

Pain-induced stress: a barrier to wound healing

Pain is an accepted feature of chronic wounds. It is known to cause distress to the patient, and, this in turn can delay healing. This article summarises what is known about chronic wound pain: when it occurs, its assessment, and management. Indeed, every patient with a wound should have an individual pain management plan, including regular review and re-assessment. The occurrence of pain during the dressing change procedure has been highlighted as one of the most frequent causes. This knowledge can focus the practitioner towards reducing or avoiding pain, thus removing one of the barriers to healing, and, improving patient quality of life.

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KEY WORDS

Delayed wound healing
Wound pain
Psychological stress

Pain is a common experience for people with chronic wounds (Krasner et al, 1995; Reddy et al, 2003). The pain can be a result of pathophysiology and/or can arise from trauma during wound care interventions, such as dressing changes (Krasner et al, 1995; Hollinworth, 2000; Price, 2006). Pain from chronic wounds can be intense and have a deleterious effect on physical functioning, cause psychological distress and reduce the quality of everyday living (Zschocke et al, 2002; Franks et al, 2003; Persoon et al, 2003; McMullen, 2004).

The minimisation of both trauma and pain should be key objectives for healthcare professionals involved in the care of patients with chronic wounds. Unfortunately, the pain of

chronic wounds is often inadequately managed (Hollinworth, 2004; Persoon et al, 2004).

There is evidence that psychological distress delays wound healing (Norman, 2003) and it is reasonable to hypothesise that minimising pain by reducing psychological stress will improve chronic wound healing. In this article, we review the evidence supporting this hypothesis and highlight the importance of taking measures to reduce pain.

The pain associated with chronic wounds

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (Mersky and Bogduk, 1994). The experience of pain is very personal and subjective (Johnson, 2006). It is a complex, multi-dimensional sensation that is difficult for patients to describe. As well as the traumatic or pathophysiological causes of pain, which arise at the wound site, the perception of pain is influenced by psychological, emotional, cognitive and social factors, as well as learned behaviours (Briggs et al, 2002; Augustin and Maier, 2003). The patient's mental state, environment and cultural background can all have an influence on perception of pain. Although the causes and

nature of wound pain are complex (Hollinworth, 2000), understanding the causes and factors affecting wound pain in an individual patient is important for effective assessment and management (World Union of Wound Healing Societies [WUHS], 2004) (Figure 1).

Wound pain can be acute or persistent (chronic). Acute pain has been described as being non-cyclic, occurring during intermittent manipulation of wounds (e.g. debridement) or cyclic, occurring during regular procedures (e.g. dressing changes) (Krasner et al, 1995). Persistent, or chronic pain has been described in many ways: 'Pain that persists over a long period of time' and, as a third pathologic emotion (Swanson, 1984). This phenomenon is more often described in terms of long-term conditions such as arthritic disease, low back pain, malignancy and so on. In the context of wounds, it has been described by Krasner (1995). The period of duration being regarded as more than seven weeks by the Quebec Task Force (Werneke and Hart, 2004), more than three months by Frank et al (2000), or, at least half the days in a 12-month period (Von Korff, 1994). Pain can arise from one of two mechanisms — nociceptive or neuroleptic. Patients with chronic wounds may experience one or both types of pain.

