Pathogenesis and Treatment of Pain in Patients with Chronic Wounds

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ABSTRACT

Pain must be managed during treatment of a patient with a chronic wound. Failure to do so will significantly impair the patient's ability to heal. Understanding the wound's etiology is essential for designing the wound-healing protocol and implementing its pain-management regimen, of which a critical part is the chronic-wound patient's self-assessed scores of pain and functionality. In this report we present a paradigm for treating all chronic wounds, which was subsequently applied to 32 consecutive patients. Our integrated-team approach to managing the treatment of wounds includes accurate evaluation of the progression of patients' pain. Directors of the pain-management team and wound team have jointly managed hundreds of patients—either hospitalized or seen in both outpatient clinical practices. The three general categories for etiologies of the 10 most common types of chronic wounds are: ischemia, neuropathy, and direct tissue damage (e.g. pressure ulcers and venous stasis ulcers). Each of these are treated with unique analgesic regimens focused on surgical/medical management of the wound: oral and parenteral medications in combinations designed to

facilitate specific additive analgesic effects and nerve blocks and implantable devices for correcting underlying wound pathophysiology. Successful treatment of pain generally results in increased functional independence and improvement of the patient's quality of life. Our integrated wound-care, pain-management team, established guidelines that delineate the causes of chronic wounds and categorize treatment options for practical clinical use. The expectation is that all pain should be resolved in all patients if both the wound-healing and pain-healthcare providers use current technologies and drugs.

INTRODUCTION

The Joint Commission for the Accreditation of Healthcare Organizations (JCAHO) has published guidelines mandating the assessment and treatment of pain in hospitalized patients. They emphasize the complexity and urgency of treating pain, particularly in patients with multiple comorbidities.[1] Comorbidities are often associated with chronic wounds and the management of pain for chronic wound patients is critical; however, the JCAHO report does not specifically address the pain experienced by these patients, which can be substantial. It is mandatory that during treatment of a patient's healing wound, pain be managed simultaneously, with the goal of attaining a painless healing wound.

The prevalence of chronic wounds in the United States is estimated to be approximately 6.5 million.[2] More than 65% of wound-care patients experience severe pain, with another 20% experiencing mild-to-moderate pain.[3] Many studies document the deficiencies associated with treating both acute and chronic pain. Reasons cited for inadequate pain management of chronic wound patients by healthcare providers include lack of training or knowledge of analgesics, fear of side effects (e.g., fatigue, decreased mental alertness) or addiction, and a prevalent attitude that complete pain relief is not a primary objective. Of the patients treated by our team, no patient had pain that could not be resolved. Significant pain is not acceptable in any patient with a wound.

Currently, pain is often considered a "fifth vital sign" in monitoring clinical recuperation, especially in post-procedural patients. Evidence indicates that factors contributing to pain decrease the immune response, with concomitant and potentially deleterious effects on infection rates and the healing process.[4] Pain management of a chronic wound is as specific as the etiology of the chronic wound itself. Just as protocols exist for treating the various categories of chronic wounds, it is critical that a set of guidelines be established to manage pain in chronic wound patients. In addition, these guidelines can provide an objective assessment of the extent of healing by noting changes in analgesic requirements. Through the use of these guidelines, patients are expected to achieve 100% healing as long as their wounds are identified and treated soon after onset and no serious morbidity is present (e.g., ischemia or osteomyelitis).

We have designed an integrated team approach to treat the pain frequently associated with chronic wounds. The team includes healthcare professionals experienced in both pain management and wound healing. The basis of the team is collaborative bedside rounds of two physicians—the director of the pain team and director of the wound team. Bedside 'rounding' of the hospitalized patients with chronic wounds, numbering at a minimum of 25 in patients at any given time, gave both clinicians the opportunity to understand each other's treatment regimen. More importantly, it resulted in enhanced quality of care and decreased length of hospital stay for the treated patients. The minimizing or elimination of pain was a critical factor that contributed to these results. Collaboration between the physician managing the pain and the wound-care provider emphasizes the importance of a team approach, which ensures comprehensive patient management. Each clinician maintains a unique understanding of wound pathophysiology from the perspective of a particular field of expertise, thus contributing significantly to the appropriate treatment regimen for each type of chronic wound and its symptoms. Subsequently, this has resulted in the current practice of patients treated on an outpatient basis in the clinical setting of either the director of the pain team or director of the wound-healing team. The patient sees both physicians once each month in the same office simultaneously.

The specific pathogenesis of the cause of pain has not been delineated previously for most types of chronic wounds. To address this issue, we have reviewed the pathogeneses of these wounds as they relate to pain. The guidelines we have established for treating pain are derived from the 10 most common causes of wounds. The 3 broad categories of the etiologies of pain in chronic wounds are: ischemia, neuropathy, and direct tissue damage (Table 1). These basic pathophysiologies have implications for selecting the appropriate pain-management treatment.

ARTERIAL INSUFFICIENCY ULCERS

Arterial insufficiency ulcers, caused by ischemia, are secondary to partial or complete occlusion (e.g., from accelerated arteriosclerosis) of the large vessels to the lower limb. Of the patients who present with ulceration and rest pain, 20% progress to amputation.[5]

Clinically, arterial insufficiency ulcers often progress in parallel with complaints of nocturnal foot pain. Ischemic rest pain is described classically as burning pain in the ball of the foot and toes, worse at night when the patient is in bed.[6] These ulcers occur frequently after minor trauma and increase in size due to inadequate blood supply to the area. Physical examination typically discloses the ischemic ulcer as characteristically shallow, well demarcated, and occasionally covered with a thick eschar.

