lynch et al., 2005a).

A cohort of participants from within Lynch et al. (2005b) were treated with 1 percent amitriptyline/0.5 percent ketamine cream for 3 weeks; they reported greater catastrophic thoughts and feelings when in pain, measured using the Pain Catastrophizing Scale, which was associated with less pain reduction with treatment and greater pain reduction with placebo ($p < .05$) (Sullivan et al., 2008).[40] Further evaluation of the individual responses showed that high scores on the measure of pain catastrophizing prospectively predicted poorer response to treatment. Fewer high-catastrophizing than low-catastrophizing individuals showed moderate or substantial reduction in pain ratings, and fewer high-catastrophizing than low-catastrophizing individuals achieved pain ratings below 4/10 (Mankovsky et al., 2012).

A phase 2 study evaluated the safety and efficacy of a combination of ketamine 2 percent and amitriptyline 4 percent (KA) in the treatment of cancer chemotherapy-induced peripheral neuropathy (CIPN) (Gewandter et al., 2014).[41] Patients were recruited from multiple sites. The

[40] Risk-of-bias assessment by committee: High (see Appendix B for more details).
[41] Risk-of-bias assessment by committee: High (see Appendix B for more details).

total population was 88 percent White, 8 percent African American, and 71 percent female. Participants were at least 1 month post chemotherapy completion and had an average 7-day pain, numbness, and tingling rating of ≥ 4. Subjects were randomized in blocks of four using computer-generated random numbers and stratified based on study site and two treatment groups (patients taking cancer chemotherapeutic taxane agents versus nontaxane agents).

Participants applied cream using a measuring device in an amount up to but not exceeding 4 g of KA cream two times per day to the area with pain, numbness, and tingling. Pain, numbness, and tingling diaries were completed for a 7-day period prior to the start of the study and after study enrollment at weeks 3 and 6. A measure of worst pain over the past 24 hours using numeric rating scale was assessed. A total of 462 subjects were enrolled (229 KA and 233 placebo). Two subjects were excluded from each group leaving 227 in KA and 231 in placebo groups whose data were analyzed on intent to treat basis. Four subjects withdrew from KA and 3 from placebo for skin-related reasons.

At the 6-week assessment, KA cream had no effect on CIPN scores (adjusted mean difference = –0.17, p = .363). In addition, there were no differences in scores for numbness or tingling in the hands and feet between the groups. Adverse events were reported in similar numbers in both groups (147 in KA group, 158 in placebo group), and when evaluated by class there was no significant difference between KA and placebo. The most common adverse events reported were hypertension, fatigue, dyspepsia, insomnia, headache, fever, musculoskeletal and connective tissue disorders, neuropathy, respiratory disorders, and a burning sensation or rash where applied.

Two randomized studies evaluated the effectiveness of 2 percent ketamine/4 percent amitriptyline cream in treating postherpetic neuralgia (84 males; 56 females) or diabetic peripheral neuropathy (65 males; 49 females) (EpiCept Corporation, 2008a,b).[42] The cream was applied twice daily for 28 days, and pain intensity scores were compared to baseline and to controls (46–57 males; 30–55 females). Patients with postherpetic neuralgia had a significantly greater change (p = .044) in pain score with treatment compared to placebo. A slightly greater change (non-significant) in pain score was found for patients with diabetic peripheral neuropathy.

Retrospective clinical studies Electronic medical records were reviewed to determine the effectiveness of 1–2 percent amitriptyline/0.5 percent ketamine for treatment of erythromelalgia (n = 36; 89 percent female) (Poterucha et al., 2013). Formulations were either in a pluronic lecithin

[42] Risk-of-bias assessment by committee (EpiCept Corporation, 2008a,b): High (see Appendix B for more details).

organogel or in a moisturizing cream with application 1–6 times daily. Among the erythromelalgia patients 75 percent had improvement, 3 percent had complete relief, 39 percent noted substantial relief, and 33 percent had some relief, while 19 percent had no relief and 6 percent had worsening symptoms (Poterucha et al., 2013).

Case reports Case reports describe moderate to complete pain/itch relief with 1 percent amitriptyline/0.5 percent ketamine for brachioradial pruritus (Poterucha et al., 2013), 5 percent amitriptyline/10 percent ketamine for ankle pain after a fall (Kopsky and Keppel Hesselink, 2011), and 2.5 percent amitriptyline/0.5 percent ketamine with severe proctodynia (Lehman and Sciallis, 2008). No adverse effects were reported in these cases.

Safety and Adverse Effects

Randomized controlled trials As described above in Lynch et al. (2005b), in a randomized placebo-controlled study of 92 subjects to evaluate the efficacy of topical amitriptyline 2 percent versus ketamine 1 percent versus a combination of amitriptyline 2 percent/ketamine 1 percent for the treatment of neuropathic pain, adverse effects were reported in 30 percent of the subjects and were evenly distributed across treatment groups.[43] The most common adverse effects were minor skin irritation at the site of application. In Lynch et al. (2003), a double-blind, placebo-controlled, four-way crossover pilot study in 20 patients to evaluate the effect of ketamine, amitriptyline, or a combination of the two in the treatment of neuropathic pain, no subjects described severe adverse effects related to ketamine, although two subjects noted skin irritation and rash at the site of application.

Clinical studies In patients treated with 2 percent ketamine/4 percent amitriptyline cream for postherpetic neuralgia (84 males; 56 females), seven reported vertigo while among those treated for diabetic peripheral neuropathy (65 males; 49 females), and two had pruritus and rash (EpiCent Corporation, 2008a,b). The percentage of patients with chemotherapy-induced peripheral neuropathy reporting adverse events was similar between the ketamine/amitriptyline treated group and the placebo group after 6 weeks (Gewandter et al., 2014).

Among 36 patients treated with 1–2 percent amitriptyline/0.5 percent ketamine for erythromelalgia, 1 showed reddening and 1 had a worsening of Raynaud phenomenon associated with erythromelalgia; no systemic effects were seen (Poterucha et al., 2013).

[43] Risk-of-bias assessment by the committee: High (see Appendix B for more details).

In vitro studies As disused in the carbamazepine and gabapentin sections above, Al-Musawi et al. (2017) conducted a toxicity analysis of commonly used topical drugs (i.e., amitriptyline, carbamazepine, gabapentin) commonly used for the treatment of neuropathic orofacial pain. After examining the effects on keratinocytes in cell culture, the authors reported that carbamazepine was cytotoxic to skin and oral keratinocytes, demonstrating significant decrease in cellular viability and cell counts, at high concentrations (1.7 mM) and with long exposure (2 hours). The authors also reported that topical gabapentin was only minimally cytotoxic to skin or oral keratinocytes at high concentrations (5.54 mM) and long exposure (24 hours). Importantly, topical amitriptyline was reported as cytotoxic to skin and oral keratinocytes at both short (30 minutes) and long (24 hours) exposure times and at low (200 μM) and high concentrations (1.8 mM).

Two-Drug Combinations: Clonidine and Pentoxifylline

Effectiveness

Randomized clinical trials A randomized, double-blind study in healthy volunteers evaluated whether clonidine in combination with pentoxifylline reduced pain after topical capsaicin. Participants were randomized to three different groups. Group 1 (n = 23): clonidine 0.04 percent and pentoxyfylline 2 percent was compared to placebo in a crossover design. Group 2 (n = 23): clonidine 0.1 percent and pentoxyfylline 5 percent were compared to placebo in a crossover design. Group 3 (n = 23): compared clonidine 0.1 percent to pentoxyfylline 5 percent. The high-dose clonidine/pentoxifylline group had a significant reduction in mean VAS scores compared to either drug alone or the vehicle (Ragavendran et al., 2016).[44]

Three-Drug Combinations: Piroxicam, Lidocaine, and Cyclobenzaprine Hydrochloride (PLC Cream)

Effectiveness

Randomized controlled trials Popescu et al. (2018) conducted an RCT involving 90 Romanian National rugby players (men and women, numbers of each not specified) who were older than 15 years, had musculoskeletal sports injuries without fracture or need for surgery, no therapy started in the past 7 days, and no use of corticosteroids.[45] Forty-seven rugby players applied a topical gel to the site of injury daily for 14 days containing piroxicam 5 mg/g, lidocaine 20 mg/g, and 5 mg/g cyclobenzaprine hydrochloride

[44] Risk-of-bias assessment by committee: Low (see Appendix B for more details).
[45] Risk-of-bias assessment by committee: Some concerns (see Appendix B for more details).

(PLC), whereas 43 players applied a topical gel with only 10 mg/g piroxicam. The study design attempted to balance the use of ice and different analgesics between the two groups, although 45.6 percent of the PLC gel group used systemic analgesics versus 65.1 percent of the piroxicam gel group. Self-reported pain was surveyed on a VAS, 0–10, with movement and with pressure after application and on days 2, 7, 14.

Compared to the piroxicam gel control, participants using the PLC gel reported a greater decrease in pain sooner with the first application and thereafter on each measurement day. Pain alleviation with application lasted longer as well. On day 14 versus day 1, a 70 percent reduction was reported for the group using the PLC gel versus 45 percent for the group using piroxicam gel. The PLC gel group had 32 percent and 57 percent of participants who were pain free with movement and pressure, respectively, compared to 2.32 percent and 6.97 percent with piroxicam gel. No adverse side effects related to the treatment were reported for either of the two groups. The PLC gel was more effective than a higher dose piroxicam (10 mg/g) gel for pain in sports injuries in young adults. Limitations of this study for assessing the specific efficacy of cyclobenzaprine is that the PLC gel also contained a considerable amount of lidocaine, an anesthetic.

Another RCT in Romania involving 256 subjects investigated the use of the PLC topical gel (appears to be the same formulation as Popescu et al., 2018) for pain control in patients undergoing extracorporeal shock wave lithotripsy (ESWL) for renal or ureteral stones (Pricop et al., 2016).[46] The three study groups received either 1 g of the PLC topical gel applied to the treatment site at different times prior to ESWL or no PLC gel: Group A (number of women/men, 42/39) 30 minutes prior, Group B (60/30) 60 minutes prior, and Group C (46/39) no treatment. VAS pain scores of Groups A (3.76 + 1.03) and B (3.40 + 0.83) were less than C (5.38 + 1.46) ($p < .0001$ for both). Groups A and especially B also needed less rescue medication (tramadol) than C during the procedure. Application 60 minutes prior to treatment seems more optimal than 30 minutes based on less need for rescue medication: 7.8 percent for A, 4.7 percent for B, and 13.6 percent for C. Although application of the PLC gel before ESWL reduced pain perception and need for opioids, cyclobenzaprine was not evaluated separately and the study did not include a vehicle control/placebo.

Safety and Adverse Effects

Randomized controlled trials Within the Pricop et al. (2016) RCT described above, no side effects or skin reactions were observed in the treated groups.

[46] Risk-of-bias assessment by committee: High (see Appendix B for more details).

Three-Drug Combinations: Baclofen, Amitriptyline, and Ketamine

Effectiveness

Randomized controlled trials Patients with neuropathic pain, numbness, and/or tingling caused by chemotherapy-induced peripheral neuropathy were prescribed baclofen 10 mg/amitriptyline HCL 40 mg/ketamine 20 mg in a pluronic lecithin organogel (n = 101; 65 percent female; 94 percent White) or a placebo (n = 102; 59 percent female; 90 percent White) twice daily for 4 weeks (Barton et al., 2011).[47,48] The primary endpoint was change in the sensory neuropathy subscale as measured by the European Organization for Research and Treatment of Cancer QLQ-CIPN20 instrument from baseline to 4 weeks. The Brief Pain Inventory did not demonstrate significant differences nor did the Profile of Mood States; however, treated patients had significant improvement in the sensory (n = 75; p = .053) and motor subscales (n = 75; p = .021) of the CIPN20 owing to improvement in symptoms of tingling, cramping, and shooting/burning pain in the hands. Blood samples were drawn on a small subset of participants (n = 8) at the end of 4 weeks of treatment to evaluate systemic absorption by measuring concentrations of drugs and their metabolites. One of the four participants in the active drug arm had detectable concentrations of amitriptyline that were below therapeutic concentrations and no detectable ketamine or baclofen. Another participant had low therapeutic concentrations of baclofen but undetectable concentrations of amitriptyline and ketamine. The range of blood concentrations considered therapeutic were not described.

Safety and Adverse Effects

Clinical studies Incidences of adverse events were similar between patients on baclofen 10 mg/amitriptyline HCL 40 mg/ketamine 20 mg gel and those on placebo (Barton et al., 2011).

Three-Drug Combinations: Ketamine, Amitriptyline, and Lidocaine

Effectiveness

Clinical studies A 1 percent ketamine/2 percent amitriptyline/5 percent lidocaine gel was evaluated in 16 patients (88 percent female) with neuropathic pain from radiation-induced dermatitis (Uzaraga et al., 2012). Patients applied ~4 mL to the painful areas three times daily until 2 weeks

[47] Risk-of-bias assessment by committee: High (see Appendix B for more details).

[48] Treatment gel and placebo gel were compounded at Gateway Health Mart Pharmacy Laboratory in Bismarck, North Dakota.

after completion of radiotherapy. A reduction in scores for intensity, sharpness, burning, sensitivity, unpleasantness, and deepness was found 30 minutes after application; reduction in burning was maintained for 2 weeks posttreatment.

In a letter to the editor the authors retrospectively examined change in the numeric rating scale after topical application of ketamine 10 percent/amitriptyline 5 percent/lidocaine 5 percent for the treatment of chronic pruritus (Lee, 2017). This was a retrospective review of medical and pharmacy records of patients prescribed the topical product between September 1, 2013, and June 30, 2016. A total of 96 patients were identified. Average numeric rating scale reduced an average of 4.61 from 8.63 to 4.19 after treatment. Authors indicate 63 percent attributed relief directly to the topical product, although it is unclear what data elements were in the medical record that allowed for such a statement. Sixteen reported mild burning and redness.

Case reports A 24-year-old male presenting with inflammatory linear verrucous epidermal nevus was prescribed 10 percent ketamine/5 percent amitriptyline/5 percent lidocaine in a Lipoderm base. After 6 weeks, one to three times daily, the patient had complete relief of pruritus and an itch rating of 0/10 down from 9.5/10 (Jaller and Yosipovitch, 2018).

Safety and Adverse Effects

Clinical studies Of 16 patients treated with 1 percent ketamine/2 percent amitriptyline/5 percent lidocaine gel (88 percent female) for neuropathic pain from radiation-induced dermatitis, 3 had irritation at grade 1–2 and 5 reported fatigue at grade 1 (Uzaraga et al., 2012).

Cardis and Pasieka (2016) describe a man in his 80s who was treated with ketamine 10 percent/amitriptyline 5 percent/lidocaine 5 percent in Lipoderm for pruritus associated with atopic dermatitis. After applying to a small test area the patient gradually increased coverage of the cream to most of his upper body. He presented to the emergency department with slurred speech, ataxia, and altered mental status and was admitted to the hospital to rule out stroke. He had persistent nonfocal findings on neurologic examination, and the temporal relationship of his symptoms to the escalating dose of the cream was identified. The authors state that amitriptyline, lidocaine, ketamine, and their metabolites were detected in the urine by mass spectroscopy. A concentration of 2,360 ng/mL was reported, but it is unclear what this concentration represents. The patient improved over the next 2 weeks and was discharged on hospital day 17.

Greater Than Three Drug Combinations, Including Ketamine, Gabapentin, Clonidine, Lidocaine, Cyclobenzaprine, Baclofen, Ketoprofen, Diclofenac, Flurbiprofen, Tramadol, Bupivacaine, Amitriptyline, Nifedipine, Ibuprofen, Pentoxifylline, Imipramine, and/or Mefenamic Acid

Effectiveness

Randomized controlled trials The safety and efficacy of three different compounded pain creams tailored for three types of pain (neuropathic, nociceptive, and mixed pain disorder) were evaluated in a clinical trial (Brutcher et al., 2019).[49] The randomized, double-blind, placebo-controlled, parallel-group clinical trial had a duration of 1 month of treatment with a compounded cream or a placebo cream. For those participants considered to have predominantly neuropathic pain (n = 133), the active cream contained 10 percent ketamine, 6 percent gabapentin, 0.2 percent clonidine, and 2 percent lidocaine. For those considered to have nociceptive pain (n = 133), the active cream contained 10 percent ketoprofen, 2 percent baclofen, 2 percent cyclobenzaprine, and 2 percent lidocaine. The active cream for those considered to have mixed pain (n = 133) contained 10 percent ketamine, 6 percent gabapentin, 3 percent diclofenac, 2 percent baclofen, 2 percent cyclobenzaprine, and 2 percent lidocaine. No significant change in average pain score on a 0–10 point numerical rating scale in the preceding week between the active cream and placebo cream in any of the three groups was found. Also, no change was found in secondary outcome measures including the SF-36 or in medication reduction. Of the 399 participants randomly assigned, 396 received treatment and 390 completed the study protocol.

Cohort studies In a retrospective analysis by Somberg and Molnar (2015a) of a large cohort of patients (n = 2,177) with chronic pain, two topical pain creams were compared to Voltaren (diclofenac sodium) gel before and after treatment using the Visual Numeric Pain Intensity Scale. The study population was 37 percent White, 24 percent Hispanic, 18 percent African American, 7 percent Native American, 3 percent Asian, and 11 percent other ethnicity; mean age of 39 ± 9 years; with chronic extremity, joint, musculoskeletal, neuropathic, or other chronic pain conditions treated with the topical creams. Cream 1 contained flurbiprofen 20 percent, tramadol 5 percent, clonidine 0.2 percent, cyclobenzaprine 4 percent, and bupivacaine 3 percent. Cream 2 contained flurbiprofen 20 percent, baclofen 2 percent, clonidine 0.2 percent, gabapentin 10 percent, and lidocaine 5 percent. Pain intensity scores improved more in the two groups that

[49] Risk-of-bias assessment by committee: Low (see Appendix B for more details).

used compounded creams as compared to Voltaren gel as follows: In the cream 1 group (n = 1,141), the score fell from 8.44 ± 1.19 pretreatment to 5.33 ± 2.01 posttreatment, $p < .001$, and by 2.93 ± 1.58 in the cream 2 group (n = 527) from 8.42 ± 1.27 to 5.50 ± 1.96 posttreatment, $p < .001$, representing an average decrease in the score of 37 percent and 35 percent. The group using Voltaren gel (n = 509) had a pain score that decreased from 7.93 ± 0.81 to 6.44 ± 1.14, $p < .001$, or an average decrease of 19 percent, which was significantly less than the other two groups. Of note, there were several limitations in this retrospective analysis, including age differences between groups and in the baseline pain intensity of patients in the Voltaren cream 2 group. In addition, physicians were allowed to choose what medication and duration of medication was prescribed.

The same authors reviewed medical records to determine efficacy of a compounded topical cream containing six or seven drugs: both contained 10 percent ketamine/2 percent baclofen/6 percent gabapentin/4 percent amitriptyline/2 percent bupivacaine/0.2 percent clonidine; one cream contained 2 percent nifedipine. A total of 283 patients with diabetic neuropathy or other chronic pain (no further description), included 78 receiving the six-drug cream and 205 receiving the seven-drug cream. Pain scores decreased by 2.4 (35 percent; $p < .001$) with the six-drug cream and by 3.0 (40 percent; $p < .001$) with the seven-drug cream (Somberg and Molnar, 2015b).

Case reports Alexander and Wynn (2007) described significant pain relief with a 6 percent gabapentin/2 percent amitriptyline/5 percent lidocaine/10 percent ketoprofen transdermal gel in a patient following gall bladder surgery.

In case reports by Safaeian et al. (2016) a topical cream with seven ingredients (diclofenac 5 percent, ibuprofen 3 percent, baclofen 2 percent, cyclobenzaprine 2 percent, bupivacaine 1 percent, gabapentin 6 percent, and pentoxifylline 1 percent), referred to as T7, was used for the treatment of radicular pain. The first patient was a 39-year-old man with 3 weeks of neck pain radiating into the left upper extremity and with 10/10 pain intensity on the NRS. He also complained of weakness, numbness, and tingling in the left arm. He was using an opiate prescription with no relief. A magnetic resonance imaging (MRI) test revealed severe stenosis at the left C6–7 neural foramen and Spurling's test (a physical maneuver used to assess nerve root radicular pain) was positive on the left. He was prescribed 1–2 grams of T7 to the neck 3–4 times per day. He was also prescribed oral gabapentin and physical therapy, which he did not use. Pain was reduced by 4 months to 6/10 and symptoms improved.

The second patient was a 47-year-old woman with chronic low back pain on opiates and other medications with a history of an L5-S1 laminectomy and fusion presenting with acute back pain (10/10 on the

NRS). There was no significant change noted by MRI and she had a negative straight leg raise test. The patient was prescribed T7, and at 3-month follow-up, she reported pain of 7/10 and 30 percent improvement in symptoms. The third case was a 65-year-old man with a history of chronic low back and radicular pain who also reported relief of pain (5/10 to 3/10) with the compounded cream T7 at 4-month follow-up. In none of these three cases was adverse events reported.

In another case report using a different combination, a 78-year-old woman with refractory postherpetic neuralgia was treated with a compounded topical cream composed of gabapentin 6 percent, ketoprofen 10 percent, amitriptyline 2 percent, and lidocaine 5 percent (Hohmeier and Almon, 2015). She experienced some relief. A new topical cream with gabapentin 6 percent, ketoprofen 10 percent, lidocaine 5 percent, and ketamine 10 percent was prescribed in addition to an oral mucosal topical agent containing gabapentin 10 percent in Orabase. The patient noted further decreases in pain but not complete resolution.

Safety and Adverse Effects

Clinical studies In the clinical study reported by Somberg and Molnar (2015b) described above, adverse events were reported in 5.7 percent of patients using a six-drug cream and in 3.8 percent of patients using a seven-drug cream including skin irritation, burning sensation at application site, rash, and flushing (Somberg and Molnar, 2015b).

Case reports In Pomerleau et al. (2014), a 23-year-old man presented to the emergency department with altered mental status after he rubbed an unknown amount of a prescribed compounded topical cream all over his body. The cream contained clonidine 0.2 percent, gabapentin 6 percent, imipramine 3 percent, ketamine 10 percent, lidocaine 2 percent, and mefenamic acid 1 percent. On presentation to the emergency department he was bradycardic with a heart rate of 46 beats/minute, blood pressure 180/87 mmHg, respiratory rate of 21 breaths/minute, and a temperature of 95.6°F. Urine toxicology screen was positive for amphetamines, tetrahydrocannabinol, and tricyclic antidepressants. It was negative for methamphetamine, cocaine, phencyclidine, barbiturates, benzodiazepines, methadone, and opiates. His skin was decontaminated with soap and water. His mental status declined, his trachea was intubated to protect his airway, and he was transported to a tertiary care facility. Upon arrival at the second hospital, he remained bradycardic and hypertensive with a maximum blood pressure of 214/139 mm Hg. He was extubated on day 2 and made a full recovery. Serum concentrations were noted as follows: clonidine 5,200 ng/mL (therapeutic range 0.5–4.5 ng/mL), lidocaine and metabolite

not detected, imipramine 13 ng/mL, and desipramine < 10 ng/mL. No analysis for ketamine was performed.

Sigillito et al. (2003) present an abstract describing a 35-year-old man who presented to the hospital after suffering a seizure. He was unresponsive and had apparently lost all brainstem reflexes. His trachea was intubated, and he was ventilated for 2.5 days. His EEG demonstrated burst suppression. A urine drug screen was positive for benzodiazepines and tricyclic antidepressants. It was later determined that the patient had applied an excessive amount of a compounded cream used for chronic pain. It was estimated that his total exposure dose of ketamine was 900 mg, baclofen 900 mg, amitriptyline 360 mg, lidocaine 900 mg, and ketoprofen 1,800 mg. Ketamine was detected in cerebrospinal fluid by gas chromatography-mass spectrometry. He improved and was discharged on the fourth hospital day.

In a case report, a 22-month-old child developed toxicity consistent with clonidine (apnea and bradycardia) following the ingestion of a topical pain cream containing clonidine 0.2 percent, ketoprofen 7 percent, lidocaine 2.5 percent, prilocaine 2.5 percent, camphor 3 percent, menthol 3 percent, ethoxydiglycol 5 percent, and gabapentin 5 percent. Serum toxicology analysis assessed clonidine levels at 2.6 ng/ml. Given the API's therapeutic range of 0.5–4.5 ng/mL, the authors noted it was unusual that the patient's serum concentration of clonidine was comparably low. Neither camphor or ketoprofen were detected, and gabapentin concentration was < 1 mcg/mL (Cates et al., 2018).

