# Pharmacologic Impact (aka "Breaking Bad") of Medications on Wound Healing and Wound Development: A Literature-based Overview

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**Abstract**

Patients with wounds often are provided pharmacologic interventions for their wounds as well as for their acute or chronic illnesses. Drugs can promote wound healing or substantively hinder it; some medications cause wound or skin reactions. A comprehensive review of extant literature was conducted to examine the impact of drug therapy on wound healing and skin health. MEDLINE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched for English-language articles published between 2000 and 2016 using the terms *drugs*, *medications*, *drug skin eruptions*, *adverse skin reactions*, *wound healing*, *delayed wound healing*, *nonhealing wound*, *herbals*, and *herbal supplements*. The search yielded 140 articles (CINAHL) and 240 articles (MEDLINE) for medications and wound healing. For medications and adverse skin effects, the search identified 256 articles (CINAHL) and 259 articles (MEDLINE). The articles included mostly narrative reviews, some clinical trials, and animal studies. Notable findings were synthesized in a table per pharmacological class and/or agent focusing on wound healing impact and drug-induced adverse skin reactions. The medications most likely to impair wound healing and damage skin integrity include antibiotics, anticonvulsants, angiogenesis inhibitors, steroids, and nonsteroidal anti-inflammatory drugs. Conversely, drugs such as ferrous sulfate, insulin, thyroid hormones, and vitamins may facilitate wound healing. Selected clinical practices, including obtaining a detailed medication history that encompasses herbal supplements use; assessing nutrition status especially protein blood levels affecting drug protein binding; and scrutinizing patient history and physical characteristics for risk factors (eg, atopy history) can help diminish and/or eliminate adverse integumentary outcomes. "Deprescribing" (discontinuing unnecessary medications) should be utilized when possible. Contemporary wound care clinicians must be cognizant of these mitigating clinical approaches.

**Keywords:** review, wound healing, pharmacotherapy, drug side effects, adverse events

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**Potential Conflicts of Interest:** none disclosed

Derived from a Southern colloquialism meaning to "raise hell," *breaking bad* aptly describes how drug therapy can affect wound healing. Although some pharmacologic agents promote and augment wound healing, many can impair wound healing through multiple phases of repair. Some drugs actually can cause or generate wounds by damaging skin integrity. Recognition of wound impairment, drug-induced skin reactions, and options to assist wound healing and avoid skin injury via targeted, judicious drug therapy is critical knowledge for contemporary wound care practitioners.

A literature review was conducted to 1) provide an overview of the impact of pharmacological therapy on wound healing and skin integrity, 2) describe the pathomechanisms of drug-induced skin reactions, 3) delineate drugs commonly and rarely associated with wound healing impairment or adverse skin reactions, 4) describe the clinical presentation for selected exemplar drug-induced skin reaction types, and 5) analyze clinical practices clinicians can use to mitigate drug effects and polypharmacy.

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## Key Points

- Commonly used pharmacologic agents can affect wound healing and skin integrity.
- Some may delay (eg, steroids and nonsteroidal anti-inflammatory drugs) and others may facilitate (eg, hemorrheologic agents) healing.
- It is important for clinicians to realize some pharmacologic agents (eg, warfarin) also can cause wounds.
- The author concludes wound clinicians need to develop a sophisticated level of knowledge regarding pharmacotherapy and its potential for hindering wound healing and/or altering skin integrity.

## Method

MEDLINE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were searched for English-language articles published between years 2000 and 2016 using the delimiting key terms *drugs*, *medications*, *adverse skin reactions*, *drug skin eruptions*, *wound healing*, *delayed wound healing*, *herbals*, *herbal supplements*, and *adverse drug events*. The search uncovered approximately 140 articles (CINAHL) and 240 articles (MEDLINE) on medications and wound healing. Searching using *medications* and *adverse skin (cutaneous) effects* identified approximately 256 (CINAHL) and 259 (MEDLINE) articles. For both aspects, the identified articles included mostly narrative reviews, but research studies (clinical trials and animal studies) were found. Studies were organized via subject type (animal versus human), design (pilot versus clinical trial), and clinical applicability. The number of articles identified was relatively limited given the time frame, but no obvious gaps in the literature were noted.

## Normal Wound Healing

Despite many obstacles and disease processes that can hamper healing, most wounds heal in an uncomplicated manner. Simply put, the human body is wired to heal. Several literature reviews[2-4] suggest that although multiple types of cells, growth factors, and bodily proteins are involved, the body progresses through 4 phases of wound healing: 1) hemostasis (immediate wounding period) involving platelets and growth factors; 2) inflammation (day 1 to day 4) during which macrophages, leukocytes, and mast cells are active; 3) proliferation (day 2 to day 21) where fibroblasts, myofibroblasts, and endothelial cells grow new tissue; and 4) remodeling (day 21 to 2 years), where the wound heals and acquires 80% of original strength. Figure 1 describes the normal healing process including the cells, proteins, and other essential components involved.

Although wound healing progresses smoothly and systematically for the majority of wounds, some wounds can get "stuck."[5] Armstrong and Meyr[2] define this condition as a chronic wound. The physiologic impairment of a chronic wound can be due to inadequate angiogenesis, impaired innervation, and impaired cellular migration. These impairments can be mediated by local and systemic factors.[2] Medications can affect any aspect of wound healing and cause impairment in 1 or more of these components.

## Medications and Wound Healing: Scope of Impact

Medications have substantive opportunity to affect wound status due to prevalence of use. According to the Centers for Disease Control and Prevention,[6] nearly 50% of Americans take 1 prescription drug monthly, 20% take 3 or more drugs monthly, and more than 11% take 5 prescription drugs monthly. When one considers 36 million Americans take herbal supplements yearly, the impact of prescribed, over-the-counter (OTC), and "natural" medicines on the American population is evident.[7,8] Given the surge of chronic illness in America, its aging population, and the occurrence of chronic illness in younger persons,[6] the potential impact of medications on wound care practice is enlarging.[4,9-11]

**Medications and wound physiology.**

*Medications that delay wound healing.* The health care literature includes multiple narrative reviews[9,10,12-22] describing the impact of pharmacologic agents on wound healing. Medications reported to delay wound healing include anticoagulants,

