# Off-label Use of Prescription Medication: A Literature Review

*Robert G. Smith, DPM, MSc, RPh, CPed*

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*From Shoe String Podiatry, Ormond Beach, Florida*

Address correspondence to:
**Robert G. Smith, DPM, MSc, RPh, CPed**
Shoe String Podiatry
723 Lucerne Cir.
Ormond Beach, FL 32174
Phone: 386-673-9933
Email: Robert.Smith@fhmmc.org

**Abstract:** The following review will describe the available literature and outline the concept and practice of off-label prescribing. Phenytoin, misoprostol, and nifedipine will be critically reviewed with emphasis on their functional components, mechanisms of action, and patient considerations regarding wound healing. Recipes of off-label medications also will be offered.

Wound management guidelines have been established to assist healthcare professionals in providing the most advantageous treatment to promote wound closure. Organized decisions that are often grounded in clinically based evidence from the medical compendium are essential tools wound care specialists employ to promote healing. Unfortunately, the multitude of advertisements for wound dressings possibly eclipses the fact that only small, poor-quality trials exist to support the use of many products.[1] Nonetheless, attempts have been made to provide the educational tools necessary for making informed decisions using evidence-based medicine to select wound care products.[2] Determining the most appropriate treatment or selection of a wound care product to satisfy a particular patient's needs requires a delicate balance between knowledge and art. *Secundum artem* is a Latin phrase meaning "according to the art." In medicine it is often taken to mean, "use your skill and judgment."

Agents that have been approved by the US Food and Drug Administration (FDA) to treat wounds include anesthetics, antibiotics, anti-infectives, enzymes for debridement, granulation stimulants, growth factors, and moisture enhancers. Numerous wound care dressings and topical medications line the shelves of pharmacies and hospitals, which makes the selection process even more difficult. Despite the plethora of approved products, some wound care patients have healthcare needs that off-the-shelf prescription medicines do not meet. Off-label prescribing of customized medicines to help promote dermal wound closure has been employed by wound care specialists to meet these needs.

The concept of off-label prescribing of approved pharmaceuticals has created much attention and led to myths and misconceptions regarding its practice. Case studies exist in the literature regarding the use of topical pheny-

toin, misoprostol, and nifedipine to treat wounds. It is for this reason that this review article has been written; to allow data from previously published literature to be presented and evaluated in the context of clinically based evidence to justify the current practice of prescribing of these agents off-label.

A review of the available literature outlining the concept and practice of off-label prescriptions is offered to serve as a foundation. Secondly, specific medications are critically reviewed regarding their mechanisms of action and patient considerations in the context of wound healing. Recommended off-label medication compounds are presented for the treatment of cutaneous wounds (Table 1).

**Table 1.** Prescription recipes for wound care compounds.

| Compounds (Reference) | Type |
|---|---|
| Misprostol 0.0024%<br>Phenytoin 5% (42) | Diabetic cream |
| Lidocaine HCl 2%<br>Misprostol 0.0024%.<br>Phenytoin 2% (43) | Topical powder |
| Metronidazole 2%<br>Misprostol 0.0024%<br>Phenytoin 5% (44) | Topical gel |
| Lidocaine HCl 2%<br>Misprostol 0.003%<br>Phenytoin 2.5% (45) | Topical gel |
| Gentamicin sulfate 0.2%<br>Misprostol 0.0024%<br>Phenytoin 5% (46) | Topical gel |
| Misprostol 0.0024%<br>Phenytoin 5%<br>Lidocaine HCl 4% (48) | Topical formula |
| Misprostol 0.0024%<br>Phenytoin 5%<br>Lidocaine HCl 4%<br>Metronidazole 2% (48) | Topical formula |

## Off-label Prescribing

Healthcare providers do not all fully understand the drug development and regulatory issues that exist. Two factors that motivate a wound care specialist to choose one therapy over another when attempting to close a particular wound are: 1) an understanding of the scientific basis for a drug's activity in a given disease state, and 2) the belief in the drug's efficacy in achieving wound closure. It is currently illegal for pharmaceutical manufacturers to promote their approved drugs for unapproved conditions.[3] Off-label or unapproved prescribing refers to a registered medicine being prescribed for a use that is not included or disclaimed in the product information.[4] Sufficient evidence exists in the medical literature to justify some off-label practices. Literature citations are identified and explored so that the misconception that off-label use of an approved medication is itself an illegal or risky endeavor for the clinicians can be addressed and any myths or misconceptions may be debunked.[3-8]