In another case report, an 18-month-old was found unresponsive and brought to the emergency department after a parent applied "one pump" (one click) of a compounded topical pain cream to the child's bottom to treat a diaper rash. In the hospital the child was bradycardic and hypotensive with decreased respiratory effort requiring endotracheal intubation and mechanical ventilation. The topical cream contained ketamine 100 mg, clonidine 2 mg, gabapentin 60 mg, mefenamic acid 10 mg, imipramine 30 mg, and lidocaine 10 mg/pump. The child improved with supportive care. A serum clonidine concentration was 9.2 ng/mL (reference range, 0.5–4.5 ng/mL) and a norketamine level of 41 ng/mL (reporting limit, > 20 ng/mL) (Sullivan et al., 2013).

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7

Additional Concerns Related to the Use of Compounded Topical Pain Creams

Previous chapters described how topical pain creams are often lauded for allowing clinicians to treat pain through multimodal actions, thus providing a greater degree of versatility than oral dosage forms (Branvold and Carvalho, 2014). Having said this, several medications for managing pain already have U.S. Food and Drug Administration (FDA)-approved topical formulations readily available in pharmacies (e.g., capsaicin, clonidine, lidocaine, diclofenac) (FDA, 2020). In other unique clinical circumstances in which pain cannot be managed by any of the available FDA-approved products, FDA regulations allow for medications to manage pain to be compounded for an individual patient.[1] While compounded topical pain creams are options in the pain management toolbox, it is critical to note that compounded medications are not necessarily safer or more effective alternatives to commercial FDA-approved products. See Chapter 6 for a review of the current evidence on the safety and effectiveness of common compounded topical pain creams.

This chapter provides an overview of certain additional risks and concerns associated with the use of compounded topical pain creams, many of which arise because of the unique regulatory landscape and minimal oversight for these preparations (see Chapter 4 for more details about gaps and opportunities in regulation and oversight). In this chapter, the committee outlines concerns related to inadequate training and expertise for individuals who compound medications, inadequate training and guidance

[1] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

for clinicians who prescribe compounded medications, and safety concerns and potential financial risks for patients.

INADEQUATE TRAINING AND EXPERTISE FOR INDIVIDUALS WHO COMPOUND

Licensed pharmacists, technicians supervised by a licensed pharmacist, and licensed physicians who compound in their own clinics are permitted to prepare compounded formulations under the auspices of state licensure and oversight (see Chapter 4).[2] However, there is reason for concern that certain individuals who compound may have inadequate training and expertise to ensure that preparations are safe and effective.

Required Knowledge and Practical Competencies for Individuals Who Compound

Traditionally, individuals who compound are required to have formal education and a foundational knowledge in a range of scientific disciplines related to chemistry, pharmacology, and biology. Over the past few decades, however, demand for compounded medications has escalated, leading to a concomitant demand for pharmacists who are trained and experienced in the practice of compounding on a larger scale. Meeting this demand is complicated by the increasingly sophisticated and technical procedures and formulations required to create the customized dosage forms and new medication therapies that are emerging (Hinkle and Newton, 2004). See Chapter 5 for an additional discussion on the art and science of compounding.

The practice of pharmacy has shifted over the past century from compounding to dispensing FDA-approved medications (Sellers and Utian, 2012). When commercial drug production began taking over the market in the 1960s and 1970s (Newton, 2003), education about compounding practices in pharmacy schools began declining. Indeed, much compounding pedagogy has now been phased out of pharmacy school curricula in favor of clinical pharmacy instruction (Kochanowska-Karamyan, 2016). Today,

[2] Section 503A of the Food, Drug, and Cosmetic Act (FDCA) mandates that compounding be performed by a licensed pharmacist or licensed physician, and under Section 503B, an individual who compounds may be a licensed pharmacist or someone under the supervision of a licensed pharmacist. USP <795> goes beyond the FDCA, recommending that anyone who compounds (1) be familiar with the United States Pharmacopeia's *Pharmacists' Pharmacopeia* and other publications that may be relevant, including the ability to interpret Material Safety Data Sheets; (2) be familiar with standard operating procedures related to compounding; and (3) be trained in the storage, handling, and disposal of hazardous drugs if they are involved in the compounding of hazardous drugs (Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9; USP, 2018).

compounding instruction is highly variable, and many pharmacy schools do not offer any didactic or practical education on compounding (Shrewsbury et al., 2012).[3] Pharmacy schools that do teach compounding often have inadequate resources and facilities and deliver instruction without standardized compounding curricula (Shrewsbury et al., 2012). Consequently, many pharmacists practicing today may not adequately understand the effect on safety and efficacy of each ingredient in a compounded preparation. In addition to theoretical knowledge, they also need practical, hands-on training in the skills needed to create compounds that are consistently and accurately prepared to ensure continuity of patient care (USP, 2008).

To develop and retain the practical skills and theoretical knowledge required, studies suggest that pharmacy students should receive more objective and quantitative evaluation of their compounding competency skills (Kadi et al., 2005) and regular, hands-on compounding instruction integrated throughout the curricula (Eley and Birnie, 2006; Mudit and Alfonso, 2017), as recommended by the American Association of Colleges of Pharmacy Council of Sections Compounding Task Force (Shrewsbury et al., 2012).[4] Compounding pharmacists would also benefit from education that extends beyond the basic skills, but relatively few currently avail themselves of specialized training or higher certification (Schommer et al., 2008). Organizations such as the Professional Compounding Centers of America and the American College of Apothecaries offer classes and certification programs (ACA, 2020; Newton, 2003; PCCA, 2020), but training on compounding sterile preparations is mostly imparted through on-the-job experience (The Pew Charitable Trusts and NABP, 2018).[5]

The evidence of minimal and unstandardized compounding instruction in pharmacy schools is cause for substantial concern as to whether current and future compounders have the requisite expertise to optimize formulations. Particular concern is warranted about the safety and effectiveness of compounded topical pain creams, given the vast range of options available

[3] It is notable that the written North American Pharmacist Licensing Examination includes compounding among its evaluated competencies (NAPLEX, 2019); however, at the time of this report, only two U.S. states require practical examination in compounding for licensure as a pharmacist: Georgia and New York (McBane et al., 2019).

[4] It is important to note that formulation scientists and compounding pharmacists are not one and the same. Formulation science is the field of pharmaceutical science that is not commonly offered in the standard pharmacy school curriculum (American Chemical Society, 2020), and there is no requirement for those who compound to gain explicit expertise in this field. Topical pain creams that are compounded by personnel without the requisite knowledge and training in tests for potency, purity, quality, and bioavailability are said to be a public health risk (The Pew Charitable Trusts, 2016).

[5] Starting in fall 2019, the Board of Pharmacy Specialties began offering an exam for pharmacists to become accredited in Compounded Sterile Preparations, though the specialty has yet to receive official recognition (Board of Pharmacy Specialties, 2020).

for active pharmaceutical ingredients (APIs) and excipients. Chapter 5 examines formulation science and its critical role in the design, development, manufacturing, and testing of pharmaceutical products and preparations.

INADEQUATE TRAINING AND GUIDANCE FOR CLINICIANS WHO PRESCRIBE COMPOUNDED MEDICATIONS

Evidence suggests that some prescribers are not sufficiently educated to properly administer and monitor the full spectrum of therapeutic medicines in their pain management toolbox (Lechenfeldt and Hall, 2018). Specifically, clinicians who prescribe compounded topical pain creams may not be adequately educated about the complex practice of compounding, the potential risks it can entail, or the lack of evidence to support the effectiveness of many compounded preparations.[6] Furthermore, there is a dearth of clinical guidance and best practices to aid clinicians in prescribing these preparations. That void has likely contributed to the emergence of online prefilled prescription pads used to market compounded topical pain creams to clinicians and patients, which are cause for additional concern.

Inadequate Compounding Education in Medical School Curricula

The amount of time devoted to pharmacotherapy and compounding education in medical schools is not generally commensurate with the increasing use and complexity of compounded medications. In fact, evidence suggests that formal pharmacotherapy education has decreased in recent years (Wiernik, 2015).[7] Medical students would also benefit more from integrated, practical pharmacological training, such as work experience with clinical pharmacologists,[8] to complement their theoretical knowledge (Lechenfeldt and Hall, 2018). Other prescribing clinicians (e.g., physician assistants, nurse practitioners) may receive even less training given their more condensed school curriculum compared with medical school.

Given that prescribers themselves are permitted to compound preparations in their offices, inadequate compounding education in medical schools is cause for concern. As briefly mentioned in Chapter 4, the scope of

[6] Additional evidence indicates that medical schools rarely assess the performance of their graduates in prescribing practices, with one study suggesting that many new clinicians feel unprepared in their prescribing skills (Lechenfeldt and Hall, 2018).

[7] In an informal poll of the chairs from 39 pharmacology schools in the United States, 35 of the chairs reported that formal training in pharmacology for medical students has decreased in recent years, and 11 chairs reported that the number of faculty who have appropriate training has also decreased (Wiernik, 2015).

[8] However, the number of clinical pharmacologists is limited; there are only four accredited clinical pharmacology fellowship programs in the United States (ACCP, 2019).

clinician compounding is largely unknown to state and federal regulators, though it is likely more frequent in certain specialties (GAO, 2016). Clinicians who compound are required to follow the federal 503A regulations and any applicable state laws (NABP, 2017),[9] but a 2016 survey found that only nine states had laws, regulations, or policies specific to physicians or other nonpharmacists who compound (GAO, 2016).

All compounding performed by physicians is regulated by state boards of medicine, but two national survey reports in 2016 suggested that many of those boards are not actively overseeing physician compounding (GAO, 2016; The Pew Charitable Trusts, 2016). Moreover, the reports found that compounding standards to ensure quality and safety are rarely applied or enforced for compounding physicians as they are for compounding pharmacists. Among state regulators who oversee compounding, the reports noted widespread confusion about oversight of physician compounding and even about whether a regulatory body exists within certain states (GAO, 2016; The Pew Charitable Trusts, 2016).

Lack of Clinical Guidance for Clinicians Who Prescribe or for Physicians Who Compound Topical Pain Creams

Very limited guidance is available for clinicians who prescribe or for licensed physicians who compound topical pain creams.[10] In fact, the committee only found a single clinical guideline or suggested best practice for prescribing compounded preparations to potential patient populations: an algorithm published by the American College of Clinical Pharmacy to aid pharmacists (and presumably extrapolatable to prescribers) in evaluating the appropriateness of nonsterile compounded drugs for a patient (McBane et al., 2019). Based on this guidance, the following relevant questions are among those to consider when prescribing compounded preparations:

- Are FDA-approved alternatives available?
- Are there studies evaluating the safety and efficacy of the compounded preparation in the specific proposed use and route of administration?
- Is the preparation for a patient in a special population (e.g., pediatric, geriatric, pregnant women)?

[9] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9; USP, 2018.

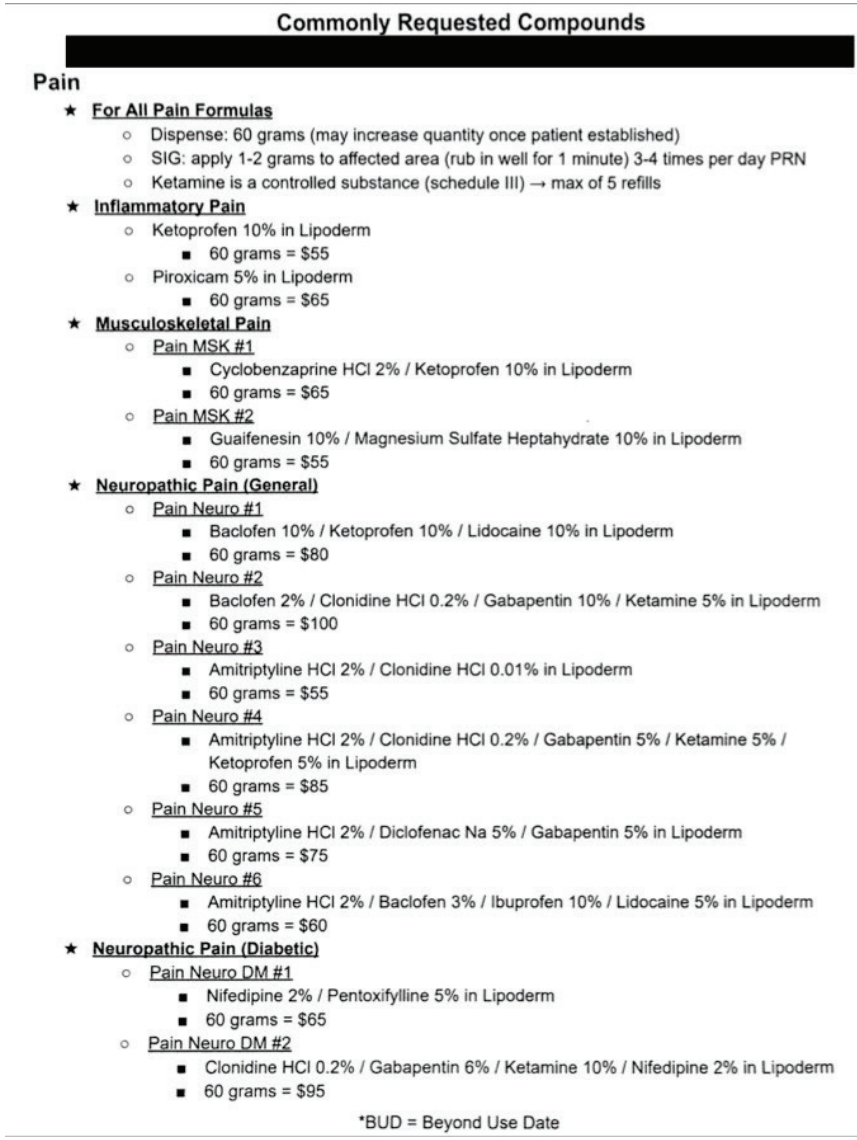
[10] In contrast, the American Veterinary Medical Association has clear recommendations for practicing veterinarians to help minimize the risk of adverse events associated with the use of compounded preparations in animals. These recommendations include limiting the use of a compounded preparation to drugs for which safety, efficacy, and stability have been demonstrated in the specific compounded form in the target species. See https://www.avma.org/policies/veterinary-compounding (accessed December 10, 2019).

Based on this single piece of professional guidance, the committee's understanding is that the ideal decision-based prescription process for compounded topical pain creams spans multiple steps. First, the prescribing clinician and patient discuss the patient's needs, assess the patient's current pain management plan, and consider whether available FDA-approved products are suitable to fulfill the patient's clinical needs. If FDA-approved products are unavailable or unsuitable, the presumable next step is for the prescribing clinician to consult with a certified compounding pharmacist to determine whether a safe and effective prescription formulation exists or can be created, based on the pharmacist's knowledge and expertise.

Once a prescription is written, the pharmacist is responsible for (1) compounding a preparation of acceptable strength, quality, and purity, and (2) ensuring that the compound has appropriate packaging and labeling in accordance with good pharmacy practices, official standards, and current scientific principles. When the patient picks up the prescription, it would be expected that the pharmacist would counsel the patient on instructions for use, risks, and safety precautions for that specific compounded preparation (USP, 2018). Unfortunately, because of lack of oversight and standardization in medical and pharmacy practice, it is unknown whether, how often, and to what degree any of these steps are taken. The lack of clinical guidelines and best practices for clinicians who prescribe compounding preparations or for physicians who compound products themselves raises great concerns with respect to the safety, quality, and effectiveness of the preparations dispensed to patients.

Use of Online Prescription Pads and Marketing

Ideally, the prescription for a compounded preparation is issued to a patient only after careful consideration of the patient's specific needs and with reasonable expectation of effectiveness (AMA, 2016). However, this clinical practice is often difficult to achieve with the increasing complexity of new therapeutics and inadequate education and guidance for clinicians about the use of compounded preparations (Wiernik, 2015). As a potential consequence, paper- or web-based preformulated prescription forms for compounded topical pain preparations seem to appeal to prescribers by making the compounding prescription process "quick and easy." These forms often list options for treating specific pain conditions and may offer preset ingredients or combinations at set or variable concentrations. In some cases, these forms are used as a marketing tool for compounded preparations to increase the volume of requests and sales (FDA, 2019b). Figure 7-1 is an example of a deidentified prescription pad that was distributed to physician offices in February 2019.



Commonly Requested Compounds

Pain

- ★ **For All Pain Formulas**
  - Dispense: 60 grams (may increase quantity once patient established)
  - SIG: apply 1-2 grams to affected area (rub in well for 1 minute) 3-4 times per day PRN
  - Ketamine is a controlled substance (schedule III) → max of 5 refills
- ★ **Inflammatory Pain**
  - Ketoprofen 10% in Lipoderm
    - 60 grams = $55
  - Piroxicam 5% in Lipoderm
    - 60 grams = $65
- ★ **Musculoskeletal Pain**
  - Pain MSK #1
    - Cyclobenzaprine HCl 2% / Ketoprofen 10% in Lipoderm
    - 60 grams = $65
  - Pain MSK #2
    - Guaifenesin 10% / Magnesium Sulfate Heptahydrate 10% in Lipoderm
    - 60 grams = $55
- ★ **Neuropathic Pain (General)**
  - Pain Neuro #1
    - Baclofen 10% / Ketoprofen 10% / Lidocaine 10% in Lipoderm
    - 60 grams = $80
  - Pain Neuro #2
    - Baclofen 2% / Clonidine HCl 0.2% / Gabapentin 10% / Ketamine 5% in Lipoderm
    - 60 grams = $100
  - Pain Neuro #3
    - Amitriptyline HCl 2% / Clonidine HCl 0.01% in Lipoderm
    - 60 grams = $55
  - Pain Neuro #4
    - Amitriptyline HCl 2% / Clonidine HCl 0.2% / Gabapentin 5% / Ketamine 5% / Ketoprofen 5% in Lipoderm
    - 60 grams = $85
  - Pain Neuro #5
    - Amitriptyline HCl 2% / Diclofenac Na 5% / Gabapentin 5% in Lipoderm
    - 60 grams = $75
  - Pain Neuro #6
    - Amitriptyline HCl 2% / Baclofen 3% / Ibuprofen 10% / Lidocaine 5% in Lipoderm
    - 60 grams = $60
- ★ **Neuropathic Pain (Diabetic)**
  - Pain Neuro DM #1
    - Nifedipine 2% / Pentoxifylline 5% in Lipoderm
    - 60 grams = $65
  - Pain Neuro DM #2
    - Clonidine HCl 0.2% / Gabapentin 6% / Ketamine 10% / Nifedipine 2% in Lipoderm
    - 60 grams = $95

*BUD = Beyond Use Date

FIGURE 7-1 Sample prescription form distributed by a local pharmacy to physician offices in February 2019.
SOURCE: FDA, 2019b.

Although they promote a factor of convenience, no publicly available evidence suggests that compounding pharmacies develop these sample prescriptions with any rationale for formulations, doses, and dosage forms; the sample prescriptions also rarely include disclosures on efficacy, safety, or potential adverse effects.[11] This gives rise to growing concern that clinicians may be "checking boxes" on these forms without adequate assessment or evaluation of the individual patient's complex clinical needs.

Prefilled prescription pads are intended for prescribers' use only, but reports of compounding pharmacies marketing compounded topical pain preparations directly to patients warrants further concern (FBI, 2018; Norton, 2019). As revealed in fraud cases brought against compounding pharmacies, there are instances of compounded topical pain preparations being prescribed to patients who maintained that they never requested nor discussed the use of the treatment with a pharmacist (FBI, 2018). This variability in initiating the prescription process calls into question the actual demand and utility of compounded topical pain creams.

Professional Risks for Prescribing Clinicians

Clinicians who prescribe a compounded medication that causes adverse effects can be exposed to liability, especially if an appropriate FDA-approved alternative is available (Gudeman, 2013). The provider is considered responsible for having selected the specific types and quantities of ingredients in the prescription (Sellers and Utian, 2012). When adverse events are caused by FDA-approved drugs, the prescribing clinician is typically protected by FDA's approval process and background support from the commercial pharmaceutical company that manufactured the drug; prescribers of a compounded preparation that harms a patient are not similarly protected. Furthermore, malpractice insurance may not cover claims that involve non-FDA-approved compounded preparations (O'Brien et al., 2013).

Additional professional risks relate to potential conflicts of interest. Financial conflicts may arise when pharmacists or clinicians who are responsible for care of a patient also have a financial stake in the compounded preparations they prescribe or produce. Navigating conflicts of interest—particularly financial conflicts—is a particular concern with respect to compounded preparations, because regulatory oversight is limited and variably enforced. Congress has sought to address financial conflicts of interest through enhanced disclosure via the Physician Payments

[11] As previously addressed in this report, individuals who compound are exempt from performing tests on the safety and efficacy of compounded preparations, in general, and based on the findings from the literature review in Chapter 6, there are limited data on the safety and effectiveness of APIs commonly used in compounded topical pain creams.

Sunshine Act, originally passed in 2010 as part of the Patient Protection and Affordable Care Act,[12] but it does not cover disclosure of payments and financial relationships between providers and compounding pharmacies or outsourcing facilities.

Conclusion 7-1

Current training requirements for pharmacists and clinicians who prescribe, formulate, and dispense compounded topical pain creams are inadequate.

SAFETY CONCERNS FOR PATIENTS

From the patient's perspective, compounded topical pain creams are associated with safety concerns including risks associated with unstandardized formulations, polypharmacy and drug–drug interactions, misuse of compounded preparations, and potential adverse events.

Unstandardized Formulations for Compounded Topical Pain Creams

Like all pain medication, each compounded topical pain cream has some potential for adverse effects or intolerance among certain populations of patients. The safety and efficacy risks associated with compounded topical pain creams are complex and difficult to assess, however. As discussed in Chapters 3, 4, and 5, a single compounded preparation may contain a large number of constituent components in a formulation, including APIs and inactive pharmaceutical ingredients (e.g., excipients, fillers).[13] All of the components carry potential risks individually and in combination, particularly those with systemic absorption. Because of the ad hoc nature of compounding, the formulations of the preparations are not standardized across different compounding pharmacies, which introduces additional risks to the patient. These risks include potential exposure to novel formulations with no demonstrated evidence for safety and effectiveness as a topical treatment.

[12] Social Security Act. § 1128G (42 U.S. Code 1320a-7h).

[13] An excipient is a pharmacologically inert ingredient used in a drug product that lends various functional properties to the product (e.g., dosage form, taste masking, drug release).

Risks Associated with Polypharmacy and Drug–Drug Interactions

In addition to taking into account the lack of evidence on safety and effectiveness of nonstandardized formulations of compounded topical pain creams, prescribers must also consider potential safety risks to the patient associated with polypharmacy and drug–drug interactions when making treatment decisions (see Table 7-1). Compounded topical pain creams often include a combination of two or more APIs (NABP, 2019),[14] which has potential safety risks. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., naproxen, meloxicam, diclofenac) and tricyclic antidepressants (e.g., amitriptyline, doxepin) are commonly used to treat pain, but with systemic absorption, their concurrent use can increase the risk for gastrointestinal bleeding and intracranial bleeding (HHS, 2019; Richlin, 1991; Shin et al., 2015). Another important consideration in treatment decisions is that many patients may concurrently use other oral medications in addition to compounded topical pain creams. Appendix G provides more information about the potential risks of polypharmacy and drug–drug interactions.

Conclusion 7-2

When making treatment decisions involving compounded topical pain creams, it is critical to consider the potential risks associated with polypharmacy, drug–drug interactions, and potential for systemic absorption.

TABLE 7-1
Potential Drug–Drug Interactions for Select APIs (Oral Administration)

Drug Product	Potentially Major or Life-Threatening Drug–Drug Interactions
Amitriptilyne	Concurrent use of NSAIDS and TRICYCLIC ANTIDEPRESSANTS may result in an increased risk of bleeding. Concurrent use of CYCLOBENZAPRINE and TRYCYCLIC ANTIDEPRESSANTS may result in increased risk of serotonin syndrome.
Baclofen	Concurrent use of TRAMADOL and CNS DEPRESSANTS may result in an increased risk of respiratory and CNS depression.
Carbamazepine	Concurrent use of TRAMADOL and SEROTONERGIC CYP3A4 INDUCERS may result in increased risk of serotonin syndrome and reduced TRAMADOL plasma concentrations.

[14] In a small survey of national pharmacies, the Professional Compounding Centers of America estimated that greater than 80 percent of dispensed compounded topical pain creams contained two or more APIs and greater than 50 percent contained three or more APIs.

