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## Exploring the Effects of Pain and Stress on Wound Healing



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### **PURPOSE:**

To enhance the learner's competence with implementing research on the effects of pain and stress on the wound healing process.

### **TARGET AUDIENCE:**

This continuing education activity is intended for physicians and nurses with an interest in skin and wound care.

### **OBJECTIVES:**

After participating in this educational activity, the participant should be better able to:

1. Interpret the interrelationships of pain, stress, and wound healing.
2. Apply strategies to minimize pain and anxiety for patients with chronic wound pain.

### **ABSTRACT**

Wound-related pain is complex, involving a multitude of physiological and psychological factors, such as emotional state, culture, personality, meanings, and expectations. The impact of pain on the individual can contribute to stress and compromise quality of life. The purpose of this article is to review the relationships among pain, stress, and wound healing.

**KEYWORDS:** pain and wound healing, stress and wound healing, pain and stress

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### **INTRODUCTION**

Pain is a common concern in patients with chronic wounds, and evidence suggests that stress responses can be deleterious to wound healing.<sup>1-3</sup> Activities important to maintain daily functioning, such as walking, standing, and climbing stairs, can often trigger and exacerbate wound-related pain.<sup>4</sup> To avoid pain, people with chronic wounds often restrict mobility and social activities, thus leading to isolation.<sup>5</sup> Even at rest, as many as 80% of patients experience substantial levels of pain on a regular basis.<sup>6,7</sup> Described as the worst aspect of having an ulcer by patients,<sup>8</sup> pain invades all aspects of everyday life,

eroding quality of life and contributing to psychological stress and anxiety.

By reading this article, clinicians will be better able to interpret the interrelationships of pain, stress, and wound healing.

## CHRONIC WOUND-RELATED PAIN

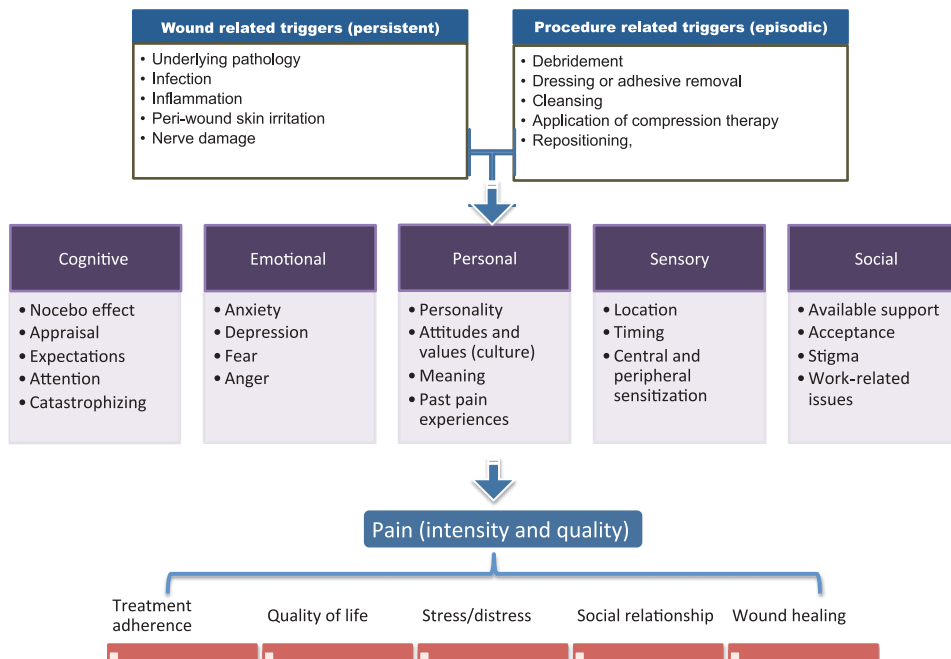
To improve the lives of individuals with chronic wound-related pain, a systematic approach is required to address the key determinants of pain and their interrelationships.<sup>3</sup> Depending on the wound etiology, the quality of pain and related patterns can be very distinctive. For example, people with diabetic foot ulcers often experience neuropathic pain characterized by burning, shooting, and stinging sensations. People with leg ulcers and coexisting ischemia may experience pain in the supine position during their sleep and exacerbated during walking (ie, claudication). Along with the underlying wound etiology, persistent inflammatory response, and local trauma (from dressing removal or cleansing) at dressing change,<sup>9</sup> a variety of patient factors are integral to the comprehensive assessment and management of wound-related pain (Figure 1). The proposed wound pain model posits that pain experience and its impact on the individual involve the interplay of physical factors (somatic input, nociception),

psychological processes (eg, beliefs, emotional and coping repertoire), and environmental contingencies (social context, cultural rules, and expectations).

