Compounding is the formulation of a personalized medication designed to meet individual patient needs. The process changes the form (powder to liquid), dose, taste or texture of a medication, and/or combines medications. Compounding was a historical part of the pharmacist’s role until large-scale production and commercialization of medications began in the 1950s as a result of increasing regulations. It is now gaining increased popularity, because it meets the growing demand for customization of medications. Podiatry, specialized pain clinics, hospice, oncology, dermatology, dental practices, veterinary medicine and others regularly prescribe compounded formulations to meet patients’ needs.

Compounded wound formulations allow for innovative approaches and can fill the niche when commercial products do not suffice. Prescribed by clinicians and designed and prepared by compounding pharmacists, these formulations consist of one or more medications combined in a carrier or base applied directly to the wound. The advantages of this single-product treatment option include addressing patient quality-of-life concerns, treating underlying impediments to wound healing and providing novel options for challenging wounds.

Compounding in Wound Care
Many of the formulations have been used for decades, and literature on the use of compounding creams for wound care dates back to before the 1990s. While success has been noted anecdotally, until recently, evidence supporting the effectiveness of compounding in wound care has been limited to animal models and case studies. The gains made in healing and addressing patient-driven concerns have begun to pave the way for more robust studies.

Compounded topical wound formulas can address several needs in one formulation and can deliver medications directly to wounds in much smaller effective doses than are required orally. The medications do not need to permeate across the epidermis and dermis, as in the case of topical medications, because wounds by definition are defects below these layers. Bases or carriers used for compounded formulations include creams, ointments, gels, powders and sprays.

The pediatric population is another group well...
served by compounded formulations. Creating formulations with small or micro-doses of locally applied medications, with choices in carriers or bases, provides options that go beyond commercially available products.

**Addressing Quality-of-life Concerns**

**Pain**

Topical pain relief is safer than oral options in individuals with acute and chronic wounds, in particular in the aging population, where alterations in opiate pharmacokinetics that occur with normal physiologic aging can lead to an increased risk of falls, sedation and constipation.\(^3\)\(^4\) Research has shown that opioid receptors are present in peripheral tissues, and it is suspected that the effectiveness of topical opioids may be greater in the presence of inflammation.\(^5\) When applied to the wound, opioid medications are delivered directly to the pain receptors and bypass the first-pass metabolism in the liver; as such, smaller doses suffice as compared with oral administration.\(^2\)\(^6\)

A number of randomized controlled studies conducted on patients with wounds in palliative care support the analgesic effectiveness of topical opioids on wounds.\(^5\) A lack of effectiveness of topical analgesics in some wounds may be the result of a lack of inflammation in some long-standing wounds, or a limited number of functional opioid receptors in ischemic leg ulcers,\(^7\) as these factors appear to be essential for pain relief efficacy.

There is little to no systemic absorption of opioids; studies have reported pain relief lasting from 4 to 8 hours.\(^1\) Opioids can be compounded with

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**Why use a compound?**

Compounded formulations for wounds are able to address:

- Managing pain
- Accessing hard-to-treat areas
- Treating rare and uncommon wounds
- Trying emerging treatments options
- Minimizing systemic exposure to medications
- Minimizing drug interactions
- Allergies to commercial products
- Administering medications in those for whom the oral route is precluded
other pain modulators to create a multi-pronged ("gun-shot") approach to addressing local and neuropathic pain by targeting the various pain mechanisms proposed in the literature, with a potential for longer-lasting pain relief. A small study supported the use of lidocaine for reducing incidental pain related to negative pressure wound therapy dressing changes. The use of oral amitriptyline is a first-line treatment option for chronic neuropathic pain, and it works well, although it may not be effective in all cases of neuropathic pain. Topical amitriptyline in wounds is an option for pain relief, and an animal study supported that it does not impede wound healing. Formulations specifically designed for comfort can alleviate persistent wound pain or incidental pain experienced with dressing changes.

Studies have shown that topical ketamine, a high potency N-methyl-d-aspartate (NMDA) antagonist, is safe and effective in patients experiencing neuropathic pain. Low doses of ketamine have minimal adverse effects on the cardiovascular or respiratory functions. Alone or in combination with gabapentin, amitriptyline, clonidine, lidocaine or ibuprofen, this non-narcotic, non-addictive medication relieves neuropathic and chronic pain by blocking the NMDA receptors in the spine. Pharmacists also suggest applying the pain-relieving compounded cream to the corresponding dorsal horn of the dermatome involved in order to address both the peripheral and central mechanisms of pain.

Secure Dressings
Dressings and ostomy appliances that fall off are of concern to both patients and wound care providers, putting the patient at risk of infection, wound desiccation, further injury, and drainage leaks on clothing, bedding or furniture. To address difficult-to-treat areas such as mucosal surfaces, and other areas where moisture and/or body topography prevent the adherence of traditional dressings (e.g., pilonidal sinuses, anal regions, pyoderma gangrenosum beneath an ostomy appliance), compounded formulations can be made using mucoadhesive polymers as a base. Designed to adhere to moist surfaces, these products can prolong the retention of medications at the wound site, promoting healing and protecting the wound from exogenous harms. When removed, these formulations do not disturb new tissue growth.

Malodorous and/or Sanguinous Wounds
Patients with fungating necrotic tumours and other palliative wounds are deeply affected by malodours. To effectively reduce odour and purulent exudates, clinicians can consider using a combination of the antifungal metronidazole and the antibiotic chloramphenicol or ciprofloxacin powdered and insufflated generously onto the wound and covered with a loose dressing. Thrombin, ferric subsalicylate (Monsel’s solution), and tranexamic acid can be added to this formulation to control a sanguinating tumour.