TABLE 7-1
Continued

Drug Product	Potentially Major or Life-Threatening Drug–Drug Interactions
Clonidine	Concurrent use of DOXEPIN and CLONIDINE may result in decreased antihypersensitive effectiveness.
Clonidine HCl	Concurrent use of DOXEPIN and CLONIDINE may result in decreased antihypersensitive effectiveness.
Cyclobenzaprine	Concurrent use of CYCLOBENZAPRINE and TRICYCLIC ANTIDEPRESSANTS may result in an increased serotonin syndrome. Concurrent use of CYCLOBENZAPRINE and TRAMADOL may result in an increased risk of respiratory and CNS depression; increased risk of serotonin syndrome; an increased risk of paralytic ileus.
Dexamethasone	Concurrent use of CORTICOSTEROIDS and NSAIDS may result in an increased risk of gastrointestinal ulcer or bleeding.
Doxepin	Concurrent use of NSAIDS and TRICYCLIC ANTIDEPRESSANTS may result in an increased risk of bleeding. Concurrent use of TRAMADOL and SEROTONERGIC AGENTS WITH ANTICHOLINGERIC PROPERTIES may result in increased risk of paralytic ileus; increased risk of serotonin syndrome.
Ketamine	Concurrent use of TRAMADOL and CNS DEPRESSANTS may result in an increased risk of respiratory and CNS depression.
Meloxicam	Concurrent use of MELOXICAM and NSAIDS AND SALICYLATES may result in increased risk of bleeding. Concurrent use of NSAIDS and TRICYCLIC ANTIDEPRESSANTS may result in an increased risk of bleeding.
Memantine	Concurrent use of MEMANTINE and SELECTED N-METHYL-D-ASPARATE ANTAGONISTS may result in increased adverse events of N-methyl-D-asperate agonists.
Naproxen	Concurrent use of NSAIDS and TRICYCLIC ANTIDEPRESSANTS may result in an increased risk of bleeding. Concurrent use of CORTICOSTEROIDS and NSAIDS may result in increased risk of gastrointestinal ulcer or bleeding.
Nifedipine	Concurrent use of NIFEDIPINE and CYP3A4 INDUCERS may result in decreased NIFEDIPINE exposure.
Orphenadrine	Concurrent use of TRAMADOL and CNS DEPRESSANTS may result in an increased risk of paralytic ileus; increased risk of respiratory and CNS depression.
Pentoxyfilline	Concurrent use of PENTOXYFILLINE and NSAIDS may result in an increased risk of bleeding.
Topiramate	Concurrent use of TRAMADOL and CNS DEPRESSANTS may result in an increased risk of respiratory and CNS depression.
Tramadol	Concurrent use of TRAMADOL and CNS DEPRESSANTS may result in an increased risk of respiratory and CNS depression.

NOTE: CNS = central nervous system; NSAIDS = nonsteroidal anti-inflammatory drugs.

SOURCE: Micromedex, 2019.

Misuse of Compounded Preparations

A patient's lack of knowledge about a compounded preparation can lead to misuse, another associated safety risk. As discussed in Chapter 4, compounded preparations from 503A compounding pharmacies are not required to be dispensed with standardized product inserts. Although some compounding pharmacies do dispense inserts with compounded preparations, particularly those practicing in states that require compliance with USP <795>, patients are likely to receive variable information about the formulation (i.e., active and inactive ingredients), how to use the preparation, and the potential for adverse reactions (FDA, 2017). Many adverse events from topical compounded pain creams reported to FDA can be attributed to the patient misusing or overdosing creams, either on themselves or inadvertently on others through skin-to-skin transmission (FDA, 2019a). See Appendix F for a list of adverse events submitted to FDA between 2003 and 2018.

Advertising and marketing by 503A compounding pharmacies and 503B outsourcing facilities may characterize their compounded preparations—implicitly or explicitly—as safe and effective, thus implying incorrectly that the medications meet FDA-approval standards (FDA, 2017).[15] Understandably, patients who are not aware of regulatory exceptions surrounding compounding may assume that compounded preparations undergo the same rigorous regulatory process as other medications prescribed by their clinicians. Patients may not even know that their medication is compounded or may not understand what compounding entails (Cowan, 2019). Moreover, many patients may not receive pharmacist counseling on the use of compounded preparations, particularly because many compounded medication prescriptions are delivered by mail or through online pharmacies (McPherson et al., 2019). This lack of awareness and education among patients further exacerbates safety concerns related to compounded preparations.

Patients would be better equipped to make their own risk–benefit assessments about using a compounded preparation if they were provided with information on its risks and potential adverse events and if they were made aware that compounded preparations have not been approved or tested by a regulatory agency. Similarly, including clear directions for use and storage of compounded drugs would likely reduce adverse events occurring from patient misuse.

[15] FDA has sent warning letters to several compounders whom they have found to make unsubstantiated efficacy and superiority claims (Gardine, 2008; Vitillio, 2008).

Conclusion 7-3

There is a need to standardize health information dispensed to patients and clinicians about compounded topical pain creams, including directions for use, APIs, excipients, and other chemicals that may impact absorption; proposed therapeutic benefits; and potential adverse effects.

Adverse Events Associated with the Use of Compounded Topical Pain Creams

As discussed in Chapter 4, little data are available on adverse events linked to compounded preparations, attributable in large part to limited federal and state-level regulations in place to document, monitor, and limit the use of compounded preparations associated with known or widespread adverse effects. In most cases, FDA may not become aware of adverse events unless a health care provider or state official notifies the agency (FDA, 2017). Studies suggest that patients, pharmacies, and clinicians will voluntarily report adverse events related to the use of the compounded preparations intermittently—if at all—so it stands to reason that a substantial number of adverse events go underreported (FDA, 2016; Kessler, 1993).

To gather additional data on adverse events, the committee submitted a data request to FDA's Adverse Event Reporting System (FAERS) in 2019 to review adverse events and case study reports involving compounded topical pain creams. See Appendix F for the detailed list of 38 adverse events that range from minor skin irritations to severe toxicity and an unfortunate death, and include suspected causes ranging from accidental misuse of the medication to API toxicity. However, owing to the voluntary nature of reporting and the limitations in the data entry process, it is uncertain whether these cases are a true representative sample of adverse effects related to use of compounded topical pain creams.[16]

Also in 2019, the committee submitted a data request to the American Association of Poison Control Centers to review potential concerns related to the safety of compounded topical pain creams. It was difficult to accurately track which reported events were related to FDA-approved

[16] FDA identified 38 adverse events reports that related to the use of a compounded topical drug by reading through report descriptions of all entries marked as *compounded*. It is important to note that there may be other FAERS cases related to the use of compounded topical drugs, but if the necessary indication box for *compounded* mediations was not checked during the data entry process, then those cases would not be represented in the full dataset.

topical creams and which where relevant to exclusive compounded topical creams. In the end, the submitted request involved a search of the National Poison Data System (NPDS) for any reported events involving the committee's specific APIs of interest used in topical (e.g., lotion, cream, gel) formulations. The data revealed that between 2014 and 2019, a total of 275 reported incidents were reported to the NPDS. The NPDS categorized 24 of those events as having a major effect, but none resulted in fatality. The vast majority (123) of these incidents were attributed to a general "unintentional" cause, meaning an overexposure or accidental exposure to the pain cream. Only 26 of these incidents were attributed to adverse reactions to APIs used (AAPCC, 2019).[17]

As illustrated by the NPDS data, it is important to remember that all medications, including FDA-approved topical pain cream products, are associated with a certain level of risk. For example, one man applied FDA-approved topical diclofenac gel to his back for back pain and, after spending prolonged time under the sun, developed a severe skin rash with blistering skin where the gel was applied (Akat, 2013). The FDA package insert for diclofenac gel—included with every prescription—warns that patients "should minimize or avoid exposure to natural or artificial sunlight on treated areas" (Endo Pharmaceuticals, 2016). A critical concern is that patients may not receive the same (or any) safety warnings when an FDA-approved product, such as diclofenac gel, is used in a compounded preparation in addition to other APIs. *It is critical for clinicians and patients to understand that when an FDA-approved product is included in a compounded preparation, that product is no longer subject to the same regulatory labeling requirements it would have when dispensed alone in a noncompounded preparation.*

In summary, as suggested by the data outlined above, it is often difficult to assess potential adverse effects or events related to the use or misuse of compounded preparations. As suggested in Chapter 4, this is likely caused, in part, by gaps in the regulation and oversight of compounded preparations. Because 503A compounding pharmacies are not required to collect or share adverse event data with FDA, without these data, it is difficult to accurately characterize the public health aspects of compounded medications. (See Box 4-3 in Chapter 4 for an additional discussion on adverse event reporting.) Additional efforts to increase the surveillance, data collection, and adverse event reporting for compounded topical pain creams is needed.

[17] These data may include both FDA-approved products and compounded formulations. Certain cases included single-ingredient creams, while others included multi-ingredient pain creams. In addition, certain cases described the ingestion of solid dosage form and an exposure to topical product/preparation. These confounders prevent clear conclusions from being made.

POTENTIAL FINANCIAL RISKS FOR PATIENTS

Potential financial risks for patients are additional consequences of the limited data on the effectiveness of many compounded topical pain creams (discussed in Chapter 6), particularly in cases where patients or their insurance companies are charged high prices for untested and potentially ineffective compounded preparations. According to a retrospective analysis of prescription claims data, ingredients commonly used in compounded topical pain creams were the most expensive ingredients used in compounded drugs for adults by total cost billed in 2013 (McPherson et al., 2016).[18]

A recent survey of almost 500 patients of compounded preparations found that almost all (95 percent) were satisfied with every aspect of the therapy except for the cost (McPherson, 2019). Given that the average duration of compounded prescription use reported by the survey respondents was 30 months, costs incurred by patients can mount quickly (McPherson et al., 2019). The out-of-pocket costs to patients for compounded preparations in general and compounded pain creams specifically have not yet been well quantified. However, some survey data are available about the average out-of-pocket costs (McPherson et al., 2019):

- Average out-of-pocket cost of compounded prescription in general: $50 for insured patients; $116 for uninsured patients
- Average out-of-pocket cost for compounded medication in general: $93
- Average out-of-pocket cost for compounded pain medications specifically: $26

Additional information about compounded topical drug costs is available from Medicare Part D data, which show that annual spending for compounded topical drugs rose more than 3,400 percent between 2006 and 2015, with the largest increase seen in 2014 (see Figure 7-2). In 2006, topical drugs accounted for 9 percent of all compounded drug spending by Medicare Part D. By 2015, spending on compounded topical drugs had reached $224.3 million, representing 44 percent of total spending

[18] The average cost of ingredients in compounded preparations in general increased from $308 to $710 (130 percent) between 2012 and 2013, while the average cost of ingredients in noncompounded prescriptions increased from $149 and $160 (7 percent) during the same period (McPherson et al., 2016). In response to the research interests of this report, the Professional Compounding Centers of America conducted a small survey to a limited number of pharmacies in their membership network and determined that the median costs for compounded topical pain creams was less than oral commercial products containing similar APIs (PCCA, 2019).

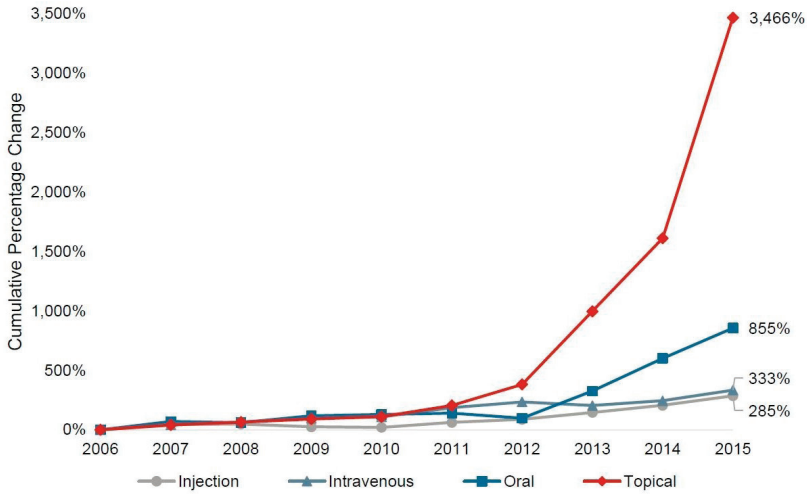


FIGURE 7-2 Growth in Medicare Part D spending on compounded drugs by form (2006–2015).
SOURCE: HHS OIG, 2016.

on compounded drugs. The costs rose dramatically during this period because the average cost of each prescription increased and the number of beneficiaries receiving these drugs increased. The average cost for each prescription grew by 720 percent from 2006 to 2015, from $40 to $331 (HHS OIG, 2016). For comparison, the average retail price for brand-name drugs increased by 188 percent during the same period (Schondelmeyer and Purvis, 2016). The dramatic shifts in the use of and spending on compounded preparations between 2006 and 2015 raised substantial concerns about fraud and patient safety (HHS OIG, 2016).

In 2015, TRICARE—the health insurance program for military personnel—discovered a nationwide compounded drug scheme that had resulted in an estimated $1.5 billion in fraudulent charges (Norton, 2019; Philpott, 2018). The majority of these schemes involved dispensing ointments or creams, with great variability in how the request for a prescription was initiated: by physicians, pharmacists, marketers, or even patients. Each of these prescriptions resulted in substantial charges to TRICARE that in some cases amounted to tens of thousands of dollars per prescription, depending on the number and type of APIs included in the compounded formulation. These compounded preparations were formulated with the intent of maximizing the amount that the pharmacist could charge to the insurer, rather than meeting patients' needs (Philpott, 2018). In response to this

activity, the U.S. Department of Justice has brought enforcement actions against hundreds of defendants for fraud and kickback schemes involving billing Medicare, Medicaid, and TRICARE for compounded topical preparations (DOJ, 2017, 2018a,b,c; U.S. Attorney's Office Eastern District of Arkansas, 2018). At the peak of this fraudulent activity, TRICARE paid about $500 million for compounded preparations in April 2015 (DoDIG, 2016). At the time of this committee's report release, TRICARE reports that it typically receives about 20,000 claims per month for compounded preparations at a cost of $10–$15 million per year (Norton, 2019).

Mounting concerns of rising costs and potential fraud related to the prescribing practices for compounded drugs, including topical pain creams, have led to policies and procedures that have increased financial risks for patients who are prescribed these preparations. Several Medicare and TRICARE policies and procedures have been changed to incorporate fraud identification training and restrict coverage only to compounds that include FDA-approved ingredients (Chavez-Valdez, 2018; DoDIG, 2016). Many insurers and pharmacy benefit managers have instituted policies to decrease the number of claims for compounded preparations because of their concerns about safety, efficacy, cost, and lack of regulatory oversight (McPherson et al., 2016).

Patients have been adversely affected by these policy changes—particularly the exclusion of certain compounded preparations from insurance coverage and consequent increases in cost. For example, some patients may no longer have access to compounded topical pain creams they need to manage their pain, because the out-of-pocket costs are prohibitive. Even if patients can afford the out-of-pocket cost, they run the risk of paying high prices for compounded topical pain creams that have little or no evidence of safety and effectiveness. Given that these policy changes were driven by a lack of evidence about the safety and effectiveness of compounded preparations, expanding the evidence base would help to mitigate financial risks to patients.

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8

Recommendations Regarding the Treatment of Patients with Compounded Topical Pain Creams

Compounded topical pain creams may have a potential role in integrative pain management plans for patients with specific clinical needs. However, three critical areas of concern related to safety and effectiveness of such compounded topical pain creams need to be addressed by stakeholders:

1. Limited evidence to describe safety and effectiveness of active pharmaceutical ingredients (APIs) commonly used in these preparations (Chapter 6)
2. Inadequate training, procedural protocols, and evidence-based guidance for pharmacists who formulate and dispense these preparations, as well as for prescribing clinicians (Chapter 7)
3. Significant gaps in federal and state-level regulation, oversight, and surveillance of non-U.S. Food and Drug Administration (FDA)-approved medications (Chapter 4)

In its review of available scientific evidence within the study scope, the committee concluded that the vast majority of APIs commonly used in compounded topical pain creams have little to no scientific evidence to support their claims of effectiveness in the treatment of various pain conditions when applied to intact skin. Furthermore, potential for systemic absorption and toxicity of many of APIs reviewed remains largely unknown. These findings give rise to substantial concerns related to excessive application of compounded topical preparations, as well as use of preparations that

contain excipients with enhancers that increase absorption of an ingredient beyond the intended site of action.

The committee also determined that selection of active and inactive ingredients used in many compounded topical preparations does not seem to incorporate the full spectrum of complexities related to skin absorption and dose. In many cases, there is no clear clinical rationale for specific combinations of APIs and dosages used. As a result, the committee concluded that the lack of publicly disclosed rationales for formulation development, inadequate labeling requirements, and (for 503A compounding pharmacies in particular) the nonstandardized surveillance procedures and protocols for ensuring appropriate reporting of adverse events underpin a substantial public health concern related to the use of these preparations.

From their research findings, the committee puts forth three overarching conclusions:

> *Conclusion 8-1: 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.*[1]

> *Conclusion 8-2: 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.*

> *Conclusion 8-3: 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.*

[1] This text has changed since the prepublication release of this report to clarify the available FDA-approved topical NSAID products.

RECOMMENDATION REGARDING TREATMENT

Recommendation 1: Caution should be used when prescribing or dispensing compounded topical pain cream preparations.

Prescribing clinicians, compounding pharmacists, and nonpharmacists who compound should exercise caution when considering inclusion of compounded topical pain creams in pain management plans, given the lack of scientific evidence to support their safety or effectiveness beyond a few limited ingredients.

RECOMMENDATIONS TO ADDRESS PUBLIC HEALTH CONCERNS

Given the public health concerns related to the use of compounded topical pain creams, the committee recommends additional research, education, and oversight to support safety, effectiveness, and use of these 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.

Pain researchers, public and private funding agencies, and relevant patient advocacy organizations should prioritize research efforts to examine the safety and effectiveness of compounded topical pain creams, including but not limited to

- Randomized, double-blind, placebo-controlled clinical trials with sufficient numbers of patients to study, both in isolation and in combinations, APIs and inactive ingredients commonly used in compounded topical pain cream formulations
- Clinical research on APIs with demonstrated effectiveness to treat pain in preclinical animal models, which may indicate a potential therapeutic effect in humans (e.g., cannabidiol)
- Obtaining high-quality evidence to inform the safety profile for all APIs that act transdermally
- Research on potential new topical or transdermal therapeutic agents to treat pain

Funding agencies that could drive these efforts include the Agency for Healthcare Research and Quality, National Center for Complementary and Integrative Health, other relevant institutes or centers of the National Institutes of Health, and Patient-Centered Outcomes Research Institute.

Patient advocacy organizations that could drive these efforts include the American Academy of Hospice and Palliative Medicine, American Academy of Pain Medicine, American Cancer Society, American Chronic Pain Association, American Society for Pain Management Nursing, Oncology Nursing Society, and U.S. Pain Foundation.

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.

Interprofessional organizations representing pharmacy, nursing, medical sectors, and other professions with prescriber authority to treat pain conditions should advocate for state-level certification of individuals who seek to begin or continue to prescribe compounded topical pain creams. Formal clinical education should be offered in parallel to continuing medical education courses for clinicians who prescribe topical pain creams.

Interprofessional organizations that could drive these efforts include the American Academy of Physician Assistants, American Association of Nurse Practitioners, American Cancer Society, American Medical Association, American Society of Anesthesiologists, and American Society of Interventional Pain Physicians.

State boards of pharmacy, local and regional schools of pharmacy, and nonprofit professional societies and organizations within the medical and pharmaceutical sectors should support and incentivize more in-depth training on compounding delivered by schools of medicine and pharmacy, as well as relevant nonprofit professional societies and organizations. These courses should:

- Review the compounding process, including the complexities of formulation science, which aim to ensure that all formulations are optimized when multiple APIs are combined.
- Examine current peer-reviewed, evidence-based conclusions on the safety and effectiveness of commonly used APIs and excipients in topical applications.
- Review the potential risks and reported adverse effects associated with the use of compounded topical pain creams.

Additional continuing medical education courses hosted by for-profit organizations should not substitute for this more in-depth training, owing to potential conflicts of interest.

Recommendation 4: Additional state-level oversight of compounded topical pain creams is needed to improve safety and effectiveness.

The National Association of Boards of Pharmacy should convene the state boards of pharmacy to unify and increase their oversight of 503A compounding pharmacies. The charge to increase oversight should also require all 503A compounding pharmacies to do the following:

- Provide a standardized insert for all dispensed compounded pain cream preparations with (1) a detailed description of the formulation, including all APIs and excipient components; (2) clear guidance for use, including how much (cream surface area and volume) and under which conditions to apply; and (3) caution for potential adverse effects.
- Report adverse events to the state boards of pharmacy and FDA through an established mechanism, such as the FDA's Adverse Event Reporting System or MedWatch.
- Monitor, record, and annually report the types, formulations, payers, and dispensing rates of compounded pain cream preparations.
- Uniformly adopt standards in United States Pharmacopeia (USP) <795> to ensure the quality of dispensed nonsterile compounded preparations.

FDA and global standards-setting organizations (e.g., USP) should collaboratively develop standard processes for testing APIs (in solitude and combinations) and excipients commonly used in compounded topical pain creams. These testing standards should include protocols to examine the mechanisms by which APIs are absorbed and released from compounded preparations, with a prioritized focus on APIs in formulations with transdermal properties that allow drugs to travel through the skin to act regionally or systemically.

Appendix A

Study Approach

In response to a request by the U.S. Food and Drug Administration (FDA), the National Academies of Sciences, Engineering, and Medicine's Committee on the Assessment of the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain Creams was charged with identifying and analyzing the available scientific data relating to the ingredients used in compounded topical pain creams and evaluating how these data translate to the safety and effectiveness of compounded topical pain creams with various combinations of those ingredients. The committee's final report will summarize the current evidence on compounded topical pain creams and offer recommendations on their use.

COMMITTEE EXPERTISE

The National Academies appointed an 11-member committee of experts to address objectives in the Statement of Task. The resulting committee included experts in a variety of disciplines and fields, including drug research and development, pharmacology, toxicology, pain management and care, drug evaluation, epidemiology, and pharmaceutical compounding and manufacturing.

MEEETINGS AND INFORMATION-GATHERING ACTIVITIES

The committee deliberated from March 2019 to February 2020, during the course of which it held four in-person meetings (March, May, July, and September) and two half-day virtual meetings. The March, May, and

September meetings included portions open to the public. The committee meeting in July was held in closed session.

In the three open-session meetings, the committee heard presentations from content experts on a wide variety of topics related to the committee's charge. These open-session meetings also included periods of public comment, to provide stakeholders with an opportunity to present the committee with any additional relevant information. The agendas for the three open-session meetings are presented in the section below.

In addition to the data collection efforts within the open-session meetings, the committee also received and reviewed a number of resources submitted by various stakeholders, including American Association of Poison Control Centers, American Chronic Pain Association, FDA, Massachusetts State Board of Pharmacy, National Association of Boards of Pharmacy, and Professional Compounding Centers of America. These resources include, but are not limited to, data on active pharmaceutical ingredients commonly used in compounded topical pain creams, literature reviews, findings from national surveys related to the cost and use of compounded topical pain creams, adverse event reports, and guidance on the federal and state regulations and oversight for compounded preparations.