In response to pain, the person may adopt a combination of deactivation or hyperactive strategies to regulate stress and emotions. Outcomes pertaining to pain include pain perception, wound healing, treatment adherence, and quality of life.

Although the exact mechanism remains elusive, an increasing body of evidence suggests a close link between stress/anxiety and pain.<sup>10</sup> In 1 study, Jones et al<sup>11</sup> examined the relationship between pain and anxiety in patients with chronic venous ulcers. A total of 190 subjects (72% were aged 60 years) participated by rating their anxiety and depression in the past week using the Hospital Anxiety and Depression Scale (HADS). Each of the 14 items on HADS is rated on a 4-point scale ranging from 0 (no, not at all) to 3 (definitely) for a total maximum score of 21 for each depression and anxiety subscales. A higher score corresponds to more emotional distress. Using 9 as a cutoff score to indicate the presence of emotional distress, 27% and 26% of the subjects were considered depressed and anxious, respectively. Pain was evaluated by a 0- to 4-point numeric scale, and a 5-point verbal rating scale indicated that 73% of the patients suffered from

**Figure 1.**  
**INTEGRATED WOUND PAIN MODEL**



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pain. Patients who expressed higher levels of anxiety also experienced more intense pain ( $P < .001$ ). In a more recent study, Woo<sup>12</sup> recruited 96 older subjects with various chronic wound types to rate their

levels of anticipatory pain before dressing change and real-time pain intensity at dressing removal, cleansing, dressing reapplication, and post-dressing change using an 11-point numerical rating scale. Anxiety was evaluated by using a validated 6-item Spielberger State-Trait Anxiety Inventory.<sup>13</sup> A repeated-measures analysis of variance demonstrated significant differences in pain ratings across various time intervals during dressing changes ( $F_{4,96} = 11.8$ ;  $P < .001$ ). Post hoc analysis using paired  $t$  tests indicated higher pain intensity at dressing removal and cleansing than baseline ( $P < .000$ ). As hypothesized, subjects who indicated feelings of anxiety were more likely to express high levels of anticipatory pain (correlation coefficient Pearson  $r = 0.674$ ). Linear regression identified anxiety and anticipatory pain as a significant predictor of mean pain scores at dressing change ( $B = 0.476$ ;  $P = .000$ ) accounting for 22.7% of variance. Although causality cannot be determined, results suggest a vicious cycle of pain, stress/anxiety, and worsening of pain. Persistent pain and related anxiety may contribute to the source of chronic stress in people with chronic wounds.

The term *nocebo effect* (opposite to placebo effect) has been coined to describe how anticipation and expectation of pain can evoke significant emotional distress and intensify pain.<sup>14</sup> In fact, a possible neural circuitry mediated by cholecystokinin has been identified that links anxiety directly to pain. Other neurobiological studies<sup>15–17</sup> have also identified additional cortical and subcortical structures including the periaqueductal gray matter, frontal cingulate and insular cortices, limbic system, amygdala, and hypothalamus that are involved in the emotional mediation of pain.

## PAIN, STRESS RESPONSE, AND WOUND HEALING

Pain and associated stress may deleteriously affect wound healing through a multitude of mechanisms.<sup>10</sup> In response to a broad range of painful stimuli, C fiber releases pain neuropeptides (substance P and neurokinin A) that activate leukocytes and other immunoreactive cells (such as glial cells) to release proinflammatory cytokines. These proinflammatory cytokines have been demonstrated to play a role in augmenting pain signals and stress response. The stress response is complex and nested within multiple parallel but interconnected mechanisms linking neuroendocrine, inflammatory,

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and nociceptive phenomena.<sup>18</sup> At the hypothalamus, the stress signal activates corticotropin-releasing hormone production leading to the secretion of adrenocorticotropic hormone (ACTH)

from the anterior pituitary gland.<sup>19,20</sup> The ACTH targets the adrenal gland and stimulates the production of glucocorticoid hormones (mainly cortisol) at the adrenal cortex and the release of catecholamine by the adrenal medulla.