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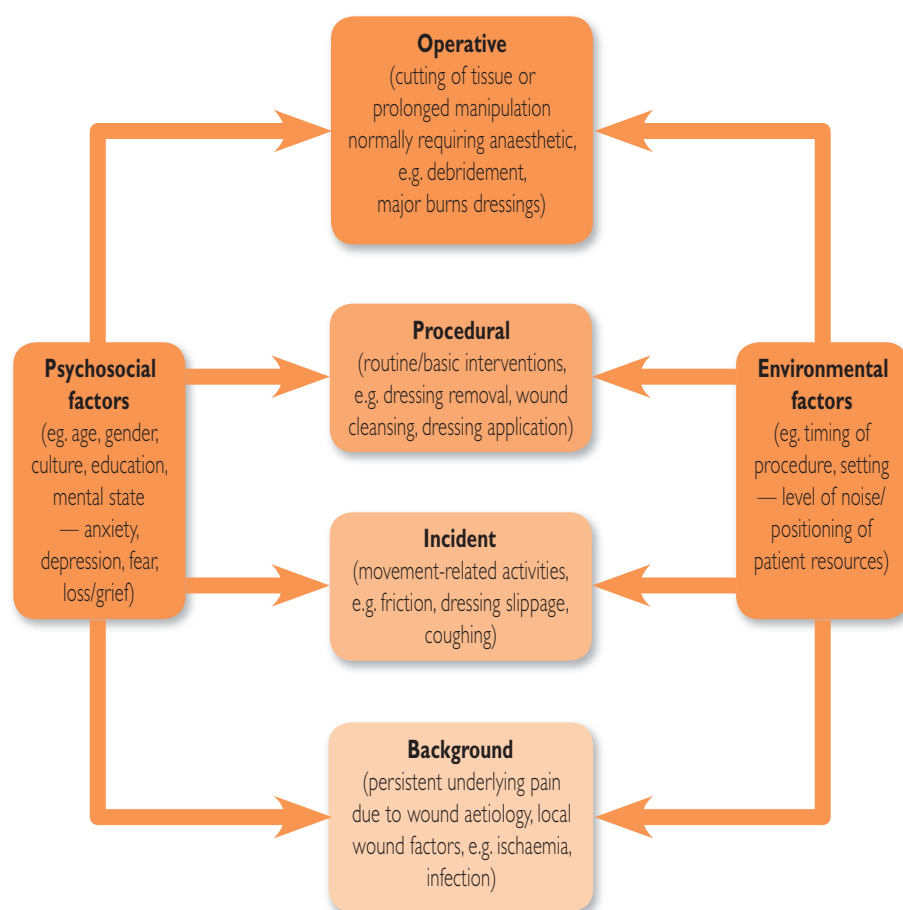


Figure 1. Factors and causes affecting wound pain. Reproduced by kind permission of WUWH, 2004.

Nociceptive pain is the normal physiological response to a painful stimulus. Receptors (nociceptors) in skin and deeper tissues detect noxious or tissue-damaging stimuli. These receptors transmit pain signals via afferent neurons to the dorsal horn of the spinal cord. Second order neurons then transmit the signals to higher centres in the brain where the signals are processed. The transmission and subsequent processing of the nerve impulses to and within the central nervous system are subject to many complex modulating influences, including psychological influences. These modify the sensation produced, which is described as pain (Johnson, 2006). Damage to cells at the site of injury causes accumulation of pain-producing substances in the extracellular fluid, which reduces the threshold for activation of the nociceptors. As a result, the tissues

become more sensitive to noxious stimuli (hyperalgesia) (American Medical Association [AMA], 2005).

Nociceptive pain can be acute (the normal physiological response) and/or persistent (chronic) and primarily involves damage to tissues. Persistent nociceptive pain may be due to an underlying condition causing ongoing ischaemia, oedema or ongoing tissue damage (Johnson, 2006). Nociceptive pain is generally localised to the wound and surrounding tissues. The nociceptive pain of a wound is typically described as sharp, stabbing, throbbing or aching (Doughty, 2004).

Neuropathic pain occurs as a result of nerve damage or dysfunction in the peripheral or central nervous system and may result in abnormal pain transmission (Johnson, 2006). Although neuropathic pain is

influenced by ongoing tissue injury, there is an assumption that the fundamental mechanisms sustaining the pain have become independent of the initial injury or damage. Neuropathic pain is generally persistent and typically described as burning, stinging, and tingling (Doughty, 2004). Neuropathic pain syndromes may be associated with referred pain, allodynia (pain induced by non-noxious stimuli or light touch), or hyperpathia (exaggerated response to painful stimuli, with continuing sensation after the pain has ceased).

Identifying the type of pain is important as interventions may not be effective in both types of pain. Nociceptive pain is usually relieved by analgesia and subsides over time. However, neuropathic pain may not respond to analgesics. Often a single mode of therapy is not successful when used in isolation and a different approach is required, e.g. the use of certain tricyclic antidepressants and anti-epileptic medications to control specific symptoms associated with nerve damage (Hollinworth, 2005). There is no evidence to support the use of one over the other.

Persistent wound pain is extremely distressing and psychological problems may become evident if the pain lasts for a continuous period of time. It can be caused by a number of factors, including wound aetiology, venous insufficiency and vasculitis, pressure from neoplasms, prolonged inflammation, hypersensitivities, or local infection (Hollinworth, 2005). Cyclic acute pain at wound dressing changes can be intense and may be responsible for considerable anticipatory distress and anxiety. Indeed, the anxiety of the painful event may be as disabling as the experience of pain itself (Fowler, 2003; Hollinworth, 2005). Cyclic acute pain may be additional to persistent pain.