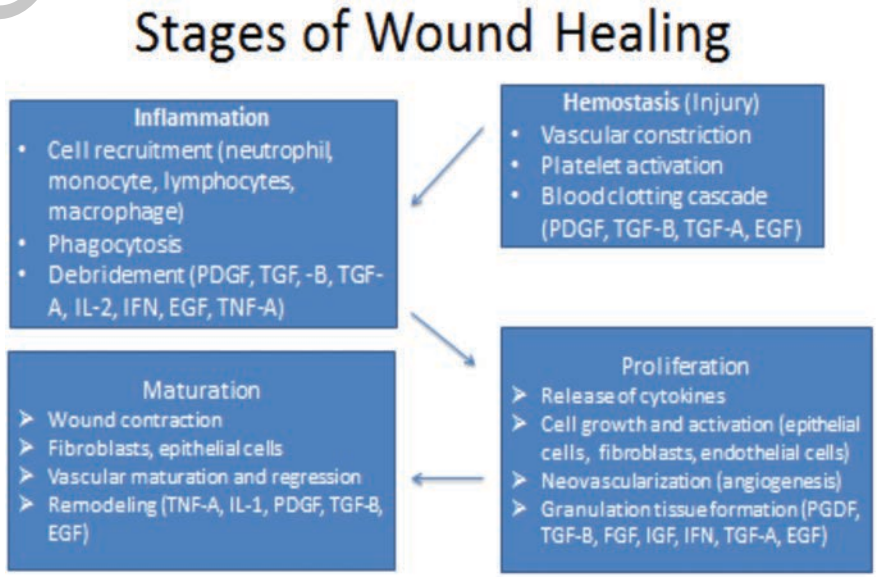


**Figure 1.** Wound healing phases synthesized.[2,4,9,10,19,58,116-123]

antimicrobials (various antibiotic classes), anti-angiogenesis agents (eg, bevacizumab, aflibercept), antineoplastic drugs, anti-rheumatoid drugs (eg, methotrexate, aspirin/non-steroidal anti-inflammatory drugs [NSAIDs]), colchicine (anti-gout drug), Dakin's solution (sodium hypochlorite), nicotine, steroids, and vasoconstrictors. Table 1 presents an extensive synthesis of their effects as reported in the literature for a variety of pharmacologic classes.[2,8-10,13-15,19,20,22-67]

Because of their ubiquity of use, 2 categories of medication require special mention: steroids and NSAIDs. Several literature reviews[14,62,68,69] support that short-term use of both categories has limited impact on wound healing. However, long-term use of steroids and NSAIDs can have marked negative impact.

Steroids are notorious inhibitors of wound healing. Noted systemic effects include hyperglycemia, osteoporosis, and mood alterations. Narrative reviews[9,70] describe how steroids alter gene expression once they cross the cell membrane and thereby alter almost every phase of wound healing. Steroids decrease the inflammatory response, fibroblast activity, and epithelial regeneration and, over time, thin the epidermis and inhibit wound contraction. NSAIDs, given long-term and especially in higher doses, can impair healing. Narrative reviews describe how NSAIDs can delay bone healing, impair ligament health,[71] and cause serious adverse skin reactions.[72] For example, in animal testing, Krischak et al[73] found diclofenac inhibited fibroblasts in 10 rats versus 10 control animals.

*Medications that facilitate wound healing.* Selected drugs and drug categories can assist wound repair. These include hemorrheologic agents (eg, pentoxifylline), hormones (estrogen), phenytoin, prostaglandins, zinc, vitamin A, and vitamin C.

Multiple narrative literature reviews[25,74,75] support that selected "natural" medications used topically also can augment wound healing. Many have been used for centuries in a variety of cultures to assist wound healing. They include aloe vera, curcumin, ginger, medicinal (eg, Manuka) honey, mucilage (slippery elm), and witch hazel. More recently, prescription pharmacologic agents have been used offlabel as topical therapy to help wounds heal. They include topical calcium channel blockers, regular insulin, nitroglycerine, opioid-related drugs, phenytoin, retinoids, sildenafil, and sucralfate[24,31,34,35,37,40-42] (see Table 1).

In a pilot clinical trial,[24] 90 patients without diabetes mellitus used topical regular crystalline insulin versus aqueous zinc on uncomplicated wounds and demonstrated topical insulin's positive healing impact. Another experimental study[31] tested topical sildenafil on healing abdominal wall wounds in 50 rats versus 50 control rats. Breaking strength and neovascularization were greater in the sildenafil group. In a randomized clinical trial,[34] chronic ulcers treated with topical sildenafil healed twice as fast in 2 weeks. Another experimental assessment[37] of topical sildenafil in acute wounds in 25 rats yielded positive healing results; both vascularization and acute inflammation strength were greater in animals treated with sildenafil. Topical nitroglycerine and aloe vera were tested topically in an ointment carrier on diabetic foot ulcers in 30 rats, and the experimental group healed significantly faster than the control group; the accelerated healing was thought to be due to increased perfusion to the animals' foot.[41] A systematic review[35] supported that topical phenytoin hastened wound healing in various chronic wounds (eg, venous ulcers, pressure ulcers). Narrative reviews[40,42] described a variety of oral systemic agents being used offlabel topically (including pentoxifylline, phenytoin, and sucralfate) with positive wound healing outcomes. Some legal issues may ensue with offlabel drug use to promote wound healing, so providers need to be clear their usage in the wound care plan is supported by credible literature and patient consent.[76]

## Drugs and Altered Skin Integrity

In addition to the fact pharmacologic agents can help or hinder wound healing, in some instances drug therapy can cause skin damage and create wounds. Multiple narrative reviews[77-79] assert cutaneous drug reactions are some of the most common adverse drug events (ADEs). Almost any medication can cause or induce skin reactions; some drug classes have ADE rates as high as 5%.[77] Adverse skin reactions are commonly categorized according to predictability or immunological characteristics. For predictability, Type A (predictable) ADEs include common reactions such as gastritis from NSAIDs or diarrhea from antibiotics and are related to the pharmacologic properties of the involved drug.[78,79] Type B ADEs involve hypersensitivity or immunologic pathomechanisms. The signs or symptoms that arise differ from the action of the drug and are not usually predictable. Tinnitus from low-dose aspirin would be an example. According to a narrative review,[78] 85% to 90% of ADEs are Type A reactions and 10% to 15% are Type B.

**Immunologic or hypersensitivity reactions.** According to the literature,[77,79,80] immunologic or hypersensitivity reactions that can occur from drug therapy can be classified into 1 of 4 types: I — immediate onset, II — delayed onset where antibodies rupture cells, III — delayed onset involving cytotoxic reactions, and IV — delayed onset caused by a T cell-mediated delayed hypersensitivity.

Type I is caused by drug/antigen-specific immunoglobulin E (IgE) antibodies that link with mast cells and basophils, precipatating immediate release of histamine/leukotrienes and subsequently causing urticaria (hives), angioedema, and possibly anaphylaxis. Potential offenders include aspirin, penicillins, neuromuscular blocking agents, quinolones, chimeric monoclonal antibodies, and platinum-based agents.