First Committee Meeting

Open Session Agenda
March 25, 2019
National Academies Keck Building
500 Fifth Street, NW, Washington, DC 20001

1:15 p.m. **Welcome and Introductions**
DEBRA A. SCHWINN, *Committee Chair*

1:20 p.m. **Sponsor Perspective on Charge to the Committee**
RUEY JU, *Study Sponsor*
U.S. Food and Drug Administration
CHARLES GANLEY, *Study Sponsor*
U.S. Food and Drug Administration

2:00 p.m. **Discussion with Committee**

2:45 p.m. **BREAK**

3:00 p.m. **Key Stakeholder Perspectives**
BARBARA EXUM, *Director*
Center for Compounding Practice and Research
Virginia Commonwealth University

CAPT. EDWARD NORTON, MSC, USN, *Pharmacy Specialty Leader*
Defense Health Headquarters

TIMOTHY MCPHERSON, *Professor*
Department of Pharmaceutical Sciences
Southern Illinois University, Edwardsville

JEFFERY FUDIN, *Clinical Pharmacy Specialist and Director*
[Remote]
PGY-2 Pharmacy Pain Residency Programs
Stratton Veterans Affairs Medical Center

4:30 p.m. **Discussion with Committee**

5:00 p.m. **Public Comments**

5:45 p.m. **ADJOURN**

Second Committee Meeting

Open Session Workshop Agenda
May 20, 2019
National Academies Keck Building
500 Fifth Street, NW, Washington, DC 20001

9:00 a.m. **Welcome and Opening Remarks**
LEIGH MILES JACKSON, Ph.D.
National Academies of Sciences, Engineering, and Medicine
DEBRA A. SCHWINN, M.D., *Committee Chair*

9:10 a.m. **Evidence-Based Pain Medicine and Pain Management**
DANIEL B. CARR, M.D.
Tufts University School of Medicine

9:30 a.m. **Discussion with Committee**

9:45 a.m. **Compounding Regulation Overview**
SARA ROTHMAN, M.P.H.
U.S. Food and Drug Administration
GREGG JONES, R.Ph.
National Association of Boards of Pharmacy

10:15 a.m. **Discussion with Committee**

11:00 a.m. **Dermal and Transdermal Background**
S. NARASIMHA MURTHY, Ph.D.
University of Mississippi

11:15 a.m. **Discussion with Committee**

11:45 a.m. **BREAK**

12:00 p.m. **Background on the Curriculum and Training for Compounding Pharmacists**
ROBERT SHREWSBURY, Ph.D.
University of North Carolina

Pharmacists and Compounders Perspectives
MARK HANUS, R.Ph.
Oakdell Pharmacy

LINDA MCELHINEY, Pharm.D.
Indiana University Health

JOHN VOLIVA, R.Ph.
Hook's Apothecary
Compounding Pharmacy

A. J. DAY, Pharm.D.
Professional Compounding Centers of America

GUS BASSANI, Pharm.D.
Professional Compounding Centers of America

12:35 p.m. **Discussion with Committee**

1:15 p.m. **LUNCH BREAK**

2:15 p.m. **Patient-Focused Perspectives**
PENNEY COWAN, *Founder and Chief Executive Officer*
American Chronic Pain Association

2:30 p.m. **Discussion with Committee**

3:00 p.m. **BREAK**

3:10 p.m. **Provider Perspectives**
JEANNINE BRANT, Ph.D., *Clinical Nurse Specialist, Oncology*
Billings Clinic

WILLIAM ZEMPSKY, M.D.
Pain and Palliative Medicine
Connecticut Children's Medical Center

ROBERT DIMEFF, M.D.
Texas Orthopaedic Associates
Texas Physician NHL Dallas Stars
Past President American Medical Society for Sports Medicine

3:30 p.m. **Discussion with Committee**

4:00 p.m. **Public Comments**

4:30 p.m. **ADJOURN**

Fourth Committee Meeting

Open Session Agenda
October 1, 2019
National Academies Keck Building
500 Fifth Street, NW, Washington, DC 20001

12:30 p.m. **Welcome**
DEBRA A. SCHWINN, M.D., *Committee Chair*

Overview of UMD-CERSI's Review of 503B Compounding Bulks List Ingredients
ASHLEE MATTINGLY, Pharm.D., BCPS, *Assistant Professor of Pharmacy Practice and Science*

Brief Review of Sample Costs for Compounded Topical Pain Creams
A. J. DAY, Pharm.D., *Vice President of Clinical Services, Professional Compounding Centers of America*

1:30 p.m. **Public Comments**

1:35 p.m. **ADJOURN**

Appendix B

Literature Review

The committee conducted a literature review to find and evaluate content related to the safety and effectiveness of 10 U.S. Food and Drug Administration (FDA) priority active pharmaceutical ingredients (APIs) used in topical formulations. These 10 APIs were selected because FDA expressed interest in these compounds (see Box B-1).

In coordination with one of the National Academies of Sciences, Engineering, and Medicine's senior research librarians, the committee constructed a literature search strategy that would produce a body of research that could inform its work. An initial search queried six databases (Medline, Embase, PubMed, Scopus, ClinicalTrials.gov, and Toxnet). Results from search one were limited to peer-reviewed articles published in the English language without any date restrictions, including human, animal, and in vitro studies. Editorials, commentaries, letters, and notes were excluded. A complete description of the syntax used can be found at the end of this appendix. This search resulted in 1,476 articles with potential relevance to the committee's charge.

In an effort to refine its search, the committee conducted a focused search to concentrate on the topical application of FDA-priority ingredients for the explicit treatment of pain. In this search, the committee also included ketamine as an API of interest. This focused search used the same six databases as the broad search, as well as the same inclusion and exclusion parameters, and produced 240 articles with potential relevance to the committee's charge.

To produce a more comprehensive report on the safety and effectiveness of ingredients used in compounded topical pain creams across a

BOX B-1
Ingredients Prioritized for Review by the U.S. Food and Drug Administration (FDA)

Given the study's broad charge to evaluate the safety and effectiveness of ingredients used in compounded topical pain cream products, the committee identified strategies to define and limit the scope of its work. In the committee's first open-session meeting, the study's sponsor, FDA, introduced a list of 37 active pharmaceutical ingredients (APIs) that have been identified in common formulations of compounded topical pain creams. Of these 37 APIs, FDA determined 10 to be of priority interest for this committee's charge.

APIs of priority to FDA:

- Amitriptyline
- Baclofen
- Clonidine
- Cyclobenzaprine
- Gabapentin
- Meloxicam
- Memantine
- Orphenadrine
- Topiramate
- Tramadol

It is the committee's understanding that the FDA-presented ingredients were identified from examples of commonly compounded topical pain medication formulas and that the list was generated through online research efforts, as well as through personal communications with other government agencies (e.g., Centers for Medicare & Medicaid Services, U.S. Department of Defense, and U.S. Department of Veterans Affairs).

broader list of compounds, the committee expanded its search strategy to include nine additional APIs. A broad and focused search were performed for these additional nine ingredients, employing the same parameters as the searches for the FDA-prioritized ingredients, but differed only in the set of ingredients queried (see Box B-2). The broad and focused searches for the additional ingredients produced 7,103 and 203 articles, respectively.

All literature results were combined and an initial screen was performed to eliminate articles not relevant to the study's scope. A total of 7,203 articles were removed for either discussing topical application to the eye, or not discussing the treatment of pain in the title, keywords, or abstract of the article. After this first screen, 1,792 articles remained and were scored based on their level of evidence as determined by the study

BOX B-2
Rationale for Selecting Additional Active Pharmaceutical Ingredients for Review

After a consideration of its study resources and timeline limitations, the committee elected to expand the scope of its review in the hopes of producing a more comprehensive report. In its consideration of which additional ingredients to review, the committee accessed various resources to determine which ingredients had the potential to add the most value to the report. Factors that influenced the committee's decisions included, but were not limited to

- Appropriate representation between and within relevant drug classes;
- Sufficient evidence base to address the committee's research questions;
- Common appearance in formulations for compounded topical pain creams in online advertisements and prefilled prescription pads;
- Representation in the National Association of Boards of Pharmacy (NABP)-reported top five dispensed compounded products from 503A and 503B pharmacies requesting an NABP inspection;
- Use in compounded topical pain cream products linked to adverse events within the U.S. Food and Drug Administration's (FDA's) Adverse Event Reporting System database;
- Relevance in the clinical practice of pain management; and
- Based on committee expertise and levels of concern for safety or toxicity.

Based on these considerations, the committee selected to examine the safety and effectiveness of 10 additional ingredients. These included

- Bupivacaine
- Cannabidiol
- Carbamazepine
- Dexamethasone
- Doxepin
- Ketamine
- Lidocaine (from FDA's drug–drug interaction considerations list)
- Naproxen
- Nifedipine
- Pentoxifylline

design. Based on the committee's research questions, the scope of the literature was limited to the topical application of any of the 20 ingredients to intact skin. This second screen for content relevance was carried out by committee members, and resulted in a total of 169 articles. See Figure B-1

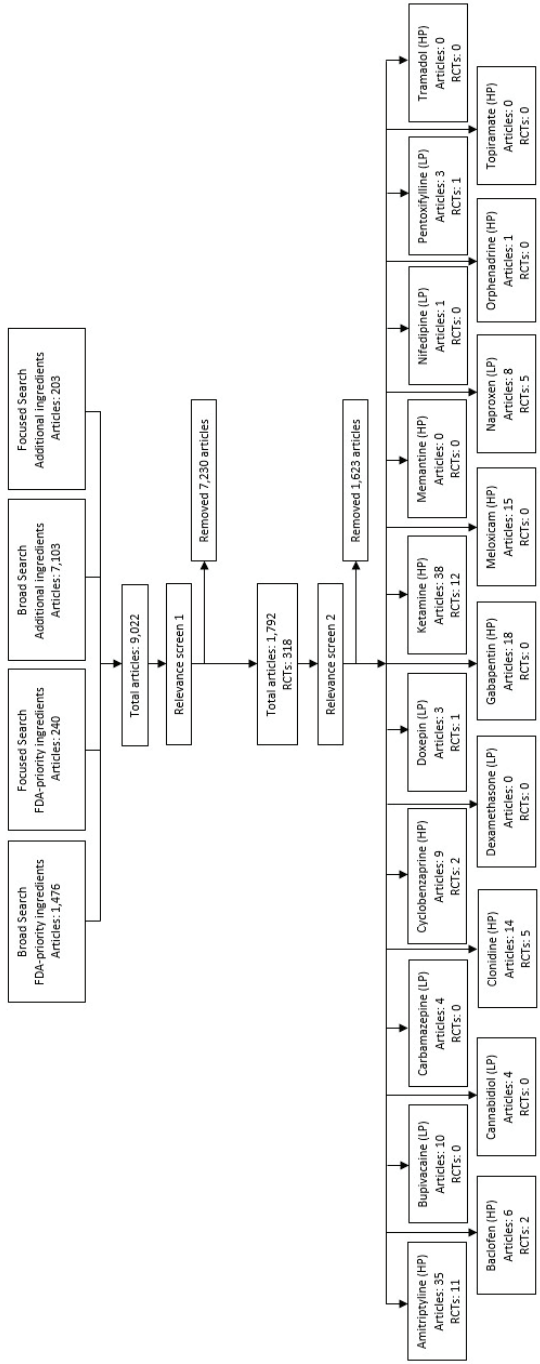

FIGURE B-1 Literature search and article selection process flowchart.

for a flowchart that depicts the inclusion of articles in the committee's literature review.

Of these 169 articles that were relevant to the study's charge, all randomized controlled trials (RCTs) (29 from the literature search, and 1 identified in a systematic review from the literature search) were evaluated for their risk of bias. Committee members used the 2019 revised Cochrane Risk-of-Bias Tool for randomized trials to evaluate each RCT for potential biases that could affect the reported outcomes.[1] Committee members assessed each RCT in five domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Committee members assigned an overall risk of bias to each RCT based on the responses in each domain. An overall assessment of "low risk of bias" meant that there was a low risk of bias in each of the domains. "Some concerns" was reached if at least one domain was judged to raise some concern of bias, but no domain was at high risk of bias. Finally, a determination of "high risk of bias" was assigned to RCTs for which multiple domains raised some concern of bias in a manner that substantially lowered confidence in the result, or if there was high risk of bias for at least one domain.

Search Strategies

FDA-Priority Ingredients Broad Search
Date performed: January 9, 2019
Articles obtained: 1,476

Databases: Embase, Medline, PubMed, Scopus, Toxnet, ClinicalTrials.gov

Search Parameters:
1900 to present
Peer-reviewed articles
English language
International

[1] For more information on the risk of bias assessment used, see Sterne, J. A. C., J. Savović, M. J. Page, R. G. Elbers, N. S. Blencowe, I. Boutron, C. J. Cates, H.-Y. Cheng, M. S. Corbett, S. M. Eldridge, J. R. Emberson, M. A. Hernán, S. Hopewell, A. Hróbjartsson, D. R. Junqueira, P. Jüni, J. J. Kirkham, T. Lasserson, T. Li, A. McAleenan, B. C. Reeves, S. Shepperd, I. Shrier, L. A. Stewart, K. Tilling, I. R. White, P. F. Whiting, and J. P. T. Higgins. 2019. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 366:I4898.

Search Terms:

1. Ingredients
    a. Amitriptyline
    b. Baclofen
    c. Clonidine
    d. Cyclobenzaprine
    e. Gabapentin
    f. Meloxicam
    g. Memantine
    h. Orphenadrine
    i. Topiramate
    j. Tramadol
2. Targeted Search Terms
    a. Drug dosage form
        i. Creams
        ii. Rubs
        iii. Topical
        iv. Skin absorption
        v. Transdermal drug administration
3. Outcomes
    a. Bioavailability
    b. Drug-related side effects and adverse reactions
    c. Effectiveness
    d. Pharmacokinetics
    e. Safety

FDA-Priority Ingredients Focused Search
Date performed: April 22, 2019
Articles obtained: 240

Databases: Embase, Medline, PubMed, Scopus, Toxnet, ClinicalTrials.gov

Search Parameters:
1900 to present
Peer-reviewed articles
English language
International

Search Terms:

1. Ingredients
    a. Amitriptyline
    b. Baclofen
    c. Clonidine

   d. Cyclobenzaprine
   e. Gabapentin
   f. Ketamine
   g. Meloxicam
   h. Memantine
   i. Orphenadrine
   j. Topiramate
   k. Tramadol
2. Targeted Search Terms
   a. Drug dosage form
      i. Creams
      ii. Rubs
      iii. Topical
      iv. Skin absorption
      v. Transdermal drug administration
3. Outcomes
   a. Drug-related side effects and adverse reactions
   b. Pharmacokinetics
   c. Pain management

Additional Ingredients Broad Search
Date performed: May 31, 2019
Articles obtained: 7,103

Databases: Embase, Medline, PubMed, Scopus, Toxnet, ClinicalTrials.gov

Search Parameters:
1900 to present
Peer-reviewed articles
English language
International

Search Terms:
1. Ingredients
   a. Bupivicaine
   b. Cannabidiol
   c. Carbamazepine
   d. Dexamethasone
   e. Doxepin
   f. Ketamine[2]
   g. Naproxen

[2] The search for articles on ketamine using this strategy was performed on May 3, 2019.

   h. Nifedipine
   i. Pentoxifylline
2. Targeted Search Terms
   a. Drug dosage form
      i. Creams
      ii. Rubs
      iii. Topical
      iv. Skin absorption
      v. Transdermal drug administration
3. Outcomes
   a. Bioavailability
   b. Drug-related side effects and adverse reactions
   c. Effectiveness
   d. Pharmacokinetics
   e. Safety

Additional Ingredients Focused Search
Date performed: April 30, 2019
Articles obtained: 203

Databases: Embase, Medline, PubMed, Scopus, Toxnet, ClinicalTrials.gov

Search Parameters:
1900 to present
Peer-reviewed articles
English language
International

Search Terms:
1. Ingredients
   a. Bupivacaine
   b. Cannabidiol
   c. Carbamazepine
   d. Dexamethasone
   e. Doxepin
   f. Ketamine[3]
   g. Naproxen
   h. Nifedipine
   i. Pentoxifylline

[3] The search for articles on ketamine using this strategy was performed on March 28, 2019.

2. Targeted Search Terms
    a. Drug dosage form
        i. Creams
        ii. Rubs
        iii. Topical
        iv. Skin absorption
        v. Transdermal drug administration
3. Outcomes
    a. Drug-related side effects and adverse reactions
    b. Pharmacokinetics
    c. Pain management

Appendix C

Commissioned Paper: Topical Dosage Form Development and Evaluation

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THE SKIN

The skin is the largest organ and a protective barrier. The skin consists of several heterogeneous layers of cells, hair follicles, and glands. To understand the key mechanisms of topical drug delivery, the skin must be viewed as having two major layers: the outer epidermis and the inner dermis. The epidermis lacks any blood vessels whereas the dermis has a rich network of blood vessels (see Figure C-1). The epidermis consists of two distinct layers: the outermost stratum corneum and the underlying viable

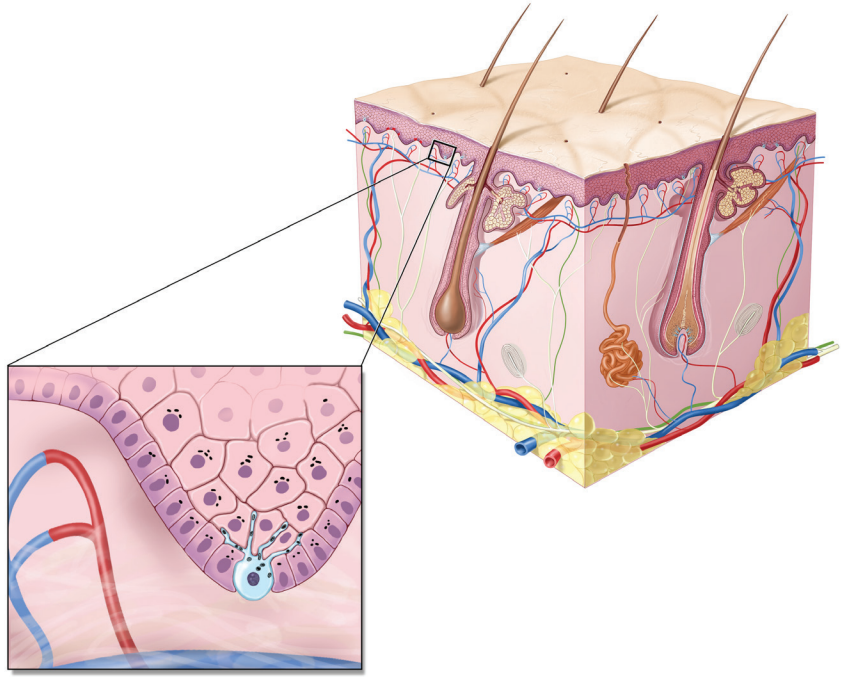

FIGURE C-1 Transverse section showing different layers and parts of human skin.
SOURCE: Copyright 2008 Terese Winslow, U.S. government has certain rights.

epidermis. The stratum corneum is constituted of tightly packed dead cells filled with keratin (see Figure C-2). The intercellular space is occupied by bilayer lamellar lipid structures (Elias, 2005). These lipid domains consist of fatty acids, cholesterol, and saturated fats called ceramides. Together, the tightly packed keratinocyte layers and intercellular lipids constitute the main barrier and keep external agents from penetrating into deeper layers of the skin. Melanin is the pigment responsible for skin color, and it protects the skin from intense ultraviolet (UV) radiation. Additionally, the skin is also associated with a great immune system to address any exposure to pathogens while also reacting to allergens. The skin surface is acidic in nature, while the inner layers are at physiological pH (Schmid-Wendtner and Korting, 2005). The pH gradient across the different layers prevents microorganisms from penetrating into deeper layers of skin. The skin tissue also has significant amounts of esterase, protease, and other enzymes that constitute a metabolic barrier (Martin and Axelrod, 1957; Park et al., 2011).

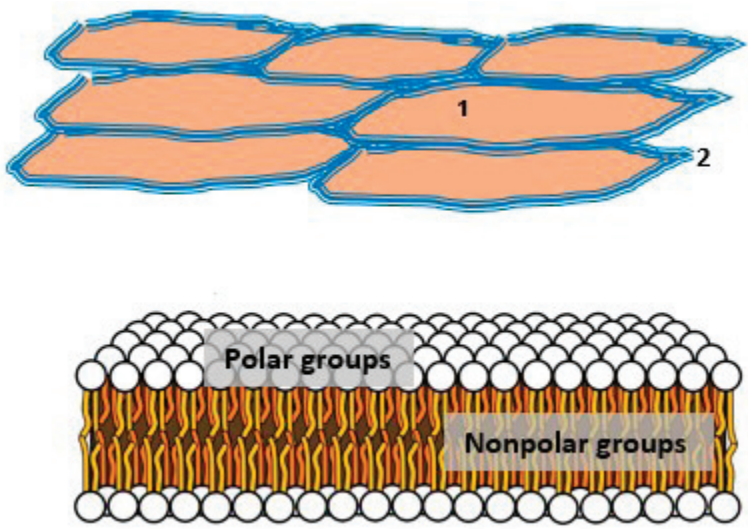

FIGURE C-2 (Top) Top view of the stratum corneum showing tightly packed keratinocytes (1) with intercellular space filled with lipids (2). (Bottom) The intercellular lipids consist of ceramides, cholesterol, and fatty acids arranged in a bilayer lamellar pattern.
SOURCE: Phospholipids aqueous solution structures by Mariana Ruiz Villarreal, LadyofHats is licensed under Creative Commons CC0.

A water gradient exists from the inside to the outside layers of the skin; it is responsible for the constant evaporation of water across the stratum corneum. Any damage caused to the stratum corneum barrier will increase the transepidermal water evaporation rate (Sotoodian and Maibach, 2012).

Over the past several decades, research has clearly shown that macromolecules could not diffuse across the skin. The carrier-medicated delivery systems, nanoparticles, micron size surfactant, and polymeric carriers cannot penetrate the skin either (Campbell et al., 2012). There are some reports showing penetration of particulate drug delivery systems owing to their charge, shape, elasticity, and other characteristics via the hair follicles. However, there is not enough strong evidence to dispute the fact that large molecules and particles would not be able to penetrate the skin. Overall, there is a strong physical, metabolic, and physicochemical barrier embedded in the skin that limits the number of drugs that can be delivered topically in effective amounts. The criteria for the molecules to diffuse into and across the skin is discussed in later sections of this article.

TOPICAL PRODUCTS

Topical products are generally available in various forms such as liquids, ointments, gels, creams, and foams. In terms of complexity, the product can be a simple homogenous viscous solution or semisolid solution, or a suspension of active pharmaceutical ingredients (APIs) in the semisolid vehicle. The microstructure of the product becomes increasingly complex with the increasing heterogeneity of the product. For example, creams are heterogeneous and are considered complex products. The complexity increases when the API or microcarrier system is dispersed in the cream base.

In compounding pharmacies, the pharmacists generally incorporate the drug into ready semisolid bases. These bases are premixed and readily available for the pharmacist, into which the API is generally incorporated with the help of an ointment spatula or triturated using a mortar and pestle. Some of the semisolid bases that are commonly used in compounding pain creams include premium lecithin organogel (PLO), oleaginous base, Vanicream base, Aquaphor base, and Eucerin base. The excipients present would determine the type of semisolid base. The gel bases are made up of hydrogel polymers such as carbomers, celluloses, and pluronics. The organogels for the delivery of lipophilic compounds are made of lipids such as lecithin. The cream bases are emulsions in which an oil and aqueous phases are mixed together to form either an oil in water (o/w) or a water in oil (w/o) emulsion. Oleaginous bases are made of hydrocarbons, oils, fats, and waxes. Water-soluble bases are generally formulated using polyethylene glycols. The consideration of a particular type of base should be based on factors such as stability, site of delivery, and target site of action. The type of base chosen could largely influence the overall performance of the product (Padula et al., 2018).

The phrase "topical products" encompasses all of the products that are intended for application on the skin, mucous membranes, and cavities. In the case of dermatological products, the products may be intended just for the purpose of **protection or hydration** of skin. Such products generally may or may not contain any active ingredients and they are intended to spread well across the entire applied area, forming a thin layer. In products that are intended for **local activity,** such as antibacterial and antifungal products, the drug must be available on the surface of the skin in its active form, and it is not required to be absorbed into the skin. In the case of products intended for **regional activity,** such as local anesthetic products and pain creams, the drug must be retained in the skin. However, the drug would eventually be cleared by dermal circulation. In the case of **transdermal drug delivery products,** the skin is only used as a port of administration for systemic delivery of drugs. For such APIs, the target site of action is located elsewhere in the

body. For example, the antianginal drug nitroglycerine is designed to be absorbed into the systemic circulation from the site of application on the skin.

POTENTIAL DRUG ABSORPTION PATHWAYS ACROSS THE STRATUM CORNEUM

There are three potential pathways for the absorption of drugs across the stratum corneum (see Figure C-3). The drug could get absorbed via the **transcellular** pathway in which the drug would need to traverse from one cell to another. The **paracellular** pathway is diffusion through the intercellular lipid domains. The third potential pathway would be the transappendageal pathway, which involves the pilosebaceous routes (hair follicle and sebaceous glands) and sweat glands (Lauer et al., 1996; Meidan et al., 2005). Because a dense capillary network surrounds the sweat ducts and hair follicles, any small fraction of a drug that makes its way into the skin via the appendageal pathway will be quickly absorbed into the circulatory system, hence explaining why it is not available in effective amounts in the skin. Therefore, the contribution of the appendageal pathway to overall dermal drug absorption is generally negligible. The most important pathways are intercellular and intracellular pathways. Although paracellular volume is relatively smaller than the transcellular route, it can still contribute significantly, provided the drug molecule meets the required criteria to propagate through the lipid pathway.