Pain management for the arterial insufficiency ulcer aims at treating the underlying ischemia. One available pain-management treatment modality is sympathetic blockade, which decreases ischemic pain by vasodilating the affected blood vessels, thereby increasing blood

Table 1. Etiologies of Pain in the 10 Most Common Chronic Wounds

CHRONIC WOUND	ETIOLOGY
Ischemic	Ischemia
Sickle cell disease	Ischemia
Diabetes	Neuropathy/Ischemia
Venous stasis disease	Tissue damage
Infection	Tissue damage
Pressure	Tissue damage
Obesity	Tissue damage
Steroids	Tissue damage
Chemotherapy	Tissue damage
Radiation	Tissue damage

flow. Specifically, a regional sympathetic block may be applied to dilate the smooth muscle in venules and arterioles, which results in a decrease in peripheral resistance and an increase in capillary blood flow. Skin capillary oxygen tension and saturation are, thus, both increased. The opening of collateral vessels secondary to the sympathetic blockade can act as a non-operative microvascular bypass that helps increase blood flow to areas of microvascular stenosis not amenable to vascular bypass procedures. By opening collateral vessels, a "steal phenomenon" is possible, in which blood flow is shunted to other vessels; therefore, the more localized the regional block, the less the "steal."

Before the advent of vascular bypass surgery, regional sympathectomy was a primary option for treatment of ischemic disease. As surgical techniques and grafts became more sophisticated, sympathetic blocks were used primarily when the medical condition of the patient or the anatomy precluded a vascular bypass. Currently, with improved fluoroscopic-guided techniques, regional sympathectomies are used increasingly for treatment of peripheral vascular disease, including painful non-healing arterial insufficiency ulcers.

In a group of 386 patients with occlusive vascular disease, including arterial insufficiency ulcers, 80% demonstrated partial to complete relief of rest pain after neurolytic sympathectomy. In those patients without pre-existing gangrene, 84% received complete or partial relief, compared to 56% of those with pre-existing gangrenous lesions. Mean duration of pain relief was 5.9 months, which coincided with the duration of the sympathetic block as measured by the cobalt sweat test. Two years after the block, 35% were alive and their skin was without ulcerations.[7]

Epidural anesthesia, lumbar sympathetic block, or spinal-cord stimulation can facilitate a sympathetic block to the lower extremities. Epidural anesthesia by way of a percutaneous catheter can be used in a hospitalized patient for up to a week before the catheter must be changed, and is most useful when a bilateral sympathetic block is indicated. Low concentrations of local anesthetic allow for a sympathetic block without a motor block, which facilitates patient ambulation. Tunneled epidural catheters can be used if long-term or home use is anticipated.

For a more specific regional sympathetic block of either lower extremity individually, a lumbar sympathetic block can be administered. This procedure is a percutaneous block of the unilateral lumbar sympathetic chain performed under fluoroscopic guidance that can be done as an ambulatory procedure. With this block, less chance of motor blockade, hypotension, and vascular steal exists, as opposed to an epidural block. The lumbar sympathetic block can be administered as a series of local anesthetic injections. If the relief obtained with the local anesthetic blocks is good but not long lasting, a neurolytic block can be administered as a chemical neurolysis or radio-frequency lesioning.

Spinal cord stimulation can inhibit central sympathetic output. It has been used to treat peripheral vascular disease, and results in increased local blood flow and promotion of healing of ischemic ulcers. This procedure entails placement of electrodes into the epidural space for stimulation of spinal cord dorsal columns. For example, with a mean follow up of 25 months following spinal-cord stimulation, ischemic pain relief is maintained in 73% of the patients.[8] In addition, patients are able to walk farther.

Oral analgesic regimens following the stepwise approach of the World Health Organization (WHO) ladder can be used in conjunction with sympathetic blocks, solely to decrease pain, either acute or chronic. If ulcer pain requires the use of frequent PRN opioids, use of an extended release opioid may provide better analgesia with fewer overall side effects.

SICKLE CELL ULCERS

Sickle cell disease originates from a substitution of glutamic acid for valine at the sixth position on the beta hemoglobin chain, which in turn, results in formation of sickle cell hemoglobin S rather than normal hemoglobin A. Hemoglobin S is capable of normal oxygen loads; however, when deoxygenated, it forms rigid and inflexible hemoglobin moieties (sickle-shaped erythrocytes). These rigid hemoglobin S moieties cause occlusion of the microcirculation, which produces hypoxemia, ischemia, and infarction leading to painful crises. The more extensive vaso-occlusive events result in systemic infarcts, including cutaneous ulcerations.

In sickle cell anemia, microcirculatory occlusion may appear as lower-extremity ulcers.[9] Although the pathogenesis is not completely understood, compromised blood flow to the muscle and bone is likely the most common origin of pain and non-healing. Sickle cell leg ulcers should always be treated as soon as they are discovered—including debridement of non-viable tissue—to prevent progression to a large, non-healing ulcer. Controlling infection is a high priority in treating these wounds. Systemic antibiotics often with debridement should be used whenever drainage, cellulitis, or both, are present. By nearly eliminating bacteria, pain often decreases.