Type II includes reactions such as hemolytic anemia and thrombocytopenia. Common drug offenders are propylthiouracil, flecainide, and amodiaquine.

In Type III, the immunologic response to the offending drug is mediated by intravascular immune complexes (drug antigens and antibodies — eg, immunoglobulin G [IgG] antibodies) in the circulation. Phagocytes attempt to remove

**Table 1. Medications with reported and potential effects on wound healing**

| Class | Mechanism of action/category | Reported effects on wound healing |
|---|---|---|
| **Anabolic steroids** | Anabolism related to hormonal effect | Theorized to help decrease weight loss |
| Oxandrolone | Anabolic effect; derivative of dihydrotestosterone | Promote weight gain and tissue growth |
| **Antibiotics (general)** | Anti-infective | Removal of inflammation caused by infection |
| Doxycycline | Anti-infective; anti-inflammatory | Accelerates healing via MMP-9 and VEGF activation |
| Tetracycline | Anti-infective; anti-inflammatory | Inhibition leukocyte chemotaxis |
| Erythromycin | Anti-infective; anti-inflammatory | Inhibition leukocyte chemotaxis |
| Neomycin | Anti-infective; Gram positive | Reepithelialization promoted |
| Polymyxin-B | Anti-infective; Gram negative | Reepithelialization promoted |
| Bacitracin | Anti-infective; Gram positive | Reepithelialization promoted and contraction inhibited |
| Gentamicin | Anti-infective; Gram negative | Reepithelialization delayed |
| Mupirocin | Anti-infective; Gram positive | Contraction inhibited |
| Silver sulfadiazine | Anti-infective; Gram positive<br>Anti-infective; Gram negative<br>Candida, fungi, *Herpes simplex* | Reepithelialization promoted and contraction mildly inhibited |
| **Antiseptics (general)** | Topical disinfective | Degrees of cytotoxicity |
| Povidone iodine (cadexomer forms of iodine may be safer) | Topical disinfective | Mild decrease of contraction; cytotoxic |
| Ethyl alcohol | Topical disinfective | Reepithelialization inhibited |
| Acetic acid 0.025% | Anti-infective; *Pseudomonas aeruginosa* | Reepithelialization inhibited and contraction inhibited |
| **Anticoagulants** | Inhibit coagulation cascade intrinsic and extrinsic pathways | Prevent fibrin deposition; avoid injury and inflammation |
| **Anticonvulsants** | Decrease electrical activity of neuronal cell membranes limiting seizures | Can affect balance of tissue growth and cessation |
| Phenytoin | Affects collagen remodeling | Decreased collagenase reduction; increased granulation tissue and angiogenesis |
| **Antihypertensive drugs** | Decrease blood pressure via inhibition of angiotensin converting enzyme (ACE) | |
| ACE-I | Inhibit deposition of collagen I in wounds | Inhibit collagen deposition in wounds; decreased granulation |
| **Anti-inflammatory drugs** | Decrease inflammatory response | |
| Dapsone | Sulfone antibiotic with anti-inflammatory effects; inhibits polymorphonuclear neutrophil leukocytes | Limits PMN-mediated injury and inflammatory response |
| **Antiplatelet drugs** | Inhibit platelet aggregation<br>Inhibit arachidonic acid pathway | Inhibition of inflammation mediated by arachidonic acid metabolites |
| **Antitumor angiogenesis inhibitors** | Decrease tumor growth via decreased blood vessel growth | Affects growth of new blood vessels |
| Bevacizumab | Humanized monoclonal antibody<br>Blocks vascular endothelial growth factor (VEGF) and impairs angiogenesis | Increased wound dehiscence<br>Infection<br>Not within 28-30 days of elective surgery |
| Sorafenib | Tyrosine kinase inhibitor; anti-angiogenesis effect | Can cause hand-foot-skin reaction; not to be used within 1 week of surgery |
| **Chemotherapeutic agents for cancer (general)** | Suppress immune response; affect both normal cells and target tumor cells | Reduced inflammatory response<br>Suppression of protein synthesis<br>Inhibition of cell reproduction<br>Increased risk of wound infection<br>Decreased fibrin deposition |

**Table 1. Medications with reported and potential effects on wound healing** *continued*

| Class | Mechanism of action/category | Reported effects on wound healing |
|---|---|---|
| **Agents for cancer** | | |
| Hydroxyurea | Classified as antineoplastic agent; used in sickle cell anemia and as anti-tumor agent/ myeloprolferative disorder | May hinder perfusion via megaloblastic erythrocytes: cutaneous, atrophy, via keratinocyte, cytotoxicity |
| **Corticosteroids** | Inhibition of gene expression<br>Long-term use more deleterious<br>Affect all phases of wound healing | Decreased inflammatory mediators<br>Decreased platelet adhesion<br>Decreased WBC recruitment and phagocytosis<br>Decreased tissue formation<br>Decreased tissue remodeling<br>NB: Local topical use of steroids may help wound healing |
| **Antigout agent** | | |
| Colchicine | Inhibition of microtubule formation | Decreased cytokine release<br>Decreased granulocyte migration<br>Decreased blood supply from vasoconstriction<br>Decreased fibroblast activity<br>Interrupted extracellular transport of procollagen<br>Increased collagenase synthesis |
| **Hemorrheological agents** | Enhanced tissue perfusion | Increased blood supply |
| Pentoxifylline | Phosphodiesterase inhibitor; acts to improve perfusion due to decreased blood viscosity; also may inhibit TNF | Enhance wound healing and flap survival |
| **Hormones** | | |
| Estrogen (topical) | Enhances collagen formation | Faster wound healing; stronger wound matrix |
| **Hormone-like drugs (prostaglandins)** | Prostaglandins are locally acting vasodilators | |
| **Misoprostol (synthetic PGE1) (topical)** | Used to prevent stomach ulcers from non-steroidal antinflammatory drugs | Facilitates collagen synthesis<br>Inhibit TNF and IL-1 |
| **Immunosuppressants** | Suppress immune system function | Decreased inflammatory response |
| mTOR inhibitors<br>Rapamycin (now called sirolimus) | Mammalian target of rapamycin (mTOR) pathway plays key role in cellular proteins important for angiogenesis, metabolism, and cell proliferation; mTOR suppression causes immune suppression | Inhibits angiogenesis<br>Inhibits fibroblast and matrix deposition (antimitotic) |
| T-cell inhibitors | Decreased T-cell activity | Decreased inflammatory response |
| Cyclosporine<br>Tacrolimus | Calcineurin inhibition<br>Decreased T cell activity | Inhibit fibroplasia and decreased wound strength |
| TNF-alpha inhibitors | TNF regulates fibroblast proliferation, prostaglandin production and angiogenesis; blockade decreases activity | Inhibit fibroplasia and new blood vessel growth |
| Infliximab<br>Adalimumab | Monoclonal antibody (chimeric)<br>Humanized monoclonal antibody | Potential for impaired surgical healing within 1 to 2 weeks before/after surgery (range 2 to 8 weeks) |
| **Nonsteroidal agents (NSAIDs)** | Affect cyclooxygenase and lipoxygenase creating anti-inflammatory effect | Retard inflammatory response |
| Ibuprofen<br>Diclofenac | Longer-term use more deleterious | Reduced wound tensile strength<br>Reduced proliferation<br>Increased bleeding risk |
| Indomethacin | | Detrimental effect on bone healing |
| **Vasoconstrictors** (cocaine-epinephrine) | Impaired microcirculation | Increased ulcer necrosis |
| **Smoking** | | |