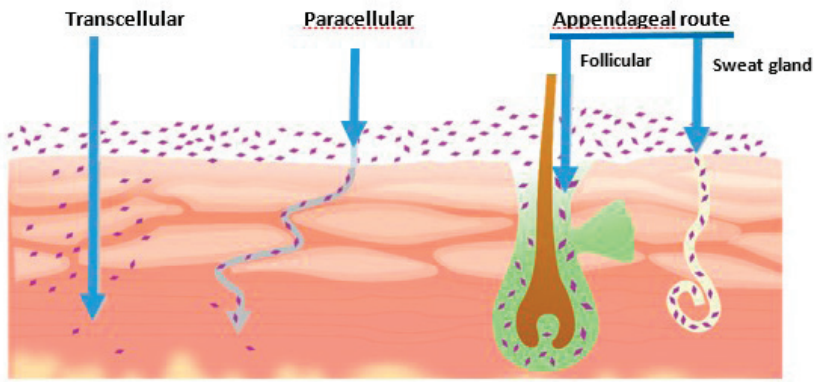

FIGURE C-3 Pathways of drug absorption across the stratum corneum layer of skin.
SOURCE: Shaker et al., 2019.

PASSIVE DIFFUSION OF DRUG

The drug undergoes passive diffusion across the skin layers along the concentration gradient, which is thermodynamically a spontaneous process. A simple approach to mathematically explain the passive diffusion of drugs across the skin layers is through Fick's first law:

$$J = D \cdot K\frac{C_d - C_r}{h}$$

Where J is the flux (rate of drug transfer per unit surface expressed mass/unit time/unit area), C_d is the concentration of drug in the formulation, and C_r is the concentration of drug in the receiver, which is generally considered as skin interstitial fluid or systemic circulation. C_d–C_r represents the concentration gradient across the barrier where h is thickness of the membrane. D is the diffusion coefficient of the drug in the stratum corneum (cm^2/sec). K is the partition coefficient of drug between formulation and stratum corneum. (Generally, the partition coefficient of drug in octanol and water system is considered in this case.)

Permeability coefficient of drug	$P = (DK/h)$
Hence rate of permeation at steady state	$J = P\ (C_d - C_r)$
Under perfect sink conditions when $C_r << C_d$	$J = P\ C_d$ (M-11)

PHYSICOCHEMICAL PROPERTIES OF ACTIVE PHARMACEUTICAL INGREDIENTS AND DERMAL ABSORPTION

The most critical physicochemical characteristics that would influence the permeation of drugs across the skin are molecular weight, partition coefficient, melting point, and charge of the penetrant molecule.

The molecules greater than 600 da are known to be poorly permeable across the skin (Barry, 2001). The larger the molecule, the less its diffusivity is in the vehicle as well as in the skin layers. Therefore, smaller molecules are preferred for passive topical delivery over larger molecules. This is the primary criteria to be fulfilled by the penetrating molecule. Most pain medications satisfy this criterion unless they are modified by association, complexation, or structural modification.

The predominant pathway for drug penetration into the stratum corneum (paracellular or transcellular pathway) is lipid in nature. Unlike the stratum corneum, the viable epidermis and dermal layers are aqueous in nature. To make its way across the stratum corneum, the API must be able to partition into the lipid domains adequately; to penetrate across the viable epidermis and dermis, the molecule should possess significant water solubility as well. Therefore, the drugs that are adequately both lipid and

water soluble are known to permeate across the skin in significant amounts. If the drug is extremely hydrophilic in nature, then it would not be able to partition into the stratum corneum. On the other hand, the drugs that are extremely lipophilic (log $P_{oct/water} > 3$) might be successful in localizing in the stratum corneum but will fail to get absorbed into the deeper layers in effective amounts. Therefore, an optimal log $P_{oct/water}$ partition coefficient value for a drug to be a good candidate for dermal product is reported to be 1–3 (Naik et al., 2000; Wiedersberg and Guy, 2014).

The melting point and the skin permeability have been known to be inversely related to each other. Generally, drugs with a melting point of less than 200°C are known to permeate relatively better than the higher melting drugs (Naik et al., 2000). Therefore, approaches to decrease the melting point such as the formation of a eutectic mixture and modification of chemical structure are considered. In a study reported by Ki and Choi, the authors observed greater permeation of the pain medication meloxicam ethanolamine compared to meloxicam, owing to the lesser melting point of the ethanolamine form (Ki and Choi, 2007).

The charge-selective nature of the stratum corneum has been well investigated. The skin has a pI[1] of 4–5. At a pH less than its pI, the surface of the skin is predominantly positively charged, whereas at a pH above pI, the skin's surface is predominantly negatively charged. Evidently, the skin is selective to negatively charged drugs at pH < pI and vice versa (Hatanaka et al., 1996).

THE FORMULATION CHARACTERISTICS AND DERMAL DRUG DELIVERY

The quality attributes and microstructure of the topical products could potentially have a significant effect on their performance and sensorial characteristics.

Some of the critical quality attributes that are considered important are drug concentration, pH, amount of drug in the suspended form, particle size, polymorphic form, shape of particles, globule size, viscosity, and texture properties (Otto et al., 2009).

Generally, the drug permeation flux increases with an increase in the concentration of the drug in the formulation vehicle. Most appropriate would be to relate the permeation flux to the thermodynamic activity of the drug. The thermodynamic activity of the drug at saturation is the unity at which a maximum transdermal flux is achieved. When supersaturated systems are formed at the applied site, the absorption flux increases further (Moser et al., 2001b). If the drug is distributed in both dispersed as well as

[1] Isoelectric point or the pH at which the charge is a net neutral.

continuous phases in a cream product, then the thermodynamic activity of the drug in both phases contributes to the performance of the topical product. Often the drug incorporated in the cream base gets localized only in one of the phases. If the drug predominantly concentrates in the dispersed phase, then the globule size of the dispersed phase becomes an important factor in determining the performance of the product (Ktistis and Niopas, 1998; Schwarz et al., 1995). If the drug is highly soluble in the continuous phase, then the globule size of the dispersed phase is not likely to have a significant influence on the drug permeation (Izquierdo et al., 2007). Friedman and coworkers demonstrated a superior permeation of steroidal and nonsteroidal anti-inflammatory drugs when delivered using a submicron emulsion vehicle as compared to conventional cream formulations indicating that reducing the size of the dispersed phase could influence the drug permeation and thus enhance the pharmacological activity of the drug significantly (Friedman et al., 1995). The efficacy of the nonsteroidal drugs, diclofenac and indomethacin, was enhanced by 40–50 percent, whereas the efficacy of steroidal drugs, which are relatively more lipophilic, was found to have been enhanced by four fold.

In topical products incorporated with poorly soluble drugs, an excess amount of drug is dispersed in the formulation due to saturation of the vehicle. The suspended drug would act like a reservoir during absorption process. The factors such as the amount of drug suspended, its particle size and distribution, shape of the particles, polymorphic form, and melting point influence the rate of dissolution of the drug in the remnant vehicle at the applied site. The smaller the diameter, the higher the specific surface area and the faster the dissolution of the particles in the formulation vehicle. As the polymorphic form of drugs could differ in their physicochemical characteristics, choosing the most appropriate form that dissolves rapidly and remains stable in the formulation is important while formulating a topical product. The X-ray diffraction studies and differential scanning calorimetric studies would shed some light on the solid-state nature of the drug.

Release of the drug is the first step in the dermal absorption process. The viscosity of a topical product is one of the major factors that determines the rate of release of the drug from the formulation (Binder et al., 2019). Indeed, it is the overall rheological behavior of the product that is known to play a significant role in determining the performance of the formulation. Generally, the topical semisolid products are shear thinning systems. This means their viscosity decreases as it is rubbed on the skin. When allowed to stand, the viscosity may or may not be recovered depending on the extent of disruption of the microstructure of the formulation. Yield stress is a property of some of the semisolids that represents their rigidity. The yield stress value determines the extrudability of the formulation from collapsible tubes and also the spreadability on the skin surface. In a study

by Binder and coworkers, the authors evaluated the effect of viscosity on drug penetration into the skin from cellulose ether-based hydrogels. It was observed that the drug penetration depth decreased as viscosity increased, suggesting a slower drug release due to an increasingly dense gel network (Binder et al., 2019).

Texture properties such as stringiness, adhesiveness, and spreadability influence the sensorial characteristics of formulation. Sensorial characteristics determine the acceptability of the formulation. Although the role of the work of adhesion has not been systematically investigated, fundamentally, it is understood that the work of adhesion represents the extent of interaction between the formulation and skin surface. There should be adequate interaction between the topical product and the skin for the product to spread and adhere to the surface of the skin so that the diffusion process continues uninterrupted.

The drying rate of the formulation is critical in determining the extent of drug delivery from a topical product. When applied in a clinically relevant dose on the skin surface, the products would start losing the volatile components immediately after application. The evaporative metamorphosis process leads to dynamic change in the viscosity of the formulation. The solvent evaporation also affects the thermodynamic activity of the API, as mentioned earlier.

The quality attributes of the product are highly dependent on the composition of the product and the manufacturing process implemented during the product's preparation. A cream product prepared using different equipment could vary in its characteristics. Despite having the same composition and process of preparation, products that are prepared using different manufacturing variables could end up with different quality attributes and thus exhibit different levels of performance.

PHARMACEUTICAL EXCIPIENTS AND DERMAL DRUG DELIVERY

The excipients play different functional roles, which in turn determine the type, structure, and stability of the semisolid base. Often, the excipients also affect the absorption of drugs. The commonly used excipients in semisolid products include solvents, viscosifying agents, emulsifying agents, penetration enhancers, stabilizers, preservatives, and organoleptic agents. The excipients used in topical products should be inert and should comply with the quality standards specified in the pharmacopoeia. The ingredients should not cause any irritation, sensitization, or irreversible perturbation of the stratum corneum barrier. Therefore, the potential physiological interaction of excipients needs to be well understood. The excipients influence the quality attributes of the topical products, physicochemical characteristics of the drug, and sensorial characteristics of the formulation as well.

Solvents play multiple roles in a topical product. Solvents help enhance the solubility of the API in the product and also facilitate drug absorption. The solvents used in the formulation could enhance drug absorption through several mechanisms. The solvent could carry the drug into the skin via solvent transport pathways (Osborne and Musakhanian, 2018). At the site of application, the solvent evaporates, leading to enhanced drug absorption owing to increased concentration. In the case of products that are already saturated with drugs (Moser et al., 2001a), incorporation of solvents with relatively higher boiling points may help to keep the drug from precipitating over a long period of time at the site of application, facilitating the absorption process. Often, the solvents are also incorporated to dissolve some of the excipients like coloring agents, preservatives, and stabilizers in the formulation.

Within the formulation, one of the potential interactions of the excipient with the API that could enhance drug absorption is through the formation of an eutectic substance. For example, the transdermal permeation of meloxicam was enhanced significantly by incorporating thymol in the formulation, owing to the decrease in the melting point. The extent of decrease in the melting point was directly dependent on the concentration of thymol (Mohammadi-Samani et al., 2013). The excipients that are present in an ionized state could also form ion pairs with the API, leading to a relatively more lipophilic drug form that could enhance the drug penetration. In one of the studies, Green and Hadgraft (1987) reported the ability of oleic acid and lauric acid to form ion pairs with cationic drugs and enhanced their transdermal permeation.

SKIN PERMEABILITY ENHANCERS

The excipients used in the topical formulations are often intended to influence the skin permeability by interacting with the stratum corneum barrier. Some excipients are known to lead to hydration and swelling of the stratum corneum to enhance the drug delivery (examples include propylene glycol, urea, and polyethylene glycol). Some excipients would enhance the skin permeability of inherently poorly permeable polar molecules by fluidizing the rigid lipid lamellar structures. The chemical penetration enhancers can be classified into different categories such as solvents, surfactants, fatty alcohols, fatty acid esters, lipids, and terpenes. Most of these enhancers have been known to enhance the permeation by fluidizing lipids in the stratum corneum and to increase the diffusivity of molecules across the stratum corneum (Williams and Barry, 2012). Azones and dimethyl sulfoxide (DMSO) are also known to disrupt the lipid domains and improve the partitioning of drugs into the stratum corneum. Solvents such as propylene glycol and transcutol enhance the solubility of the drug in

the stratum corneum. Oleic acid is known to induce phase separation in the stratum corneum lipid domains. For example, amitriptyline, one of the topical pain medications formulated in combination with other drugs, was found to permeate 4- and 5-fold more in the presence of fatty acids such as oleic acid and linoleic acid (Jain and Panchagnula, 2003). The permeability enhancers should be used in optimal concentration. When used in higher amounts, the permeability enhancers could affect the formulation properties as well as potentially cause skin irritation (Haque and Talukder, 2018).

In Vitro Evaluation of Topical Products

In Vitro Release Testing

The topical products applied on the skin are required to release the drug from the formulation so that it is available for absorption at the site of application. The release rate of the drug is governed by the viscosity and heterogeneity of the topical product. The drug release rate would be significantly affected in the case of any thermodynamic instability in the formulation. A drastic drop in the viscosity of the formulation due to phase separation of the cream could lead to the rapid release of the drug concerning dose dumping. Therefore, in vitro release testing is considered an excellent tool to test the product's performance, stability, batch-to-batch variability, and influence of changes in the composition (Nallagundla et al., 2004; Tiffner et al., 2018; USP, 2019).

The in vitro release testing is generally performed using the USP II dissolution apparatus or Franz diffusion cells. In some cases, the use of flow through the apparatus has been demonstrated too (Chattaraj and Kanfer, 1996). The various apparatus that is used for in vitro testing of dermatological products are shown in Figure C-4. In principle, the in vitro release testing involves separation of the formulation from the receiver fluid using a nonrate controlling, nonbiological membrane. Generally, a filter membrane or a dialysis membrane would be used so the rate of release of the drug from the formulation is governed only by the quality attributes of the product (FDA's SUPAC-SS guidance) (FDA, 1997). The release rate of drug from the formulation is determined by sampling and quantitative analysis of the receiver fluid at different time points. The in vitro release rate is the slope of the amount of drug released from the formulation to the square root of time (Higuchi, 1961, 1962).

In Vitro Permeation Testing

Furthermore, the performance of topical formulations is evaluated by subjecting them to in vitro skin permeation testing studies using a suitable

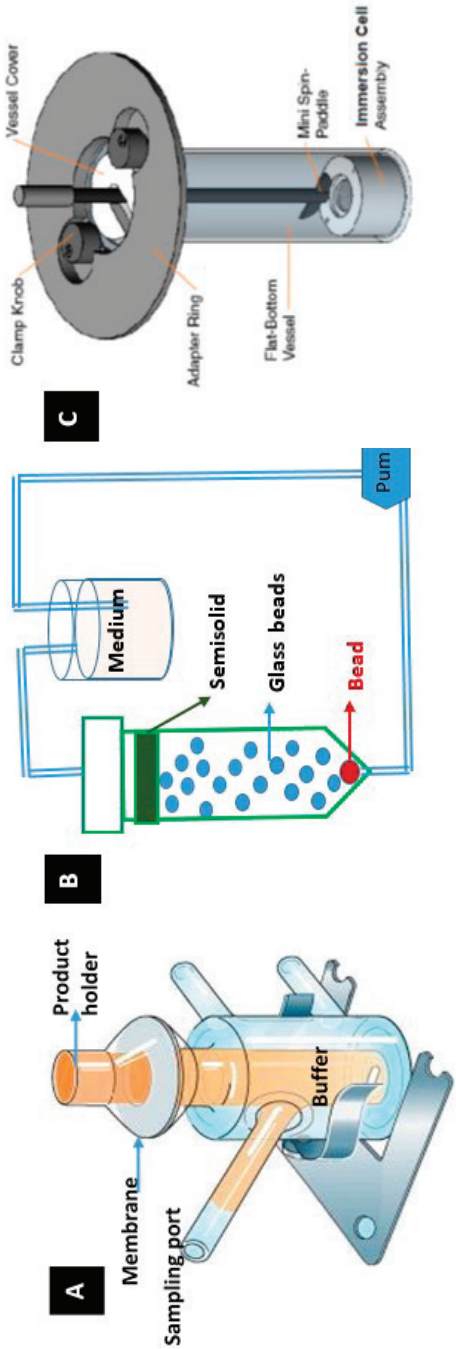

FIGURE C-4 Instruments for performing in vitro release testing of topical semisolid products. A. Franz diffusion cell. The formulation would be placed in the donor compartment and the buffer in the receiver compartment. The donor and receiver are separated using a nonbiological membrane with known porosity. B. USP IV dissolution apparatus is a flow-through type model. C. USP II dissolution apparatus with immersion cell for filling the semisolid product. The buffer is filled in the flat bottom vessel and the paddle is used for stirring.
SOURCES: PermeGear, 2018; © 2014 United States Pharmacopeial (USP) Convention.

skin model. In vitro permeation testing is performed using Franz diffusion cells across an appropriate skin model. The skin is sandwiched between donor and receiver compartments with the epidermis facing upward. The receiver fluid would be a buffer system that would serve as a perfect sink. The receiver compartment fluid is withdrawn at different time intervals and analyzed for the amount of drug permeated across the skin (Friend, 1992). Generally, two types of dosing protocols are reported in the literature. Finite dosing would mean the application of a clinically relevant dose applied on the skin surface using a suitable application technique. The objective of applying a finite dose is to mimic the in vivo phenomenon of postapplication metamorphosis of the product (Kasting and Miller, 2006). In an infinite dose study, an excess dose is applied on the skin, and the permeation study does not exactly reflect the in vivo situation.

There are several skin models used in dermal and transdermal delivery research. Excised skin from rodents and other animals have been the most common. However, the permeation studies across rodent skin can lead to an overestimate of the drug's permeability. This is generally attributed to differences in stratum corneum thickness and composition of the intercellular lipid domain (Bond and Barry 1988a,b; Bronaugh et al., 1982; Wester and Noonan, 1980). Nevertheless, such skin models would serve as great and inexpensive tools during product development and optimization (Scott et al., 1986). Porcine ear skin has been suggested as a valid model for human skin in vivo (Sekkat et al., 2002). Sekkat and coworkers performed a systematic biophysical evaluation study and observed that the barrier function of the pig ear skin model closely resembled the human skin in vivo. However, additional evidence is needed to demonstrate that porcine ear skin has comparable permeability characteristics to drug molecules as that of human skin.

Excised human skin is most commonly obtained from cadavers or from patients undergoing plastic surgery. Skin from the abdominal region, breast, thigh, or back is most convenient, due to the availability of adequate area for performing multiple replicates (Rougier et al., 1987). The use of dermatomed human cadaver skin for bioequivalence testing of topical products is increasing in the pharmaceutical industry as regulatory agencies are accepting the study data (Abd et al., 2019).

Variability in skin permeability due to age, sex, region, processing, storage, and diffusion study protocols are common issues seen in the case and of all these skin models. An adequate number of replicates should be implemented in the study design to generate reliable data that helps draw valid conclusions.

DRUGS USED IN COMPOUNDED PAIN CREAMS

Compounded topical creams typically use a combination of two or more medications to achieve multiple complementary effects (Keppel Hesselink and Kopsky, 2017). Common APIs used in compounded topical creams are listed in Table C-1. The key physicochemical characteristics influencing the dermal penetration of drugs are also tabulated. Apparently, all are small molecules and meet the size criteria to be a candidate for topical administration. However, for most of the molecules, not all of the other physicochemical characteristics seem to favor permeation. Either the log P is out of the 1–3 range or the molecule has a high melting point or an unfavorable dissociation constant (pKa).

TABLE C-1
Physicochemical Properties of APIs Commonly Used in Pain Medications

Drug	Mol. Wt (g/mol)	Log P (Oct-water)	Melting Point (°C)	pKa
Amitriptyline	277.40	4.92	197	9.4
Baclofen*	213.66	1.3	207	9.62 and 3.67
Bupivacaine	288.43	3.41	107	8.2
Cannabidiol	314.46	—	66	—
Carbamazepine	236.27	2.45	191	13.9
Clonidine	230.09	1.59	130	8.12
Cyclobenzaprine*	275.39	5.2	218	8.47
Dexamethasone	392.46	1.83	262	12.42
Doxepin	273.38	–0.548	184	8.96
Gabapentin	171.24	–1.1	166	3.68 and 10.70
Ketamine	237.73	3.12	92.5	7.5
Lidocaine	234.34	2.44	68.5	8.01
Meloxicam	351.40	3.43	254	4.08
Memantine	179.31	3.28	258	10.27
Naproxen	230.26	3.18	153	4.15
Nifedipine	346.30	2.20	173	3.93
Orphenadrine	269.39	3.77	156	8.91
Pentoxifylline	278.31	0.38	105	—
Topiramate	339.36	–0.5	125	8.6
Tramadol	263.38	1.34	181	9.4

* Zwitter ionic in nature.

SOURCES: Sources for the data in this table include DrugBank, 2020; Expert Committee on Drug Dependence, 2017; Plumley et al., 2009; PubChem, 2020.

Owing to greater lipid partitioning ability, generally the un-ionized moiety is more permeable across the lipid pathways over the ionized counterpart. Depending on the pKa, the drugs undergo dissociation to different extents (Chantasart et al., 2015). For example, Watkinson and coworkers reported a significant order of magnitude decrease in the permeability coefficient of ibuprofen (pKa = 4.41) across the skin when the pH was increased from 4 to 7 owing to the significant increase in dissociation of ibuprofen into its ion (Watkinson et al., 1993). The skin surface is acidic in nature (pH 4–5). Skin is not only capable of resisting any change in pH upon exposure to extreme pH formulation, but it also has the ability to drive the formulation to come into homeostasis with the skin's pH (Levin and Maibach et al., 2007). Therefore, the percent of the un-ionized drug present at skin pH is critical in determining the absorption. Although the ionized form of drug generally gets absorbed by polar pathways in the skin, it is relatively many-fold smaller than the amount that could get absorbed via nonpolar pathways.

In the case of formulations with a combination of drugs of different pKa, it is challenging to adjust the pH to favor the permeation of all of the drugs. For example, in a topical pain product containing amitriptyline (pKa 9.4) and ketamine (pKa 7.5) if the formulation pH happened to be 9, most of the ketamine (96.93 percent) would exist in ionized form. But at the same pH only 28.47 percent of amitriptyline would exist in ionized form. If meloxicam or nifedipine are in combination with the above drugs, they would exist almost completely in an ionized state at a pH of 9, which could hamper their penetration significantly.

When oppositely charged medications are combined in the same formulation, they tend to form ion pairs. Ion pairing is generally known to favor the absorption of drugs owing to the relatively higher partitioning ability of neutral ion pairs compared to the charged moieties of the API. Valenta and coworkers have used an ion-pairing mechanism to enhance the delivery of a local anesthetic, lignocaine (Valenta et al., 2000). The advantage of an ion-pairing mechanism is jeopardized if the size of the complex exceeded the acceptability limit of the skin. Particularly, when APIs have multiple ionizable groups, they will be combined; the chances of forming larger ion pair complexes are even higher. The ion pairing could happen between excipient and the API as well. Jain and Panchagnula reported an enhanced permeation of amitriptyline owing to ion pairing with oleate (Jain and Panchagnula, 2003).

PERMEATION STUDIES OF PAIN MOLECULES

Some studies in the literature have specifically discussed the permeation of APIs from topical pain products. In one of the studies by Wang and Black

(2013), the investigators studied the permeation of a few pain medications from cream formulations across excised trunk skin from human cadavers. The objective was to compare a custom-made cream base against respective reference cream products. The amount of drug present in the respective reference cream products and the amount of drug permeated in the creams are given in Table C-2. The amount of pain medication permeated was less than 1 percent of the applied dose (except ketamine, which was a little more than 1 percent). The custom-made cream did not enhance the permeation of pain medications significantly compared to the reference creams (Wang and Black, 2013).

In another study, Bassani and Banov investigated the absorption of ketamine, gabapentin, clonidine, and baclofen across the human cadaver trunk skin (see Table C-3). All of the drugs permeated poorly except ketamine hydrochloride, which achieved a 35 percent permeation across the skin (n = 3) (Bassani and Banov, 2016).

Sznitowska and other researchers investigated the effect of absorption promotes on percutaneous permeation of baclofen, a zwitterion. Baclofen

TABLE C-2
The Amount of Drug Absorbed Across the Human Cadaver Skin from Topical Pain Creams (n = 6 ± SD)

Active Pharmaceutical Ingredient	% w/w API in the Cream Formulation	% Absorbed (dose 50 mg of formulation across 1.77 cm^2 in 48 h)
Bupivacaine hydrochloride	1	0.28 ± 0.11
Diclofenac sodium	3	0.84 ± 0.23
Gabapentin	6	0.38 ± 0.43
Ketamine hydrochloride	10	1.03 ± 0.32
Orphenadrine citrate	5	0.13 ± 0.05

SOURCE: Wang and Black, 2013.

