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How oral medications affect wound healing

By Jeffrey M. Levine, MD, AGSF, CWSP

THE ART OF WOUND CARE is as old as human civilization, yet given the advances in medical science of recent decades, surprisingly few oral medications are available that directly improve healing. The addition of an effective oral formulation to heal wounds would be immensely beneficial to the wound care field because of ease of use and acceleration of healing time.

Of the oral medications available for wound care, most target ancillary aspects such as pain management, infection mitigation, and nutrition. There are several reasons for this, the first being the challenge of study design in patients with confounding factors that include multiple comorbid illnesses.[1] In addition, a wound healing treatment must meet the FDA requirement of full closure during a fixed investigational period with statistical significance.[2]

This article describes oral pharmacologic agents intended to build new tissue and aid in wound healing, and discusses oral medications that interfere with wound healing. A detailed discussion of the pharmacology of pain management, treatment of infection, and role of nutritional supplements including micronutrients is beyond the scope of this article.

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Anabolic agents

Optimum nutrition is a well-recognized component of wound healing.[3] Patients with wounds are often in a hypermetabolic or catabolic state. Pressure injuries, for example, commonly occur in debilitated patients with involuntary weight loss and protein-energy malnutrition. With a loss of 30% or more of lean body mass, the body will shunt resources from a wound to basic functions, essentially halting the healing process.[3] The same principles apply to wounds other than pressure injuries. A major strategy, therefore, has been directed toward development of anabolic medications intended to increase body weight and muscle mass.

Four major anabolic hormones potentially impact wound healing:[4]

- human growth hormone (HGH)
- insulin-like growth factor-1 (IGF-1), also called somatomedin C
- insulin
- testosterone and its analogues.

Produced in the anterior pituitary gland, **HGH** has powerful anabolic effects, including accelerated cell proliferation, stimulation of IGF-1, and production and stimulation of uptake of amino acids into cells. Other metabolic activities of HGH include increased fat metabolism, increased protein and nucleic acid synthesis, increased insulin resistance, and decreased cortisol receptor activity. Although HGH has been shown to increase skin thickness in healthy humans and increase the rate of reepithelialization of skin graft donor sites, little or no data have shown that it has a positive impact on wound healing in humans.[4] Significant complications include increased insulin requirements, fluid retention, hypercalcemia, and increased metabolic rate. In addition, because HGH isn't available in oral form, it must be administered parenterally.

Somatomedin C, another name for IGF-1, is similar in its physiologic effects to insulin.[4] It's produced in the liver, and its anabolic activity is directly related to HGH. It's recognized as a general wound healing stimulant and causes fewer adverse reactions than HGH, but its short half-life limits its clinical usefulness. Like HGH, it's not available in oral form.

Insulin, a hormone produced in the pancreas, has anabolic activities in addition to its effect on glucose and fat metabolism. Clinical trials in burn patients have shown that insulin stimulates protein synthesis and increases net nitrogen uptake, but the effects on wound healing haven't been well studied in humans.[4] In addition, insulin must be delivered parenterally.

Testosterone, a steroid hormone produced in the testes in men and by the ovaries and adrenal glands in women, has both masculinizing and anabolic properties. Even before the molecule was identified, topically administered testicular paste was considered a potential accelerator of wound healing.[5] Testosterone's anabolic properties include increasing skin thickness and muscle size and strength. Decreased production of testosterone is associated with increased age, injury, trauma, and chronic illness. Testosterone deficiency leads to catabolism and impaired healing, but exogenously delivered testosterone hasn't been demonstrated to have a positive direct effect on wound healing.[4] Anabolic steroids are produced by modification of the testosterone molecule to decrease androgenic adverse reactions while taking clinical advantage of its ability to stimulate protein synthesis and new tissue formation.[4]

Oxandrolone is a synthetic derivative of testosterone with both anabolic and androgenic properties. It's the only FDA-approved oral anabolic steroid for restoration of lost body weight. Adverse reactions include cholestatic jaundice, increased risk of prostatic hypertrophy and cancer in men, and virilization in women. The prescribing information contains a boxed warning for peliosis hepatis, liver cell tumors, and blood lipid changes.