First, the decision of whether to use a drug for an off-label purpose is a matter of medical judgment and not one of regulatory approval. The FDA has never had the authority to regulate the practice of medicine.[5] To build on this, a policy statement was issued in the December 1982 *FDA Drug Bulletin* specific to the use of approved drugs for unlabeled indications: "The Federal Food, Drug, and Cosmetic [FD&C] Act does not, however, limit the manner in which a physician may use an approved drug." Additionally, once approved for marketing, a physician may prescribe a drug product for uses or in treatment regimens or patient populations that are not included in the approved labeling. Further, the FDA may accept clinical studies conducted outside the United States in support of safety and efficacy for drugs, biological products, and medical devices. The FDA will accept a foreign clinical study involving a drug or biological product not conducted under an investigational new drug (IND) application only if the study conforms to the ethical principles contained in the 1989 version of the Declaration of Helsinki. Another consideration regarding off-label prescribing is that many wound care products are considered medical devices. The FDA was prohibited from intruding into medical practice with respect to off-label use of medical devices when Congress enacted section 214 of the Food and Drug Administration Modernization Act (FDAMA).[5] Finally, a review of the Medicare Benefit Policy Manual, chapter 15, section 50.42 endorses the practice of off-label prescribing.[8] Approved drugs used for indications other than what is identified on the official label may be covered under Medicare if the insurance carrier determines the use to be medically acceptable and that its use is consistent with the drug compendia, authoritative medical literature, and accepted standards of medical practice.[8]

The practice of off-label prescribing of drugs and medical devices plays an important therapeutic role in many disease states, including psychiatric disorders, human immunodeficiency virus (HIV), and diseases in children and other patient populations that are underserved by approved medicines. When medications and devices are used off-label for medical treatment, their primary purpose is to benefit the individual patient. Within the scope of medical practice, the clinician's primary purpose and intention when using a product off-label is to enhance the wellbeing of the patient with an expectation of success. It is clear that rapid developments in medical science often outpace the speed with which regulatory authorities like the FDA can move to implement new legislation.[5] Physicians may safely prescribe any drug off-label provided he or she practices a standard of care based on sound evidence.[6,7] Williams[8] states that off-label drug use may constitute the current standard of care, and failure to provide or discuss off-label therapy with patients may be considered malpractice.

Uniformly accepted specific guidance to assist clinicians attempting to make decisions about the appropriateness of such prescriptions does not exist. Given the lack of FDA approval for off-label uses, many off-label uses of drugs are published in the literature as case reports, which allows other clinicians the opportunity to learn and use these treatments on a greater number of patients.[3] One might surmise that these case studies are not given the same degree of scientific scrutiny that are required for labeled indications from drug manufacturers.[7] Gazarian et al[4] outline consensus recommendations for evaluating appropriateness of off-label use of medicines.

Compounding pharmacists create alternate methods of delivery like transdermal gels, ointments, or solutions of approved medications to provide for patients with unique health needs; thus, compounding pharmacists create off-label medications. While the FDA and Federal Trade Commission (FTC) enforce laws that prohibit making unsubstantiated claims regarding safety and efficacy in pharmacists' marketing materials, off-label dispensing of approved medications is not considered malpractice. When a licensed practitioner writes a prescription for a compounded drug, the medication is normally needed as soon as possible. As a matter of public health policy, it is clear that individual compounded medications should be exempted from the FDA approval process because requiring approval would be neither cost-effective nor in the best interest of the patient. State pharmacy boards regulate compounded medications and are not subject to federal laws designed to regulate mass-produced drugs. Therefore, pharmacists should observe the same principles and levels of evidence when dispensing off-label medications that a physician applies when prescribing off-label drugs.

## Medication Classes and Wound Healing

Medications may exert their effects by either assisting or interfering with the specific phases of wound healing. The effect of a particular medication on the wound healing process may depend on its mechanism of action, dosage, and route of administration in relation to the specific phase of the wound healing process.[10] Specific medications of interest to the wound care specialists include misprostol, nifedipine, and phenytoin.

