

Electrical stimulation for pain reduction in hard-to-heal wound healing

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DOI:

[10.12968/jowc.2021.30.7.568](https://doi.org/10.12968/jowc.2021.30.7.568)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Milne, J, Swift, A, Smith, J & Martin, R 2021, 'Electrical stimulation for pain reduction in hard-to-heal wound healing', *Journal of Wound Care*, vol. 30, no. 7, pp. 568-580. <https://doi.org/10.12968/jowc.2021.30.7.568>

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Title: ~~Choosing an Single-use~~ electrical stimulation devices for wound healing

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Commented [JS1]: GENERAL:

Highlights in yellow are gaps for me to fill in as I proceed.

Comments in green are directed to authors.

Comments not highlighted are general – for anyone to comment on

NOTE – choice of journal is probably JWC

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Abstract: [to be reviewed and edited during later drafts]

Despite many notable treatment advances in wound management over the past 30 years, chronic wounds are becoming increasingly burdensome. One major unresolved issue is poor patient compliance to the accepted gold standard treatments, for example because wound pain can make many treatments intolerable. Approaches are therefore needed that not only stimulate wound healing but have the potential to improve compliance through the early resolution of pain

Electrical stimulation is one such treatment technology that has the potential to achieve this. Electrical stimulation is one of the most evidence-based technologies in wound management with 8 meta analyses and 29 RCTS published to date. It has been proven to be effective in accelerating healing in multiple wound types and is also shown to be beneficial in reducing wound pain. It is safe to use with minimal side effects. Despite this wealth of supportive evidence, electrical stimulation has not been adopted into everyday practice. This may be due to the complexity around the different forms of electrical stimulation, the confusion caused by the multiple theories that have been communicated on mode of action over the years, and a lack of awareness of the extensive and growing evidence base. Compounding these obstacles, most technologies have been clinic or research based, complicated to use and in some cases cause an unpleasant sensation; these features may have proved a major barrier to uptake of electrical stimulation devices in the past.

This review aims to clarify the use of electrical stimulation in wound healing and to explain the aspects of the technology that are important to consider and how these variables can impact the patient. This will be useful when choosing which device and settings to use. In conclusion, electrical stimulation is a technology platform that should be part of the armamentarium to address the many challenges of treating chronic and complex wounds.

Keywords: [TBC – depends on choice of journal]

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Introduction

Hard-to-heal wounds, those that remain unhealed after 12-weeks, are a major resource burden affecting 1.3% of the total adult population of the UK ¹ and 15% of the Medicare population in the US where annual expenditure on wounds costs over \$8.6billion.² Although wound management protocols, techniques and products have improved outcomes over recent decades, the problem posed by chronic wounds is far from solved. As the Western populations live for longer with an increasing burden of co-morbid conditions, the incidence of hard-to-heal wound is set to grow, with a corresponding burden on already stretched clinical systems [ref to be added]. Chronic wounds are often resource intensive requiring frequent dressing changes. Because of their typical long duration there is a protracted need for nursing visits and dressing resources. Approaches that may speed up wound healing would be of benefit not only to improve patient quality of life but also to reduce the financial and resource burden.

Patients with hard-to-heal wounds, by definition, have many barriers to efficient healing. Although some of these are non-modifiable, such as patient age or the presence of co-morbid conditions, several barriers that impact on the efficiency of healing are modifiable. Overcoming these barriers will also bring about improvements in the rates of wound healing.

One of these modifiable barriers is patient pain. This article describes the need to reduce patient pain whilst simultaneously stimulating wound healing. One treatment that appears to tackle both issues simultaneously is electrical stimulation and this article presents the case for adoption of electrical stimulation. Electrical stimulation covers a wide range of variables (different devices, settings, modes of delivery, waveforms etc). We also present a framework to help clinicians to decide which aspects of electrical stimulation are important and what to consider when choosing the best devices for the individual patient.

Wound pain is a barrier to patient compliance to treatment

One major barrier common to many hard-to-heal wounds, is wound pain.³ In 69% of patients, wound pain was cited as the worst thing about having a leg ulcer.⁴ Wound pain ~~comprises can be~~ categorised into ~~temporary-procedural~~ pain and 'persistent' wound pain. The former is associated with pain during dressing changes, debridement and cleansing procedures whereas persistent pain (sometimes termed chronic wound pain) represents the ~~underlying degree of pain experienced~~ present continuously during everyday activities at rest or during activity.^{5,6} It is widely acknowledged that ~~between~~ 50% and 60% of patients with chronic wounds experience persistent pain related to their chronic wound^{5,7} [add others as I come across them]. Arterial ulcers are believed to be most frequently painful with studies reporting between 82-100% of patients experiencing persistent or temporary pain. [refs from Price et al, but these are quite old now so maybe look for another ref], followed by venous leg ulcers and diabetic foot ulcers, both of which have been reported to be painful in between 50-64% of cases.^{5,8}

Not only is persistent pain a common experience for patients with chronic wounds, but the pain intensity is also often high. A study investigating a variety of chronic wounds in geriatric patients reported that of patients experiencing pain with their wound, 35% of them were suffering a pain intensity ≥ 5 (out of a "worst possible" pain score of 10).⁷ The most painful wounds were found to be arterial ulcers with a mean pain score of 6.07 (out of a maximum of 10), followed by venous leg ulcers (5.45). Patients experiencing the highest levels of pain, were those with multiple chronic wounds of different aetiologies.⁷

Commented [JS5]: There are other ways of categorising pain for example Background pain, breakthrough pain and procedural pain. Do you have a preference which method of categorisation is used?

Ref for this in Bechert and Abraham 2009

Commented [as6R5]: I think procedural and persistent are good choices. I don't think a reference is needed for the categorisation.

Commented [JS7]: This ref is Price et al who has reviewed several studies from the late 1990s and given a range of % of patients who experience pain divided by wound type. Maybe insert other more recent papers, if identified.

Commented [as8R7]: I found it difficult to find papers specifically about pain in leg ulcers but QOL papers such as this one were very helpful: Herber OR, Schnepf W, Rieger MA. A systematic review on the impact of leg ulceration on patients' quality of life. *Health Qual Life Outcomes* 2007;5:44.