In vitro and animal studies, as well as small therapeutic trials, have shown that oxandrolone has positive effects on collagen synthesis, tensile strength, and bone and matrix formation. This would seem to have great promise for wound healing, but orally administered oxandrolone hasn't met these expectations.[6]

In one of the few major, randomized, placebo-controlled clinical trials with oral medication for pressure injuries, oxandrolone was tested in Veterans Affairs spinal cord units across the country.[7] The study was designed to test the efficacy of oxandrolone to heal chronic pressure injuries of the pelvic region that hadn't responded to standard or other treatment methods. Study outcomes were full closure of a pressure injury with proof of efficacy, as well as information on the rate of healing and economic analysis on potential cost reduction. The investigators found no discernible evidence of facilitating wound healing or benefit in keeping a healed wound closed, with no more beneficial effect above the usual standard of care.[7]

Appetite stimulants

Given the close association of nutrition with the wound healing process, it makes sense that increased oral intake of nutrients and weight gain is beneficial.[8] Protein-energy malnutrition can result from either the catabolic state of acute illness or the cytokine-associated anorexia/cachexia syndrome often seen with aging patients and those with chronic illness. Nutritional strategies are therefore a critical component of a plan to heal wounds, with nutrient intake calculated to include consideration of both the stress response and the increased requirements of

wound healing.[9] This includes protein, calories, amino acids, and micronutrients. Whenever weight loss is noted, reversible causes should be considered with interventions aimed at provision of adequate protein and calories.[8] The differential diagnosis of weight loss includes the catabolic state associated with acute illness, cytokine-mediated cachexia, starvation, age-related loss of muscle mass, depression, malabsorption, and hyperthyroidism.

If weight loss continues despite implementation of standard environmental and nutritional interventions, orexigenic drugs (appetite stimulants) should be considered.[10] One of the most commonly used oral medications for appetite stimulation is megestrol acetate, a synthetic progesterone originally used as therapy in women with breast cancer. Megestrol improves appetite and body weight in people with HIV/AIDS, although the precise mechanisms for weight gain are unknown.[9] Adverse reactions include venous thromboembolism (VTE), glucose intolerance, abdominal pain, and increased low-density lipoprotein.

Dronabinol is a synthetic delta 9-tetrahydrocannabinol, the active ingredient of marijuana. It's been shown to be beneficial in patients with AIDS, cancer-related cachexia, and Alzheimer disease.[9] Adverse reactions include paranoid reaction and somnolence.

Other oral medications used for increased appetite and weight gain include mirtazapine, an antiserotonergic compound indicated to treat major depressive disorder, and cyproheptadine, an antihistaminic and antiserotonergic agent. Atypical antipsychotics including clozapine, olanzapine, risperidone, and quetiapine are also known to cause moderate weight gain but haven't been recommended for cachexia or protein-energy malnutrition.[11] In short, evidence linking weight gain from orexigenic agents to improved wound healing is very limited.

The utility of complementary approaches, such as nonvitamin, nonmineral, oral supplements for wound care, isn't well established.

Menopausal hormone therapy

Estrogen can exert substantial influence on the physiology and composition of skin and may have a key role in maintaining skin integrity and structure. Several studies in both humans and animals suggest that estrogen deprivation is a substantial factor in delayed wound healing.[12] Estrogen deficiency amplifies inflammatory responses and delays angiogenesis, whereas exogenous estrogen promotes reepithelialization and matrix deposition by fibroblasts and increases local vascularization. Menopausal hormone therapy (MHT) has been associated with stroke, breast and other cancers, and VTE. Although theoretically beneficial for accelerated wound healing, MHT hasn't been recommended for this purpose.

A new class of pharmaceuticals may hold promise for wound healing: the selective estrogen receptor modulators.[13] Examples include tamoxifen and raloxifene. These compounds exert tissue-specific agonist/antagonist activities that mimic estrogen effects while minimizing adverse reactions. Their use in wound healing, however, requires more investigation.[12]

Oral medication for lower-extremity wounds

The first step in formulating a treatment plan for lower-extremity wounds is to address the underlying illness and issues of diet and lifestyle. The diagnosis is critical for prescribing considerations because various disorders can lead to lower-extremity wounds, such as deep vein thrombosis, atherosclerosis, thrombophilic disorder, vasculitis, hemoglobinopathy, malignancy, hypertension, diabetes mellitus, and dyslipidemia. Vascular or podiatry consultations may be indicated for lower-extremity wounds. Once these steps are completed, oral medication can be considered.