Psychological stress

Human beings display a collection of physical and behavioural responses to stressful physical or psychological

situations. These serve to remove the stressor and re-establish homeostasis. While the stress response is adaptive in the short term (it increases one's chances of survival) prolonged exposure to stressful situations (and the accompanying physiological stress response) eventually become maladaptive and increases the risk of harm.

In the case of wounds, this suggests that stress-induced changes in the immune system following acute wounding would accelerate wound healing, e.g. by enhancement of the immune system and reducing the risk of infection. However, if the stress persists (e.g. pain from a chronic wound) the immune response may be suppressed, increasing vulnerability to infection (Kiecolt-Glaser et al, 1995; Miller et al, 2002).

Over the past 30 years, more than 300 studies have been carried out on stress and immunity in humans, and together they have shown that psychological challenges are capable of modifying various features of the immune response (Segerstrom et al, 2004). The effect on immune function is complex and dependent

on the nature of the stressor. The effects of psychological stress on immune function have been explored

There is evidence from a number of studies in humans (summarised below) to link psychological stress with adverse effects on wound healing and tissue repair, and these support the view that depressed immune function and the resultant depression of pro-inflammatory cytokines are involved.

by Segerstrom et al (2004) and this has helped to clarify the effect of psychological stress on immune function, according to the type of stressor (Figure 1).

Although studies have demonstrated that immune suppression related to chronic stress may impair immune responses to infectious diseases and delay

wound healing, there is a danger of oversimplification. The effect of stress should, more accurately, be considered as one of dysregulation of the immune function and not one of global suppression (Robles et al, 2004). Individuals who have experienced more recent stressful events show exaggerated immune changes in response to minor stressors. Stressful events, even those of short duration (e.g. < 30 minutes), can lead to transient changes in the function of the immune response (Kiecolt-Glaser, 2002). However, severe stressful events can produce long-term immune dysregulation, which may last for weeks or even years after the event (Kiecolt-Glaser, 2002). Many stressors have been shown to give rise to long-term changes in pro-inflammatory cytokines, notably IL-6, which has been linked to a broad array of health problems such as rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus (SLE) and chronic obstructive pulmonary disease (COPD) (Kiecolt-Glaser, 2002).

Psychological stress and wound healing

The biochemical processes occurring during wound healing and the way in which these may be affected and modified by stress is complex and, at present, unclear. However, one aspect is of particular importance with regard to the effects of psychological stress — immune function. This is important both for preventing infection and, if disturbed, having an adverse effect on the processes involved in tissue repair and wound healing. It is known that psychological stress, if prolonged, can lead to raised levels of the stress hormone cortisol. A consequence is a depression in immune function and changes in the levels of various inflammatory cytokines and enzymes involved in tissue repair. Changes in these levels could offer a plausible explanation of how reduced rates of wound healing occur with pain-induced psychological stress (Kiecolt-Glaser, 1998).

There is evidence from a number of studies in humans (summarised

- ▶▶ Acute time-limited stressors (e.g. public speaking) result in up-regulation of the natural immunity in preparation for possible infection, injury or both. The effect is consistent with a redistribution of immune cells into compartments in which they will be most effective.
- ▶▶ Brief naturalistic stressors (e.g. academic exams) tend to suppress cellular immunity while preserving humoral immunity. The profile of cytokine production is changed. There is a decrease in cytokines which stimulate natural and cellular immune functions and an increase in cytokines which stimulate natural and humoral immune functions.
- ▶▶ Stressful event sequences involve a focal event (e.g. loss of a spouse, major disaster). However, the subsequent period over which a person is affected is uncertain. Such stressors have not been robustly associated with changes in the immune system and their affects may be influenced by the kind of event.
- ▶▶ Chronic stressors (e.g. living with a disability, unemployment or caring for someone with dementia) have been shown to have negative effects on all aspects of the immune system. Living with persistent pain falls into this category.
- ▶▶ Distant stressors (e.g. traumatic events such as combat exposure or abuse occurring years in the past) have not been studied a great deal, and any affects on immune function are uncertain.

Figure 1. Categories of psychological stressors.

below) to link psychological stress with adverse effects on wound healing and tissue repair, and these support the view that depressed immune function and the resultant depression of pro-inflammatory cytokines are involved.