**Table 1. Medications with reported and potential effects on wound healing** *continued*

| Class | Mechanism of action/category | Reported effects on wound healing |
|---|---|---|
| (Nicotine)<br>Note: nicotine replacement therapy does **not** impair healing | Agonist at nicotinic cholinergic receptors; nicotine constricts blood vessels | Decreases red blood cells, fibroblasts<br>Increased scarring<br>Increased platelet adhesion |
| **Ascorbic acid** (Deficiency) | Essential cofactor for hydroxylation of proline and lysine | Poor wound healing due to impaired collagen synthesis<br>Decreased tensile strength<br>Increased capillary fragility |
| **Natural medications (some oral; some topical)** | From plant, tree and herbaceous sources | Variety of purported effects |
| Aloe vera (topical) | Gel from succulent aloe plant; assists collagen formation | Promotes faster wound healing and is soothing; improves collagen production; antimicrobial |
| Cayenne pepper | Enhances blood circulation; helps vascular integrity | Relieves pain with short-term topical use |
| Curcumin | From turmeric shrub; purported to be antibacterial/viral/fungal; anti-inflammatory | Promotes faster wound healing |
| Ginger | Produced from rhizome of *Zingiber officinale* plant | Promotes faster wound healing |
| Goldenseal | Promotes healing by antimicrobial effect | Increases granulation |
| Honey (medicinal) | Produced from Manuka tree *(Leptospermum)* | Inhibits excessive inflammation; promotes autolytic debridement; generally non-toxic to cells |
| Plaintain | Antioxidant | Promotes wound healing |
| Tea tree oil (topical) | Anti-inflammatory | Helps with healing with antimicrobial effects; may be active with MRSA |
| Turmeric | Antioxidant; stimulates immune response | Anti-inflammatory; antimicrobial |
| **Offlabel topical agents** | | Drugs used topically may affect wound healing |
| Calcium channel blockers<br>Nifedipine | Affects calcium channels in blood vessels | Increased vascular perfusion and wound healing |
| Insulin topical (regular) | Antidiabetic agent with growth factor effect | Accelerates wound healing process |
| Morphine and morphine blockers | Opioid narcotic and opioid narcotic blocker | Affect wound healing processes via opioid receptor impact |
| Naltrexone (topical) (animal studies) | Antagonizes opioid receptors from opioid receptors | Assists with wound contraction |
| Nitroglycerine (glyceryl trinitrate) (topical) | Organic nitrate; increases vasodilation | Accelerates wound healing |
| Phenytoin topical | Anticonvulsant | Promotes granulation tissue formation; stimulates collagen, protein, and hydroxyproline synthesis |
| Retinoids (tretinoin) | Anti-acne agent | Increases granulation tissue; increases angiogenesis |
| Sildenafil (Topical and oral [animal studies]) | Phosphodiesterase Type 5 inhibitor; increases nitric oxide release | Accelerates wound healing and tissue perfusion; increases granulation |
| Sucralfate (topical) | Anti-ulcer (agent); coats gastric mucosa | Inhibits inflammatory cytokines; stimulates angiogenesis |

Synthesized from: [2,8-10,13-15,19,20,22-67]
Disclaimer: Please note that medications may have different trade and generic names in Canada and other foreign countries.

| Table 2. Drugs rarely causing skin eruptions[77] |
|---|
| Antacids |
| Antihistamines |
| Atropine |
| Benzodiazepines |
| Corticosteroids |
| Digoxin |
| Ferrous sulfate |
| Insulin |
| Laxatives |
| Local anesthetics |
| Muscle relaxants |
| Nitrates |
| Nystatin |
| Oral contraceptives |
| Propanolol |
| Spironolactone |
| Theophylline |
| Thyroid hormones |
| Vitamins |

them and end up in the skin, kidneys, and vessel walls. Examples include serum sickness and vasculitis. Potential drug culprits are antitoxins, penicillins, cephalosporins, sulfa agents, and phenytoin.

Type IV reactions include contact dermatitis, Stevens Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN).[79] Possible offenders are allopurinol, lamotrigine, anti-epileptics, and antibiotics.

**Types of drug-induced skin damage.** Numerous narrative reviews describe the manifestations of skin eruptions related to drug therapy. They include exanthems, fixed drug reactions, blistering responses, psoriasiform responses, immune-mediated reactions (eg, SJS and TEN), and hematologic/vasculitic reactions. Other dermatologic drug events such as photosensitivity, pigmentary disorders, and urticaria/angioedema are not addressed herein due to space constraints. Selected drugs and drug classes are rarely associated with adverse skin reactions (see Table 2). Conversely, other drugs and drug classes are commonly associated with the various forms of skin damage (see Table 3) How the drug reactions present clinically will be addressed herein, although the comprehensive treatment for each of the drug-induced skin reactions is beyond the scope of this article.