Additionally, opioids are currently the analgesic of choice in treatment of pain associated with sickle cell vaso-occlusive crises.[10] Multiple routes of administration of opioids are available; however, intravenous patient-controlled analgesia (PCA) use is a preferred method for treating acute painful crises. PCA de-

vices allow patients to self-administer small doses of opioids for needed pain relief, and thus, bypasses the delay of calling nurses to the bedside and awaiting their return with pain medication.

A subset of patients with sickle cell ulcers will not receive adequate pain control with the intravenous PCA. For this group, epidural analgesia can be used to control their painful crises. In the setting of an acute painful crisis, the epidural catheter is placed while the patient is deeply sedated. Epidural analgesia with low-dose opioids alone, or in combination with local anesthetics, provides effective relief for patients who do not benefit from intravenous opioids. Addition of a local anesthetic not only enhances the analgesia, but also causes vasodilatation that can locally prevent sickle cell occlusion. Epidural PCA can abort acute chest syndrome by decreasing pain and improving oxygenation.

There exists a growing interest in the role of cognitive behavioral therapy as a treatment modality for pain associated with sickle cell anemia and sickle cell ulcers. The aim of cognitive behavioral therapy is to replace the patients' anxiety and distress with a sense of hope and mastery over their pain.[11] Psychological intervention can bring about a decrease in the frequency and intensity of acute painful crises. Nevertheless, most patients continue to require the pain team and wound team to work with the hematologist treating their sickle cell disease.

NEUROPATHIC FOOT ULCERS IN PATIENTS WITH DIABETES

Neuropathic ulcers are caused by pressure or injury in the lower extremity in areas of sensory deficit. Ischemia and infection contribute to the pain that results from these ulcers. It has long been known that a high percentage of patients with diabetes have neuropathic symptoms.[12] The symptoms associated with neuropathic pain are paroxysmal, burning, shooting, sharp, and lancinating pain. This pain follows a dermatomal distribution; the patient may have concomitant hyperesthesia, allodynia (a painful response to non-painful stimuli), or both, as well as aching, cramping, and tingling.[13] Pain also can occur in areas of sensory deficit; this condition is known as anesthesia dolorosa.

The classic clinical presentation of the diabetic neuropathic foot is a warm, dry foot with hyperkeratotic tissue. The classic neuropathic ulcer is commonly under a metatarsal head, surrounded by thick hyperkeratosis; has a pink, punched-out base that bleeds easily; and is painless.[14] Diabetic foot ulcers can occur on the plantar and dorsal surfaces of the foot as well as the toes.[15]

Neuropathies are often caused by axonal degeneration and segmental demyelination. This condition results in selective loss of large fibers (e.g., A-beta) that have an inhibitory effect on pain transmission from the periphery, according to the Gate Control Theory of Pain, with preferential regeneration of smaller fibers (e.g., A-delta and C) that have stimulatory input regarding pain sensation. The sum total of these changes is increased pain sensation from the periphery. One peripheral expression of neuropathic pain is formation of a neuroma, which results in abnormal spontaneous uncoordinated neuronal firing. Changes at the levels of the dorsal root ganglia, dorsal horn neurons, and brain itself have all been associated with neuropathic pain.[16]

Prevention of neuropathy in patients with diabetes is ideal. The Diabetes Control and Complications Trial demonstrated that intensive diabetes treatment (frequent insulin injections, or a subcutaneous insulin pump and frequent glucose monitoring) delays the onset effectively and slows the progression of long-term neurologic complications, including neuropathic pain.[17] Electrophysiologic abnormalities associated with diabetic neuropathy can be delayed or prevented by intensive treatment of diabetes, and the risk for clinical neuropathy can subsequently be reduced by as much as 64%.[18]

Neuropathy in patients with diabetes is often painful and should always be treated immediately.[19-21] Tricyclic antidepressants (TCAs) are among the first-line analgesics used for relief of neuropathic pain. Their mechanism of action involves inhibition of the reuptake of serotonin and norepinephrine in the descending inhibitory tracts of the spinal cord. Amitriptyline demonstrates the ability to relieve the pain of diabetic neuropathy independent of mood elevation.[22] However, amitriptyline can cause many complications, such as sedation, urinary retention, and orthostatic hypotension. Desipramine has the least anticholinergic side effects of the first-generation tricyclic antidepressants and causes relatively little sedation. It also has been demonstrated to be analgesic in diabetic neuropathy.[23]

Anticonvulsants have been used to treat neuropathic pain for many years. Both phenytoin and carbamazepine prove effective as neuropathic pain medications, but each causes numerous side effects.[24,25] Newer formulations of anticonvulsants that treat the pain of diabetic neuropathy, but with significantly fewer side effects, have been developed recently. Gabapentin (Neurontin®, Parke-Davis, Vega Baja, Puerto Rico) is one example of these new anticonvulsants shown recently to be effective for symptomatic treatment of painful neuropathy,[26,27] including diabetic neuropathy.[28] The only statistically significant side effects were dizziness and somnolence.