Kiecolt-Glaser et al (1995) studied the effect of stress on the healing of acute punch biopsy wounds in the carers of patients with Alzheimer's disease. Wound healing was shown to take significantly longer in caregivers than controls (48.7 vs 39.3 days, $p < 0.05$). Caregivers reported significantly more stress on the Perceived Stress Scale (PSS) than did control subjects on study entry (20.5 vs 13.7, $p < 0.002$). Consistent with the differences in rates of wound repair, leukocytes in peripheral blood from carers produced significantly less IL-1 β in response to lipopolysaccharide stimulation than did cells from controls.

In a study carried out by Glaser et al (1999), skin blisters were induced in the forearms of 36 women by suction. After removal of the blister roofs, a blister well containing serum was created above the blister and aspirated at five and 24 hours after wounding for analysis. Women with higher stress scores (PSS) demonstrated lower production of two key cytokines (IL-1 α and IL-8). Raised salivary cortisol levels were evident in the women who reported the highest levels of stress.

Ebrecht et al (2003) demonstrated a significant negative correlation between the speed of healing of a punch biopsy wound and both perceived level of stress (PSS) and emotional distress (General Health Questionnaire). This study included 24 male non-smokers and monitored wound repair using high-resolution ultrasound scanning. As in the Glaser et al (1999) study, slow wound healing appeared to be associated with elevated levels of cortisol in saliva. Importantly, this study considered a number of potentially confounding health behaviours, i.e. alcohol consumption, exercise, healthy

eating and sleep influences, and found no correlation of these factors with healing speed at any point.

Broadbent et al (2003) showed that stress (PSS) in 36 patients before undergoing elective open surgery for inguinal repair significantly impaired inflammatory response and tissue

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repair processes in wounds during the 20 hours following the operation, as determined by lower levels of matrix metalloproteinase and IL1 in wound fluid. Greater worry about the operation was associated with greater pain and poorer and slower recovery following surgery.

Kiecolt-Glaser et al (2005), in a study of 42 couples who had been married for an average of 13 years, provided further evidence for the sensitivity of wound healing to everyday stressors and found that this was related to levels of inflammatory cytokines in wound fluid. In a crossover trial, the couples were admitted to a hospital research unit twice, each time for 24 hours, with wound healing being assessed the day following discharge. During the first admission the couples underwent a structured social support interaction; during the second visit they discussed marital disagreement. Blister wounds healed more slowly and local cytokine production (IL-6, TNF α and IL-1 β) was lower at wound sites following marital conflict than after social support interactions. Blister wounds in couples who demonstrated consistently higher levels of hostile behaviours across both interactions were found to heal at only 60% of the rate of couples who demonstrated lower levels of hostility.

Two studies of students suggest that even the transient, predictable and relatively benign stress of examination can have significant consequences for skin repair and wound healing.

In a study carried out by Marucha et al (1998), students ($n = 11$) took on average three days longer (a 40% increase) to completely heal a 3.5 mm punch biopsy wound during examinations than when on holiday. This decline in healing was associated with a 68% decline in the production of IL-1 mRNA.

In a study of 27 students, Garg et al (2001) showed that perceived psychological stress arising from exams was associated with a decline in the ability of the epidermis to recover its barrier properties following skin stripping with cellophane. In the period following exams, when stress was assumed to be at a lower level, recovery of the epidermal barrier was more rapid ($p < 0.001$) than during the exam period.

Psychological stress can be induced in the continued presence of chronic pain, but it can also be induced by the anticipation of pain (e.g. as a result of waiting to have a dressing changed). These psychological effects may, in turn, through depression of immune functions, have detrimental local effects on the biological processes involved in wound repair and thus delay wound healing. Direct evidence that pain from chronic wounds is associated with psychological stress and wound healing is limited. However, two studies in patients with chronic venous ulcers do suggest, when taken together, that poor mental state is associated with pain and delayed wound healing.

Jones et al (2006) explored the prevalence of depression in patients with chronic venous ulcers in nine trusts in the northwest of England. Of the 190 patients included in the study, 73% suffered some degree of pain and 14% reported suffering

pain constantly. Using a cut-off value of nine on the Hospital Anxiety and Depression Scale (HADS), 27% were identified as depressed and 26% were identified as anxious. Pain and odour were both significantly associated with anxiety and depression (all $p \leq 0.002$). This study highlights the importance of minimising the pain of a patient with a chronic wound in order to improve their mental state and quality of life.