Commented [as9]:

As well as having a serious impact on sleep quality^{4,7} and quality of life^{5,8} wound pain also can be a major reason why patients can't tolerate some of the most effective treatments. Pain or discomfort can therefore lead to lack of compliance of patients with prescribed therapy including some gold standard therapies (**Figure 1**).^{9,10} For example, many patients with venous leg ulcers that need compression already experience persistent wound painful and compression can exacerbate this pain. This is particularly true in the early stages of compression therapy, before any improvement in healing is noted.^{11,12} A key factor in deciding when to use lower levels of compression is wound pain, despite lower levels of compression being less efficacious compared with 4-layer compression systems.¹² Treatment-related pain appears to be a significant issue. In a study by Briggs et al, 44% of patients with venous leg ulcers were unable to tolerate compression bandaging for the treatment of venous leg ulcers (VLU) half of whom cited wound pain as the primary reason for their resulting non-compliance. Of the remaining patients who were able to tolerate compression, almost half (47%) reported that the treatment was painful and although the patients persevered for as long as possible with the treatment, a large proportion either stopped treatment or switched to a lower level of compression as a means of managing the wound pain associated with the treatment.¹³

In the same study, approximately 20% of patients with venous, arterial or mixed ulcers, reported increased wound pain following application of a range of different dressing types including anti-microbials, hydrogels and hydrofibres. Approximately a quarter of patients felt that the process of wound cleansing also worsened wound pain.¹³

Another intervention, advised in particular for patients with oedematous wounds, is leg elevation to relieve venous hypertension and increase ulcer blood flow.¹² This should reduce persistent wound pain and does in some patients; however, an early report by Hoffman et al (1997) reported that leg elevation, in some cases, worsened wound-related pain.⁴ This would lead to non-compliance for many patients affected in this way.

[what about exercise/ambulation? To what extent is exercise prescribed or advised to patients with hard-to-heal wounds? To what extent does pain dictate the amount of exercise tolerated?]

[What about NPWT? Should we go here? Can Accel-heal be used along-side NPWT?]

It is clear that many aspects of the interventions and treatments that are necessary for efficient wound healing can exacerbate wound pain, leading to reduced ability of patients to tolerate the treatment. In many cases, steps taken by the patient to avoid pain, for example removal of compression bandages or failure to elevate the lower leg, can be interpreted as non-compliant behaviour by HCPs, leading to a breakdown in the relationship between the patient and the caregiver.⁹ This appears to be particularly true of compression bandaging, the current gold standard treatment of VLU but is also true of a wide range of treatments, depending on the patients' perceived wound pain and their tolerance threshold. Under these circumstances, HCPs may have little option but to provide less effective treatments (passive e.g. simple wound dressing or lower levels of compression). In effect, this reduces the armamentarium upon which the HCP can rely, and can have a direct effect on the efficiency of healing; wounds were found to take twice as long to heal when patients were not concordant with their prescribed therapy¹⁰ and ulcers of long duration are much less likely to heal.^{14 15} Individuals with VLU that are not receiving effective compression are at risk of prolonged non-healing.^{4 16} Addressing patient pain can lead to improved concordance with otherwise poorly tolerated treatments, leading to improved healing rates.⁹ The positive effect of reduced pain on patient quality of life would also be of significant benefit.

Commented [JS10]: Authors - is this something you have observed with patients? That wound / limb pain can prevent patients from complying with elevation?

Commented [JS11]: In this section, I've tried to widen the scope to chronic wounds in general rather than be limited to VLU only at this stage. Other than those already covered, can you think of any other types of treatment or aspects of treatment where wound pain would cause problems with compliance? Some discussion of pain during ambulation in Bechert and Abraham, this is in the context of breakthrough pain. I have found more info on wound pain – need to see Made Easy piece for details.

Pain management in chronic wounds

Effective clinical pain management and the recognition of the experience of acute and chronic pain are of the utmost importance to people with a chronic wound.¹⁷ It is widely recognised that optimal pain management should ideally be incorporated as an integral part of wound management⁶ however current commonly used pain management approaches are far from optimal.^[need a couple of good refs].

Many pain management approaches are based on the WHO analgesic ladder, originally developed for the management of cancer pain¹⁸ but widely adopted as a model to cover any type of 'chronic pain', including by the British National Institute for Clinical Excellence (NICE).¹⁹ This model adopts a step-wise approach to pain management, starting with non-opioid analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). If these provide ineffective pain control, cause side-effects or if they have been in use for a prolonged period, escalation to opioid painkillers may be necessary. ^[In reality, many patients with persistent chronic wound pain do not receive adequate management from non-opioid analgesics (either oral or topical) and need escalation.]²⁰ Some commentators have suggested that patients with wounds with moderate (4-6 out of 10) wound pain should be offered weak opioids like codeine or tramadol, with or without addition of acetaminophen and NSAIDs, as appropriate. For patients with a high level of wound pain (>6-10 out of 10) patients should be stepped up to opioid analgesics such as morphine, hydromorphone, oxycodone, fentanyl, and buprenorphine.²⁰ Opioids are commonly used in the US to manage persistent wound pain.²¹ ^{[Need some information here to describe how common is the use of opioids pain killers in patients with chronic wounds, in the UK].}

Although the model laid out by the WHO is widely acknowledged, there are many barriers to its adoption in the management of persistent wound pain. These barriers relate to the inadequate pain alleviation²², ^{[access to the medication[ref], concerns over analgesic-related adverse events or harms²³ and a reluctance of patients to progress up the ladder.]}²² Firstly, there are concerns that the currently available analgesics may not be fully efficacious in managing the type of pain typical of persistent wound pain. The agents described above are most effective against nociceptive pain, as opposed to neuropathic pain more common in chronic wounds, caused by damaged (e.g. during the injury process) or pathological defects of the nerves (e.g. caused by prolonged uncontrolled diabetes).⁵ ^[In one study, 30 out of 37 patients with VLU prescribed morphine still reported wound pain of 4 or 5 out of 5, suggesting a lack of effective pain management in a large proportion of patients.]⁴ There are also some concerns that some opioid analgesics (in particular) may have a negative impact on the actual biological process of wound healing, reducing the efficacy of the healing process itself. Although the physiological effect of opioids on wound healing is not fully understood and remains to be more fully investigated, some studies have shown that wounds treated with opioids heal more slowly than those not treated with opioids.²¹

In terms of access to analgesics, patients who receive routine wound care from community nurses may not have ready access to opioid painkillers or alternative pharmaceutical approaches such as the use of certain tricyclic ^[anti-depressants or anti-convulsants]⁵ because of ^[prescribing restrictions].

There are also obvious concerns regarding the safety of long-term use of opioid analgesics. In the UK, NICE guidelines specifically warn of the over-reliance on pharmaceutical approaches to pain management. Not only may these be less successful if the complexity of the patient's individual needs are not also taken into account but there is the ^[risk of serious harms and dependence].¹⁹

Commented [JS12]: Authors- please advise if this is the case for your practice.