Pharmacologic risk factor interventions for patients with peripheral arterial disease (PAD) include antihypertensive therapy and low-density lipoprotein cholesterol-lowering therapy with statins. Treatment of diabetes mellitus must be individualized, balancing the deleterious effects of elevated hemoglobin A1C with the potential harms of hypoglycemia.

Antithrombotic therapy, particularly antiplatelet monotherapy, with aspirin or clopidogrel has benefits in patients with symptomatic PAD.[14] Cilostazol is an inhibitor of phosphodiesterase-III that reduces platelet aggregation, enhances vasodilation, and improves claudication symptoms in patients with

PAD.[14] Although theoretically these antithrombotics can improve wound healing by improving circulation, little data support routinely prescribing these medications for lower-extremity wounds.[14]

Pentoxifylline is a pharmaceutical with diverse properties. This xanthine derivative is an antioxidant, vasodilator, and hemorrheologic agent that increases erythrocyte flexibility and improves microcirculation and oxygen delivery.[15] Other effects include inhibition of inflammatory mediators, decreased cytokine release, and suppression of leukocyte function. One Cochrane database review recommends pentoxifylline for venous ulceration in combination with compression modalities to increase the chances of healing.[16]

Complementary approaches

Complementary approaches to healthcare encompass a wide range of modalities with a history of use or origins outside conventional Western medicine. Examples are acupuncture, biofeedback, folk medicine, special diets, meditation, and yoga, to name a few. In recent decades, complementary therapies have significantly increased among all age groups in the United States.[17] However, the utility of complementary approaches, including nonvitamin, nonmineral, oral supplements for wound care, isn't well established.

Complementary approaches to cutaneous wound healing include phytotherapeutics (also known as ethnobotanicals) or plant-based medicines that have significant pharmacologic effects.[18] Numerous compounds have been described, including aloe vera, mimosa, echinacea, chamomile, ginseng, jojoba, tea tree oil, garlic, and ginkgo; however, all of these are administered topically.[18]

Triphala is an ayurvedic herbal formula taken orally and recommended for numerous medicinal effects including wound healing, but scientific studies are limited.[19] Another compound that has been reported for oral administration is curcumin (diferuloylmethane). It's the major bioactive component of turmeric—a common spice used for centuries in South Asian countries in cooking and traditional medicine. Some reports suggest that curcumin is a naturally occurring anti-inflammatory agent that has analgesic and prohealing effects on burns and other wounds.[20] Curcumin can be administered either topically or orally, but because of bioavailability issues, the optimum dosage and delivery route are still not established.

Drugs that interfere with wound healing

Four commonly accepted phases of wound healing are coagulation, inflammation, proliferation, and wound closure with matrix remodeling and scar formation.[21] Many growth factors and cytokines are involved, and each of these steps is vulnerable to disruption by specific oral medications. (See *Selected oral medications that can inhibit wound healing*.) These medications can contribute to delayed wound healing, wound dehiscence, and infection.

Coagulation (hemostasis), the first step in wound healing, is mediated by platelet-derived growth factor, transforming growth factor, and other coagulation factors. Oral anticoagulants such as warfarin and the newer anticoagulants such as apixaban, rivaroxaban, and dabigatran can inhibit coagulation factor production. Antiplatelet medications such as aspirin, clopidogrel, and dipyridamole can inhibit platelet aggregation. Cytotoxic agents such as methotrexate can suppress hematopoiesis and cause thrombocytopenia. Any of these medications can potentially inhibit the early stages of wound healing.[21]