Cole-King and Harding (2001) studied the relationship between the healing of acute wounding (punch biopsy) and anxiety and depression, assessed using a nine-point cut-off on the HADS in 53 patients with chronic leg ulcers. Delayed healing was associated with a higher mean HADS score ($p = 0.035$). Patients scoring in the top 50% of the total HADS score were four-times more likely to have delayed healing than those in the bottom half (95% CI=1.1 to 15.1). This study suggests that paying attention to the factors associated with anxiety and depression in patients with chronic wounds can improve the healing rate. Although these two studies do not provide direct evidence of a link between pain control and delayed wound healing, they support the hypothesis that by reducing wound pain, and thus mental stress, wound healing rates can be improved.

Some evidence for an association between pain and delayed wound healing has been shown in a recent study by McGuire et al (2006). In this prospective five-week study of 17 women undergoing elective gastric bypass surgery, post-surgical pain intensity was found to be significantly associated with subsequent delayed healing of a 2.0mm punch biopsy wound.

When considered together, all the above studies suggest that psychological stress, both brief and transient or persistent, can delay the healing of wounds and that the depression of pro-inflammatory cytokines is involved in this. However, the evidence for a causal link between psychological stress and wound healing comes mostly from studies of acute

wound healing. Chronic wound healing does not follow the same pattern as that of acute wounds (Enoch and Price, 2004) and it is not clear whether reductions in immune function and changes in levels of pro-inflammatory cytokines as a result of psychological stress follow the same pattern in chronic wounds as in acute wounds.

It is known that pro-inflammatory cytokines, such as IL-1, IL-6 and TNF α , are found at significantly higher concentrations in wound fluid from non-healing ulcers compared to healing leg ulcers, and it is possible that wound healing in chronic ulcers is impaired

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by the presence of these high levels of inflammatory mediators (Trengeve et al, 2000). However, it is unknown whether chronic stress reduces these high levels of cytokines in chronic wounds, and if so, whether this change is beneficial to wound healing. Although a relationship between pain, psychological stress and adverse chronic wound healing is probable, more research is clearly needed in this area.

Managing psychological stress and pain

Although many clinical factors can contribute to the pain of chronic wounds, pain during dressing changes is one of the most frequent causes. Two surveys illustrate this. The first was a 1999 survey of UK nurses who had an interest in wound management (Hollinworth, 2000). There were 373 respondents (37% response), of whom 81% stated that patients experienced most pain during dressing removal. A

smaller number (7%) identified wound cleansing as a cause of pain, with 6% identifying pain simply as a result of dressings being *in situ*. Although leg ulcers, infected wounds and superficial burns, cuts, and abrasions were considered to be particularly painful at dressing times (in that order), pressure ulcers, arterial leg ulcers and skin-graft donor sites were also cited.

In the second survey of nursing and medical practitioners conducted in Germany, Austria and Switzerland between 2000 and 2001 (447 respondents, 15% response), dressing removal and wound cleansing were perceived to be the most painful wound care interventions (Kammerlander and Eberlein, 2002). These surveys demonstrate the importance nurses place on avoiding trauma to the wound and adjacent skin during dressing changes and, thus, reducing pain.

Pain should be a priority and assessed, managed and re-evaluated effectively during treatment of a patient with an acute or chronic wound. Failure to do so can cause considerable distress both at the time of treatment and during the periods before treatment in anticipation of the painful experience. A critical part of a wound management regimen is the chronic wound patient's self-assessed scores of pain and functionality (Freedman et al, 2003). Understanding the cause and nature of pain (i.e. whether it is nociceptive, neuroleptic or both) is also important for providing the most appropriate pain relief on an individual patient basis.

Measurement tools for the assessment of pain have been outlined and categorised into four areas (Australian and New Zealand College of Anaesthetists [ANZCA], 2005):

- ▶▶ Uni-dimensional
- ▶▶ Categorical
- ▶▶ Numerical
- ▶▶ Multidimensional.

The body of evidence was discussed in the ANZCA article to support the use of any of these four scales, and

should be given consideration when developing guidelines for the assessment of pain to standardise the management of pain. Although the Anzca article is aimed at acute pain, it does make the cross over to chronic pain.

Unresolved pain negatively affects wound healing and impacts on quality of life (Franks et al, 2003). Recognising this, a consensus document representing the views of an international expert working group, was published by the WUWHS in 2004 (WUWHS, 2004). This educational initiative promotes principles of best practice for minimising pain in wound dressing-related procedures. The principles presented in this consensus document are based on statements from two seminal documents: the European Wound Management Association's (EWMA) position document *Understanding Wound Pain and Trauma: An International Perspective* (Moffatt et al, 2002) and a supplement to *Ostomy Wound Management* entitled *Practical Treatment of Wound Pain and Trauma: A Patient-centred Approach* (Reddy et al, 2003).