Commented [as13R12]: It is the case that systemic analgesia and anti-inflammatories are generally ineffective but there is little empirical evidence.

Commented [as14]: The use of opioids for leg ulcers is not common in the UK. There is little or no published evidence of oral analgesia effectiveness. Most literature is about the use of topical agents impregnated in dressings or applied as gels. I have been writing a paper on VLU pain and its management with Leeanne and have appended a relevant section in a separate document. I am happy for it to be changed and used in some form in this paper but will be publishing it with Leeanne later so we need to be careful to avoid plagiarism.

Commented [JS15]: Should I include this or delete?
"In 1997, a study investigating wound pain in patients with VLU, reported that of patients describing 'horrible' or 'excruciating' pain, only 50% were receiving morphine-based analgesia; 27% had been prescribed no analgesia whatsoever and the remainder were being prescribed only mild analgesics."

Commented [as16]: I don't think there is evidence to support this statement. I think the research focuses on nociceptive pain and the pain-relieving drugs in use are not effective even though a significant proportion of wound pain is likely to be nociceptive.

Commented [as17]: This sounds like there is mechanical damage as the tissues deteriorate but I think it is more complicated than that. It is likely that the neuropathic pain is due to ischaemia resulting from small blood vessel damage in the wound bed Jin J. Neuropathy and Ankle Mobility ... [1]

Commented [as18]: I could find no papers exploring the use of gabapentin or amitriptyline for ulcer pain, which is weird when we consider that neuropathic pain is involved. It might be worth noting that there is little or no research ... [2]

Commented [JS19]: Authors – do you agree that there is there a reluctance among HCPs to prescribe these drugs to patients with wound pain? Or is it a prescribing issue i.e. the wound is managed by the nurse who does not have the ... [3]

Commented [JS20]: Authors - Is this the case? I should think that physicians usually prescribe these things – do you think this 'access' issue is a reason that too few people receive appropriate pain relief?

Commented [as21R20]: I would think it has a lot to do with lack of efficacy and the type of patient involved – many will have comorbidities and be on many drugs per day. Chance of compliance with poorly effective analgesics ... [4]

Commented [JS22]: Authors – please can you advise. How worried are HCPs about this in practice specifically for chronic wound patients?

Commented [as23R22]: There is an opioid expert working group meeting at the MHRA (commenced Feb 2019) to explore benefits and risks of opioid medicines. It might be good to say at this stage that the situation is complex ... [5]

It seems clear that although adoption of the WHO analgesic ladder, based on a pharmaceutical approach, is important in the management of wound pain, it does not completely solve the issue of persistent wound pain; so what are the alternatives? Topical application of analgesics has been explored but has been found lacking; although there is some evidence to suggest that delivery of topical pain killers (ibuprofen dressings) may offer pain relief to people with painful venous leg ulcers²⁴ these are not widely commercially available and are not a practical option for most people. In another example, topical application of morphine gel onto chronic wounds was found to be effective but only for a 2-hour window following application, meaning that pain management was not continuous.²⁵

In the UK, NICE recommend that HCPs “be familiar with the range of non-pharmacological interventions that are effective for reducing symptoms in people with chronic pain”.¹⁹ It is clear that an alternative, non-pharmacological approach to the management of persistent wound pain during treatment is needed.

Alternative approaches to address pain and non-healing

Ideal approaches should alleviate wound pain in the short-term, improving patients’ tolerance to their prescribed wound treatments and improving patient compliance to their wound management plan. Improved compliance would lead to improved efficacy of healing, because the chosen treatment would be given chance to work; therapies that promote wound healing would be able to reduce patient pain over the medium to long-term as a direct consequence of the progress towards healing. The cumulative effect of a reduction in pain and wound progressing towards healing would be an improvement in patient quality of life (**Figure 1**).

However, there is an additional opportunity for therapies, that in addition to reducing wound pain, can also have a direct stimulatory effect on the wound healing process. The resulting long-term benefit in both wound progression and pain alleviation, may be doubly beneficial.

One such option may be electrical stimulation. Electrical stimulation for wound management is understood to be effective in the management of hard-to-heal wounds. It has been reported to alleviate patient wound pain^{26–30} and has been shown to improve healing outcomes.³¹ (**Figure 1**) The overall effect also improves patient quality of life [ref]. These clinical outcomes will be explored in more detail in a later section.

Explaining electrical stimulation – a variety of formats for a variety of applications

Electrical stimulation is used in a wide variety of clinical applications and can be considered a ‘catch all’ phrase that covers many different functional therapies encompassing a wide range of tailored stimuli. Some of the ways in which electrical stimuli can differ is in the physical response that it evokes when applied to a patient. For example, in order for some clinical therapies to work, they need to evoke a response from the motor nerves (i.e. causing a muscle twitch) or a response from sensory nerves (i.e. causing a physical sensation). Importantly, other types of electrical stimulation can work at a ‘sub-sensory’ level, meaning that the patient may not feel any stimulation (**Figure 2**).

There are many ways in which the electrical stimulus can be tailored to achieve specific clinical goals. Variables include the **intensity** of the electrical stimulus, typically represented as the current (measured as amps or microamps) although this can also be represented as power (measured as voltage). Another important variable is the **duration** of the stimulus; i.e. how long the electrical stimulus lasts for, often measured in microseconds, representing pulses of current. There is a well characterised relationship between the intensity of electrical current applied, and the duration of

Commented [as24]: I would include this with the other section about the likely efficacy of analgesics and anti-inflammatories. Same mechanism of action so doesn’t seem to warrant a different section.

each pulse, so that current and frequency, in combination, define the size of the stimulus, and thus the extent of the patient's physical response. This is called the strength-duration curve (**Figure 2**). Essentially, the graph shown in **Figure 2** describes the well-characterised relationship where (for example) a higher current with a shorter duration may evoke the same physical response as a lower current applied for a longer duration. [need a ref – probably some kind of text book.]

With regard to wound healing, electrical stimulation therapies can work to influence wound healing on a **sub-sensory level** of stimulation. This means that some of the types of electrical stimulation that can be effective in wound healing are different to those used for some other clinical applications, for example electrical muscle stimulation (EMS, used in physiotherapy), pain relief (trans-epidermal nerve stimulation, TENS) or neuromuscular electrical stimulation (NMES). These treatments all rely on *externally applied* electrical stimulation, as opposed to implanted electrical stimulation devices, such as cochlea implants and pacemakers, which are not described in this review. With therapies like EMS or TENS, their purpose is to stimulate muscle twitch (EMS) or to activate the appropriate nerve thus evoking a sensory response. They therefore need to deliver a relatively high stimulus to evoke an appropriate response in the patient's body. However, electrical stimulation devices used in wound management can be effective at much lower currents and shorter pulse durations (higher frequency). Electrical stimulation devices used for wound healing *do not need* to evoke the physical responses required for other types of electrical stimulation therapy. This is represented in the strength-duration curve shown in **Figure 2**, where sub-sensory levels of stimulation that have been used clinically for wound management, [ref] is within the green shaded area. Conversely, the typical currents and durations required for functional EMS or TENS therapy, place these therapies in the sensory or motor domains of the strength-duration curve (**Figure 2**).