A search profile was compiled using key terms to perform Boolean logic electronic searches to identify relative primary literature citations from 1967 to 2009 (Figure 1). Further, a manual review of citations' references lists and bibliographies was undertaken to gather any additional information that might have led to further material for this review. Citations (n = 317) were reviewed and evaluated as defined by the search limita-

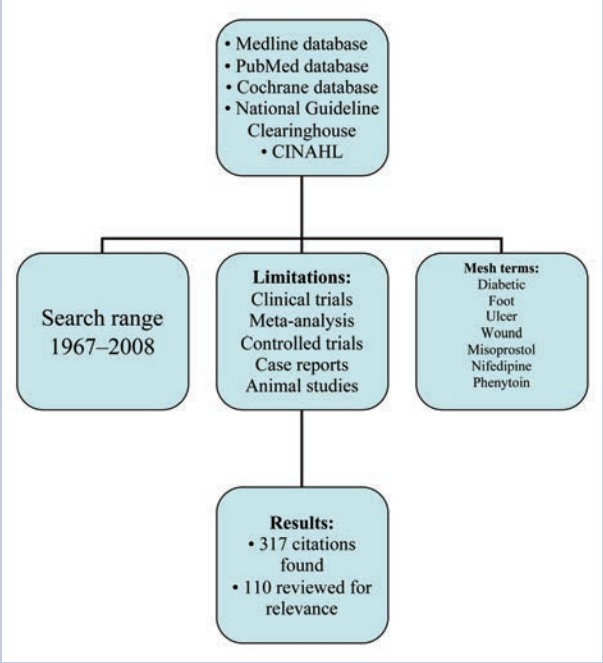


**Figure 1.** Citations (n = 317) were reviewed and evaluated as defined by the search limitations. Accounting for duplication, 35% (n = 110) of the citations were reviewed for significance and relevance for inclusion in this review.

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**Misoprostol.** Misoprostol [15-deoxy-16-hydroxy-16-methyl-PGE1] is a synthetic prostaglandin E1 analog with an additional ester group at C1.[11] As a therapeutic agent misoprostol embodies various pharmacological features that contribute to its pharmacodynamic actions. It seems to inhibit the acid secretion by means of direct action on parietal cells. The inhibition of adenylate cyclase may be dependent on guanosine-5'-triphosphate (GTP).[12] The significant cytoprotective actions of misoprostol are related to several mechanisms, which include: increased secretion of bicarbonate; decrease in the volume and pepsin content of gastric secretions; enhancement of mucosal blood flow as a result of direct vasodilatation; stabilization of tissue lysozymes/vascular endothelium; and improvement of mucosal regeneration capacity.[13]

Misoprostol's potential pharmacological benefits in cutaneous wound healing may be explained by reviewing the role of prostaglandins in wound healing. Products of the earliest cellular events are activated upon tissue injury. Phospholipase stimulate the release of arachidonic acid, ultimately leading to the production of prostaglandins, leukotrienes, and other factors. Histamine released from platelets and circulating mast cells increases vascular permeability and indirectly stimulates vasodilation through the production of prostaglandins E1 and E2. Prostaglandins cause vasodilation through activation of the adenylate cyclase pathway via the production of cyclic adenosine monophosphate.

Several investigations have been conducted evaluating pharmaceutical developed prostaglandin E1 (PGE-1), misoprostol, and its action on wounds.[14-19] Milio et al[14] performed one of the first, and one of the few human investigations that focused on the efficacy of intravenous PGE-1 in the treatment of lower extremity venous ulcers. This randomized, single-blinded, placebo controlled trial of 87 consecutive patients observed healing time for venous ulcers.[14] The treatment group (n = 44) received 60-mg of PGE-1 diluted in 250-mL of saline solution, while the placebo group (n = 43) received just 250-mL of saline solution over a 20-day span. Also, both groups were treated with elastic bandaging and local therapy. The main outcome of the study was the percentage of ulcer recovery at the conclusion of the 120-day period of observation and time to healing.[14] The investigators concluded that the study demonstrated that treatment with PGE-1 is effective on lower extremity venous ulcers; however, the authors concluded that the mechanism with which PGE-1 favors healing of venous ulcers remains to be verified.[14]