Glucocorticoid hormones participate in many key physiological functions. For example, cortisol has been shown to influence the activity of the immune system by suppressing cellular differentiation and proliferation, down-regulating gene transcription, and reducing expression of cell adhesion molecules that are essential for cell trafficking.<sup>19,21</sup> In the presence of cortisol, T cells become less responsive to interleukin 1 (IL-1) signaling for the production of growth factor that facilitates T-cell proliferation. To maintain equilibrium, a negative feedback mechanism is built in to stop the production of ACTH by elevated cortisol.<sup>22</sup> Such mechanism, however, is rendered dysfunctional by psychological stress.<sup>23–25</sup> McBeth et al<sup>26</sup> documented uninhibited production of corticotropin-releasing factor, ACTH, and corticosteroid under prolonged stress in subjects with chronic pain conditions.

Overproduction of cortisol and catecholamines as a result of the stress response can have a significant impact on wound healing due to alteration in the immune system and tissue hypoxia.<sup>27</sup> Ebrecht et al<sup>2</sup> studied healing of dermal biopsy sites among 24 subjects. They reported that perceived stress and emotional distress were negatively correlated to wound healing rates between days 7 and 21 after the biopsy ( $P < .05$ ). Subjects who expressed optimism were more likely to achieve faster healing, but the result was not statistically significant. Slow-healing subjects (below median healing rate) rated higher levels of stress during the study ( $P < .05$ ) and higher cortisol levels 1 day after biopsy than the fast-healing group ( $P < .01$ ). Glaser et al<sup>28</sup> examined psychological stress and the levels of proinflammatory cytokines in experimentally induced skin blisters on the forearm of 36 women (mean age, 57.2 [SD, 6.6] years). The specimens were aspirated and analyzed within 24 hours of blister formation. Women who reported more stress on the Perceived Stress Scale produced significantly lower levels of IL-1 ( $P < .03$ ) and IL-8 ( $P < .04$ ).

Kiecolt-Glaser et al<sup>27</sup> compared wound healing in 13 older women (mean age, 62.3 years) who were stressed from providing care for their relatives with Alzheimer disease and 13 controls matched for age (mean age, 60.4 years). All the subjects acquired a wound from a 3.5-mm punch biopsy at the same

anatomical location (nondominant forearms). Time to achieve complete wound closure was increased by 24% or 9 days longer in the stressed caregiver versus control groups ( $P < .05$ ). Caregivers' peripheral blood leukocytes exhibited a diminished ability to express the IL-1 gene in response to lipopolysaccharide stimulation in vitro.

Interleukins play an important role to protect the host against infection and prepare injured tissue for repair by enhancing phagocytic cell recruitment and activation.<sup>29</sup> In another study, Garg et al<sup>30</sup> observed the skin barrier recovery rate from damage caused by tape stripping in 27 university students. Serial assessments were performed on 3 occasions: after winter vacation when stress level was low, during examination week with high stress levels, and after spring vacation when stress level waned. Consistent with their hypothesis, the investigators reported that barrier recovery was significantly slower during the high-stress compared with the low-stress period ( $F_{12,2} = 18.87$ ,  $P < .001$ ). The correlation coefficient for the relationship between stress and barrier recovery was significant ( $r = 0.42$ ;  $P = .03$ ), indicating the higher the stress, the slower was the barrier recovery rate. The negative impact of stress on wound healing has also been shown in a patient who underwent gastric bypass surgery.<sup>31</sup>

Broadbent et al<sup>1</sup> investigated the relationship between psychological stress and wound repair in 36 patients following inguinal hernia operation. They reported that perceived stress before the operation was a significant predictor of low IL-1 levels in wound fluids ( $P = .03$ ), accounting for 17% of the variance. In contrast, worry about the operation significantly predicted lower levels of matrix metalloproteinase 9 in the wound fluid ( $\beta = .38$ ,  $P = .03$ ), as well as increased pain over the first 20-hour postoperative period ( $\beta = .51$ ,  $P = .002$ ). However, the investigators followed the subjects only for 20 hours after the surgery; the long-term effect of stress on the immune system and wound healing remains unanswered.