While some electrical stimulation devices designed to operate via sensory nerve stimulation, such as TENS devices, have been used to improve wound healing, patients reported a sensation that they described as unpleasant. This negatively affected compliance to this particular treatment.³² [need to describe in more detail]. Devices which cause an unpleasant sensation, in addition to an already persistently painful wound, may not be the ideal approach. Conversely, use of electrical stimulation device that operate in the 'subsensory' domain, are less likely to cause unpleasant sensations and have the additional benefit of not having twitchy muscles. This also means that patients will often not feel any sensation, relating specifically to the operation of the device. [ref] There is a need to more precisely categorise the electrical stimulation devices that operate in the sub-sensory and sensory domains. One option is to adopt the recently coined term 'electroceutical' that encompasses all bioelectric medicine that uses low level electrical energy to affect and modify specific functions of the body. Unlike the universal term 'electrical stimulation', 'electroceutical' implies a more accurately targeted clinical application more akin to its pharmaceutical equivalent. [The low level of electrical energy, the specific dosage delivered and the specific mode of action differentiates electroceutical treatment from the traditional understanding of electrical stimulation]. Indeed, this new therapeutic area is now subject to considerable research and investments by major pharmaceutical companies for a wide range of clinical applications; many of these new devices are implantable, so to differentiate between electroceutical wound healing devices which are applied to the skin and implantable electroceutical devices, the descriptive term "externally applied electroceutical" (EAE) is appropriate. **Figure 2** illustrates the part of the strength-duration curve typically stimulated by EAE devices.

Electrical stimulation triggers bioelectric signalling in normal cells and acute wounds

Electrical impulses in the human body are of course needed to stimulate nerves and muscles; this is only the tip of the iceberg. Each and every cell in the human body (indeed, in every living thing) is

Commented [as25]: There is quite a lot of evidence about implanted spinal cord stimulation for difficult to control pain so it might be better not to divide into internal and external.

Commented [JS26]: Need to reference the Accel-Heal evidence here, preferably a paper which mentions the sub-sensory aspect or mentions the current/duration]

Commented [JS27]: I also need more information about the electrical parameters of the competitor devices to understand where they land on the strength-duration curve. Do you have any information? I need current and duration of pulse.

Note – See Polak et al 2013 for HVPC stimulus details. See draper et al for proof that HVPC causes a sensation (pins and needles). This has been developed in the Mde Easy piece – review.

Commented [JS28]: Need Accel-heal ref that mentions about lack of sensation

Commented [JS29]: Need a ref – maybe a general one in the field of electroceuticals, rather than a wound specific one.

finely tuned to tiny electrical stimuli.³³ The normal homeostatic situation is for cells to be 'charged' because they contain and are surrounded by electrically charged ions. This 'charge' is the foundation of 'bioelectric signalling'. The ions involved in bioelectric signalling are predominantly calcium (Ca^{2+}), chloride (Cl^-), potassium (K^+) and sodium (Na^+) that are present in our blood and interstitial tissues.³³ These ions can't permeate freely from the inside to the outside of a cell (or vice versa) but have to be let in or out via 'voltage-gated' channels, doors in the cell membrane that open or close in response to electrical stimulation.³⁴ **(Figure 3)** When an electrical current of an appropriate strength is delivered, it opens (or closes) the voltage-gated channels and allows a flow of ions from one place to another along an electrical gradient (from $-$ to $+$). These ion flows activate various second messenger cascades (protein signalling events) inside the cells that regulate gene expression and ultimately change cell behaviour! This process is known as bioelectric signalling.

This process can occur in all tissues of the body including the skin. The uninjured human epidermis acts as a "battery" keeping negatively charged ions in the superficial layers of the epidermis and positively charged ions in the deeper layers.³³ This creates a difference in electric potential (electrical gradient) across the epidermis, termed the trans-epithelial potential. When the skin is wounded and the epithelium breached, this electric potential is disrupted and a small electric current (i.e. flow of ions from positively charged areas to negatively charged areas) is generated. This current is identifiable immediately around the wound and is called the 'current of injury'. It can reach up to 100-200mV in strength. This current is enough to surpass the threshold potential of most cells, triggering bioelectric signalling and fundamentally influences the cellular behaviours essential for normal wound healing.^{33,35,36}

Some of the cell behaviours known to be regulated by bioelectric signalling include behaviours necessary in many stages of the wound healing process, the inflammatory phase, proliferative phase and remodelling phases of healing **(Figure 3)**.³⁵ Electrical stimulation can activate macrophages and stimulate the production and release of growth factors.^{37,38} Proliferation and migration of many cell types can be stimulated including fibroblasts,³⁸ endothelial cells³⁹ and keratinocytes,⁴⁰ all important in the proliferative phase of healing, for the production of granulation tissue and for re-epithelialisation.³⁷ Electrical stimulation promotes angiogenesis,^{37,41} essentially a combination of endothelial cell proliferation, migration and morphogenesis, collagen matrix formation³⁷⁻³⁹ as well as wound contraction and cellular differentiation, and organisation of the extracellular matrix,^{35,41} all important in the remodelling phase of healing **(Figure 3)**.

Bioelectric stimulation in chronic wound healing

Following the wounding of the skin the resulting flow of ions across the epidermal breach can only last for so long. Healing is believed to be arrested when the current flow ceases e.g. when the wound has been present for a protracted period.^{28,29} The current ceases altogether when the wound dries out and this is thought to be one reason why moist wound healing gives better results.³³ Other potential aberrations in chronic wound healing caused by inherent problems with bioelectric signalling are currently poorly explored and not fully understood.

In a non-healing wound, this inherent bioelectric signalling can be jump-started through the use of therapeutic electrical stimulation. This appears to stimulate the healing process by artificially providing an electrical stimulus similar to that seen in the normal current of injury **(Figure 3)**.