The remaining investigations were conducted as animal observations of surgically induced wounds.[15-19] de Oliveira et al[15] investigated the influence of misoprostol on healing of colonic anastomoses in Wistar rats particularly regarding changes in collagen levels. The animals received misoprostol intragastrically at a dosage of 200-mcg/kg body weight diluted in 0.9% saline twice daily by means of a stomach tube. Their results demonstrated that misoprostol administration increased the hydroxyproline concentration on postoperative day 14 without interfering in the inflammatory response, which was verified by histopathological study. Three investigations centered on topical application of PGE-1 and skin flap viability.[16-18] All of these investigations observed a beneficial effect of topical application of prostaglandins as defined by augmented skin flap viability.[16-18] A final animal observational investigation focused on the application of misoprostol powder suspended in saline in a 1:1000 concentration on a surgically prepared wound.[19] This investigation offered data concluding that when applied daily to an acute surgical wound, topically applied misoprostol results in decreased healing time.[19] Additionally, the authors offered the assumption that prostaglandins exert their greatest effect in the inflammatory phase of wound healing, while acknowledging that their investigation was preliminary and called upon further studies to validate the use of misoprostol in chronic wounds.[19]

**Nifedipine.** Nifedipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester used as an antianginal medication that belongs to a class of pharmacological agents known as calcium channel blockers. Nifedipine is a calcium ion influx inhibitor that inhibits the transmembrane influx of calcium ions into both cardiac muscle and smooth muscle without changing serum calcium concentrations. Recalling that cellular calcium metabolism appears to regulate extracellular matrix production as well as other critical steps in wound healing[20,21] leads to the inference that nifedipine as a calcium channel blocker could potentially be an attractive agent to study with regard to its influence on the wound healing process. The report by Lupo et al[22] describing the dose-dependent antioxidant activity of nifedipine and other calcium channel blockers when compared to α-tocopherol further validates the influence of these drugs on the wound-healing process.

Several investigations have evaluated nifedipine and

its influence on the wound healing process.[20–29] An even distribution of both animal and human investigations are present in the literature and include case reports, retrospective studies, and prospective, randomized, blinded studies.[23–29] These investigations have reviewed the topical application of nifedipine on surgically prepared wounds,[23–25] a chronic wound,[26] a hypertrophic wound,[26] and anal fissures.[27–29]

A review of the studies of the animal wound models reveals similar investigational methods were used.[23–25] All three investigations used healthy Wistar rats (150 g–250 g).[23–25] One investigation evaluated the co-founder of diabetes by comparing their study group of diabetic rats with normal rats.[23] Surgically-applied incisional and excisional wounds were evaluated and topical nifedipine was applied to the wounds.[23–25] An interesting aspect was that two investigations examined calcium channel blocker application in the wounds of animals treated with systemic dexamethasone.[24,25]

Corticosteroids affect cells by altering gene expression after crossing the cell membrane where they bind to cytoplasmic receptors and translocate into the cell nucleus. The inhibitory effect on gene expression over many cells allows for corticosteroids to affect almost every phase of wound healing.[10] The degree of gene expression inhibition is related to the particular corticosteroid's potency. The most prominent effects are seen when corticosteroids are administered during the early inflammatory phase.[10] Collectively, the findings and results of these three animal studies are similar.[23–25]

The effects of nifedipine were evaluated in the three different phases of the wound-healing process. Topical nifedipine significantly improved the inflammatory phase,[23–25] significantly improved the process during only the maturation phase in diabetic rats,[23] and did not affect the proliferation phase.[23–25] Nifedipine enhanced normal healing by increasing the tensile strength of 10-day-old granulation tissue. There was no significant change in hydroxyproline level, collagen level, or glycosaminoglycan content in the granulation tissue.[25] This finding validates the tissue model findings of Lee and Ping[20] who concluded that the cellular calcium metabolism appears to regulate extracellular matrix production and that hypertrophic disorders of wound healing may respond to therapy with calcium antagonist drugs. Finally, the application of topical nifedipine was able to overcome steroid depression of wound healing.[24,25]

Torsiello and Kopacki[26] described their experience with transdermal nifedipine in two patients. The first patient was a 43-year-old woman with a nonhealing right heel wound. The formula used for this wound was 8% nifedipine in pluronic lecithin organogel administered by the patient twice daily. The authors used wound size as an outcome indicator for healing time. They observed a 6- to 8-week healing time with the therapeutic invention compared to previous accounts for the same wound in which a healing time of 4 to 5 months was observed. The second case report described an 8-year-old boy with a linear hypertrophic scar contracture. A nifedipine 2% pluronic lecithin organogel formulation was applied twice daily. After surgical invention and applications of transdermal nifedipine complete wound healing occurred in 3 to 4 weeks. The authors acknowledged that the exact mechanism of action of the influence of transdermal nifedipine on the wound-healing process remains to be determined. The authors believe that the same pharmacological action of smooth muscle relaxation occurs in the skin vasculature and creates a localized peripheral vasodilatation and increases flow to the localized area, which accelerates epithelialization and possibly microvascular neogenesis.