Addressing the Causes of Non-healing Wounds
The observation that children developed overgrowth of gingival tissue with long-term use of phenytoin, an anti-epileptic drug, led to the use of this tissue-stimulating medication in wounds, including pressure ulcers, vascular leg wounds.
and those of other etiologies. This medication works to stimulate fibroblast proliferation, enhances tissue granulation, inhibits collagenase activity, promotes collagen deposition and decreases wound exudate production. Wounds stalled at the granulation phase may respond to phenytoin in a compounded topical formulation, although the evidence has been deemed inconclusive due to research flaws. Phenytoin alone can be insufflated to a moistened wound or combined with other medications to meet a broader range of needs.

For patients with diabetic wounds with vascular compromise refractory to standard treatments, nifedipine, propranolol, verapamil and diltiazem are calcium channel blockers that, when used topically in compounded formulations, can increase local vascular perfusion by relaxing local blood vessels. A synergistic effect occurs when pentoxifylline is compounded with these calcium channel blockers, resulting in increased blood viscosity, and increased blood flow and oxygen delivery to the wound.

Inflammation and Infection

To treat localized bacterial infections and speed healing, a number of antibiotics alone or in combination can be incorporated into compounded formulations. Topical compounded antibiotic formulations have been found to be non-cytotoxic and tissue compatible, easy to apply and remove, and cost effective. They can result in decreased time to heal and reduction of biofilms. Selections are based on culture and sensitivity results and can include metronidazole, clindamycin, aminoglycosides, vancomycin and rifampin. Wounds with fungal infections can be successfully treated with compounded clotrimazole.

Misoprostol is a synthetic prostaglandin that stimulates and modulates inflammation in wounds stalled in the inflammatory phase, inhibits IL-1 and tumour necrosis factors (TNFs) and promotes collagen synthesis. It can likewise be added to a compounded wound formulation.

Compounding enables the use of over-the-counter (OTC) products that may have medicinal properties and have the capability and ability to interact with other components. Essential oils such as tea tree oil, St. John’s Wort, lavender and oregano oil, for example, can be and are used at the request of some providers. Other compoundable over-the-counter products with bioactive medicinal properties that may influence wound healing include zinc oxide, green propolis extract, alkaloids, flavonoids, tannins, terpenoids, saponins, aloe vera and phenolic compounds. Aloe vera was shown to have effects on wound healing and pain reduction in a small randomized, blind, placebo-control trial.

Rare and Challenging Wounds

Pyoderma gangrenosum typically poses a challenge to wound care professionals and patients. Sometimes found in difficult-to-heal areas such as those adjacent to ostomy stomas, it presents further challenges. There is evidence that supports the use of the tumour necrosis factor alpha (TNF–α) inhibitor infliximab compounded in a sterile aqueous gel or as a solution for treatment-refractory chronic wounds. In a small study by Streit and colleagues, its use was based on the observation that TNF–α was present in high levels in chronic wounds and decreased as wounds heal. Results showed 12 out of 14 four-month-old ulcers in the study responded to the treatment with infliximab, some with 50% reduction in wound surface in four weeks.

Wounds in patients with connective tissue diseases such as scleroderma and dermatomyositis can be complicated by the deposition of calcium deposits in the wound. These calcium nodules are extremely painful and cannot be debrided. A compounding pharmacist can formulate a 10% sodium thiosulfate solution, shown to be effective as an initial intervention in this type of rare wound.
Financial Considerations
Clinicians must consider the financial implications of using compounded formulations for wound care. Most formulations will need a secondary dressing to secure the product in place and protect the wound. In addition, more frequent dressing changes may be necessary to renew the product as it is absorbed into the wound; and in the case of pain compounds, this will need to be tailored to individual patient response.

In most provinces, third-party payors such as insurance companies and provincial drug plans will not cover the cost of compounded medications, even when the individual medications are found on formularies. There may be provincial exceptions for palliative patients with wounds.

How to Choose a Compounding Pharmacy
The use of compounded products requires a prescription, and clinicians are advised to consult and work with the compounding pharmacist as part of a multidisciplinary wound care team. Compounding pharmacists work with prescribers to design and formulate topical treatments to meet the unique needs of the patient. In formulating combinations of medications, they consider drug interactions, secondary effects of topical medications that can be mitigated with additional products, and underlying comorbidities such as end-stage renal failure. Pharmacists can also assist by doing a specific patient pharmacological review for medications that are known to have an inhibiting effect on wound healing, or that may be complicating a wound presentation with a drug-induced skin reaction, and will advise on substitutions in these cases. They are a critical part of any team-based approach to holistic patient care.

The compounding pharmacy chosen must have access to the appropriate resources to meet patient and clinician needs. Canadian pharmacists can opt for membership to the Professional Compounding Centres of America (PCCA), which can provide helpful resources. The PCCA provides members with a Pharmacy Consulting Department, an extensive database of compounded formulas, and accredited courses and continuing education for pharmacists and prescribers (www.pccarx.com).

Conclusion
The use of compounded topical treatments can provide treatment options when commercially available products have not met the needs of patients with wounds. Making a compounding pharmacist part of a multidisciplinary wound care team serves to capitalize on the knowledge and skills of a professional with the expertise to create solutions to unique and individualized problems.

References


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