Previous studies examined healing of artificial or experimentally induced wounds that are relatively small and superficial, so interpretation of these studies warrants careful deliberation. In a clinical study, Woo and Sibbald<sup>32</sup> followed 111 older subjects with either leg or foot ulcers prospectively for 4 weeks. Pain was acknowledged as a significant problem in 68 subjects (61.3%). Although pain medications were typically prescribed, a number of subjects did not take these agents because of fear of addiction.

## INTERVENTIONS TO IMPROVE WOUND-RELATED PAIN

To improve pain management, education was provided to dispel misconceptions about pain (Table 1). Specific pharmacological

**Table 1.**  
**STRATEGIES TO MINIMIZE WOUND-RELATED PAIN AND ANXIETY<sup>3</sup>**

Strategies	Objectives and Treatment Options
Education	<ul style="list-style-type: none"> <li>• Web-based learning</li> <li>• Face-to-face education               <ul style="list-style-type: none"> <li>• Explain mechanism of pain</li> <li>• Dispel misconceptions about pain</li> <li>• Address concerns about addiction</li> <li>• Emphasize the availability of multiple strategies</li> </ul> </li> </ul>
Pharmacological	Topical: <ul style="list-style-type: none"> <li>• Topical ibuprofen (dressing)</li> <li>• Morphine gel</li> <li>• Topical lidocaine (as a compression)</li> </ul> Systemic: <ul style="list-style-type: none"> <li>• Nociceptive pain: acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, or acetaminophen for mild to moderate pain</li> <li>• Opioids for moderate to intense pain</li> </ul> Neuropathic pain: <ul style="list-style-type: none"> <li>• Serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, anticonvulsants</li> </ul>
Local wound care	<ul style="list-style-type: none"> <li>• Atraumatic interface (silicone)</li> <li>• Sequester: remove inflammatory mediators</li> <li>• Protect periwound skin</li> <li>• Treat infection</li> </ul>
Anxiety reduction	<ul style="list-style-type: none"> <li>• Relaxation</li> <li>• Imagery</li> <li>• Distraction</li> <li>• Education: reduce nocebo effect</li> <li>• Music therapy</li> <li>• Support group</li> </ul>
Cognitive therapy	<ul style="list-style-type: none"> <li>• Cognitive behavior therapy</li> <li>• Problem-solving skills</li> <li>• Positive thinking</li> </ul>
Therapeutic alliance	<ul style="list-style-type: none"> <li>• Communication techniques: eg, reflective listening</li> <li>• Goal setting</li> <li>• Align expectation</li> <li>• Demonstrate empathy</li> <li>• Being authentic</li> </ul>
Empowerment	<ul style="list-style-type: none"> <li>• Allow individual to call "time out"</li> <li>• Respect individual's choices</li> <li>• Maximize autonomy: active participation</li> <li>• Functional focused therapy</li> </ul>

agents were prescribed to address nociceptive or neuropathic pain. Pain associated with dressing changes was addressed by careful selection of wound dressings, application of topical

analgesics during dressing changes, and use of systemic analgesics. The average pain intensity score was reduced from 6.3 at baseline to 2.8 at week 4 ( $P < .001$ ). To examine the relationship between pain and wound healing, pain intensity scores were

compared among those who achieved wound closure by the end of data collection and those who did not. The mean pain intensity score was 1.67 for subjects who achieved wound closure, as compared with an average score of 3.21 among those who did not achieve complete wound closure ( $P < .041$ ). Based on the finding of the study, the authors surmised that wound healing can be enhanced by optimizing pain management. Future research is required to answer the question.

Pain is a multidimensional experience including sensory, cognitive, affective, and behavioral components. McCaffery<sup>33</sup> reminds us that pain is whatever the patient says it is. Effective management of pain not only requires the use of pharmacological agents, but also mindful attention to personal and social factors that may account for the variability in pain experience. A therapeutic relationship between the healthcare provider and the patient can enhance treatment adherence to optimize patient outcomes.<sup>34</sup> As a crucial step to cultivate a therapeutic alliance, clinicians should first acknowledge that anxiety and pain are common experiences at dressing changes. Although patients should be informed that these symptoms are part of a normal response, emphasis should be placed on available treatment options and achievable goals to minimize these symptoms.