The last two human accounts focus on the use of topical nifedipine as nonsurgical treatment of chronic anal fissures.[27,28] One report was a retrospective chart review with telephone follow-up of 88 patients. The other report was a prospective, randomized, double-blinded study of 110 consecutive patients.[27,28] Both investigations concluded that chronic anal fissures can be simply and effectively treated with topical nifedipine with either injectable botulinum toxin[27] or as a compounded formula with lidocaine.[28] The treatment was demonstrated to be safe and effective with a low recurrence rate. Perrotti et al[28] chose healing of the chronic anal fissure as the primary outcome measure defined as epithelialization or formation of a scar observed under anoscopy. Their control group received 1.5% lidocaine and 1% hydrocortisone acetate and the treatment group received 1.5% lidocaine and 0.3% nifedipine applied every 12 hours for 6 weeks. Clinical healing was achieved in 55 patients in the nifedipine group at 42 days. The final account is a critical narrative of the clinical investigation by Perrotti et al.[28]

Merenstein and Rosenbaum[29] demonstrated the effectiveness of topical nifedipine by highlighting the 46 patients who were in the control group and did not experience healing were offered nifedipine treatment, resulting in a 82% (n = 38) healing rate. Also, none of the patients in the nifedipine group experienced systemic side effects—only one patient in the secondary treat-

ment group experienced slight local hyperemia, which improved when treatment was completed.[29] Finally, Merenstein and Rosenbaum emphasized that this topical formulation is an extremely safe, well tolerated, and effective treatment that has the potential to provide clinicians with a reliable nonsurgical method for treating chronic anal fissures.

**Phenytoin**. Phenytoin sodium is an antiepileptic drug. Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is sodium 5,5-diphenyl-2, 4-imidazolidinedione. It has been reported that phenytoin's main action in wound healing is its modification of collagen remodeling by decreasing collagenase activity.[10] Also, collagen synthesis is not significantly affected by phenytoin, although it does inhibit wound contraction.[30] Finally, Spaia et al[31] report that studies historically have shown that phenytoin stimulates fibroblast proliferation, decreases collagenase activity, increases epidermal and keratinocyte growth factor receptors and collagen disposition, accelerates initial inflammatory responses, induces new vessel formation, speeds the decrease of microbial colonies thus decreasing bacterial contamination, reduces wound exudate, and improves healing.[31-37] A limitation of Spaia et al's case report is that the exact amount of phenytoin applied to this patient's wound was not quantified as it is only referred to as "1–2 ampoules of a commercial preparation."[31]

In order to explore this pharmacological action, systematic searches of PubMed, Medline, Cinahl, and the Cochrane library were performed. The medical literature is replete with citations describing the clinical effect of topical phenytoin on wound healing. Given that this compound has been rigorously investigated, a summary of published accounts to emphasize and report on the most important points is presented.[35-37]

Bhatia and Prakash[35] offer a thorough review on topical phenytoin for wound healing. This review begins with a historical perspective on the use of topical phenytoin over time. The review recounts animal studies, cell cultures, case reports, retrospective studies, and prospective controlled comparison human observational findings.[35] The types of wounds investigated with regard to topical phenytoin and its effects on healing in this review include abscesses, ballistic wounds, decubitus ulcers, diabetic foot ulcers, pressure ulcers, surgical induced, tropic ulcers, and venous stasis ulcers with regard to topical phenytoin and its affects on healing.[35] The authors acknowledge that despite the extensive investigation of topical phenytoin for wound healing the best method of delivery of topical phenytoin remains unknown.[35] The authors explore the safety issues by stating that side effects from topical phenytoin are rare and then provide detailed accounts of adverse effects including generalize rash and hypertrophic granulation tissue both of which resolved with stoppage of treatment.[35] Finally, the issue of phenytoin's systemic absorption is evaluated. This review concludes that the systemic absorption of topical phenytoin is not significiant. The authors further explain that most studies that have monitored serum phenytoin levels during topical application have shown undetectable levels.[35]

Younes et al[36] conducted an intriguing observational investigation that is relevant to cutaneous wound healing and is pivotal to wound healing events associated with individuals who have diabetes. These researchers tested wound bed preparation with 10% phenytoin ointment and observed split-thickness skin graft survival. Sixteen patients with diabetes and large, lower extremity foot ulcers underwent wound bed preparation with phenytoin ointment followed by split-thickness skin graft application. The product was compounded with phenytoin powder and levigated with white petroleum to a final concentration of 10% (W/W). Younes et al offered a qualifying statement to their observations remarking that comparison of their results to those of other groups using various growth factors was not possible because of the different methodologies and different ways of measuring outcomes that were used. Finally, in order to minimize the potential risk of wound sepsis due to the patient's co-morbidities and ulcer size, the authors recommended that adequate surgical debridement and broad spectrum antibiotics be initiated before any wound therapy.