Clinical efficacy of electrical stimulation in wound management

Wound healing response

The clinical effect of electrical stimulation on chronic wound healing has been widely investigated with a number of comparative studies including 29 randomised controlled trials³¹ (Figure 4). Systematic reviews and meta-analyses have confirmed that electrical stimulation has a clear beneficial effect on wound healing^{31,32} and is safe.³² [other meta-analyses]. One systematic review of 21 RCT studies that confirmed benefit and safety of electrical stimulation to accelerate wound healing, compared to healing with no electrical stimulation, irrespective of the type of ulcers.³² In other meta-analyses of multiple randomised studies, electrical stimulation has proven to reduce wound area [refs]⁴² and to increase the rate^{43,44} and chance of healing [refs].

While some meta-analyses have included randomised studies from any type of chronic wound,^{31,42,44} there is a particularly strong body of evidence emerging to support the use of electrical stimulation in pressure ulcers.⁴³ This is reflected in the fact that the National Pressure Ulcer Advisory Panel (US), European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance, jointly advise clinicians to “consider the use of direct contact (capacitive) electrical stimulation to facilitate wound healing in recalcitrant Category/Stage II pressure ulcers as well as any Category/Stage III and IV pressure ulcers”. This strong recommendation is based on a body of evidence classed as grade A (strongest level of evidence).⁴⁵ Most recently, a randomised study published by Polak et al (2016)⁴⁶ reported that treatment of pressure ulcers with electrical stimulation, in addition to standard wound management, resulted in a reduction of wound area at 4 and 6-weeks compared to standard wound management alone. Other randomised studies have demonstrated the effectiveness of electrical stimulation in the specific wound aetiologies VLU⁴⁷ and DFU⁴⁸, with many others investigating mixed cohorts of patients with different types of chronic wounds [list the other RCTs?].

Pain management response

In addition to the improved wound healing outcomes described above, electrical stimulation has a simultaneous beneficial effect on wound pain. Clinical studies have reported a rapid and prolonged reduction in chronic wound pain in patients who have been treated with electrical stimulation.^{26–28,30,49} Leloup et al (2015) observed a statistically significant drop in pain levels within the first three days of electrical stimulation, from an average pain score of 5.3 (out of 10) to 3.6 by day 3 and further still to 2.2 by day 5 following the initiation of treatment. This effect might be most marked in patients with a high level of wound pain; Santamato et al (2012)⁴⁹ studied a group of patients with particularly painful leg ulcers, with a mean pain score at baseline of 9 out of a maximum score (worst pain) of 10. Within 5 days of treatment, patients receiving electrical stimulation, reported a significantly reduced pain level, of only 3.4 (vs 7.8 in the control group who did not receive any electrical stimulation). After 15 days of treatment this had fallen further to a pain score of 1.6 (vs 6.6 in the control group).

Consistent with the reduced level of pain, several studies have reported a reduced need for analgesics to manage wound pain following commencement of electrical stimulation.^{26,27} Nair et al²⁷ (2018) reported a reduced need for opiate analgesics. Eighty-three percent of patients taking tramadol at the beginning of the study, were able to stop taking this painkiller following treatment with electrical stimulation, and a further 15% were able to dramatically reduce their intake.

- [Mode of action of e-stim wrt pain relief – S100 aspects also to be explored]

[One of the most likely mechanisms for pain relief by electrical stimulation is enhanced wound healing. There are several reports of electrical stimulation improving wound healing in chronic

Commented [JS30]: Update if I find any more.

Commented [JS31]: Girgis et al 2019 – need to buy
Lala et al 2016 – need to buy
Will add once purchased and reviewed.

Commented [JS32]: Girgis et al 2019 – need to buy
Lala et al 2016 – need to buy

Commented [JS33]: Add Girgis et al and Lala et al as these are two other meta-analyses on PU specifically.

Commented [JS34]: Please advise if you need more detail in this section i.e. describing the specific outcomes and statistics that came out of some key individual studies.

Commented [JS35]: This is a key area that needs some input. In terms of mode of action, the S100 work is important to include.
I would also like some insight into how much of the MoA from TENS can be extrapolated to wound E-stim generally. For example, TENS provides pain relief via the gate theory of pain. Is it possible that this can be possible for a sub-sensory stimulation? Or is gate theory by definition dependent on the provision of a sensory stimulus?

Commented [JS36]: This section is modified from an existing pain relief document.

ulcers by stimulating blood flow in the wound bed and the surrounding skin [7-9].⁵⁰ Electrical stimulation improves re-innervation of damaged tissues as well as general wound repair.^{40,50}

However, there are reports of pain reduction immediately on application of electrical stimulation devices [refs] and one of the suggested benefits is that pain reduction is enough to allow full compression therapeutic bandaging. This suggests there must be a more immediate effect of electrical stimulation than a gradual pain reduction that would be achieved by wound healing. The mechanism of actions underlying these more immediate effects is not well understood.

Variables to consider when choosing an E-stim device

Despite the wealth of evidence in support of E-stim, several major hurdles have historically prevented wide adoption (Figure 5). These include poor adherence by patients to their electrical stimulation therapy,³² the difficulty of choosing and applying appropriate settings by HCPs^{32,51} and treatment limitations which mean that E-stim can only be delivered during routine dressing changes.⁵² These are described in more detail below:

Maximising adherence to treatment

E-stim devices used for wound healing have included devices which are designed to be used at a sensory level. Many patients describe the sensation as unpleasant. This appears to be particularly true when TENS machines have been used for the purposes of wound healing³² but may also be the case for HVPC devices which often cause a prickling sensation.⁵³ The nature of the stimulation typically applied as part of a TENS and HVPC treatment regime delivers a stimulus well within the sensory domain and TENS occasionally within the motor domain. Figure 2. We hypothesise that use of subsensory EAE devices may be of benefit by reducing the likelihood of unpleasant sensation associated with some types of E-stim. This may improve patient compliance.

Another aspect of adherence to treatment depends on the extent to which patients are able and willing to comply with often onerous and complicated treatment regimes, on top of all the other medications they may be taking. Many devices require the patient to self-administer the electrical stimulation at several separate time points per day and to continue this regime for several days. A significant proportion of patients are not adherent with these schedules. In a study by Peters et al (2001)⁴⁸ 25% of the patient cohort were non-compliant to the prescribed periodic use of ES in the home, even under the controlled conditions of a formal clinical study. It is possible that the degree of non-compliance with these 'manual' electrical stimulation treatments may be higher. Automatic systems which deliver therapy without the need for any intervention from either patients or caregivers, may be preferable to avoid non-compliance arising from patients forgetting to apply the treatment or not managing to factor it into their day.

Ease of choosing and setting stimulation parameters

When using many E-stim devices, the device requires that the user (typically the clinician) choose and set an appropriate level of stimulation. Specific pre-programmed devices are preferable to multi-functional devices with a very high number of settings where there is room for error in setting inappropriate parameters.