Other classes of drugs also are used to treat neuropathic pain. Mexilitene, an analog of lidocaine, can be given orally and demonstrates an analgesic effect on chronic painful diabetic neuropathy.[29] It is most effective against burning or stabbing types of pain. Capsaicin, a topical analgesic derived from chili peppers, was studied by the Capsaicin Study Group.[30] Patients with diabetes who have peripheral neuropathies demonstrated decreased pain, but had localized adverse effects such as burning and rash. N-methyl-D-aspartate (NMDA) inhibitors,[31] clonidine,[32] lidocaine patches,[33] and tramadol[34] have all been used with varying success in patients with diabetic neuropathic pain. Invasive techniques such as spinal-cord stimulation have been used in refractory cases.[35] The use of opioids for neuropathic pain is controversial.

VENOUS ULCERS

Venous ulcers are secondary to reflux between the deep and superficial venous system in the lower leg. Venous reflux results in an increase in venous pressure, venous dilatation, increased capillary permeability, and extravasation of fluids and proteins. Ultimately, skin breakdown occurs and an ulcer forms. Sixty-four percent of patients with venous ulcers report distressing or excruciating pain.[36]

Surgical management of venous stasis ulcers frequently includes intermittent debridements to remove non-viable tissue and stimulate granulation tissue formation, epithelialization, and contraction. The use of local anesthetic combination creams such as EMLA® (eutectic mixture of local anesthetics: lidocaine 2.5% and prilocaine 2.5%) (AstraZeneca,

Table 2. Typical Chronic Analgesic Regimen

ANALGESIC	SITE OF ACTION	CLINICAL EFFECT
Set dose, extended-duration opioid	Opiate receptors	Maintenance of analgesic levels within therapeutic window (more efficient analgesia with less side effects)
Non-steroidal anti-inflammatory drugs	Peripheral pain receptors	Analgesia; anti-inflammatory
Tricyclic antidepressants	Descending spinal cord inhibitory tracts	Analgesia; sleep promotion
Fast-onset, short-duration, PRN opioid	Opiate receptors	Analgesia for episodic breakthrough pain

Table 3. Common Extended-Duration Opioids

EXTENDED-DURATION OPIOID	DOSING INTERVAL	EQUIPOTENT DOSE [10 mg IV MORPHINE (ms)]
Methadone	6 hours	20 mg po/10 mg IV
Continuous release fentanyl patch (Duragesic, Janssen Pharmaceutica*)	72 hours	100 mcg/hour = ms IV 3 mg/hour
Extended release oral oxycodone (OxyContin, Purdue Pharma†)	12 hours	30 mg
Extended release oral morphine (MS Contin, Purdue Pharma‡)	12 hours	30 mg
Extended release oral morphine (Kadian, Faulding Laboratories§)	24 hours	30 mg
Levorphanol	6-8 hours	4 mg po/2 mg IV

*Titusville, New Jersey
†Stamford, Connecticut
‡Stamford, Connecticut
§Piscataway, New Jersey

Wilmington, Delaware, USA) demonstrated improvement in patient pain scores, as well as reduction of a number of required procedures and a higher wound-healing success rate, likely due to performing more effective debridements.[37] Venous leg ulcer patients treated with bilayered human skin equivalent (HSE) also showed improvement in health-related, quality-of-life variables, including decreased pain.[38]

In direct contrast to arterial insufficiency ulcers, venous ulcers do not respond to sympathetic nerve blocks; venous congestion can worsen with the use of these techniques. The primary pain-relieving modalities used to treat pain caused by chronic venous stasis ulcers are systemic analgesics. A systemic analgesic regimen for chronic pain uses the protocol recommended by the WHO analgesic ladder.[39] This protocol is a tiered system whereby less-potent drugs are used first, and drug potency is increased until the patient is comfortable with minimal side effects. If lower-tier medications are ineffective, then higher-tier medications are added to the regimen in a stepwise fashion. First-tier medications include non-opioids such as non-steroidal anti-inflammatory drugs, acetaminophen, tricyclic antidepressants, and tramadol. Second-level medications include "weak" opioids, such as combination drugs with acetaminophen and codeine, oxycodone, or hydrocodone. Third-tier medications

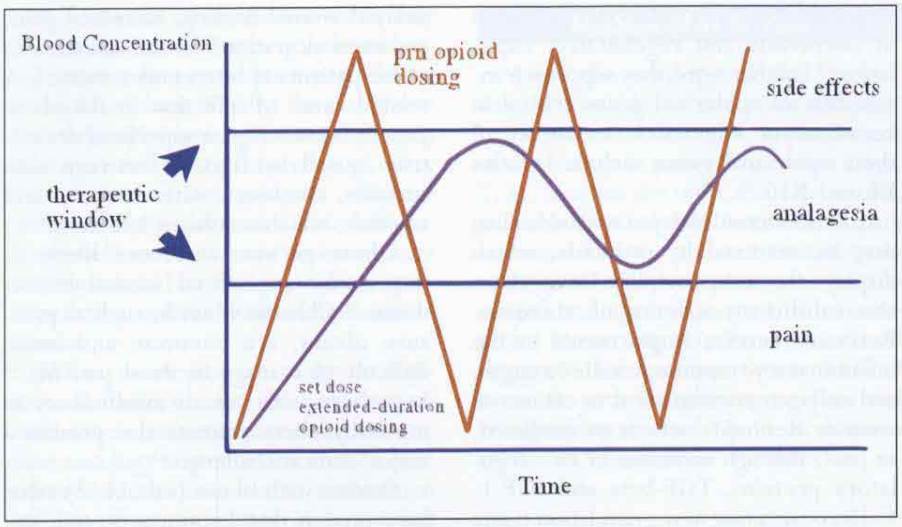


Figure 1. Blood concentrations with different opioid dosing regimens. Prescribing the long-acting opioids on a set-dose basis helps maintain more effective blood levels than administering the medications on an as-needed basis.

include all other opioids, both short- and long-acting.