TABLE C-3
The Amount of Drug Absorbed Across the Human Cadaver Skin from Topical Creams (n = 3 ± SD)

Active Pharmaceutical Ingredient	Percent Drug Absorbed Across the Cadaver Skin	
	Lipoderm	Lipoderm ActiveMax
Ketamine	35.48 ± 9.03	45.52 ± 2.42
Clonidine	3.955 ± 2.60	4.38 ± 0.95
Gabapentin	0.41 ± 0.34	0.19 ± 0.08
Baclofen	0.27 ± 0.27	0.10 ± 0.08

SOURCE: Bassani and Banov, 2016.

is one of the commonly used drugs in neuropathic pain management via topical administration alongside other pain management drugs. The drug was found to be poorly permeable across the full-thickness cadaver skin. All of the highly efficient lipophilic and hydrophilic permeation enhancers such as oleic acid-propylene glycol, oleic acid, azone, ethanol, sodium lauryl sulfate, propylene glycol, and dimethyl sulfoxide failed to enhance its permeation significantly for up to 30 hours (Sznitowska et al., 1996).

It is evident from the above reports that APIs used in the compounded pain creams are poorly permeable and require appropriate enhancement strategies to improve their delivery into and across the skin. In the above studies, the absorption did not differ significantly with the use of different types of bases. A rational selection of base composition might be one of the factors needed to be considered in optimizing dermal delivery of pain medications. For example, Lehman and Raney (2012) studied the permeation of ketoprofen across excised human skin at finite dose conditions, from different formulation bases. The performance of Pentravan base (Vanishing o/w base) was compared with the PLO gel. The ketoprofen permeation from Pentravan base (~13.12 percent) was almost 4-fold higher than the PLO gel (~3.63 percent). This study demonstrated the importance of utilizing the appropriate formulation base for the development of a pain product.

The bioavailability of drugs from topical products also depends on the area of application. Any accidental or intentional application of medicated creams over a larger skin surface area can be associated with a potential risk of toxicity. Pomerleau and coworkers reported a case of severely elevated levels of clonidine in a 23-year-old patient who had rubbed a specially compounded medicinal cream over his entire body (Pomerleau et al., 2014). The formulation contained clonidine 0.2 percent w/w, gabapentin 6 percent w/w, imipramine 3 percent w/w, ketamine 10 percent w/w, lidocaine 2 percent w/w, and mefenamic acid 1 percent w/w. The patient suffered severe hypertension, bradycardia, and altered mental status.

SUMMARY

The physiochemical characteristics of the API are critical in determining the suitability of a drug for dermal delivery. Only a few of the drugs currently used come close to meeting all of the criteria to penetrate the skin. Moreover, the use of multiple drugs increases the potential for drug–drug and drug–excipient interactions influencing the dermal absorption of actives. The skin barrier can be modulated using formulation approaches, compositional approaches, and chemical permeation enhancers to improve the delivery of drugs. There is a need to determine appropriate methods and approaches to evaluate the topical cream products. In vitro release testing and in vitro permeation testing are great tools to compare the compounded

products with benchmark reference products. However, the fact that there are no exact reference products or FDA-approved products available for the comparison of compounded products complicates the challenge significantly. Preclinical and clinical studies are necessary to determine the safety and efficacy of compounded products.

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Appendix D

Glossary

Absorption: The process of assimilating substances into cells or across the tissues through diffusion or osmosis. In the case of compounded topical medications this assimilation could happen with the active pharmaceutical ingredient or with the excipient.

Active pharmaceutical ingredient (API): Any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure and function of the body of humans or other animals. Elements of a drug that are not API are called inert pharmaceutical ingredients.[1,2]

Acute pain: A complex, unpleasant emotional, cognitive, and sensory experience that is usually correspondent with the degree of tissue damage and that lessens as the injury heals.

Adjuvant: A medication that enhances the effectiveness of pain treatments.

[1] Definition from the United States Pharmacopeia.
[2] Definition adapted from the U.S. Food and Drug Administration (FDA).

Adverse event: An adverse event is any undesirable experience associated with the use of a medical product or preparation in a patient.[3]

Analgesia: A loss of pain sensation in an individual.[4]

Anesthesia: A process that reduces or eliminates pain and sensation, usually given during a painful procedure. Anesthesia may be local, regional, or general.

Bioavailability: The fraction of the administered dose of a drug that reaches the bloodstream for systemic circulation.

Bioequivalence: The therapeutic and pharmacokinetic uniformity of two drug products delivered at the same molar dose and under the same conditions.

Breakthrough pain: A sudden increase in pain that "breaks through" pain relief provided by ongoing analgesia. The duration is usually short, and while the level of pain may be severe the type of pain and the source of pain are usually not a symptom of a new or worsening condition. Typically the type of pain and the location of pain in these cases are shared with the chronic or acute pain condition that proceeded the breakthrough. Also called a pain flare.

Bulk drug substance: Any substance that is intended for incorporation into a finished drug product or preparation and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body, but the term does not include intermediates used in the synthesis of such substances.[5]

Cancer pain: Can be caused by the cancer itself or by the surgery, treatments, or tests used to diagnose and treat cancer. The amount and duration of pain varies, depending on the source. Pain from the cancer tumor can be caused by pressing on nerves, bones, or organs. There is no distinction between cancer pain and acute or chronic pain in the underlying neural processes.

[3] Definition adapted from FDA.
[4] Definition from the International Association for the Study of Pain.
[5] Definition adapted from FDA.

Chronic pain: Pain that extends beyond the period of healing or pain that is not explained by the identified pathology. It is pain that often disrupts sleep and normal living, ceases to serve a protective function, and instead degrades health and functional capability. Although injury often initiates chronic pain, factors (pathogenetic, physical, environmental, or affective) may perpetuate it and lead to disability and maladaptive behavior.

Chronic regional pain syndrome: A chronic pain condition that most often affects one limb, usually after injury, and is characterized by prolonged or excessive pain and changes in skin color, temperature, and/or swelling.

Clinical trial: Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

Compounded preparation: A nonsterile or sterile drug or nutrient preparation that is formulated in a licensed pharmacy, outsourcing facility, or other health care–related facility in response to or anticipation of a prescription or a medication order from a licensed prescriber. Federal law permits compounding; however, these drugs are not U.S. Food and Drug Administration approved for safety and effectiveness.

Compounder: An individual who makes compounded preparations. Compounders can be pharmacists, physicians, or individuals under the supervision of a pharmacist, and may practice in a variety of health care facilities, including pharmacies, hospitals, clinics, and outsourcing facilities.

Compounding: Drug compounding is often regarded as the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient. Compounding includes the combining of two or more drugs. Compounded drugs are not U.S. Food and Drug Administration approved.[6]

Compounding pharmacy: A pharmacy that makes compounded preparations in response to or anticipation of a prescription order for an individual patient.

Cream: A semisolid oil-in-water emulsion for application to the skin. Creams are spreadable and easily rub into the skin without a greasy residue, and can be washed off with water.

[6] Definition from FDA.

Difficult to compound: A condition of both sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act that precludes the use in compounding of those drugs appearing on the list of drugs with a demonstrable difficulty to compound.

Drug: For the purposes of this report, considered a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease by affecting the structure or any function of the body.[7]

Erythromelalgia: A rare vascular peripheral pain disorder characterized by episodes of pain, redness, and swelling in various parts of the body, particularly the hands and feet.

Evidence based: Evidence for efficacy or effectiveness should be based on designs that provide significant confidence in the results. The highest level of confidence is provided by multiple well-conducted randomized experimental trials, and their combined inferences should be used in most cases. When evaluations with such experimental designs are not available, evidence for efficacy or effectiveness cannot be considered definitive.

Excipient: A pharmacologically inactive ingredient used in the formulation of a drug that lends various functional properties to the drug formulation (i.e., dosage form, drug release, etc.).

Formulation: A selection and mixture of active pharmaceutical ingredients and inactive ingredients, which ideally takes stability, form, and strength into consideration.

Gel: Also referred to as jellies, is a semisolid dosage form that appears transparent or translucent, and employs either a hydrophobic or hydrophilic base.

Inert pharmaceutical ingredients: An inert, or inactive, ingredient is any substance, other than an active ingredient, which is intentionally included in a product. It is important to note, the term *inert* does not imply that the chemical is nontoxic.

Local: Refers to a specific site on the body. Local effects are achieved by administering a drug directly to the location where a therapeutic effect is desired, while avoiding absorption into circulating biological fluids.

[7] Definition from FDA.

Lotion: While similar to a cream, this dosage form has a more liquid consistency. The lower viscosity may provide a cooling effect to the area where applied as solvents in the lotion evaporate.

Mechanism of action: Describes the process by which a drug functions to produce a pharmacological effect.

Neuropathic pain: A type of pain that results from a lesion or a disease of the somatosensory system.

Nociceptive pain: A type of pain that results from somatosensory signals from an intact nervous system in response to potential or actual tissue damage.

Nociplastic pain: A type of pain that may arise without any clear evidence of actual or threatened tissue damage.

Off-label: A drug is considered off-label, for example, when an approved drug product is prescribed for a condition, or in a dose other than that for which it received its approval.

Ointment: A greasy semisolid dosage form that exerts occlusive properties over the outer layer of the skin, thereby increasing drug transfer across the skin.

Outsourcing facility: A facility that is engaged in the compounding of nonsterile or sterile drugs that has elected to register as an outsourcing facility per requirements of section 503B of the Federal Food, Drug, and Cosmetic Act. An outsourcing facility may or may not obtain prescriptions for identified individual patients.

Pain: An unpleasant sensory and emotional experience associated with subjective perception and interpretation of actual or potential tissue damage, or stimuli described in terms of such damage. There are many medically recognized qualifiers to pain including acute, chronic, myofascial, musculoskeletal, neuropathic, and high impact.[8]

Paste: A stiff semisolid dosage form that contains finely powdered solids. Some pastes may also have occlusive properties.

[8] Definition from the International Association for the Study of Pain.

Patch: A patch (not preferred terminology, but it is commonly used) or transdermal delivery system is a preparation of drug substance(s) in a carrier device that is applied topically. The drug substance is designed to be released in a controlled manner over a specified period of time. The carrier device is removed after use.[9]

Penetration enhancer: An excipient or a vehicle that aids in absorption through the skin.

Permeation: Penetration of and spreading throughout an organ, tissue, or space.

Pharmacokinetics: The science of drug absorption, distribution, metabolism, and excretion.

Systemic: Refers to the entire body. Systemic effects rely on the distribution of drugs by biological fluids that circulate throughout the body.

Tolerance: The capacity of the body to endure or become less responsive to a substance (such as a drug) or a physiological insult especially with repeated use or exposure.

Topical: A drug delivery method of applying the drug to the skin that aims to confine the therapeutic effect to the surface of the skin or within the skin, with no or minimal systemic absorption.

Transdermal: A drug delivery method of applying the drug to the skin that relies on absorption across the skin to blood vessels in deeper layers of the skin in order to achieve systemic distribution, which results in systemic delivery of the drug and systemic therapeutic effects.

U.S. Food and Drug Administration (FDA)-approved drug product: The finished dosage form that contains a drug substance, generally, but not necessarily in association with other active or inactive ingredients, and has received FDA approval for safety and effectiveness. An FDA-approved drug product will appear in FDA's *Orange Book*.

Vehicle: A component of the excipients that is used as a carrier or diluent in which liquids, semisolids, or solids are dissolved or suspended.

[9] Definition from the International Association for the Study of Pain.

Appendix E

503A and 503B Distribution Supplement

503A

Total estimates of 503A compounding pharmacies vary based largely on how a compounding pharmacy is defined. In a 2016 report, The Pew Charitable Trusts reported a total of more than 32,000 pharmacies in the United States that compound. This value was derived from the listing of pharmacies that report compounding functions in the National Council for Prescription Drug Programs Provider Database as of 2015. Submission of this information to the database was optional, and may not represent the true (and current) number of pharmacies that compound (The Pew Charitable Trusts, 2016). However, this estimate does not provide clarity on the extent of compounding services offered. The American Pharmacists Association estimates that there are approximately 7,500 pharmacies in the United States that *specialize* in compounding (American Pharmacists Association, 2020), a substantially lower estimate than the total 503A compounding pharmacies that perform any compounding.

503B

The value of 503B outsourcing facilities are reflective of those registered with the U.S. Food and Drug Administration as of February 2020. See Table E-1.

TABLE E-1
Distribution of 503B Outsourcing Facilities by State

State	Registered 503B Outsourcing Facilities
AL	2
AK	0
AR	4
AZ	4
CA	6
CO	4
CT	2
DC	0
DE	0
FL	9
GA	0
HI	0
IA	0
ID	1
IL	0
IN	0
KS	2
KY	0
LA	0
MA	2
MD	0
ME	0
MI	0
MN	1
MO	2
MS	0
MT	0
NC	1
ND	0
NE	0
NH	0
NJ	4
NM	0
NV	1
NY	6
OH	2
OK	1
OR	0
PA	2
RI	0
SC	4
SD	0
TN	3
TX	9
UT	0
VA	0
VT	1
WA	0
WI	0
WV	0
WY	0

SOURCE: FDA, 2020.

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FDA (U.S. Food and Drug Administration). 2020. *Registered outsourcing facilities*. https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities (accessed March 31, 2020).

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Appendix F

Adverse Events Table

The following is a set of 38 adverse event reports identified in the U.S. Food and Drug Administration's (FDA's) Adverse Event Reporting System (FAERS). This dataset describes one or more adverse event experiences resulting from the use of a topical compounded pain creams. Owing to the limited information collected, the data below can give a snapshot of the potential concerns related to insufficient labeling, systemic toxicity, and overall misuse (accidental and intentional) of these medications. See Chapters 4, 6, and 7 for additional discussions on what is known about the safety of compounded topical pain creams.

TABLE F-1
Adverse Events Table—Summarized Data

Patient Demographics/ Condition	Drugs Present in Compound	Suspected Cause of Adverse Event (SKRI-1; C-1-5)	
22y female; patient died after suspected single application of CPCs	Musculoskeletal + bupivicaine compound (no strength noted) No dosage instructions or possible side effects on the prescriptions	Drug toxicity	
14m male; accidental ingestion of grandmother's CPC (prescribed for diabetic foot pain)	Gabapentin 5%; lidocaine 5%; clonidine 2%; ketamine (nondocumented percentage); baclofen 0.4%	Misuse	
18m male; application of father's CPC (prescribed for neck pain) to treat diaper rash	Ketamine 100 mg; clonidine 2 mg; gabapentin 60 mg; mefenamic acid 10 mg; imipramine 30 mg; and lidocaine 10 mg	Misuse	
22m female; cream was prescribed to another family member for an unknown indication, accidental ingestion of CPC	The concomitant medications were ketoprofen, lidocaine, prilocaine, camphor, menthol, ethoxydiglycol, and gabapentin	Misuse	
26m male; accidental ingestion of his mother's CPC	Ketamine 10%, clonidine 0.2%, gabapentin 6%, diclofenac 5%, baclofen 2%, cyclobenzaprine 2%, menthol 1%, nifedipine 2%, and bupivacaine 1%	Misuse	
2y female; accidental dermal exposure	Pregabalin 2.5% (w/v), ketamine 10%, gabapentin 8%, and clonidine 0.3%	Misuse	

	Physical Response	Publication (If Available)
	Mother filed report to FDA after discovering her daughter's body. She suspects her daughter received the CPCs in the mail without a doctor's visit. According to autopsy report daughter died of toxic effects of ketamine and cyclobenzaprine.	N/A
	EMTs reported the boy had pinpoint pupils, was only responsive to painful stimulation, and had slow and inadequate respiration. He was put on an endotracheal intubation respirator. After several hours on the respirator he experienced bradycardia (HR 58 bpm). He was admitted to the pediatric ICU and weaned off of respiration and vasoactive support for 2 days before he was discharged.	Lucyk, S. N., L. S Nelson, R. S. Hoffman, M. A. Howland, and M. Su. 2014. Ingestion of compounded ointment leading to significant toxicity in a child. *Clinical Toxicology* 52(7):801.
	Within 20 minutes boy was unresponsive and gasping; was admitted to pediatric ICU and put on an endotracheal intubation respirator. Vital signs returned to normal over the next 12 hours. Blood taken returned with a serum clonidine level of 9.2 ng/mL (reference range, 0.5–4.5 ng/mL) and a norketamine level of 41 ng/mL (reporting limit, > 20 ng/mL). He was discharged the next morning.	Sullivan, R. W., M. Ryzewski, M. G. Holland, and J. M. Marraffa. 2013. Compounded ointment results in severe toxicity in a pediatric patient. *Pediatric Emergency Care* 29(11):1220–1222.
	In the ED the patient was noted to have intermittent excitation with altered level of consciousness (somnolent condition), followed by periods of apnea, a depressed gag reflex, miosis, and pale, warm, dry skin. An EKG after intubation revealed sinus bradycardia with a rate of 75 BPM, nonspecific T-wave inversions, and a first-degree block with a PR interval of 178 milliseconds with normal QRS and QTc durations. After the patient was transferred to a pediatric ICU her vital signs indicated that the patient was comatose. Fluid resuscitation and "meticulous supportive care" allowed the patient to be extubated after 14 hours and released without incident after 3 days.	Cates, A. L., S. M. Wheatley, and K. D. Katz. 2018. Clonidine overdose in a toddler due to accidental ingestion of a compounding cream. *Pediatric Emergency Care* 34(4):e79–e81.
	Patient developed hypotension and drowsiness but when given IV fluid his symptoms completely resolved overnight.	Henretig, F., et al. 2014. Toxicity from compounded analgesic creams. *Clinical Toxicology* 52(7):801–802.
	Became drowsy, once at the ER she became apneic and was intubated; patient was discharged within 24 hours.	Lange, R. 2017. Apnea in a child following dermal exposure to compounded pain cream. *Clinical Toxicology* 55(7):733.

continued

TABLE F-1
Continued

Patient Demographics/ Condition	Drugs Present in Compound	Suspected Cause of Adverse Event (SKRI-1; C-1-5)	
2y male; accidentally smeared his body with CPC	Nifedipine 2%, clonidine 0.2%, 10% ketamine, 5% diclofenac, baclofen 2%, gabapentin 6%, cyclobenzaprine 2%, menthol 1%, and bupivicaine 1%	Misuse	
22y female; over application of CPC, followed by wrapping area in plastic wrap	Lidocaine 10% and tetracaine 10%	Misuse	
23y male; over application of a CPC	Clonidine 0.2%, gabapentin 6%, imipramine 3%, ketamine 10%, lidocaine 2%, mefenamic acid 1%	Misuse	
34y female; intentional ingestion while on methadone	Bupivicaine 90 mg, clonidine 0.9 mg, cyclobenzaprine 90 mg, flurbiprofen 450 mg, and ketamine 450 mg	Misuse	
35y male; prescribed cream for relief of chronic pain, over application of CPC	Ketamine 900 mg; baclofen 900 mg; amitriptyline 360 mg; lidocaine 900 mg; and ketoprofen 1,800 mg	Misuse	
36y male; used expired CPC on his calf muscles	Neuromax pain cream (ketamine 15%, gabapentin 6%, clonidine 0.2%, prilocaine 7%, baclofen 3%, diclofenac 2%)	Misuse	

	Physical Response	Publication (If Available)
	A call came from a health care facility to Poison Control. Patient was brought in after he smeared three areas on his body with a topical pain cream; he was difficult to awaken with low BP and had very docile behavior. HR 130, BP 69/32, 12 lead EKG, improved with maintenance fluids to 110/59.	N/A
	Patient had progressive downward course with seizure, decreasing responsiveness, and gradual loss of brainstem reflexes, variability in BP and HR, and elevated intracranial pressure. CT scan showed evolution of severe profound cerebral edema. Patient was declared brain dead and removed from life support at a later date (dates are redacted). She then died.	Unknown
	Patient presented with HR 46 bpm, BP 180/87, respiratory rate 21 breaths/min., temperature 95.6; he had a decreased level of consciousness with response to painful stimuli, slurred speech, disorientation, mydriasis, and regular bradycardia. The patient spent 2 days in the hospital; at 6 month follow-up he had made a full recovery.	Pomerleau, A. C., et al. 2014. Dermal exposure to a compounded pain cream resulting in severely elevated clonidine concentration. *Journal of Medical Toxicology* 10(1):61–64.
	She was intubated for airway protection when she was brought to the ED. She awoke and was extubated the next day.	Henretig, F., et al. 2014. Toxicity from compounded analgesic creams. *Clinical Toxicology* 52(7):801–802.
	Over 2 hours patient lost all brainstem reflexes, and required intubation and mechanical ventilation for 2.5 days. He was discharged neurologically intact after 4 days.	Sigillito, R. J., V. E. Tuckler, K. W. Van Meter, and J. Martinez. 2003. Near fatal accidental transdermal overdose of compounded ketamine, baclofen, amitriptyline, lidocaine and ketoprofen: A case report. *Journal of Toxicology and Clinical Toxicology* 41(5):672.
	A short time after application he had an out of body experience, lost feeling in extremities, and passed out. Upon ER presentation he had limited brain stem reflexes but normal MRI; initial tests showed acute ischemic stroke secondary to basilar occlusion. 24 hours after admission patient woke up.	N/A

continued

TABLE F-1
Continued

Patient Demographics/ Condition	Drugs Present in Compound	Suspected Cause of Adverse Event (SKRI-1; C-1-5)	
58y female; prescribed for chronic neck pain and oral ulcers, purposeful overdose and misuse of CPC	Topical medication for chronic neck pain: amitriptyline 3%, baclofen 0.5%, diclofenac 3%, and lidocaine 5% 3 to 4 times daily as needed; and a topical lidocaine gel for oral ulcers	Misuse	
85y male; prescribed for severe intractable pruritus secondary to atopic dermatitis, over application of CPC	10% ketamine, 5% amitriptyline, and 5% lidocaine (KAL) compounded in a Lipoderm base	Misuse	
Adult (age unknown) female; accidental over application of CPC	Ketamine 3%, aloe 0.5%, amitriptyline 2%, baclofen 1%, estriol 0.1%, gabapentin 2%, lidocaine 2%	Misuse	
14y female; CPC prescribed for knee pain acerbated by running	5F diclofenac3, gabapentin, lidocaine	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
29y female; prescribed for oral mucosa for dental pain	Pentoxifylline 3%, diclofenac 3%, bupivacaine 1%, gabapentin 6%, baclofen 2%, ibuprofen 3%, ketamine 10%	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	

	Physical Response	Publication (If Available)
	She was using the cream twice as often as instructed on her neck and in her mouth since she had run out of the lidocaine gel prescribed for her oral ulcers. She presented with acute onset altered mental status from serotonin syndrome. 5 days after she stopped using the cream she returned to cognitive baseline. Serum nortriptyline/amitriptyline level that was drawn at 6 am on the second day was found elevated at 288 ng/mL (amitriptyline 231 ng/mL).	Ellison, C. 2017. Staying topical: An unusual case of serotonin syndrome. *Journal of Clinical Psychopharmacology* 37(5):633–635.
	A highly functioning man in his 80s with a history of Parkinson's disease presented to the ED with slurred speech, ataxia, and altered mental status (resulting in confirmation of toxic encephalopathy). Four days prior to presentation, his dermatologist prescribed several new medications to manage severe intractable pruritus secondary to atopic dermatitis. Over the ensuing 2 weeks on the inpatient service, the patients' mental status improved to baseline, and he was discharged on hospital day 17.	Cardis, M. 2016. Safety of topical neuromodulators for the treatment of pruritus. *JAMA Dermatology* 152(12):1390–1391.
	Patient was instructed to apply CPC to vulvar area 3 times daily, but accidentally applied full 3 ml syringe intravaginally prior to reading the instructions. She was instructed to go to the ER but declined. She said she never felt anything other than a little sedated.	N/A
	Area of application became swollen, formed hives, and extremely painful.	N/A
	Presented to the ER with seizure-like activity (rhythmic shaking of her arms and legs), testing revealed a nonanion gap metabolic acidosis, and EEG demonstrated nonspecific findings consistent with toxic metabolic encephalopathy. A comprehensive urine drug screen demonstrated the presence of propofol, caffeine, topiramate, doxepin, ibuprofen, lidocaine, baclofen, and ketamine. Observed uneventfully and released on day 4.	Swartzentruber, G. S., et al. 2014. Inappropriate application of compounded topical pain medication cream leading to significant neurotoxicity. *Clinical Toxicology* 52(7):692–693.