Most often, devices designed to deliver electrical therapy are designed to deliver a set voltage. In practice, when applied to the human body, voltage is converted into current and it is the electrical current, the flow of energy through the patient's tissue, that causes the physiological, sensory and physical effects of the electrical stimulation therapy. Current can be influenced by the resistance of the patient's tissue, itself influenced by many factors including level of hydration, level of peri-

Commented [JS37]: Robin you referenced these in your document (the one on pain and TENS but I don't have them in the Mendelet folder. Please can you send them. Thanks

•Biedebach MC. Accelerated healing of skin ulcers by electrical stimulation and the intracellular physiological mechanisms involved. *Acupuncture & electro-therapeutics research* 1989;14(1):43-60. [published Online First: 1989/01/01]

•Kloth LC. Electrical Stimulation Technologies for Wound Healing. *Advances in wound care* 2014;3(2):81-90. doi: 10.1089/wound.2013.0459

•Feedar JA, Kloth LC, Gentzkow GD. Chronic dermal ulcer healing enhanced with monophasic pulsed electrical stimulation. *Phys Ther* 1991;71(9):639-49. [published Online First: 1991/09/01]

Commented [JS38]: Can include some TENS gate theory papers here but also review the French study (if it has been published)

Commented [JS39]: Need to work in the gene expression story here with short-term reduction in inflammation.

Commented [JS40]: Review Avrahami et al about practicalities of applying in clinic only.

Avrahami R, Rosenblum J, Gazes M, Rosenblum S, Litman L (2015) The effect of combined ultrasound and electric field stimulation on wound healing in chronic ulcerations. *Wounds* 27(7): 199-208

This kind of device is said by Ovens to be a challenge in the community. See Ovens 2017 paper.

wound oedema, room temperature (sweat) and the types of tissue in the immediate vicinity.⁵⁴ This means that one set level of voltage, might result in delivery of a range of currents depending on the patient's unique and changing condition and environment. An increased current, resulting from the same voltage but through tissue with different resistance, might explain why some patients feel an unpleasant sensation at one given device setting, when some patients feel very little sensation.

Given the importance of avoiding an unpleasant sensation, due to the impact this has on compliance to treatment, one solution is to use a current-controlled device, in which, the electronics within the device continually measure the current that is delivered and automatically adjusts the voltage to ensure the current is always applied. This is important as it automatically compensates for the different makeup of tissues in different body locations, in different patients, perhaps with different levels of hydration or peri-wound oedema, all of which can influence the delivery of bioelectricity, without needing direct intervention from the clinician or patient. The appropriate current is already programmed in the device and there is no need for clinicians to decide on an appropriate level of electrical stimulation.

Ability of patients to manage their own treatment in their own home

Being able to manage wounds in patients' own homes, rather than outpatient clinics or hospital is important in terms of saving resources, to ensure a more continuous and uninterrupted treatment and for patient convenience. To achieve this, devices that are safe and appropriate for use in the home are needed.

Historically, e-stim would be applied episodically, often limited to routine dressing changes which may have been conducted during out-patients visits. This was limited by the lack of portability of the devices that were used to deliver the treatment and other design limitations, for example use of devices not designed for use along-side open wounds and wound dressings.⁵² More recently, portable, user friendly pocket-sized devices have been developed. Because they can be used to deliver uninterrupted treatment between dressing changes, as opposed to episodic treatment, these new devices are believed to be advantageous. Their small size makes them discrete, an important consideration in the patients' quality of life.

Patterns and magnitude of E-stim waveform

Another way in which the delivery of E-stim can vary is in the pattern and magnitude of electrical stimulation they deliver to the wounds. There is an emerging evidence base to suggest that different parameters may lead to different wound healing responses, although the 'ideal' parameters remain to be definitively proven. The weight of evidence is in favour of pulsed current waveforms rather than continuous direct current.^{31,55} Khouri et al (2017) published a meta-analysis in which they compared the efficacy of electrical stimulation devices which had pulsed or direct electrical impulses on wound healing and identified that pulsed waveforms resulted in better wound outcomes. This was true for both low voltage and high voltage waveforms.³¹ Pulsed current can have a monophasic (unidirectional) or biphasic (bidirectional) waveform.⁵⁵ While both monophasic and biphasic pulses were found to significantly improve the rate of healing, the effect was more marked for monophasic waveforms.⁵¹

There is less certainty about the 'ideal' intensity of the electrical stimulation. Although high voltage pulsed currents appeared to perform marginally better than low voltage pulsed currents,³¹ both performed better than direct electrical impulses. Some commentators would suggest that instead of voltage, a more representative measure might be electrical 'charge' measured in Coulombs (C). Kloth et al, supported by other commentators,⁴⁶ reported that the most appropriate charge is 250-500 $\mu\text{C}/\text{sec}$. [Kloth et al] [would need to expand]

Commented [JS41]: Is this actually the case? Is there any evidence for this? I'm struggling to find references.

N.B. RCTs aren't reliable in terms of their description of treatment because they are artificially designed around the need to collect data at intervals. Treatment interventions often occurred in the clinic due to the need for formal wound assessments at given time points rather than being provided at the clinic because of a limitation of the E-stim device used.

Commented [JS42]: Is this correct? Do you know of any evidence to support this?

Commented [JS43]: Presumably from Kloth et al. [need to find] 'The dosage range of 250–500 IC/s represents a small window of electrical energy that has been shown to pro... [6]

Commented [JS44R43]: Can anyone help me to assign a microCoulombs/sec value to Accel-Heal to see if it's in the range hypothesized by Kloth et al to be efficacious. Without a corresponding value, it is not possible to put Accel-Heal in its correct context.

Commented [JS45R43]: Synapse is doing this via third party contractor

Conclusions

Chronic wounds remain a major resource and humanistic burden. New approaches are needed to tackle the growing problem. Electrical signalling is a natural part of the normal wound healing process triggered by wounding of the epidermis. This signalling is a fundamental part of many of the cellular responses needed when healing a wound. This natural electrical signalling can cease in a hard-to-heal wound but can be triggered artificially through device-mediated electrical stimulation. As well as kick-starting the healing process electrical stimulation may also provide a means of actively reducing pain as well as increasing the rate of wound healing. Reduction in pain is likely to improve ability of patients to tolerate effective wound management treatments for example compression for the management of VLU. There are many options for electrical stimulation for wounds presently available. We suggest that a preferred option, can be categorised as ‘externally applied electroceutical’ (EAE) treatment. This treatment delivers, low intensity, pulsed current at a sub-sensory level. This stimulates the patient’s bioelectric signalling pathways to trigger healing events but avoids any unpleasant sensation that may exacerbate an already painful wound. In addition, for greatest efficacy (uninterrupted use), and greatest resource savings (provision in a home-care setting) portable and intuitive devices are particularly advantageous. We also suggest that pre-programmed devices that require no intervention from either patients or caregivers, can improve compliance to the electrical stimulation, thus improving outcomes. We hope that these insights will be of benefit to clinicians when choosing which electrical stimulation device and protocol is most suited to their patients’ needs.