The guidelines to follow when developing a chronic pain analgesic regimen begin with use of a combination of medications to decrease the side effects of any one of the included drugs separately (Table 2). When considering appropriate drug combinations, use of drugs that work on pain pathways at different points provide additive or synergistic results. If analgesia requires use of more potent medications from the WHO ladder, extended duration opioids frequently maintain analgesic blood levels within the therapeutic window more efficiently than do short-acting opioids (Table 3). Prescribing the long-acting opioids on a set-dose basis also helps maintain more effective blood levels than administering medications on an as-needed basis. PRN dosing maintains the analgesic blood levels in the therapeutic window for approximately one third of the time. Therefore, for the remaining two thirds of the time, the patient is either over-dosed and experiencing side effects, or under-dosed and in pain (Fig. 1).

Patients with venous stasis ulcers may require opioid use. These drugs can be readily administered.

PRESSURE ULCERS

Patients with pressure ulcers (59.1% to 68.2%) experience severe pain associated with their ulcers.[40] Spinal cord injury patients and those who require long-term ventilation are especially susceptible to pressure ulcers. Pain management for these patients is mandatory, and often ignored.

Patients who require pain management while being weaned from mechanical ventilation present a somewhat paradoxical situation, in that pain medications with significant potential for causing respiratory depression—such as opioids—are frequently required when maximization of respiratory effort is needed most. Several analgesic regimens may be used to help resolve this problem. Potent non-opioid analgesics such as intravenous ketorolac (Toradol®, Roche Labs, Nutley, New Jersey, USA) can provide effective pain relief with no respiratory depressant effects. Ketorolac is a parenteral nonsteroidal anti-inflammatory drug whose potency is comparable to that of morphine. Agonist-antagonist opioids have ceiling effects for respiratory depression. They have an agonist effect on the kappa opioid receptors leading to analgesia, and an antagonist effect on the MU opioid receptors that facilitate respiratory depression. Important to remember is that MU receptor antagonism can cause withdrawal symptoms in patients on chronic opioid therapy. Regional or central axis anesthesia (spinal or epidural) is another way of providing not only analgesia, but also anesthesia with minimal respiratory depression.

Spinal cord injury patients may experience partial sensation in an area that contains a pressure ulcer, which requires analgesics for somatic nociceptive pain. However, some patients with spinal cord injury lack sensation in a specific area, but can develop central pain in the region encompassing the area. The incidence of central pain in patients with spinal cord injuries can vary between 10%-90%, with approximately 30% of patients experiencing disabling pain after a traumatic injury.

Central pain is a category of neuropathic pain secondary to injury to the main ascending pain pathway in the spinal cord—the spinal thalamic tract. Clinically, patients experience a constant, burning dysesthesia with intermittent, acute lancinating exacerbations. Hyperesthesia (an exaggerated response to stimuli) and allodynia may be prominent.

Treatment regimen for central pain is currently incomplete. Neuropathic pain medications, such as anticonvulsants and tricyclic antidepressants, can provide a degree of analgesia. However, nerve blocks, neuroablative techniques, and neuromodulation (stimulators) have failed to provide good results consistently. Use of opioids for these patients is controversial; the risk of addiction exists and responsiveness of central pain to opioid analgesia is debatable. Analgesic responses to opioids sometimes require side effect-precluding dosages.

WOUNDS ASSOCIATED WITH INFECTION

Colonized bacteria are the most common reason for the presence of pain in a wound. In patients who were not previously opioid dependent, less pain after wound debridement is typically observed. Presence of bacteria results in the release of mediators of inflammation (e.g., prostaglandins) from inflammatory cells that sensitize peripheral pain receptors (nociceptors) in the area. The sensitized nociceptors have a lower threshold for stimulation, which results in the infected area feeling tender and more painful. In specific surgical procedures, it is preferable not to treat bacterial colonization; an example is a tracheostomy. In contrast, when treating a patient with a chronic wound, the following five indicators in which treatment of bacterial colonization is appropriate are: 1) fever, 2) presence of diabetes, 3) elevated white blood cell count, 4) cellulitis, and 5) non-closure of the wound.

Infection inhibits wound healing and increases the risk of bacteremia and osteomyelitis because it delays epidermal maturation.[41] Both of these conditions are significant sources of pain. Another mechanism by which bacteria may impair wound healing is through the de-

crease in, and alteration of vascular endothelial growth factor (VEGF) receptors by the bacterial wall products. VEGF has a crucial role in the proliferative phase of wound healing by stimulating angiogenesis and endothelial cell proliferation.[42] This process can result in more pronounced pain associated with the wound, because a decrease in VEGF corresponds to an increase in bacteria, which in turn causes greater pain.