continued

TABLE F-1
Continued

Patient Demographics/ Condition	Drugs Present in Compound	Suspected Cause of Adverse Event (SKRI-1; C-1-5)	
33y female; prescribed for SI joint area pain	Ketoprofen 10%, baclofen 5%, gabapentin 5%, Keta 5%	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
37y female; CPC used to numb area prior to a skin treatment	Benzocaine 20%, lidocaine 6%, tetracaine 4%	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
37y female; prescribed CPC for shoulder pain	Compounded cream bupi/clon/doxe/gaba/pent (1-K) 1/0.2/5/6/3%	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
39y male	Amantadine 10%, ibuprofen 20%, dexamethasone 0.4%, lidocaine 1%	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
44y female; applied CPC cream in gynecologist office to numb reddened, broken, inflamed skin	Benzocaine, tetracaine, lidocaine (no strengths given)	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	

	Physical Response	Publication (If Available)
	After first application patient could not straighten leg, could not walk, and experienced very painful nerve twitching on the inner part of right leg. The twitching lasted about 1.5 days, completely resolved on day 3.	N/A
	About 10–20 minutes after application patient felt burning on leg and then chest tightening and difficulty breathing. Fingers and hands turned blue and patient became chilled.	N/A
	After first week pain subsided; however, rash appeared. Patient talked with pharmacists who said the rash may be due to DMSO in the cream.	N/A
	Patient experienced a bruise-like purple discoloration to the skin in the maxillary region of the body, which tingled and burned. When patient attempted to self-medicate with aloe vera, further irritation occurred.	N/A
	Within 5 minutes of application patient experienced tachycardia, diaphoresis, and chest pressure; after 15 minutes, abnormal involuntary movements with spasms including neck and jaw. Observed in doctor's office for more than 2 hours then transferred to the ER where benzodiazepine was given IV and symptoms alleviated but returned the next day and progressively worsened. Out of work for 6 months, still has occasional twitches and spasms, but mostly resolved 2 years later.	N/A

continued

TABLE F-1
Continued

Patient Demographics/ Condition	Drugs Present in Compound	Suspected Cause of Adverse Event (SKRI-1; C-1-5)	
48y male; prescribed CPC for frozen shoulder	Baclofen 2%, cyclobenzaprine 2%, diclofenac 3%, gabapentin 6%, bupivacaine 2% in a Versapro cream base	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
49y female; prescribed CPC for chronic pain in ankles, knees, wrists, hands, shoulder, and neck	Diclofenac 5%, baclofen 2%, cyclobenzaprine 2%, bupivacaine 1%, lidocaine 5%, prilocaine 2.5%, imipramine 3%	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
50y female; prescribed cream for tarsal tunnel syndrome in both feet	Concentrations/ingredients are unknown, compound was called Jonas Neuropathy Cream #3	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
54y male; applied anesthetic CPC prior to ablative laser therapy	23% lidocaine and 7% tetracaine mixed in ointment base	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
57y female; used CPC numbing cream prior to skin tag removal procedure	Lidocaine and benzocaine (strength not given)	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	

	Physical Response	Publication (If Available)
	Patient applied 1–2 grams of pain cream to shoulder for 10 days, four times per day, then noticed rash/hives develop on shoulder. Hives spread from shoulder to top of neck down to wrist on right side.	N/A
	After application pain in shoulder increased, face became flushed, red, and swollen, felt disoriented, and she had trouble breathing. Event abated after use stopped.	N/A
	After 1 week of applying CPC three times per day, resulted in dizziness, nausea, vomiting, and inability to get out of bed. After she stopped using the cream her symptoms have improved but she is still in pain and unable to work.	Unknown
	Immediately after application of cream the patient developed a diffuse eruption of vesicles and bullae (ranging in size from 1 to 15 mm) on a well-demarcated erythematous base. The lesions resolved after less than 1 week with gentle skin care. Patient developed postinflammatory hyperpigmentation, which faded over 2 months.	Alok, V., and R. Markus. 2011. Immediate vesicular eruption caused by topical 23% lidocaine 7% tetracaine ointment in a patient scheduled for laser therapy: A new adverse drug reaction. *Journal of Cosmetic Dermatology* 10:307–310.
	Patient experienced red ulcerating nodules and was very itchy where cream was applied for about 1 week. Full recovery in about 1 month.	N/A

continued

TABLE F-1
Continued

Patient Demographics/ Condition	Drugs Present in Compound	Suspected Cause of Adverse Event (SKRI-1; C-1-5)	
58y male; prescribed CPC for tennis elbow	Diclofenac 3%, baclofen 2%, cyclobenzaprine 2%, lidocaine 2%	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
Late 50s/early 60s female; prescribed CPC for joint damage	Ingredient amounts were not listed on label, ketoprofen, lidocaine, and hydrocodone in a Van-Pen base	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; suboptimal compounded preparations) Inadequate labeling	
63y male; prescribed CPC for pain from degenerative disk disease in his neck	Compounded cream #180 GM keta/bupi/dicl/doxe/gaba/pent (7) 10/1/3/3/6/5	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
65y female; prescribed CPC for rectal pain (included rectal tenesmus, burning and nerve pain)	XYREM (500 mg/ml solution) sodium oxybate, baclofen,	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
66y female; CPC prescribed for pain in foot	Baclofen 2%, diclofenac 5%, gabapentin 6%, tetracaine 3%	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	

	Physical Response	Publication (If Available)
	He only used the cream three times before he experienced an irregular heartbeat. The tachycardia continued for about 10.5 hours.	N/A
	After three applications pain became worse and spread to other joints. Patient experienced edema in lower legs and knees, with stasis pigmentation, coldness in her legs, and abnormal sensations in her hands. These symptoms persist to a lesser extent after she stopped using the cream.	N/A
	After using the cream for more than 2 weeks patient described the skin on his neck becoming bright red and dried out as though sunburned.	N/A
	After application of the cream she developed a rash that spread and she reported urinating blood.	N/A
	After 3 days of use patient started seeing small blood like blisters. On the fourth day it has progressed to a rash full of blisters and she stopped using the cream. Severe swelling with hives, deep blisters, and darkening (blackening) of toes and side of outer foot. Condition improved after patient stopped applying the cream but she is still having some swelling, peeling, and itching 1 month later.	N/A

continued

TABLE F-1
Continued

Patient Demographics/ Condition	Drugs Present in Compound	Suspected Cause of Adverse Event (SKRI-1; C-1-5)	
66y male; CPC prescribed for nerve pain in feet	BENZ20%LIDO6%TETR4%PLO (K)	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
66y male; prescribed for CPC for tendonitis of left foot to be applied four times/day	120 Gm CMP DBCT Lipoderm	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
70y female; prescribed for idiopathic itching, rash, shingles, and neuralgia	Compounded cream (gabapentin/lidocaine/ clonidine/ketamine topical cream, percentages or mg of each API not given), patient was also taking the following oral medications: neurontin (gabapentin) 100 mg per day increased to 200 mg, and ibuprofen 200 mg. During this time the patient was also taking paracetamol (Norco 5/325 mg), cephalexin monohydrate (Keflex 250 mg), and using Neosporin (bacitracin zin, neomycin sulfate, polymixin b sulfate, 800 mg) daily	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
72y female; condition unknown	Emla cream—topiramate 2.5%, meloxicam 0.09%, in a base of Lidocaine 2.5%, Prilocaine 2.5%	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	

	Physical Response	Publication (If Available)
	Patient experienced chemical burns to foot skin.	N/A
	After 6 days the patient noticed his foot skin looked like it had undergone a bad chemical burn but without pain, areas ranged from red to purple with some blistering and peeling.	N/A
	The patient began taking gabapentin (Neurontin), ibuprofen, and applying the compounded cream 2–4 times per day for postherpetic neuralgia. She doubled the amount of Neurontin at the advice of her pharmacist and initially it worked but left her feeling dizzy and weak. The pain relief did not last and she developed abdominal pain. The outcome of these events was not recovered.	N/A
	Allergic response to lidocaine, leg skin redness and blistering; patient was advised to stop using the cream.	N/A

continued

TABLE F-1
Continued

Patient Demographics/ Condition	Drugs Present in Compound	Suspected Cause of Adverse Event (SKRI-1; C-1-5)	
74y female; prescribed cream to be applied perivaginally for chronic pelvis neuritis with vaginal pruritus; patient had 2-year history of Alzheimer's dementia	6% gabapentin, 10% ketamine, 10% ketoprofen, 3% lidocaine, and 0.6% clonidine	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	
75y male; prescribed cream containing gabapentin for pain after a lumbar discectomy procedure, to be applied to his entire back and left lower extremity three times daily	10% ketamine, 3% imipramine, 2% lidocaine, 1% mefenamic acid, 0.2% clonidine, gabapentin (unknown dose)	Reaction due to unknown cause (e.g., allergy to the API or excipient; drug–drug interactions; systemic toxicity; suboptimal compounded preparations)	

NOTE: API = active pharmaceutical ingredient; BP = blood pressure; bpm = beats per minute; CPC = compounded pain cream; CT = computed tomography; DMSO = dimethyl sulfoxide; ED = emergency department; EEG = electroencephalogram; EKG = electrocardiogram; EMT = emergency medical technician; ER = emergency room; FDA = U.S. Food and Drug Administration; HR = heart rate; ICU = intensive care unit; IV = intravenous; intravenously; KAL = ketamine, amitriptyline, and lidocaine; MRI = magnetic resonance imaging; PR = a PR interval in electrocardiography is the measure of time in milliseconds between the onset of atrial depolarization and the onset of ventricular depolarization; QRS = a QRS complex is the combination of three of the graphical deflections seen on a typical electrocardiogram (the Q, R, and S waves); QTc = corrected QT interval; a QT interval is a measurement made on a electrocardiogram used to assess some of the electrical properties of the heart; SI = sacroiliac.

Considerations for data extracted from the FAERS database:

These adverse event reports were identified in the FAERS database by the study sponsor, FDA. FDA identified 38 adverse events reports that relate to the use of a compounded topical drug by reading through report descriptions of all entries marked as *compounded*. It is important to note that there may be other FAERS cases related to the use of a compounded topical drugs, but if the necessary indication box for *compounded* mediations was not checked during the data entry process, then those cases would not be represented in the full dataset.

For full submitted data please see the Public Access File for the Committee on the Assessment of the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain Creams at the National Academies website at https://www8.nationalacademies.org/pa/managerequest.aspx?key=HMD-HSP-18-18 (accessed April 9, 2020).

	Physical Response	Publication (If Available)
	Within the first 2 weeks of cream use, her behavior became increasingly erratic prompting a visit to primary care. Believing that her unusual behavior and altered mental status was a consequence of dementia, both risperidone and lorazepam were prescribed. Six days later, she applied the cream over her upper body, arms, perineum, and vulva. She soon became markedly agitated, expressing homicidal ideation toward her husband by burning down the house, and suicidal ideation.	Soumoff, A. A., D. L. Cook, and C. C. Clark. 2018. Delirium following topical application of compounded creams containing multiple analgesic medications in geriatric patients: Two new cases. *Psychosomatics* 59(1):81–89.
	From onset of cream use, he had an altered mental status and delirium. He became increasingly angry and paranoid with decreased need for sleep. During hospital week 1, despite discontinuation of the cream, he frequently became hostile and combative. Over the last few days of his 13-day hospitalization, his mental status and behavior returned to baseline with no cognitive deficits.	Soumoff, A. A., D. L. Cook, and C. C. Clark. 2018. Delirium following topical application of compounded creams containing multiple analgesic medications in geriatric patients: Two new cases. *Psychosomatics* 59:81–89.

Appendix G

Potential Adverse Effects from Oral Administration of 20 Active Pharmaceutical Ingredients Commonly Used in Compounded Topical Pain Creams

As discussed in Chapter 6, evidence is inadequate to quantify the extent to which the active pharmaceutical ingredients (APIs) reviewed in this report are absorbed and present at local, regional, or systemic levels. Given the limited data, little is known regarding the relative risk for adverse effects caused by systemic absorption. To consider the potential safety concerns for the systemic absorption of APIs in this report, below is a summarized list of the known adverse events derived from the U.S. Food and Drug Administration (FDA)-approved product labels and data derived from Micromedex, a pharmaceutical database resource.

TABLE G-1
Adverse Events Associated with Systemic Absorption of Active Pharmaceutical Ingredients Used in Compounded Topical Pain Creams

Drug Product	Formulation(s)	Drug Class	FDA-Approved Pain Indications	Off-Label/Non-FDA Uses for Pain	
Amitriptyline	Oral	Tricyclic antidepressants	None	Fibromyalgia, postherpertic neuralgia	
Baclofen	Oral, intrathecal	Skeletal muscle relaxant	Muscle spasms	Trigeminal neuralgia, peripheral neuropathy	
Bupivacaine	Injection	Local anesthetic	None	Pain	
Cannabidiol	Oral	Cannabinoid	None	None	
Carbamezapine	Oral	Anticonvulsants	Trigeminal neuralgia	None	
Clonidine	Transdermal	Alpha-2 adrenergic agonist	None	None	
Clonidine HCl	Epidural, oral	Alpha-2 adrenergic agonist	None	Muscle spasms	
Cyclobenzaprine	Oral	Skeletal muscle relaxant	Skeletal muscle spasm	Fibromyalgia	
Dexamethasone	Oral, ophthalmic, injection	Adrenal corticosteroid	None	None	
Doxepin	Oral, topical	Tricyclic antidepressants	None	Chronic pain	
Gabapentin	Oral, topical	Anticonvulsants	Postherpetic neuralgia	Fibromyalgia, diabetic peripheral neuropathy	

	Example Adverse Effects from FDA-Approved Label	Example Adverse Effects from Micromedex (2019)
	Cardiovascular, the CNS and neuromuscular, anticholinergic, allergic, hematologic, gastrointestinal, and endocrine adverse reactions (Sandoz, 2014)	Black box warning for increased suicidal thoughts; cardiac arrhythmias
	Drowsiness, dizziness, and weakness (Metacel Pharmaceuticals, 2019)	Gastrointestinal bleeding
	Excitation and/or depression of the CNS system as well as cardiovascular adverse reactions (Pfizer, 2012)	Cardiac arrest, respiratory depression
	Somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, malaise, asthenia, rash, sleep disorders, and infections (GW Pharmaceuticals, 2018)	Increased suicidal thoughts; increased liver enzymes
	Dizziness, drowsiness, unsteadiness, nausea, and vomiting adverse reactions. The most severe reactions observed have been in the hemopoietic system, skin, liver, and cardiovascular system (Novartis, 2009)	Stevens-Johnson syndrome, toxic epidermal necrolysis, atrioventricular block, syncope, liver failure
	Dry mouth, drowsiness, fatigue, headache, lethargy, and sedation (Boehringer Ingelheim Pharmaceuticals, 2011)	Atrioventricular block
	Dry mouth, drowsiness, dizziness, constipation, and sedation (Boehringer Ingelheim Pharmaceuticals, 2009)	Atrioventricular block
	Drowsiness, dry mouth, fatigue, and headache (McNeil Consumer Healthcare, 2013)	Cardiac dysrhythmia, heart block, myocardial infarction, syncope
	Allergic reactions, cardiovascular, dermatologic, endocrine, fluid and electrolyte disturbances, gastrointestinal, metabolic, musculoskeletal, neurological/psychiatric, and ophthalmic adverse reactions (Fera Pharmaceuticals, 2004)	Cardiomyopathy, hyperglycemia, pancreatitis
	Burning/stinging at the site of application, drowsiness, dry mouth, pruritus, and fatigue (Bioglan Pharma, 2002)	Ventricular arrhythmia, thrombocytopenia, suicidal thoughts, kidney damage
	Dizziness, somnolence, and peripheral edema (Pfizer, 2010a)	Stevens-Johnson syndrome

continued

TABLE G-1
Continued

Drug Product	Formulation(s)	Drug Class	FDA-Approved Pain Indications	Off-Label/Non-FDA Uses for Pain	
Ketamine	IV, IM	Local anesthesia	None	Acute pain	
Lidocaine	Rectal, topical	Local anesthetic	Postherpetic neuralgia	Diabetic neuropathy, acute pain	
Meloxicam	Oral	NSAID	Osteoarthritis, rheumatoid arthritis	None	
Memantine	Oral	NMDA receptor antagonist	None	None	
Naproxen	Oral	NSAID	Rheumatoid arthritis, osteoarthritis	None	
Nifedipine	Oral	Calcium channel blocker	None	None	
Orphenadrine	Injection, oral	Skeletal muscle relaxant	Musculoskeletal pain	None	
Pentoxyifyline	Oral	Vasoactive phosphodiesterase inhibitor	None	None	
Topiramate	Oral	Anticonvulsants	Migraine prophylaxis	None	
Tramadol	Oral	Opioid agonist	Chronic pain	Cancer pain	

NOTE: CNS = central nervous system; FDA = U.S. Food and Drug Administration; HCl = hydrochloride; IM = intramuscular; IV = intravenous; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug; REMS = Risk Evaluation and Mitigation Strategy.

	Example Adverse Effects from FDA-Approved Label	Example Adverse Effects from Micromedex (2019)
	Cardiovascular, respiratory, ocular, genitourinary, psychological, neurological, and gastrointestinal adverse reactions (JHP Pharmaceuticals, 2012)	Bradyarrhythmia, cardiac dysrhythmia, respiratory depression
	Application site reactions such as irritation, erythema, and pruritus (Scilex Pharmaceuticals, Inc., 2018)	
	Diarrhea, upper respiratory tract infections, dyspepsia, and influenza-like symptoms (Boehringer Ingelheim Pharmaceuticals, 2012)	Black box warning for increased risk of cardiovascular events, gastrointestinal bleeding and ulceration
	Dizziness, headaches, confusion, and gastrointestinal adverse effects (Forest Pharmaceuticals, 2013)	Cerebrovascular accident, seizures, kidney failure
	Gastrointestinal, the CNS, dermatologic, cardiovascular and special senses disturbances (visual and hearing) adverse reactions (Roche, 2007)	Black box warning for increased risk of cardiovascular events, gastrointestinal bleeding and ulceration
	Peripheral edema, headache, dizziness, fatigue, nausea, and constipation adverse reactions (Bayer Healthcare, 2011; Pfizer, 2010b)	Myocardial infarction, ventricular arrhythmia, suicidal thoughts, kidney damage
	Dry mouth, tachycardia, palpitation, urinary hesitancy or retention, and blurred vision (3M Pharmaceuticals, 2006)	Palpitations, tachyarrhythmia
	Cardiovascular, digestive, and nervous system adverse reactions (Validus Pharmaceuticals, LLC, 2016)	Thrombocytopenia
	Paresthesia, anorexia, and weight loss (Janssen Pharmaceuticals, Inc., 2017)	Dermatologic: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
	Constipation, nausea, dizziness, and headache (Johnson & Johnson, 2009)	Black box warning for addiction, abuse, misuse. Required REMS by FDA. Respiratory depression, accidental ingestion, sedation, coma, and death if used with benzodiazepines or alcohol

TABLE G-2
Potential Drug–Drug Interactions for Select APIs (Oral Administration)

Drug Product	Potentially Major or Life-Threatening Drug–Drug Interactions
Amitriptilyne	Concurrent use of NSAIDS and TRICYCLIC ANTIDEPRESSANTS may result in an increased risk of bleeding. Concurrent use of CYCLOBENZAPRINE and TRYCYCLIC ANTIDEPRESSANTS may result in increased risk of serotonin syndrome.
Baclofen	Concurrent use of TRAMADOL and CNS DEPRESSANTS may result in an increased risk of respiratory and CNS depression.
Carbamazepine	Concurrent use of TRAMADOL and SEROTONERGIC CYP3A4 INDUCERS may result in increased risk of serotonin syndrome and reduced TRAMADOL plasma concentrations.
Clonidine	Concurrent use of DOXEPIN and CLONIDINE may result in decreased antihypersensitive effectiveness.
Clonidine HCl	Concurrent use of DOXEPIN and CLONIDINE may result in decreased antihypersensitive effectiveness.
Cyclobenzaprine	Concurrent use of CYCLOBENZAPRINE and TRICYCLIC ANTIDEPRESSANTS may result in an increased serotonin syndrome. Concurrent use of CYCLOBENZAPRINE and TRAMADOL may result in an increased risk of respiratory and CNS depression; increased risk of serotonin syndrome; and an increased risk of paralytic ileus.
Dexamethasone	Concurrent use of CORTICOSTEROIDS and NSAIDS may result in an increased risk of gastrointesinal ulcer or bleeding.
Doxepin	Concurrent use of NSAIDS and TRICYCLIC ANTIDEPRESSANTS may result in an increased risk of bleeding. Concurrent use of TRAMADOL and SEROTONERGIC AGENTS WITH ANTICHOLINGERIC PROPERTIES may result in increased risk of paralytic ileus and increased risk of serotonin syndrome.
Ketamine	Concurrent use of TRAMADOL and CNS DEPRESSANTS may result in an increased risk of respiratory and CNS depression.
Meloxicam	Concurrent use of MELOXICAM and NSAIDS AND SALICYLATES may result in increased risk of bleeding. Concurrent use of NSAIDS and TRICYCLIC ANTIDEPRESSANTS may result in an increased risk of bleeding.
Memantine	Concurrent use of MEMANTINE and SELECTED N-METHYL-D-ASPARATE ANTAGONISTS may result in increased adverse events of N-methyl-D-asperate agonists.
Naproxen	Concurrent use of NSAIDS and TRICYCLIC ANTIDEPRESSANTS may result in an increased risk of bleeding. Concurrent use of CORTICOSTEROIDS and NSAIDS may result in increased risk of gastroinstestinal ulcer or bleeding.
Nifedipine	Concurrent use of NIFEDIPINE and CYP3A4 INDUCERS may result in decreased NIFEDIPINE exposure.
Orphenadrine	Concurrent use of TRAMADOL and CNS DEPRESSANTS may result in an increased risk of paralytic ileus; increased risk of respiratory and CNS depression.

TABLE G-2
Continued

Drug Product	Potentially Major or Life-Threatening Drug–Drug Interactions
Pentoxyfilline	Concurrent use of PENTOXYFILLINE and NSAIDS may result in an increased risk of bleeding.
Topiramate	Concurrent use of TRAMADOL and CNS DEPRESSANTS may result in an increased risk of respiratory and CNS depression.
Tramadol	Concurrent use of TRAMADOL and CNS DEPRESSANTS may result in an increased risk of respiratory and CNS depression.

NOTE: CNS = central nervous system; NSAIDS = nonsteroidal anti-inflammatory drugs.

SOURCE: Micromedex, 2019.

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Appendix H

Expanded Discussion on Special Populations to Consider in Pain Management

ELDERLY AND PEDIATRIC POPULATIONS

Overall findings from the pain research field suggest that pain experienced by pediatric and geriatric populations is understudied and often inadequately managed. Estimates suggest that more than half of older adults in the United States experience regular bothersome pain (Kaye et al., 2010; Patel et al., 2013). Similarly, pediatric studies suggest that up to one-third of children and young people experience chronic or recurrent pain that is often underrecognized and undertreated (King et al., 2011; McCarthy and Rastogi, 2017).[1]

Certain U.S. Food and Drug Administration–approved pain products may be unsuitable for elderly or pediatric patients—individuals who may have difficulty swallowing oral medications and/or who lack the muscle mass to receive frequent injections (Liu et al., 2014). In addition, the functionality of organ systems (either in developing or aging patients) and the absorption profiles of skin are of great relevance, and a simple extrapolation of pharmacokinetic or pharmacodynamics data from healthy adults is likely to be inadequate. As a result, pain management plans for these populations tend to be more complex and may result in suboptimal treatments.

Adding complexity to the situation, pain products formulated for adults may not be appropriate in infants and children who have sensitivities or allergies, or who need more palatable or age-appropriate formulations

[1] Evaluating and managing pain is particularly challenging in neonates, in preverbal children, and in children with complex neurodevelopmental needs (Quinn et al., 2018).

(Berde et al., 2012; Liu et al., 2014; McBane et al., 2019; O'Donnell and Rosen, 2014). Elderly patients who have comorbidities that require polypharmacy further complicates health providers' efforts to effectively and appropriately treat their pain (Borsheski and Johnson, 2014).[2] Importantly, the prevalence of chronic pain is likely to increase as Americans live longer, which may profoundly affect morbidity and health care expenditures,[3] and although pain management is a critical part of palliative care, studies suggest that pain experienced by people at end of life is often inadequately assessed and treated (IOM, 2011; Wilkie and Ezenwa, 2012).