*Exanthems.* Multiple narrative literature reviews[77,81,82] explain that exanthems (a skin reaction that "bursts forth") are characterized by erythema (redness), morbilliform (resembling measles), or maculopapular lesions (most common exanthema presentation). Exanthems are most frequently caused

| Table 3. Common drug offenders per reaction[43,77,115] | |
|---|---|
| **Skin reaction** | **Drug categories/names** |
| **Blistering reactions** | ACE inhibitors (captopril, enalapril) |
| | Antibiotics (cephalosporins, penicillins, sulfa agents, tetracyclines, vancomycin) |
| | Gold/sodium aurothiomalate |
| | Lithium |
| | Loop diuretics (eg, furosemide, bumetanide) |
| | Nonsteroidal anti-inflammatory drugs (NSAIDs) |
| | Penicillamine |
| | Thiazide diuretics (eg, hydrochlorothiazide) |
| **Exanthems** | Allopurinol |
| | Antimicrobials (anti-tubercular drugs, cephalosporins, erythromycin, gentamicin, nitrofurantoin, penicillins, sulfa) |
| | Barbiturates |
| | Captopril |
| | Furosemide |
| | Gold salts |
| | Lithium |
| | Phenothiazine |
| | Phenytoin |
| | Thiazides |
| **Fixed drug eruptions** | ACE inhibitors |
| | Allopurinol |
| | Antimicrobials (cephalosporins, clindamycin, metronidazole, penicillins, sulfa, tetracyclines, trimethoprim) |
| | Barbiturates |
| | Benzodiazepines |
| | Calcium channel blockers |
| | Carbamazepine |
| | Fluconazole |
| | Lamotrigine |
| | NSAIDs |
| | Paclitaxel |
| | Proton pump inhibitors (PPIs) |
| | Salicylates |
| | Terbinafine |
| **Psoriasisiform eruptions** | ACE inhibitors |
| | Beta blockers |
| | Chloroquine and hydrochloroquine |

**Table 3. Common drug offenders per reaction[43,77,115]** *continued*

| Skin reaction | Drug categories/names |
|---|---|
| | Digoxin |
| | Gold |
| | Interferons |
| | Lithium |
| | NSAIDs |
| | Penicillamine |
| | Terbinafine |
| | Tetracyclines |
| | Tumor necrosis factor (TNF) – alpha blockers |
| Stevens-Johnson Syndrome (SJS) | Barbiturates |
| | Beta-lactam antibiotics (penicillins, cephalosporins) |
| | Carbamazepine |
| | Chlorpropamide |
| | Co-trimoxazole |
| | Gold |
| | $H_2$ antagonists |
| | Lamotrigine |
| | Leflunomide |
| | Macrolides |
| | NSAIDs |
| | Phenothiazines |
| | Phenytoin |
| | Rifampicin |
| | Sulfonamides |
| | Tetracyclines |
| | Thiazides |
| Toxic epidermal necrolysis | Allopurinol |
| | Anti-tubercular agents |
| | Barbiturates |
| | Carbamazepine |
| | Gold |
| | Griseofulvin |
| | Lamotrigine |
| | Leflunomide |
| | Nitrofurantoin |
| | NSAIDs |
| | Penicillins |
| | Phenytoin |
| | Salicylates |
| | Sulfonamides |
| | Tetracyclines |
| Vasculitis reactions | Allopurinol |
| | Aspirin |
| | Beta-lactam antibiotics (carbapenems, cephalosporins, monobactams, penicillins) |
| | Carbamazepine |
| | Co-trimoxazole |
| | Diltiazem |
| | Erythromycin |
| | Furosemide |
| | Granulocyte colony stimulating factor (G-CSF) |
| | Granulocyte macrophage stimulating factor (GM-CSF) |
| | Gold |
| | Hydralazine |
| | Interferons |
| | Methotrexate |
| | NSAIDs |
| | Penicillamine |
| | Propylthiouracil (PTU) |
| | Retinoids |
| | Sulfasalazine |
| | Sulfonamides |
| | Thiazides |
| | Thrombolytic agents |

by penicillins, especially ampicillin, and sulfonamides. Exanthems account for 90% of all drug rashes[77,81,82] (see Figure 2).

*Fixed drug reaction.* Fixed drug reaction is characterized by erythematous and edematous plaques or frank bullae, often with a dark post-inflammatory pigmentation. The defining feature of this eruption is the recurrence of lesions at exactly the same spot with drug re-exposure. Narrative drug reviews[79,82,83] have described drugs that commonly cause this response are anticoagulants, NSAIDs, antimicrobials (especially sulfonamides and tetracyclines), barbiturates, acetaminophen, and antimalarials (see Figure 3).

*Blistering.* Blistering reactions include skin lesions that are erythematous with crusting and scaling. Large, tense blisters on a red base also can occur. Idiopathic pemphigus and bullous pemphigoid are examples. Narrative reviews[77,84] and a Cochrane systematic review[85] note drugs causing this response include penicillamine, penicillins, cephalosporins, angiotensin-converting enzyme (ACE) inhibitors, NSAIDs, and diuretics (see Figure 4).

*Psoriasiform reactions.* Psoriasiform-type drug reactions present as psoriatic type lesions on previously uninvolved

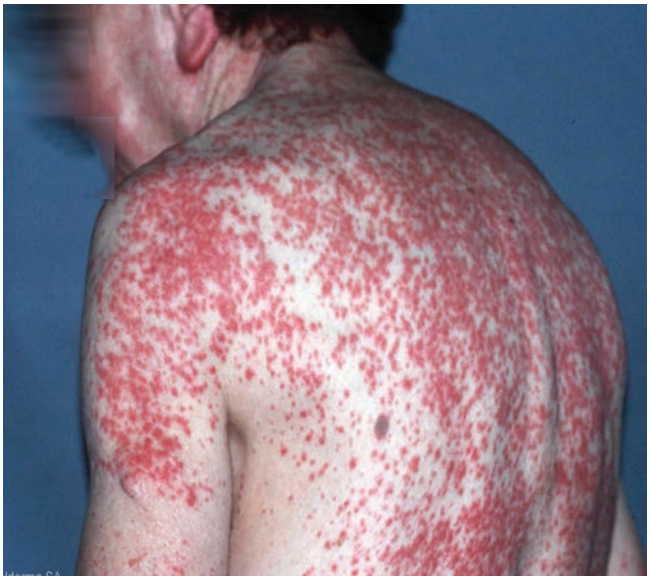

**Figure 2.** Drug reaction: exanthem (maculopapular). *(Used with permission of DermQuest (www.dermquest.com/image-library/image/5044bfd0c97267166cd64da9).*