Obtaining deep-tissue biopsies is extremely valuable in treating infected wounds.[43] Infection-induced ulcer pain management relies mainly on chronic analgesic regimens as described previously. However, we emphasize that the presence of bacteria is often the #1 untreated etiology of pain in wound patients. Simple, sharp debridement often alleviates this pain.

RADIATION-INDUCED ULCERS

Radiation therapy disrupts the normal wound-healing process. Delays in wound healing occur because of changes in local vasculature and decreases in collagen production.[44] Vascular abnormalities include stasis and occlusion, vascular wall edema, and possibly a reduction in angiogenesis.[45] Radiation appears to alter fibroblasts permanently by either slowing the maturation of collagen or diminishing collagen production.[46] Collagen production is decreased by changes in the levels of specific growth factors [e.g., beta (transforming growth factor—TGF-beta) and platelet derived growth factor (PDGF)].[47]

Radiation-induced ulcers are often painful. They appear along with changes in the skin, formation of keratoses, epidermal atrophy, and inflammatory dermal and subcutaneous fibrosis.[48] From our experience, ulcers that result from radiation therapy often progress to Stage IV and even to the bone. This problem is often due to clinicians' reluctance to treat them immediately after onset.

Pain management for radiation ulcers mainly requires chronic analgesic regimens as discussed previously.

STEROID-INDUCED ULCERS

Corticosteroids are well known for delaying most aspects of wound healing significantly, although little is understood regarding their mechanisms. Steroids lower TGF-beta and insulin-like growth factor-1 (IGF-1) to below basal levels, which subsequently delays the migration of fibroblasts and regenerative capillaries.[49] Furthermore, they suppress transcription of epidermal genes critical in keratinocyte migration—examples of these epidermal genes include keratins K6 and K16.[50]

Corticosteroid-delayed wound healing may be reversed by retinoids, which displays the unique ability to overturn the inhibitory effects of steroids. Retinoids reverse impairments in the inflammatory response, tensile strength, and collagen accumulation in cutaneous wounds. Retinoids' actions are mediated, in part, through increases in two regulatory proteins, TGF-beta and IGF-1. Cells constituting new granulation tissue synthesize these proteins. The proteins act as local mediators of the cellular response that regulates intercellular interactions.[49]

Pain management for steroid-induced ulcers is treated primarily with chronic analgesic regimens, as described earlier.

CHEMOTHERAPY-INDUCED ULCERS

Chemotherapy is effective in suppressing tumor growth by killing rapidly dividing cells.[51] However, the majority of chemotherapeutic anti-neoplastic agents interfere with deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or both, production; protein synthesis; and collagen production. Most anti-neoplastic agents studied experimentally have demonstrated a deleterious effect on wound healing when administered in the perioperative period. In addition to aggravating the existing ulcers, these agents can induce ulcers based on the damaging effects described above.

Chemotherapy-induced, ulcer pain management relies mainly on chronic analgesic regimens as described previously.

OBESITY-INDUCED ULCERS

Morbidly obese persons have an increased incidence of non-healing wounds secondary to multiple etiologies. Common reasons for non-healing wounds in obese patients include: 1) higher incidence of venous reflux and thus venous ulcers; 2) higher incidence of diabetes and, therefore, diabetic foot ulcers; 3) pressure ulcers that often emerge after complicated surgery for which the patient requires prolonged bed rest; and 4) wound infection, which results in delayed wound healing, increased pain, and even ulceration. Wound infection in obese patients is often under-treated. A related cause of infection in the obese patient is intertrigo, a superficial dermatitis caused by friction between skin surfaces, combined with moisture and warmth, which results in infection.[52]

Obese persons are more likely to experience superficial wound breakdown.[53] Chronic wounds, such as pressure ulcers, are common and more difficult to manage in these patients.[54] Leg ulcers with venous insufficiency in morbidly obese patients also present a major clinical challenge.[55]

Studies with obese (i.e., *ob/ob*) mice have proven that Leptin, a protein encoded for by the *ob* gene, which has an inhibitory effect on appetite, also has an important role in wound healing.[56,57] Obese mice are much slower to heal their wounds than non-obese mice. Leptin regulates the T-lymphocyte response,[58] enhance phagocytosis,[59] as well as many other functions in a healing wound.[57-59] Therefore, Leptin-deficient *ob/ob* mice have delayed healing of their wounds. Although *ob/ob* mice exhibit obesity similar to morbid obesity in humans,[60] further clinical studies should be undertaken.

Obesity-induced ulcer pain-management relies mainly on chronic analgesic regimens as described above.

PATIENTS WITH SPECIAL CONSIDERATIONS

Several groups of wound patients require special considerations when administering chronic analgesic regimens: the elderly, patients on methadone maintenance as part of the recovery from drug addiction, and those using cocaine.