To reduce anxiety, healthcare professionals should have effective communication skills to educate patients about pain mechanisms.<sup>35</sup> There is a need to reinforce the belief that patients with chronic wounds do not have to live with persistent or temporary pain and foster their active participation in assessment, treatment, and coping behaviors.<sup>36</sup>

Although no one is immune to the feelings of anxiety before a potentially painful procedure, strategies that allay anxiety may lessen the pain experience. In addition to pain, clinicians should pay attention to other sources of anxiety that may be associated with stalled wound healing, fear of amputation, body disfigurement, repulsive odor, social isolation, debility, and disruption of daily activities. Cognitive therapy that aims at altering anxiety by modifying attitudes, beliefs, and expectations by exploring the meaning and interpretation of pain concerns has been shown to be successful in the management of pain.<sup>37</sup> This may involve distraction techniques, imagery, relaxation, or altering the significance of the pain to an individual. Patients can learn

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to envision pain as less threatening and unpleasant through positive imagery by imagining pain disappearing or conjuring a mental picture of a place that evokes feelings and memories of comfort, safety, and relaxation.<sup>38,39</sup>

Relaxation exercises can help to reduce anxiety-related tension in the muscle that contributes to pain. The primary task of the caregiver is to help the individual gain an insight into factors that increase or decrease anxiety and pain. By minimizing anxiety-provoking factors, the person may develop a sense of control instead of continuing with a helpless and hopeless attitude to symptoms. Connections made among thoughts, feelings, and behaviors may assist patients in acquiring awareness of their own responses and create a rationale for skill development. The focus of treatment is to reframe the patient's internal dialogue and interpretation of the existing concern, so that the problem is perceived as being controllable.

Education is a key strategy to empower patients and to improve wound-related pain control. Only a small proportion of patients are cognizant of factors contributing to their chronic wounds and treatment strategies to improve their conditions.<sup>40</sup> Inadequate information and healthcare provider misconceptions, such as patients always exhibiting signs indicating the existence of pain, using single pain strategies to manage pain, addiction to pain medications, and the fact that the intensity of pain can be determined by the underlying pathology, are all barriers to effective pain management. These misconceptions can hinder optimal pain management and should be addressed while being sensitive to the patient's beliefs. Patients are reluctant to report pain and take medications because of fear of addiction and adverse effects from analgesia. Culturally, some individuals believe that good patients do not complain about pain and that healthcare providers are too busy to manage their pain.<sup>35</sup> Pain is perceived by some individuals to be unavoidable and is integral to growing old, perpetuating a sense of helplessness and hopelessness about pain. In a pilot study,<sup>41</sup> 5 patients with chronic wounds described dressing change pain as being more manageable after receiving educational information. Pain-related education is a necessary step in effecting change in pain management by rebuking common misconceptions and myths that may obstruct effective pain management.

Patients should be informed of various treatment options and be empowered to be active participants in care. Being an active participant involves taking part in the decision making for the most appropriate treatment, monitoring response to treatment, and communicating concerns to healthcare providers.

## FUTURE RESEARCH

Although various strategies may be useful to mitigate anxiety and pain, future research must validate an interventional approach that can easily be translated into clinical practice. Review of the literature highlighted the deleterious effect of stress on healing of acute wounds. Little is known about the effect of chronic stress on healing of chronic wounds. Longitudinal studies and multilevel modeling controlling for potential confounding variables will help to shed some light on causality and exposure-response relationships.

## CONCLUSIONS

Pain is a common symptom for persons with chronic wounds. As an unpleasant physical and emotional experience, pain induces stress leading to a cascade of physiological events that stall wound healing. Several strategies to reduce stress and anxiety may be effective to stop the vicious cycle of pain, stress, and exacerbation of pain.

Pain and stress are intricately linked in patients with chronic wounds. Unresolved pain predisposes individuals to stress and associated physiological responses that can impair wound healing. Clinicians must be vigilant of anxiety and stress when assessing for pain. Although various strategies may be useful to mitigate anxiety and pain, future research must validate an interventional approach that can easily be translated into clinical practice. ●

## PRACTICE PEARLS

- Pain is common in people with chronic wounds.
- Pain is a common source of anxiety in people with chronic wounds.
- Together, pain and anxiety can have a negative impact on wound healing.
- Multiple strategies can be used to reduce pain and related anxiety: consider education, types of dressings, communication techniques, and empowerment.

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