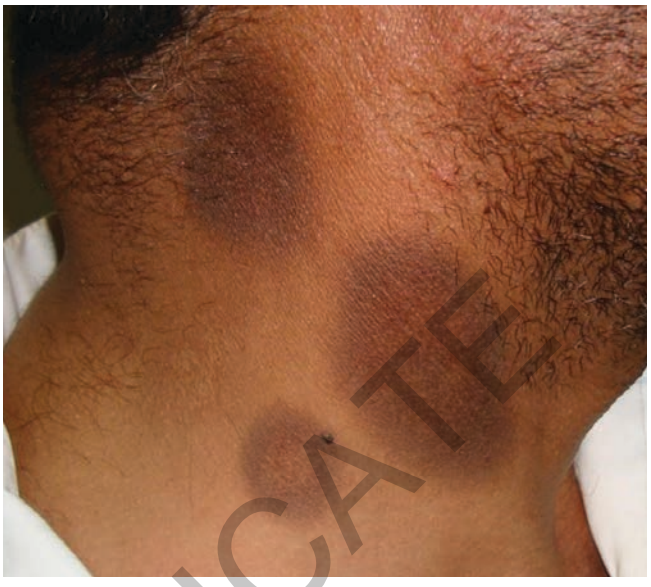

**Figure 3.** Drug reaction: fixed drug reaction. *(Used with permission of DermQuest (www.dermquest.com/image-library/image/5044bfd1c97267166cd6732f).*

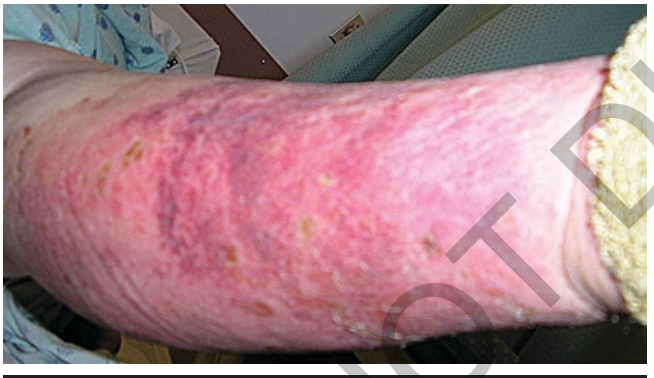

**Figure 4.** Drug reaction: blistering/bullous reaction (resolving lesions).

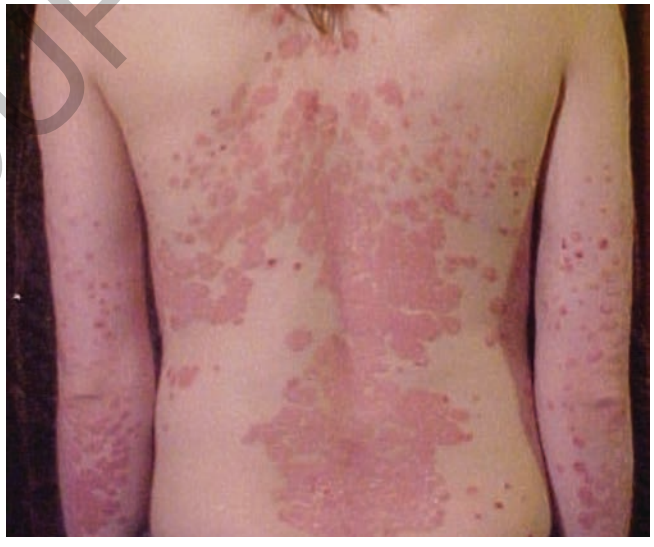

**Figure 5.** Psoriasis appearance. Available at: https://en.wikipedia.org/wiki/psoriasis#/media/File:psoriasis_on_back1.jpg (used with permission).

skin or exacerbation of preexisting psoriatic lesions. The lesions include limited or generalized erythematous plaques with large, thick, silvery scales, pustular lesions, or erythroderma. Several literature reviews[86,87] note drugs commonly involved are NSAIDs, antimalarials, ACE inhibitors, and beta blockers (see Figure 5).

*Immune-mediated reactions.* Immune-mediated adverse cutaneous drug reactions include SJS and TEN. The disorders are categorized or codified based on the percentage of skin detachment.[88] Multiple literature reviews[89-93] suggest they are variants on a spectrum of disease. SJS presents with fever, malaise, myalgia, and skin eruptions (blisters, papules, erythematous areas) affecting <10% of the body. Skin changes also involve body mucosa such as mouth, genitals, and eyes (see Figure 6).

TEN presents with fever, malaise, nausea, vomiting, myalgia, arthralgia, and skin changes.[94] Lesions can be erythematous bullae, and the skin detaches in sheets (>30% of body is affected). As in SJS, TEN also affects the body mucosa[94] (see Figure 7).

*Hematologic-associated dermatologic ADE.* Hematologic-associated dermatologic ADE can be dramatic in their fullest manifestations. Two (2) disorders can result from drug therapy: warfarin-induced skin necrosis and heparin-induced thrombocytopenia (HIT) syndrome.

Warfarin-induced skin necrosis classically occurs 3 to 5 days after a dose of warfarin. It can begin with red painful plaques that can progress to hemorrhagic blisters, ulcers, and frank skin necrosis (the most serious in this category).

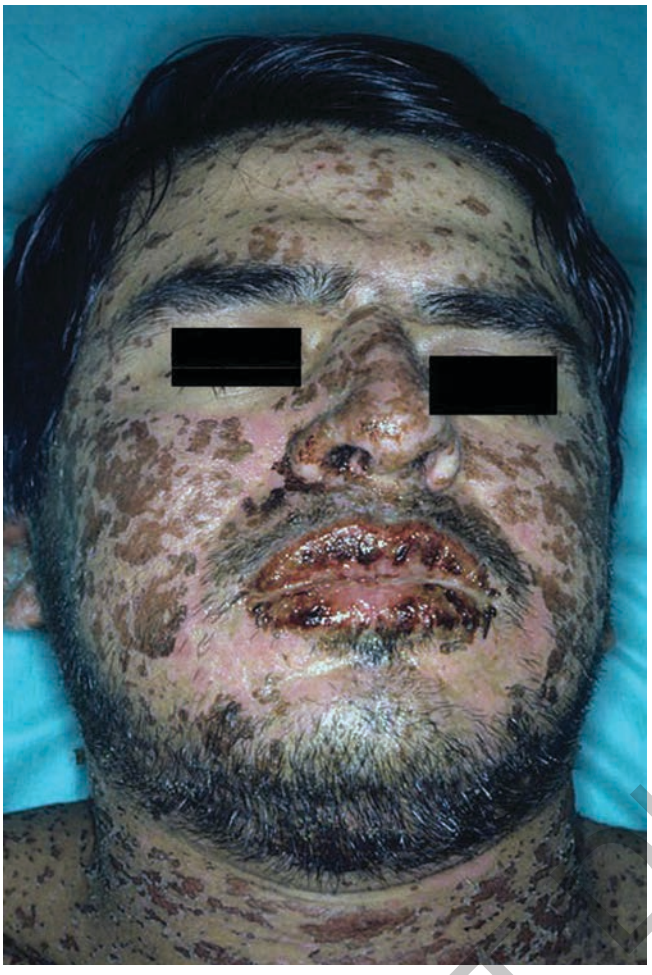

**Figure 6.** Drug reaction: Stevens-Johnson Syndrome. Available at: https://commons.wikimedia.org/wiki/file:stevens-johnson-syndrome.jpg (used with permission).