Use of extended-duration opioids by these patients can result in a prolonged duration of drug action, as well as greater potential side effects—such as respiratory depression, because of the unique physiology, pharmacodynamics, and pharmacokinetics of the elderly. When elderly patients who experience pain from chronic wounds are unable to tolerate the use of long-acting opioids, several techniques may be implemented for dosing analgesics. Extending the dosing schedule to intervals longer than usual may be helpful; e.g., dosing medications every 12 hours that normally last for 6 to 8 hours. If, despite this schedule, the patient continues to not tolerate the use of long-acting opioids, use of short-

acting opioids on a set-dose basis may provide the same effect; e.g., administering codeine or oxycodone every 6 hours around the clock. Finally, the use of set-dose non-opioids such as tramadol, again at an increased dosing interval (e.g., every 6 to 8 hours) can generate effective analgesia with decreased side effects. Tramadol's mechanism of action appears to be mediated by both opioid-receptor stimulation and inhibition of monoamine uptake.

When developing an analgesic regimen for chronic-wound patients on methadone maintenance, the unique pharmacology of methadone must be considered. Methadone has an elimination half-life of approximately 24 hours, but its analgesic half-life is only 6 hours. As methadone is a long-acting opioid, the maintenance dose can either be incorporated into the overall chronic analgesic regimen as the extended-duration opioid (dosed 4 times a day), or methadone maintenance can be retained at once-a-day dosing as the patient's baseline, either adding methadone or another extended-release opioid to the regimen in addition to the maintenance dose.

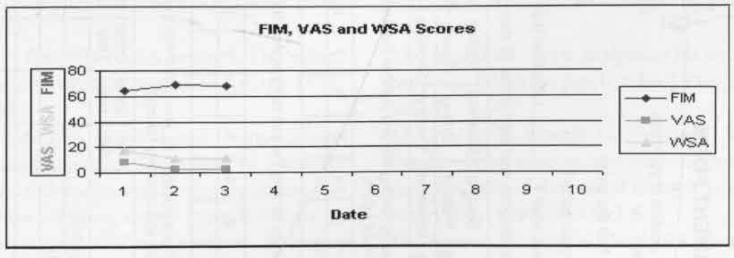
For patients on chronic methadone maintenance for previous opioid abuse, tolerance to pain is a critical factor. In these patients, tolerance is characterized by a shortened duration and decreased intensity of analgesia. These patients are expected to need higher doses of opioids than is normally the case.

The estimate is that 5 million people use cocaine regularly in the United States.[61] Intravenous cocaine users may often require wound debridement because of infection in venous areas surrounding injection sites. Cocaine is a local anesthetic that enhances sympathetic nervous system activity by inhibiting norepinephrine uptake into ganglionic nerve endings, direct actions on dopamine receptors, or both. Cocaine is metabolized in the blood and excreted in the kidneys after approximately 2 hours and, therefore, approximately 5 half lives, or 10 to 12 hours, should pass before safely taking an acutely intoxicated patient to the operating room for non-emergent surgery. Complications of acute cocaine toxicity include myocardial infarction, arrhythmia, cerebrovascular accidents, hyperthermia, and seizures. Patients with this condition require maintenance of their level of catecholamine; in particular, epinephrine use should be monitored.

MEASUREMENT OF PAIN

After the etiology of the chronic wound is established and a pain-management treatment initiated, measurement of any change in pain is imperative (Figs. 2, 3). To attain the most accurate results, we have devised and instituted a pain assessment form, updated continuously each time the patient returns to the wound-healing physician (see Pain Assessment Form, Fig. 3). Pain is assessed using a Verbal Analogue Score (VAS) of 0 to 10, with 0 signifying no pain and 10 signifying the worst pain. In addition to the VAS, two other variables are included: the patient's Modified Functional Independence Measurement (MFIM) and wound surface area. The MFIM, derived from the Functional Independence Measurement (FIM™, Uniform Data System of Medical Rehabilitation, Division of UB Foundation Activities, Inc., Buffalo, New York, USA) indicates a patient's ability to perform basic self-care and locomotion, and is measured on a scale of 0-70, with 70 signifying complete independence and 0 signifying complete dependence. To prevent bias, the patient is solely responsible for assigning the rating of their pain and MFIM (see Fig. 2). The person assessing the patient should not infer results based

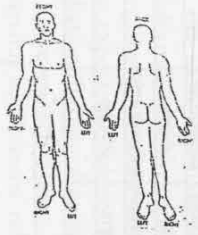
	10/17/02	11/14/02	11/21/02
VAS* (0 = no pain, 10 = worst pain)	**8**	**2.5**	**2.5**
Modified Functional Independence Measurement (MFIM)			
SELF CARE			
A. Eating	7	7	7
B. Grooming	7	7	7
C. Dressing-Upper	7	7	7
D. Dressing-Lower	7	7	7
E. Toileting	7	7	7
TRANSFERS			
F. Bed, Chair, Wheelchair	6	7	7
G. Toilet	7	7	7
H. Tub, Shower	6	7	7
LOCOMOTION			
I. Walk/Wheelchair	6	7	6
J. Stairs	4	6	6
TOTAL MFIM SCORE (range 0-70)	**64**	**69**	**68**
WSA† (cm^2)	**17.52**	**11.17**	**11.25**
Analgesics used	/	1. oxycontin	1. oxycontin
		20 bid	20 bid
		2. Percocet	2. Percocet
		6/day	6/day
		3. Desipramn	3. Desipramn
		25 qhs	25 qhs



*VAS = Average Verbal Analogue Score
†WSA = Wound Surface Area

Figure 2. Modified Functional Independence Measurement (MFIM) Form.

Print Full Name _____



PAIN ASSESSMENT FORM

Please indicate the location of your pain on the figure provided:

How long have you had this pain?