Shaw et al[37] offered results from their systematic review of the clinical effect of topical phenytoin on wound healing. A total of 347 references were located through database, journal, and handsearching; however, only 14 randomized controlled trials were suitable for review.[37] Two of these papers were of high quality using the Van Tudler (VT) method and methodologically sound: Pai et al[39] who performed a double-blind study of topical phenytoin treatment of diabetic ulcers; and Simpson et al[40] who investigated the use of diphenylhydantoin in the treatment of venous stasis ulcers.[37-40] The remaining 12 papers scored between 10–14 with the VT method and were deemed to be low to moderate quality, providing at best level 2 (n = 9) and level 3 (n = 2)

evidence for the effectiveness of phenytoin in the treatment of wounds.[37] Shaw et al point out in these described 14 studies, the sample size ranged from 30 to 102, which is typical of many wound care studies and was not directly related to the VT score.[37] Also, the randomization process was inadequately described in many of the studies, with subjects often assigned to treatment groups rather than being randomized through a truly independent process.[37] Another finding of this review was that 12 out of 14 studies reported a statistically significant reduction in wound area in the phenytoin-treated group when compared with the control groups in various wounds. A final acknowledgement made in this review indicated that it is easy to be critical of the design of the studies reviewed but presenting solutions to the highlighted problems associated with the particular design is much more difficult.[37]

## Clinical Application

It is the duty and responsibility of both the wound care specialists and the dispensing pharmacist to make certain that any off-label use of a drug is supported by credible, evidence-based medicine. It was the purpose of this review to offer data regarding the off-label use of misoprostol, nifedipine, and phenytoin. Formulas do exist and are presented in Table 1 for compounding topical preparations such as powders, creams, and gels using one if not all of the medications reviewed. Some formulas incorporate either metronidazole or gentamicin as anti-infectives or as odor controlling substance or lidocaine as a local anesthetic. Questions that present themselves are: "How was the effective concentration of each component of the each formula decided upon?" and "Are the concentrations based on animal studies, cell cultures, or anecdotal information from wound care experts in the field?"

Several limitations must be acknowledged when applying some of the literature citations to clinical practice. The foremost is that wound healing rates in rats may not be directly comparable to humans because normal rates are not equivalent between species. Levenson et al[41] reported that incisions in rats may heal more slowly than wound models predict.[41] Secondly, chronic wounds exhibit significant differences from acute wounds in both immunohistochemistry and histopathology. Therefore, it would be difficult to apply the clinical findings of surgically induced wounds to chronic wounds. Thirdly, in many of the literature accounts, one cannot exactly determine the amount of active drug applied directly to the wound. A drug-specific concern regarding phenytoin is the added expense of ordering and monitoring drug levels to insure that a patient does not become toxic.

Despite the fact that some studies rely on measures of statistical power to legitimize data, it remains that many of these studies have small sample sizes. This phenomenon is typical of many wound care studies, and may impart some statistical bias in the results.

It is an optimistic outlook that experts from wound healing societies will develop policy documents to outline procedures for documenting and dispensing off-label medications for wound healing. Criteria should be developed and embraced by wound care specialists and guidelines should be offered for prescribing appropriate off-label medications. These criteria should offer validated and uncontested data in support of particular off-label medications. Available literature and existing compounded recipes[42-47] should attest to the drug's safe and effective use in treating a particular type of wound.

## Conclusion

The concept of off-label prescribing of approved pharmaceuticals to treat cutaneous wounds has generated substantial attention. Studies have reported the use of topical misoprostol, nifedipine, and phenytoin to treat wounds. The purpose of this article is in part to serve as a foundation and a review of the available literature outlining the concept and practice of off-label prescribing. In addition, specific medications were reviewed with an emphasis on their mechanisms of action and patient considerations in the context of wound healing. Finally, details and compounding recipes of these medications can be found throughout the literature.

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