GENDER, RACE, AND ETHNICITY

The experience of pain and the quality of pain management are also shaped by sociodemographic factors of gender, race, and ethnicity (Mossey, 2011). In the United States, women and racial and ethnic minorities report more pain complaints than men (Dahlhamer et al., 2018; Mansfield et al., 2016) and experience chronic illnesses (e.g., diabetes, cancer) associated with chronic pain, aging, and disability more frequently and at an earlier age than their White male counterparts. Women who are pregnant commonly experience chronic pain, but the evidence-based guidance on how to best provide safe and effective pain management in pregnant women is understudied, as is the potential effect on their unborn children (Ray-Griffith et al., 2018; Shah et al., 2015). To complicate matters further, gender differences in response to analgesics suggest that biological, sociocultural, and psychological mechanisms underline those differences.

Racial and ethnic minorities who experience certain chronic illnesses associated with chronic pain are more likely to have poorer overall access to primary care and are less likely to be referred for specialty pain care, as compared to nonminority patients (Ezenwa and Fleming, 2012). When their pain is assessed, women and patients of color received less medication for pain (including opioids) and suboptimal pain care in all clinical settings (Green et al., 2003, 2005). Variability in clinicians' attitudes toward women and racial/ethnic minorities are suggested to reflect clinicians' implicit, conscious, and unconscious biases that further complicate pain therapy for those groups (Green et al., 2003; Hoffman et al., 2016).

[2] Older adults commonly experience pain caused by health conditions associated with aging, such as musculoskeletal conditions, Parkinson's disease, Alzheimer's disease, cancer, joint surgeries, compression fractures, and advanced chronic diseases such as end-stage renal disease (Husebo et al., 2016; Smith et al., 2010).

[3] The prevalence of chronic pain will increase as the global population ages, driving increases in morbidity and health care expenditures. For example, by 2030, the number of hip and knee replacements is expected to grow by 174 percent (572,000 procedures) and by 673 percent (3.48 million procedures), respectively (Kurtz et al., 2007).

ADDITIONAL SUBPOPULATIONS

In addition to the patient populations listed above, there are additional subpopulations who may also experience disparities in accessing quality pain care, pain assessment, pain treatment, or outcomes of care. For example, many patients living in underserved communities (e.g., rural or urban areas) receive their care in the primary care arena and may have difficulty accessing specialized multidisciplinary and multimodal pain care (Eaton et al., 2018). The potential absence of health services, health care insurance, and other resources (e.g., wealth, positive social support), as well as the potential presence of specific stressors (e.g., social roles, comorbidities), can influence health care access and use, quality of care, and short- and long-term health outcomes (Leeds et al., 2017; Nguyen et al., 2005).

Managing chronic and acute pain experienced by people with current or prior substance use disorder can be challenging because of both the patients' attitudes and providers' practical and ethical concerns related to addiction and drug-seeking behavior (Cheatle et al., 2014). Other populations that may have more complex management pain plans include patients with an increased risk of kidney-related complications, or individuals with spinal cord injuries, patients with cognitive disorders (e.g., Alzheimer's), military veterans, or individuals for which English is not their first language (Davison, 2019; Hama and Sagen, 2012; IOM, 2011; NASEM, 2017).

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Appendix I

Biographical Sketches for Committee Members, Fellow, Consultants, and Staff

COMMITTEE

Debra A. Schwinn, M.D. (*Chair*), is a professor of anesthesiology, pharmacology, and biochemistry at the University of Iowa (UI). She served as the dean of the UI Carver College of Medicine (2012–2016), the associate vice president for medical affairs at UI (2016–2019), and is currently the president-elect of Palm Beach Atlantic University (2020). Dr. Schwinn is a member of the National Academy of Medicine and Association of American Physicians, the past chair of the Board of Trustees of the International Anesthesiology Research Foundation, and the past chair of the Sarnoff Cardiovascular Research Foundation Board of Directors. Her molecular pharmacology laboratory focused on mechanisms underlying alpha1-adrenergic receptor regulation and modulation in cardiovascular disease, including the biological effects of genetic variants of these stress receptors. In parallel, over the past few decades, her clinical studies have focused on perioperative genomics, a relatively new field aimed at identifying genetic variants that predict increased risk for perioperative adverse events. Prior to moving to UI in 2012, Dr. Schwinn was a professor and the chair of anesthesiology and pain medicine, the Allan J. Treuer Endowed Professor in Anesthesiology, and an adjunct professor of pharmacology and genome sciences at the University of Washington in Seattle. Prior to that period, she spent her entire career at the Duke University Medical Center. Dr. Schwinn served for many years on the National Institutes of Health (NIH) National Institute of General Medical Sciences advisory council and the external advisory board for the NIH Pharmacogenomics Research Network.

Stephen Byrn, Ph.D., is the Charles B. Jordan Professor of Medicinal Chemistry in the Department of Industrial and Physical Pharmacy at Purdue University in West Lafayette, Indiana. Dr. Byrn set in motion the development of the field of solid state chemistry of drugs with his books, short courses, and papers on the subject, the first of which were first published in the mid-1970s. He has also educated more than 50 Ph.D. students and postdoctoral fellows and taught a wide range of courses at Purdue. Dr. Byrn has had numerous grants, including one of the first 13 National Institutes of Health Centers for AIDS Research. Dr. Byrn is the co-founder of Purdue's graduate programs in regulatory and quality compliance. These programs now constitute the Biotechnology Innovation and Regulatory Science MS program. He is also the co-founder of the Purdue-Kilimanjaro School of Pharmacy Sustainable Medicines in Africa project in Moshi, Tanzania. Dr. Byrn has served as the chair of the Pharmaceutical Sciences Advisory Committee to the U.S. Food and Drug Administration and chaired several United States Pharmacopeia committees. Dr. Byrn is also the co-founder of Solid State Chemical Information, Inc. (SSCI), a cGMP research and information company. SSCI, Inc. is now owned by Albany Molecular Research Inc. Dr. Byrn has taught a range of courses and short courses involving medicinal chemistry, industrial pharmacy, physical pharmacy, and solid state chemistry. Dr. Byrn is an elected fellow of the American Association of Pharmaceutical Scientists (AAPS) and has received several awards for his research and entrepreneurial activities including the AAPS David Grant Award for Research Achievement and the AAPS Wurster award in pharmaceutics and formulation. Dr. Byrn also received the Purdue University Morrill Award.

Diana D. Cardenas, M.D., M.H.A., is a professor and the chair emeritus of the Department of Physical Medicine and Rehabilitation at the University of Miami Miller School of Medicine. She has years of experience with the Spinal Cord Injury (SCI) Model Systems, a program sponsored by the National Institute on Disability, Independent Living, and Rehabilitation Research, having served as the principal investigator (PI) of the SCI Model System in Seattle from 1990 to 2006, as well as for the South Florida SCI Model System (2011–2015). Her research focus is pain and other secondary conditions of SCI. She is the vice president of the Foundation for Physical Medicine and Rehabilitation, which fosters rehabilitation research. She was elected to the National Academy of Medicine in 2004. A 1969 graduate of The University of Texas at Austin, Dr. Cardenas earned her medical degree at The University of Texas Southwestern Medical School in Dallas in 1973. She completed her internship and residency in physical medicine and rehabilitation medicine at the University of Washington (UW) in 1976, and joined the UW faculty in 1981. She was the clinical director of the UW Medical Center's Spinal Cord Injury Service, and director of the UW

Rehabilitation Medicine Spinal Cord Injury Clinic. In 2001 she earned a master's degree in health administration from UW. In 2006 she was recruited to the University of Miami Miller School of Medicine as the founding chair of the Department of Physical Medicine and Rehabilitation where she served until her retirement in 2015. She continued to conduct research in pain as the co-PI of the South Florida SCI Model System until 2019. She is widely published and is the recipient of the 2020 American Spinal Injury Association Lifetime Achievement Award.

Barbara Insley Crouch, Pharm.D., is the executive director of the Utah Poison Control Center (UPCC). She has been the director of the UPCC since 1992. She holds a bachelor's degree in pharmacy from the Philadelphia College of Pharmacy and Science, a master of science in public health from the University of Utah, and a doctor of pharmacy jointly administered by The University of Texas at Austin and The University of Texas Health Science Center at San Antonio. She completed a clinical toxicology fellowship at the University of Maryland School of Pharmacy and Maryland Poison Center. She held faculty positions at the University of California, San Francisco, School of Pharmacy and the Philadelphia College of Pharmacy and Science prior to joining the University of Utah in 1990. Her primary academic appointment is a professor (clinical) in the Department of Pharmacotherapy, College of Pharmacy. She established a 2-year fellowship in clinical and applied toxicology for doctor of pharmacy graduates. Her research interests include the epidemiology of poisonings and facilitation of communication to improve patient care.

Edmund J. Elder, Ph.D., R.Ph., is the director of the Zeeh Pharmaceutical Experiment Station in the School of Pharmacy at the University of Wisconsin–Madison (UW). Dr. Elder obtained 16 years of experience in the pharmaceutical and drug delivery industry prior to joining UW in 2006. As the director of the station, he is responsible for providing pharmaceutical and biopharmaceutical research and development support and educational programs for researchers, both on and off campus. Dr. Elder also serves as the scientific advisor to the U.S. Food and Drug Administration Regulated Research Oversight Committee in the UW Institute for Clinical and Translation Research (ICTR) and serves as the chemistry, manufacturing, and controls advisor for the ICTR Investigational New Drug/Investigational Device Exemption Consultation Service, which provides support for campus researchers pursuing regulatory filings related to their clinical research. Dr. Elder also holds appointments as an affiliate in the Pharmaceutical Sciences Division at the UW School of Pharmacy and is the course director for Biotechnology Operations in the MS in Biotechnology Program at the UW School of Medicine and Public Health.

John T. Farrar, M.D., Ph.D., has been involved in clinical research for more than 25 years, with a major focus on the study of the efficacy of pain therapeutics and on novel methodology in the design and execution of clinical trials. As a neurologist and a pharmacoepidemiologist, he has been involved in numerous studies including randomized controlled trials (RCTs), cohort studies, and methodologic studies of pain and associated symptoms such as fatigue, depression, and quality of life in clinical research and practice. His research has been funded by the National Institutes of Health, the U.S. Food and Drug Administration (FDA), private foundations, and industry sources. Currently, he is the principal investigator of an FDA-funded contract to use large datasets to study the relative efficacy of acute drug treatments for pain and the HEAL Initiative Early Phase Pain Investigation Clinical Network Clinical Specialty site. He also directs the evaluation component of the University of Pennsylvania's current Clinical and Translational Science Award, and is a collaborator with the data coordinating center for the U54 multicenter Multidisciplinary Approach to the Study of Chronic Pelvic Pain study and the Hemodialysis Opioid Prescription Effort study. Nationally he has served as a member and the chair of the Anesthetic and Life Support Drugs Advisory Board for FDA, on the National Research Council Panel on Handling Missing Data in Clinical Trials, and on the Institute of Medicine Committee on Advancing Pain Research, Care, and Education. He also serves as an associate editor for the journal *Pharmacoepidemiology and Drug Safety*. At the University of Pennsylvania Perelman School of Medicine, he has co-directed the Biostatistical Analysis Center and the Master of Science in Clinical Epidemiology program for more than 10 years. In addition, he continues to see pain patients, predominately in a palliative care setting.

Carmen Green, M.D., is a tenured professor of anesthesiology with joint appointments in the Medical School's Department of Obstetrics and Gynecology and the Department of Health Management and Policy in the School of Public Health at the University of Michigan. She was co-director for the Community Liaison Core and the director of the Healthier Black Elders Center for the Michigan Center for Urban African American Aging Research at the University of Michigan Institute for Social Research. Her research focuses on pain management outcomes, physician decision making, and access to care, and she has documented disparities due to age, race, gender, and class across the life span as well as disparities in hospital security being called for Black patients and their visitors. She has also found community-based structural barriers to health and pain care, including clear disparities in access to pain medication for Blacks, women, and low-income individuals with chronic pain. Her leadership in developing and diversifying the health professional pipeline includes service on faculty and

advisory boards for programs designed to achieve a critical mass of minorities and women in biomedical science. She has been selected for several fellowships focusing on aging, health care, and health policy, including the Robert Wood Johnson Health Policy Fellowship at the National Academies of Sciences, Engineering, and Medicine, where she worked as a health policy analyst on the U.S. Senate's Health Education, Labor, and Pensions Committee and the Children and Families Subcommittee. She is an elected fellow of The New York Academy of Medicine, the Gerontological Society of America, and the Association of University Anesthesiologists. Her work has informed the policy agenda and she has provided expert testimony to state and federal entities.

Friedhelm Sandbrink, M.D., is the national program director for pain management within the Office of Specialty Care Services in the Veterans Health Administration (VHA). Dr. Sandbrink completed his residency in neurology at Georgetown University in Washington, DC, and a fellowship in clinical neurophysiology at the National Institutes of Health (NIH). He is board certified in neurology, clinical neurophysiology, and pain medicine. He is a clinical associate professor in neurology at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, and an assistant clinical professor of neurology at The George Washington University in Washington, DC. Dr. Sandbrink joined the U.S. Department of Veterans Affairs (VA) in 2001 and since then has been leading the comprehensive interdisciplinary Pain Management Program within the Neurology Department at the Washington VA Medical Center. He was appointed deputy national program director at the VHA in 2014. After serving in an acting capacity (since October 2016), he became the national program director for pain management in September 2018. He participates in many VHA and national pain management initiatives, and was involved in writing the Pain Management Best Practices Federal Inter-Agency Task Force Report in 2019 (by the U.S. Department of Health and Human Services) and the VA/U.S. Department of Defense Clinical Practice Guidelines for Opioid Therapy and for Low Back Pain.

Vinod P. Shah, Ph.D., joined NDA Partners as an expert consultant in 2016. He had 30 years of experience at the U.S. Food and Drug Administration (FDA), working in different divisions, until he retired as a senior research scientist in the Office of Pharmaceutical Sciences in 2005. During his career at FDA, he developed several regulatory guidances for industry in areas such as dissolution, SUPAC, bioanalysis, bioequivalence, biopharmaceutics, and topical drugs. In addition to his career at FDA, Dr. Shah worked at Sarabhai Chemicals, Baroda, India. He served as scientific secretary of the International Pharmaceutical Federation (FIP), as adjunct faculty at JSS

University, India, and an adjunct professor at the College of Pharmacy, University of Kentucky. Dr. Shah is a former Biopharmaceutics Expert Committee member of the United States Pharmacipeia (USP). He was the co-chair of USP's Advisory Panel on Dosage Form Performance—Topical/Dermal, and Distinguished Pharmaceutical Scientist/Consultant at USP in Biopharmaceutics. He is a member of the steering committee of Non-Biological Complex Drugs (hosted at Lygature, The Netherlands), and the founder and chairman of the Society of Pharmaceutical Dissolution Science International. In addition, Dr. Shah was a board member of the Product Quality Research Institute from 2013 to 2017 and holds two honorary doctorates from Semmelweis University, Hungary, and the University of Medicine and Pharmacy "Carol Davila" Bucharest, Romania. Dr. Shah was the president of the American Association of Pharmaceutical Scientists (2003). He is a recipient of FDA's Distinguished Service Award, FIP's Lifetime Achievement in Pharmaceutical Sciences Award, the American Association of Pharmaceutical Scientists's (AAPS's) Distinguished Pharmaceutical Scientist Award, AAPS's Global Leader Award, and the Marquis Who's Who Albert Nelson Marquis Lifetime Achievement Award.

Joyce S. Tsuji, Ph.D., DABT, FATS, is a board-certified toxicologist and a fellow of the Academy of Toxicological Sciences. She specializes in assessing exposure and risks associated with chemicals, and in communication of scientific issues. Dr. Tsuji has worked on projects in the United States and internationally for industry, trade associations, the U.S. Environmental Protection Agency (EPA) and state agencies, the U.S. Department of Justice, the Australian EPA, municipalities, and private citizens. Her experience includes toxicology and risk assessment related to a wide variety of chemicals in the environment, workplace, food, consumer and personal care products, pharmaceuticals, and medical devices. She has designed and directed dietary and environmental exposure studies and community programs involving health education and biomonitoring for populations potentially exposed to chemicals in the environment, including soil, water, and food-chain exposures. She has served on expert panels on toxicology and health risks issues for the National Academy of Sciences/National Research Council (including the Board on Environmental Studies and Toxicology), the Institute of Medicine, and federal and state agencies. Dr. Tsuji earned her B.S. in biological sciences from Stanford University, and a Ph.D. focused in environmental physiology from the Department of Zoology, University of Washington.

Carol S. Wood, Ph.D., is a distinguished staff scientist in the Environmental Science Division of Oak Ridge National Laboratory. She has more than 20 years of experience as a toxicologist, with extensive work performing risk assessments of inhalation/pulmonary and oral toxicity from exposure to

a variety of chemicals. Her past work has included developing acute exposure guideline levels and provisional advisory levels, in which health-based exposure levels are developed for priority toxic chemicals. These projects often used toxicokinetic data and physiologically based pharmacokinetic models for extrapolating animal toxicology data to humans. Dr. Wood is a past president of the American Board of Toxicology. She is certified in general toxicology by the American Board of Toxicology. She served on the National Academies of Sciences, Engineering, and Medicine's Committee on the Review of Clinical Guidance for the Care of Health Conditions Identified by the Camp Lejeune Legislation, the Committee on Spacecraft Exposure Guidelines, and the Committee on Gulf War and Health: Volume 11 (Generational Health Effects of Serving in the Gulf War); she currently serves on the Committee on Toxicology. Dr. Wood received her M.S. in toxicology from Mississippi State University and her Ph.D. in toxicology from Oregon State University.

NATIONAL ACADEMY OF MEDICINE FELLOW

Dima Qato, Pharm.D., Ph.D., M.P.H., is an associate professor in the Department of Pharmacy Systems, Outcomes, and Policy and an affiliate in the Center for Pharmacoepidemiology and Pharmacoeconomic Research at the University of Illinois at Chicago (UIC), and the 2018 National Academy of Medicine Fellow in Pharmacy. Her research focuses on access and safe use of medications in vulnerable populations, including refugee and immigrant populations. She uses population-based methods to better understand the underlying mechanisms responsible for the use, underuse, and unsafe use of medications; how these patterns may influence health outcomes and health disparities; and what can be done from a community and policy perspective to address these growing public health problems. Her work focuses on the growing prevalence and impact of pharmacy deserts; the increasing and widespread use of polypharmacy and potentially harmful drug–drug interactions among people of all ages, including teens and the elderly; and the systems-level transformation needed to combat these trends that have received significant attention from national news outlets, care providers, and community-based advocacy groups. Dr. Qato earned a doctor of pharmacy degree from UIC, a master's degree in public health from the Johns Hopkins Bloomberg School of Public Health, and a doctor of philosophy degree from the UIC School of Public Health.

CONSULTANTS

S. Narasimha Murthy, Ph.D., is a professor of pharmaceutics and drug delivery and the associate director of the Pii Center for Pharmaceutical

Technology at the University of Mississippi School of Pharmacy. Dr. Murthy is also the founder-director of a nonprofit research organization, Institute for Drug Delivery and Biomedical Research in Bangalore, India (http://www.IDBresearch.com). Transcutaneous drug delivery is one of the main areas of Dr. Murthy's research. His research programs are funded by the National Institutes of Health, the U.S. Food and Drug Administration, and pharmaceutical companies. He has published more than 100 research papers and presented more than 200 scientific posters in various national and international scientific meetings. He has authored 2 books and more than 15 book chapters. He is serving on the editorial board of several journals including *AAPS PharmSciTech*, *Drug Development and Industrial Pharmacy*, and the *Journal of Pharmaceutical Sciences*. Dr. Murthy has received several awards such as the New Investigator award and Cumberland Researcher of the Year from the University of Mississippi, the Global Indus Technovator award from the Massachusetts Institute of Technology, the Endowed Chair for Research at Ohio Northern University, and he was inducted as a fellow of the American Association of Pharmaceutical Scientists in 2017. The American Association of Indian Pharmaceutical Scientists has also honored him with the Distinguished Scientist award.

Anna Nicholson, Ph.D., M.A., M.Phil., is the founder and lead writer of Doxastic, a science writing firm based in Chapel Hill, North Carolina. She founded Doxastic after completing graduate degrees and a postdoctoral fellowship in linguistics, philosophy, and cognitive science at Indiana University Bloomington, Trinity College Dublin, and University College Dublin. Doxastic supports clients seeking to disseminate the latest advances in research, translate knowledge into improved practice and better outcomes, and shape health policy toward broader access to care. For clients including the National Academies of Sciences, Engineering, and Medicine and the Harvard Medical School Center for Global Health Delivery, she has provided writing support for meeting proceedings and consensus studies spanning a range of pressing issues in global and public health. Recent areas of focus have included infectious disease threats, the opioid use disorder epidemic, community-based health care delivery systems, and medical and public health preparedness for disasters and emergencies.

NATIONAL ACADEMIES STAFF

Leigh Miles Jackson, Ph.D. (*Study Director*) is a senior program officer for the Health and Medicine Division's Board on Health Sciences Policy (HSP) and serves as the study director for two U.S. Food and Drug Administration–sponsored consensus studies related to compounded drug products—one that focuses on the utility of treating patients with compounded

bioidentical hormone therapy, and another that focuses on the safety and effectiveness of compounded topical pain creams. Prior to her work on HSP, Dr. Jackson served on the Board on Higher Education and Workforce where she directed the consensus study *Minority Serving Institutions: America's Underutilized Resource for Strengthening the STEM Workforce*. Prior to this, Dr. Jackson worked in the Health and Medicine Division and directed the reports *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research* and *Advancing the Power of Economic Evidence to Inform Investments in Children, Youth, and Families*. Prior to joining the National Academies, she was a developmental psychopathology and neurogenomics research fellow at Vanderbilt University, where she investigated the role of chronic sleep disturbance and specific epigenetic modifications on the health outcomes of adolescents. Dr. Jackson has a bachelor's degree in chemistry from Wake Forest University and a Ph.D. in molecular and systems pharmacology from Emory University.

Claire Giammaria, M.P.H., is an associate program officer for the Health and Medicine Division's Board on Health Sciences Policy (HSP). She has worked for HSP since 2010, during which time she has helped staff consensus studies, standing committees, roundtables, and forums on a variety of topics. Most recently, she was the lead on a stand-alone workshop on medical product shortages during disaster events. Prior to working for the National Academies, she worked for the American Civil Liberties Union on privacy and health care issues. She attended Grinnell College, where she majored in biology, and the University of Michigan, where she received her master in public health with a concentration in policy and genetics.

Andrew March, M.P.H., is a research associate for the Health and Medicine Division's Board on Health Sciences Policy (HSP). He came to HSP after completing his master in public health at the Universitat Pompeu Fabra in Barcelona. Mr. March received his bachelor's degree in biology and Spanish from Roanoke College. His previous research experience includes sickness absence trends in working women and health care access in migrant populations.

Justin Jones, M.A., is a senior program assistant for the Health and Medicine Division's Board on Health Sciences Policy. He has a bachelor's degree in history from the University of Maryland and a master's degree in sociology from the University of Glasgow. His previous research experience focused on racial disparities within the lesbian, gay, bisexual, and transgender community of Scotland and the gender pay gap among Scottish universities. Prior to working at the National Academies, he worked

with several STEM-focused organizations, including the National Science Foundation and the American Association of Medical Colleges.

Andrew M. Pope, Ph.D., is the senior director of the Board on Health Sciences Policy. He has a Ph.D. in physiology and biochemistry from the University of Maryland and has been a member of the National Academies of Sciences, Engineering, and Medicine staff since 1982, and of the Health and Medicine Division staff since 1989. His primary interests are science policy, biomedical ethics, and environmental and occupational influences on human health. During his tenure at the National Academies, Dr. Pope has directed numerous studies on topics that range from injury control, disability prevention, and biologic markers to the protection of human subjects of research, National Institutes of Health priority-setting processes, organ procurement and transplantation policy, and the role of science and technology in countering terrorism. Since 1998, Dr. Pope has served as director of the Board on Health Sciences Policy, which oversees and guides a program of activities that is intended to encourage and sustain the continuous vigor of the basic biomedical and clinical research enterprises needed to ensure and improve the health and resilience of the public. Ongoing activities include Forums on Neuroscience, Genomics, Drug Discovery and Development, and Medical and Public Health Preparedness for Catastrophic Events. Dr. Pope is the recipient of the Health and Medicine Division's Cecil Award and the National Academy of Sciences President's Special Achievement Award.