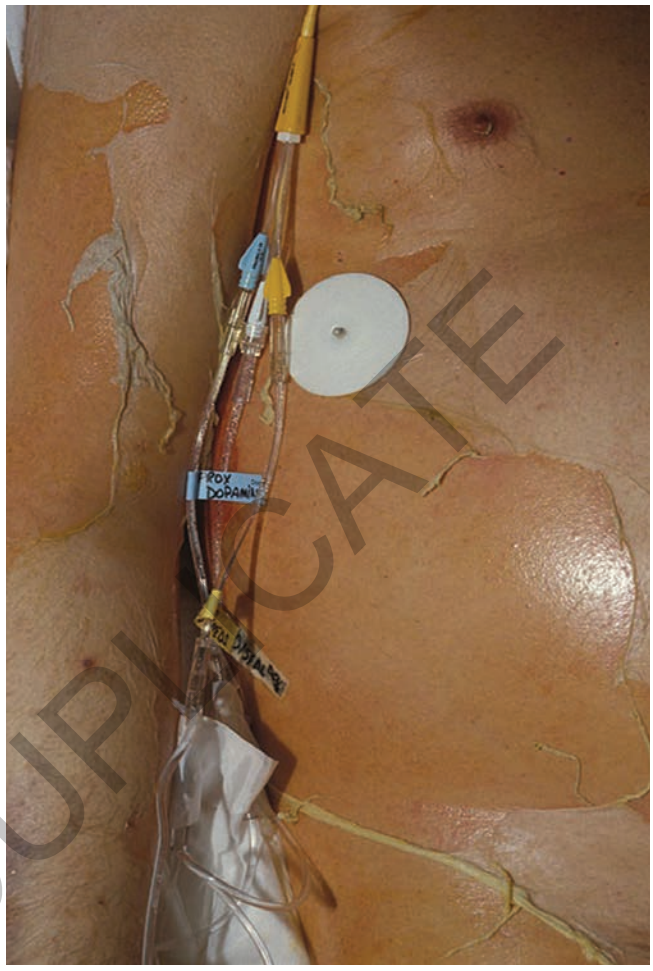

**Figure 7.** Drug reaction: toxic epidermal necrolysis. Available at: https://commons.wikimedia.org/wiki/file:toxic-epidermal-necrolysis.jpg (used with permission).



Narrative reviews and case reports support that the disorder results from an imbalance in procoagulation-anticoagulation factors and is frequently but not always seen in patients with protein C and protein S deficiencies[95-100] (see Figure 8).

HIT syndrome necrosis (specifically HIT II) is caused by antibodies reacting to the heparin drug components that form antibody complexes and serve to destroy platelets.[95] The patient will develop decreased platelets and possible venous and arterial thrombosis. A "4Ts Score" can be used to assist with diagnosis (thrombocytopenia, timing of platelet fall, thrombosis and sequelae, and ruling out other causes for thrombocytopenia).[101] HIT lesions can begin as reddened painful areas that can progress to large bruised areas or serosanguinous bullae. Depending on severity, literature reviews and case reports note the lesions may become necrotic[102,103] (see Figure 9).

Hematologic/vasculitic drug-induced response presents with maculopapular rash, palpable purpura, petechiae, and systemic symptoms such fever, urticaria, and arthralgias. Drugs commonly involved include hydralazine, minocycline, propylthiouracil, antimicrobials, diuretics, phenytoin, and allopurinol[82,104] (see Figure 10).

## Clinical Practices That Mitigate the Effect of Drugs on Wound Healing/Wound Generation

Because chronic wounds and dermatologic ADEs are relatively common, knowledgeable clinicians of all disciplines have to be cognizant of a drug's potential to cause wounds or impair wound healing and utilize strategies to minimize this risk as much as possible. Some general management approaches can assist with this endeavor. Multiple narrative reviews suggest addressing several specific components for any wound patient, especially in the presence of a nonhealing wound.

1. Obtain a detailed medical history, noting any past occurrences of drug sensitivity, contact dermatitis, connective tissue disease, atopy history (eg, asthma, eczema), or previous wound healing delays.
2. Review a detailed accurate medication history including dose, intervals, and start date.

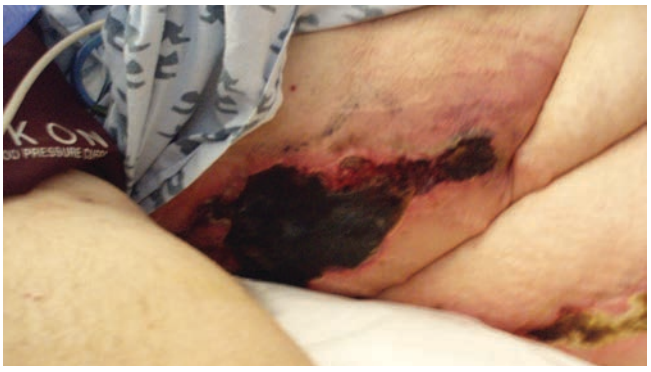

**Figure 8.** Drug reaction: warfarin-induced skin necrosis.

3. Obtain a history and document use of all OTC medications.
4. Document use of herbals or "natural" medications (eg, St. John's Wort, echinacea).
   a. Ask what form is ingested (teas, liquid extracts, capsules).
   b. Ask if the patient is using any topical, natural, or herbal products on the wound bed or skin.
   c. Ask if the patient spaces herbals away in time from other drugs (eg, St. John's Wort, ginkgo biloba) to avoid drug interactions; some natural therapies interact with the cytochrome P450 (CYP450) drug metabolism system.
5. Ask about recent use or reception of vaccines or contrast dye media.
6. Identify "red-flag" prescription medications for potential drug interactions (eg, warfarin, digoxin, lithium, cyclosporine, protease inhibitors).
7. Note the following for people with a new onset dermatologic adverse drug event:
   a. The time of medication use relative to onset of skin reaction;
   b. The physical manifestations of the skin reaction owing to previously described characteristics and etiologies.
8. Educate patients with an adverse dermatologic drug reaction about avoiding the drug in the future and clearly document the drug reaction type and patient instructions given in the patient history. If the reaction is serious enough, the clinician should recommend a Medic-Alert bracelet for the patient and notify regulatory authorities such as the Food and Drug Administration's (FDA) Adverse Event Reporting System (www.fda.gov).
9. Analyze medical history/current status for other hidden factors potentially affecting drug therapy and wound healing for patients with refractory wound healing:
   a. Is malnutrition present?
   b. Does the protein insufficiency affect drug protein binding (eg, dilantin/phenytoin) and consequently drug toxicities?