Selected oral medications that can inhibit wound healing

Medication	Class
Apixaban	Factor Xa inhibitor
Aspirin	NSAID
Azathioprine	Immunosuppressant antimetabolite
Capecitabine	Nucleoside metabolic inhibitor with antineoplastic activity
Celecoxib	Selective COX-2 inhibitor/NSAID
Clopidogrel	Platelet aggregation inhibitor
Corticosteroids	Immunosuppressant
Cyclosporine	Immunosuppressant
Dabigatran	Direct thrombin inhibitor/anticoagulant
Dipyridamole	Platelet aggregation inhibitor
Ibuprofen	NSAID
Methotrexate	Antimetabolite
Mycophenolate	Immunosuppressant
Naproxen	NSAID
Rivaroxaban	Factor Xa inhibitor/anticoagulant
Valdecoxib	Selective COX-2 inhibitor
Warfarin	Vitamin K antagonist/anticoagulant

Nonsteroidal anti-inflammatory drugs (NSAIDs) are relatively inexpensive and often prescribed for pain management. Many are available over the counter. Other medications in a similar class include selective cyclooxygenase-2 (COX-2) inhibitors such as celecoxib and valdecoxib. Their mechanism of action is inhibition of the inflammatory mediator prostaglandin E2, the lipid mediator of inflammation in the wound healing process.[21] Animal studies have demonstrated an antiproliferative effect on blood vessels, delaying healing rates.[22] Because of the inhibition of inflammation that is a critical component of wound healing, NSAIDs and selective COX-2 inhibitors should be used with caution.[23]

Chemotherapeutic agents not only target rapidly dividing cancer cells, but also inhibit wound healing. Adverse reactions can include delayed inflammatory phase of healing, decreased fibrin deposition and collagen synthesis, and delayed wound contraction.[21] Methotrexate is an oral chemotherapy agent and immunosuppressant used to treat malignancies and autoimmune diseases. When prescribed for autoimmune disorders, methotrexate and azathioprine are sometimes classified as disease-modifying antirheumatic drugs (DMARDs), and all have a potential negative impact on wound healing.[24]

Immunosuppressants are often prescribed to prevent organ rejection and to treat autoimmune diseases such as systemic lupus erythematosus and psoriasis. Oral immunosuppressants include cyclosporine, azathioprine, and mycophenolate. These medications interfere with T cells and other inflammatory mediators and can therefore impede wound healing. Reducing the dosage or avoiding these drugs altogether is recommended until complete wound healing occurs.[25]

Given the advances of recent years, it's surprising that so few oral medications are available to improve wound healing.

Corticosteroids impact wound healing by stabilizing lysosomes within neutrophils, inducing anti-inflammatory proteins, and inhibiting cytokine release and chemotaxis.[24] Other effects include fibroblast dysfunction, reduced collagen production, angiogenesis, reepithelialization, and decreased wound tensile strength.[24] Clinical consequences can be severe and include delayed wound healing, dehiscence, infection, and permanent weakening and atrophy of the skin. Other systemic complications of oral corticosteroids include drug-induced diabetes mellitus. Although some evidence suggests that androstenediol can reverse the inhibitory effects of steroids on wound healing, corticosteroids should be avoided if possible in patients with healing wounds.[26]

Looking to the future

The historian Guido Majno eloquently stated that the art of healing is one of humankind's greatest creations.[27] In addition, wound care is arguably the oldest of the healing arts. Given the scientific and technologic advances of recent years, it's surprising that so few oral medications are available to improve wound healing.[28] (See *Nursing practice pearls*.) An oral medication that accelerates wound closure would not only improve patient care, but would also decrease healthcare expenditures. ■

Nursing practice pearls

- Oral pharmaceuticals that directly enhance wound healing are uncommon.
- Oral anabolic steroids have shown limited effectiveness in wound healing.
- Evidence linking oral orexigenic agents (appetite stimulants) such as megestrol acetate and dronabinol to improved wound healing is also limited.
- MHT, although theoretically beneficial, hasn't shown promise for accelerated wound healing.
- The only oral medication that has shown possible use for lower-extremity wounds is pentoxifylline for venous ulcers in combination with compression modalities.
- Many classes of oral medication can inhibit wound healing, including anticoagulants, NSAIDs, chemotherapeutic agents, DMARDs, immunosuppressants, and corticosteroids.

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Jeffrey M. Levine is an attending physician at Mount Sinai Beth Israel Medical Center and Icahn School of Medicine at Mount Sinai, New York, N.Y.

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