Readers are referred to the consensus documents (Moffatt et al, 2002; Reddy et al, 2003; WUWHS,

2004) for more detailed information on understanding the causes of pain, its assessment and management, including the use of analgesic and wound dressing options. The following statement from the WUWHS document (2004) highlights the need to consider pain on an individual patient basis:

Every person and every wound should have an individualised management plan: uncontrolled pain should signal an immediate adjustment to the plan. Wounds differ in their origins and prospects of healing, which has potential implications for the likelihood and severity of pain experienced, and should guide the choice of treatment options and strategies used in dressing-related procedures. The aim is to treat all causes of pain and the clinician will need to consider the patient's level of background and incident pain prior to any clinical intervention.

With regard to dressing removal and selection, the consensus document advises using dressings that promote moist wound healing (e.g. hydrogels, hydrogel sheets and hydrofibres) and are known to be comfortable when *in situ* and atraumatic on removal (i.e. soft silicones). In a study of 5850 patients with chronic or acute wounds, 80%

(both types) experienced moderate or severe pain during dressing changes (Meaume et al, 2004). By switching to a non-adherent dressing, pain was reduced during dressing changes in 88% of patients with chronic wounds and 95% of patients with acute wounds. Dressings using soft-silicone adhesives are ideal for the treatment of most types of wounds where adherence or secondary trauma has been identified as a real or potential problem (Thomas, 2003). Such atraumatic dressings are clearly appropriate for use in patients who experience pain during dressing changes. The use of a skin preparation before the application of the dressings will reduce trauma on removal, as will the use of an adhesive removing spray.

As well as paying attention to pain at dressing changes, clinicians should address the issue of persistent pain and psychological stress, which may be present before and during dressing changes (Hollinworth, 2004). Simple changes in clinical practice, based on awareness of the psychological factors that may influence the pain experience, can result in major improvements for the patient (Price, 2006). A number of non-pharmacological interventions may be considered (Figure 2), although evidence on which to use in a given situation is lacking. Therefore, as with all aspects of patient care, the involvement of the multidisciplinary team, e.g. pain management team and pharmacy, is vital. If appropriate, the patient's family can also be involved, depending on the individual patient. Emotional support to the patient and adopting a sensitive, caring approach are important. The various methods of controlling pain will be the subject of another article.

Conclusion

Pain is a common cause of distress in patients with chronic wounds and can severely impact on quality of life. There is increasing evidence that psychological stress causes dysregulation of immune function and this can impair the normal wound healing process. However, more research is needed to confirm

- ▶▶ Education/instruction
- ▶▶ Relaxation strategies or breathing exercises
- ▶▶ Meditation or prayer
- ▶▶ Distraction (music)
- ▶▶ Imagery
- ▶▶ Hypnosis
- ▶▶ Biofeedback
- ▶▶ Acupuncture
- ▶▶ Pain-reducing dressing (soft silicone)
- ▶▶ Self-dressing changes
- ▶▶ Time-outs during dressing changes
- ▶▶ Positioning, elevation, immobilisation, or rest
- ▶▶ Pressure-reducing devices/positioning devices
- ▶▶ Hot or cold applications
- ▶▶ Physical therapy
- ▶▶ Transcutaneous electrical nerve stimulation (TENS)
- ▶▶ Support groups or counselling

Figure 2. Non-pharmacological interventions for the management of pain (Fowler, 2003).

Key Points

- ▶ Pain is common in chronic wounds; even neuropathic ulcers can be painful.
- ▶ Wound pain is known to be a stressor, and pain-induced stress can delay healing.
- ▶ All patients with a wound should have an individual pain assessment and management plan which is regularly reviewed and adjusted as necessary.
- ▶ Minimising wound trauma and pain, particularly at dressing change, must be key objectives for the practitioner.

whether the same applies to the healing of chronic wounds. Wound pain is a major contributor to psychological stress, and minimising pain should be a key priority in wound management. Dressing changes are the most frequent cause of pain and particular attention should be given to the use of a dressing regimen that reduces the likelihood of trauma to the wound and surrounding skin.

Local guidelines should be put in place to regulate and aid decision-making. However, each individual patient should be treated according to the assessment findings to ensure that the most effective outcome is achieved.^{WUK}

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