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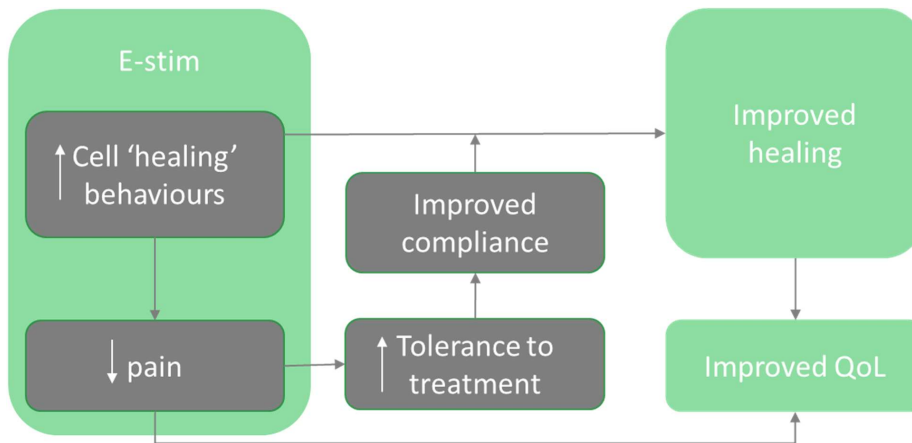
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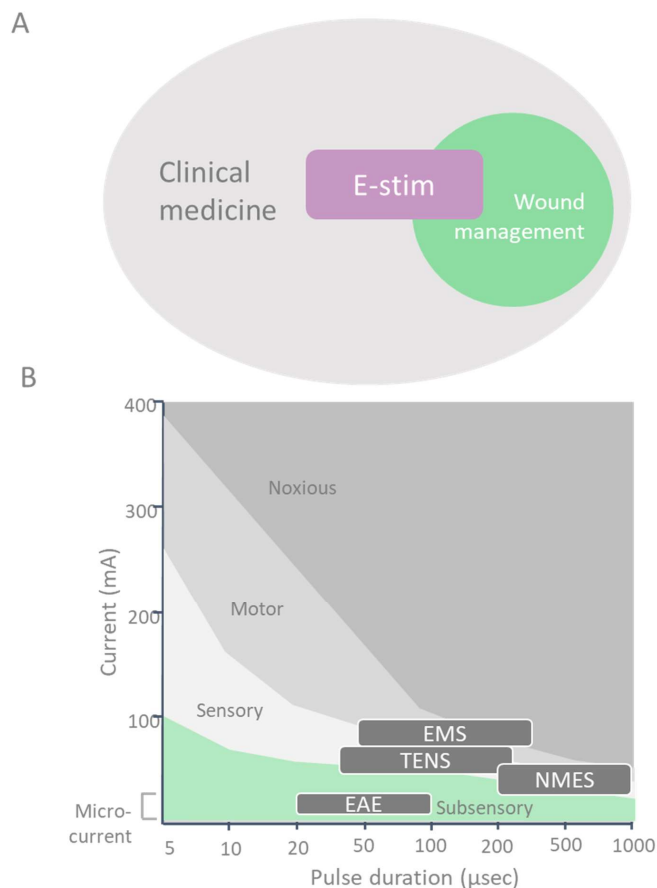
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Figure 1. Impact of Electrical stimulation on wound healing



Application of electrical stimulation to chronic wounds can help to reduce pain²⁶ as well as promoting wound healing processes.³¹ Reduced pain²⁶ leads to an increased patient tolerance to wound treatment,¹³ leading to improved compliance with treatment.¹³ This leads to more efficient wound healing. The combined effect of reduced pain and improved healing include improved patient quality of life [ref for E-stim having this effect].

Figure 2. The landscape of electrical stimulation for clinical applications



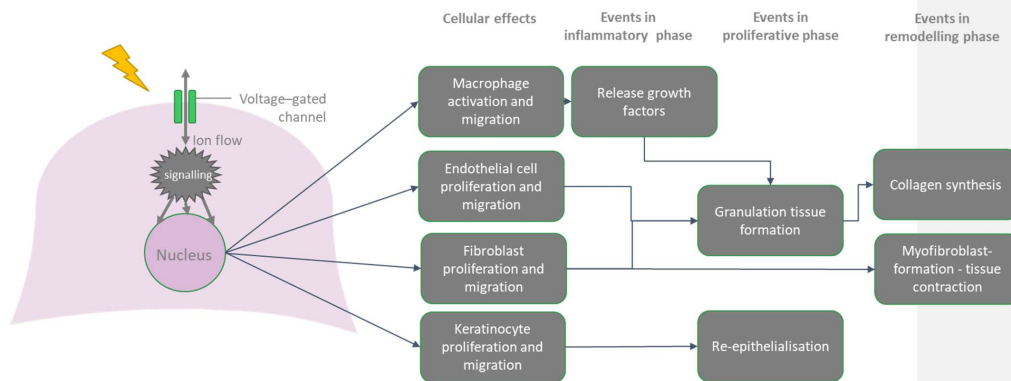
- A.** Wound management forms one small part of a much larger general field of medicine. Electrical stimulation therapy has applications not only in wound management but also in other clinical applications. Note: these bubbles are for illustrative purposes only and are not drawn to scale.
- B.** Electrical stimulation is an umbrella term that covers a wide range of different functional therapies. Types of therapies shown for comparison are related to physiotherapy (electrical muscle stimulation, EMS, neuromuscular electrical stimulation, NMES) and pain relief (trans-epidermal nerve stimulation, TENS). TENS has also been used in wound healing. The graph describes the relationship between the current applied (y-axis) and the duration of each electrical pulse (x-axis). This combination of parameters defines the extent to which the patients can feel the electrical stimulation. Conventional TENS devices deliver a high enough current at a pulse duration long enough for sensory stimulation (i.e. the patient feels a sensation). Therapies such as EMS and NMES deliver a current at a pulse duration long enough to evoke a motor response (e.g. a muscle twitch) as well as a sensory response. However, some e-stim devices, here categorised as externally applied electroceuticals (EAE) used in wound management do not need to evoke a sensory or motor response and can have a physiological effect below the threshold for sensory detection.