How often does the pain occur?

_____ Several times a week? _____ Less than 3 or 4 times per month?

Circle the words that describe your pain (circle as many as you need):

Dull ache	Sharp	Burning	Crushing	Tingling	Gnawing	Flicking
Itching	Stabbing	Pricking	Cutting	Pulsing	Pressing	Cramping
Nagging	Stinging	Squeezing	Pinching	Shooting	Boring	Electric

Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours:

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain

Please rate your pain by circling the one number that best describes your pain at its average:

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain

Which medications have you tried for your pain? Are they helpful? For how long? Which ones are you currently taking?

	No Help	Some Help	Great Help	How Long	Now Taking	Current Dose
Acetaminophen (Tylenol)						
Amitriptyline (Elavil)						
Aspirin						
Baclofen						
Butorphanol (Stadol)						
Carbamazepine (Tegretol)						
Carisoprodol (Soma)						
Clonazepam (Klonopin)						
Codeine						
Cyclobenzaprine (Flexeril)						
Desipramine (Norpramin)						
Diazepam (Valium)						
Fentanyl (Duragesic)						
Fluoxetine (Prozac)						
Gabapentin (Neurontin)						
Haloperidol (Haldol)						
Hydrocodone (Vicodin)						
Hydromorphone (Dilaudid)						
Ibuprofen (Motrin, Advil)						
Ketorolac (Toradol)						
Levorphanol (Levo-Dromoran)						
Lorazepam (Ativan)						
Meperidine (Demerol)						
Methadone						
Morphine						
MS Contin						
Nabumetone (Relafen)						
Naproxen (Aleve)						
Nortriptyline (Pamelor)						
Oxycodone (Percocet)						
OxyContin						
Pentazocine (Talwin)						
Phenytoin (Dilantin)						
Promethazine (Phenergan)						
Propoxyphene (Darvon)						
Trilisate						
Tylenol with Codeine						
Other:						

Does the pain affect your activity in these different areas?

_____ School _____ Work
_____ Household Chores _____ Social Interactions
_____ Leisure _____ Sexual Activity

What treatment have you already tried for your pain? Are they helpful for how long? Which ones are you currently using?

	No Help	Some Help	Great Help	How Long	Now Taking
Surgery					
Nerve Blocks					
Epidural Injections					
PCA Pump					
TENS Unit					
Trigger Point Injections					
Ethyl Chloride Spray					
Brace					
Exercise					
Physical Therapy					
Acupuncture					
Relaxation Training					
Chiropractic Therapy					
Biofeedback					
Hypnosis					
Massage					
Psychological Counseling					
Other:					

What makes your pain better? _____

What makes your pain worse? _____

Does your pain interrupt your sleep?

_____ Yes _____ No _____ Sometimes

Are your bowel movements:

_____ Regular _____ Irregular _____ Constipated

What other medical problems do you have (e.g., Angina, bronchitis, diabetes, depression, etc)?

a.
b.
c.
d.

What medications are you taking for these problems?

_____ Drug _____ Dose _____ Frequency

a.
b.
c.
d.

Do you, or have you, used tobacco and/or alcohol?

_____ yes _____ no

Do you, or have you, used illicit drugs?

_____ yes _____ no

Are you allergic to any medications or substances?

_____ yes _____ no

If "yes," please describe: _____

What is your current employment status? _____

Do you have a pending settlement about disability, worker' compensation, or other legal matters?

_____ yes _____ no

If "yes," briefly describe:

_____

_____

_____

Patient Signature: _____ Date: _____

Physician Signature: _____ Date: _____

Figure 3. Pain Assessment form. This form, or a similar form, should be given to every patient with a wound upon initial evaluation and during follow up.

on the patient's subjective statements, but instead should make their assessment on the basis of the forms completed by the patient.

Pain assessment was measured for 32 consecutive patients with chronic wounds. Eighteen of these patients experienced pain. On a scale of 0-10, the average pain experienced by these patients was 5.08. The long-term change in this average allows for an overall view of the clinic's performance in managing its patients' pain.

This preliminary study suggests pain is decreased when an integrated wound-management team is involved in treatment, based on results tabulated from the forms of patients with multiple pain scores. The decrease in pain was generally correlated with a decrease in wound surface area and an increase in the patient's MFIM. As a typical example, one patient experienced a decrease in VAS from 8 to 2.5, a decrease in wound-surface area from 17.52 cm^2 to 11.25 cm^2, and an increase in MFIM from 64 to 68 over a 5-week period. This correlation implies that pain management facilitates healing of the wound and healing results in less pain. In either scenario, decreased pain is likely an indicator of wound healing. This pain assessment form is an unbiased, accurate method that should be used to measure the change of pain in patients with chronic wounds.

SUMMARY

With any analgesic regimen, to treat the underlying etiology of the pain is critical. With all chronic wounds, removing local infection, which usually requires surgical debridement, is the most important part of the pain management regimen. Analgesia for wound-care patients can be problematic due to age, concomitant disease, and the diverse causes promulgating the pain. A strong understanding of the pathophysiology of the pain, and all the treatment options available, is essential for effective analgesia. Regular discussions between the pain and wound-care physicians can result in a significant decrease in patient morbidity and, often, in decreased length of hospital stay.

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