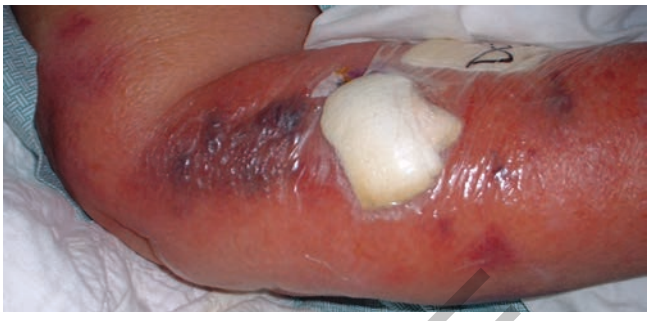

**Figure 9.** Drug reaction: heparin-induced thrombocytopenia syndrome.

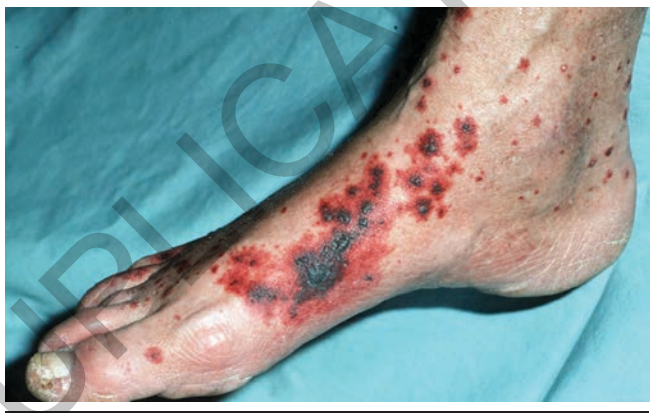

**Figure 10.** Vasculitic appearance.
*(Used with permission of DermQuest (www.dermquest.com/image-library/image/5044bfd0c97267166cd64e2d).*

**Table 4. Practice implications: ARMOR mnemonic[113]**

| | |
|---|---|
| Assess | **A:** Assess Beers criteria, use of beta blockers, pain meds, antipsychotics |
| Review | **R:** Review drug-drug and drug-disease interactions; adverse drug event |
| Minimize | **M:** Minimize number of meds related to patient's functional status |
| Optimize | **O:** Optimize for renal/hepatic status |
| Reassess | **R:** Reassess functional/cognitive status 1 week after changes and periodically |

   c. Does the patient have fatigue, pain, or mouth ulcers?[105]
10. Consider chronic diseases and associated drug therapy for elderly persons with, or at risk for, nonhealing wounds:
   a. How may aging affect drug metabolism and excretion?
      1) Note that both kidney and liver function decrease with aging, so function needs to be monitored (eg, use creatinine clearance to monitor kidney function in the elderly as opposed to creatinine level).

2) Note use of high-risk drugs in the elderly and avoid use as per the Beers criteria (antipsychotics such as haloperidol, hypnotics (diazepam), diuretics (eg, furosemide).[106]
3). Note use of worrisome drugs commonly used in specific chronic conditions (eg, disease-modifying, antirheumatic drugs (DMARDS) such as methotrexate and sulfasalazine in rheumatoid arthritis).[107]

b. Assess patients of all age groups with multiple comorbidities and particularly the elderly with chronic wounds or at risk for skin reactions[108-110] to:
1) Reduce polypharmacy as much as possible. Wound specialists need to interact with primary care providers to continually assess need and "deprescribe"[111];
2) Educate patients that polypharmacy is not only receiving excess drugs, but also going to more than one pharmacy. The latter is risky and should be avoided[112]; and
3) Put on ARMOR and assess the wound patient to review and revise drugs being prescribed[7,113] (see Table 4 for ARMOR mnemonic).

## Discussion

Wound clinicians need to develop a sophisticated level of knowledge regarding pharmacotherapy and its potential for hindering wound healing and/or causing altered skin integrity. Conversely, judicious use of topical or systemic therapy can facilitate wound healing. Lack of regard for pharmaceutical adverse effects can hinder positive wound and skin outcomes.

Narrative literature reviews describe agents that can help wound healing (eg, vitamins, minerals [zinc, iron], and hormones [estrogen]). Wound clinicians need to recognize categories of drug agents that are higher on the list of risk offenders for wound healing and/or adverse skin events. These include antibiotics (penicillins, sulfa agents), anticoagulants, nicotine (via smoking), steroids, and drugs that decrease blood flow (eg, vasoconstrictors).[2,43,77,82,88] However, most drugs have the potential to either delay wound healing and/or cause skin eruptions in certain circumstances (eg, too high dosing, allergic states, impaired renal or liver function, and malnutrition).

A noteworthy implication for clinical practice is patient use of herbal supplements and other nontraditional substances. The literature suggests vigilance for usage because these products may hinder wound or skin health (even when used alone) or interact with traditional medical therapy, causing adverse events. As the United States becomes increasingly diverse, the use of nontraditional therapies likely will increase. Clinicians need to ask what is being used and how it is consumed (topical or oral use).

Another aspect of care related to wound healing in particular is the increasing analysis of offlabel topical drug therapy. For persons with recalcitrant wounds that have not responded to other adjunctive therapies, judicious offlabel topical use of systemic (oral or injectable) drugs may add to the science of care. Clinicians need to review the literature for research testing such agents as topical insulin, phenytoin, and sildenafil. Patient consent, ethical clearance, and full information are necessary.

## Conclusion

A review of the relevant literature shows certain medications substantively impede wound healing and possibly cause wound and skin damage. Some drug classes are more frequent offenders and demand that wound professionals be cognizant of the risks of their use. Wound care clinicians must be aware of their patient's overall drug therapy, not just what is being administered to their wound. The nonhealing wound has been called a major snowballing threat to public health and the American economy,[114] so the stakes are high. Clinical approaches to mitigating the effects of drugs "breaking bad" on the intact skin and a healing wound need to be in the armamentarium of every wound care clinician. ■

**For the full list of references, please view the article online at: www.o-wm.com/article/ pharmacologic-impact-aka-breaking-bad**

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