Commented [JS46]:

Query - I know the voltage delivered by the Accel-heal device is modified to ensure the correct current is delivered but roughly what kind of voltage are we talking about?

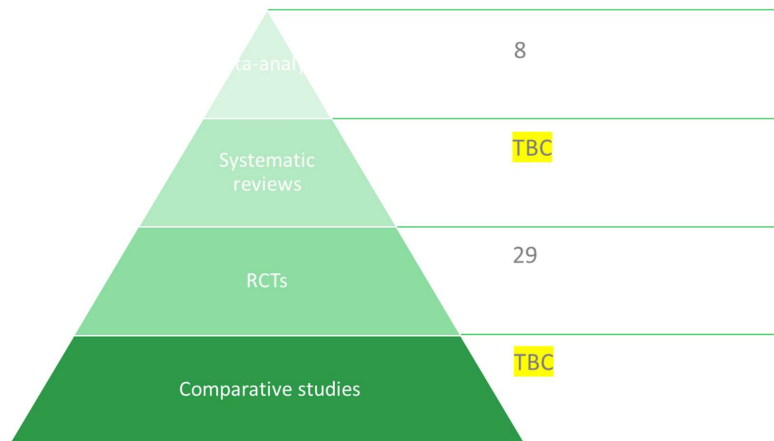
In wound devices that are called 'high voltage' exactly how high do they mean?

Figure 3. Bioelectric signalling and its role in wound healing



Individual cells can respond to a small electrical stimulus by opening or closing voltage-gated channels in their cell membranes. The electrical stimulus can be delivered as part of the electrical current that occurs when the epithelium is breached during wounding or can be applied artificially through device-mediated electrical stimulation. The flow of ions into and out of a cell affects its internal biochemistry, which in turn activates cell signalling mechanisms. The end products are changes in gene expression which can give rise to a variety of different cellular effects, often depending on the type of cell stimulated. Normal wound healing follows 3 over-lapping phases of healing, the inflammatory, proliferative and remodelling phases. In normal wound healing, endogenous microcurrents, activate gene expression to change the cell behaviours needed to progress through the phases of healing. [add refs to legend consistent with main body of text]

Figure 4. Evidence-base for electrical stimulation for wound healing



[Note to self. Need to:

- Review 'systematic reviews' and 'comparative studies' on PubMed.
- Add all of the references to the reference list via Mendeley]
- For RCTs see Khouri et al and check Pubmed for any newer ones
- For Meta-analyses, see list in notebook

Figure 5. Important considerations when choosing the most appropriate E-stim device

Maximising adherence to treatment	Ease of choosing and setting parameters	Ability to manage treatment at home	Waveform
<ul style="list-style-type: none">• Sub-sensory - no uncomfortable sensation• Can be used along-side other treatments• Automatic as opposed to manual function	<ul style="list-style-type: none">• Simple to set - <i>no need for complex decision making</i>• Current controlled as opposed to 'voltage controlled' - <i>no need for adjustment</i>	<ul style="list-style-type: none">• Suitable for home setting• Wearable• Discrete	<ul style="list-style-type: none">• Sub-sensory preferred over sensory• Pulsed current preferred over direct current

Page 5: [1] Commented [as17] **amelia swift** **04/11/2019 12:22:00**

This sounds like there is mechanical damage as the tissues deteriorate but I think it is more complicated than that. It is likely that the neuropathic pain is due to ischaemia resulting from small blood vessel damage in the wound bed Jin J. Neuropathy and Ankle Mobility Abnormalities in Patients With Chronic Venous Disease. *JAMA* 2014;311(24):2549.

Diabetic neuropathy tends to be focused in peripheries and many ulcers are more proximal. Not sure the diabetes link is appropriate here although it is possibly related.

Page 5: [2] Commented [as18] **amelia swift** **04/11/2019 12:34:00**

I could find no papers exploring the use of gabapentin or amitriptyline for ulcer pain, which is weird when we consider that neuropathic pain is involved. It might be worth noting that there is little or no research about this. One systematic review I found included 1 paper where gabapentin had been used in critical limb ischaemia but it wasn't for ulcers.

Page 5: [3] Commented [JS19] **Jenny Smith** **02/07/2019 12:03:00**

Authors – do you agree that there is there a reluctance among HCPs to prescribe these drugs to patients with wound pain? Or iss it a prescribing issue i.e. the wound is managed by the nurse who does not have the control to prescribe these types of drugs. Also see comment below?

Page 5: [4] Commented [as21R20] **amelia swift** **04/11/2019 12:45:00**

I would think it has a lot to do with lack of efficacy and the type of patient involved – many will have comorbidities and be on many drugs per day. Chance of compliance with poorly effective analgesics is very low. There are a few consensus statements in the US to support safe prescribing of opioids in response to the development of risk averse prescribing behaviours resulting from the 'opioid crisis' e.g. Drew DJ; Gordon DB; Morgan B; Manworren RCB (2018) '[As-Needed" Range Orders for Opioid Analgesics in the Management of Pain: A Consensus Statement of the American Society for Pain Management Nursing and the American Pain Society.](#) *Pain Management Nursing.* 19(3):207-210,.

Page 5: [5] Commented [as23R22] **amelia swift** **04/11/2019 12:52:00**

There is an opioid expert working group meeting at the MHRA (commenced Feb 2019) to explore benefits and risks of opioid medicines. It might be good to say at this stage that the situation is complex and changing as evidence is collated and experts consulted. Also should mention Public Health England's report into prescribed medicines <https://www.gov.uk/government/publications/prescribed-medicines-review-report> which states that 13% of the adult population have been prescribed opioids for non-cancer pain, with 540,000 receiving ongoing prescriptions for three years or more. In 2017 Cathy Stannard told an Addiction conference that GPs and nurse prescribers needed to be part of the conversation about the challenges of appropriate opioid use (<https://rcni.com/nursing-standard/newsroom/news/prescribing-nurses-need-to-be-part-of-conversation-about-potentially-addictive-drugs-122036>) which suggests that their voice was not being heard at that time. A more recent paper by Alison Moore quotes clinical nurse specialists being concerned about over-use of opioids (<https://rcni.com/nursing-standard/features/opioid-misuse-breaking-prescription-addiction-cycle-149836>) and so we can probably conclude that there are increasing concerns and efforts to find a way forward.

Page 11: [6] Commented [JS43] **Jenny Smith** **04/07/2019 22:20:00**

Presumably from Kloth et al. [need to find] 'The dosage range of 250–500 IC/s represents a small window of electrical energy that has been shown to produce very favorable wound-healing results in four studies which

12,17,18,20

