



# Supporting the Patient Journey

There are alternative methods of pain management  
in wound care.

BY WINDY COLE, DPM AND EMMA WOODMANSEY, PHD

Successful wound management outcomes primarily focus on objective measures such as rate of wound healing, number of ulcer-free days, occurrence of infection, amputation rates, recidivism, and mortality. This information can be obtained through data mining of electronic medical record (EMR) systems or wound care registries, but these commonly reported parameters rarely consider the patient experience. There is a push within the wound management community supporting the collection of patient-reported outcomes measures (PROMs) and patient-reported experience measures (PREMs).

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Through surveys and interviews, patients can provide useful information on all aspects of their care including overall satisfaction of treatments, symptoms and severity, quality of life, mental health, and social interactions. By analyzing this data, healthcare professionals and organizations can better understand if services and procedures are contributing to the health status of a given patient population.<sup>1</sup> Additionally, this information can be used to determine treatment algorithms, drive policy, impact health service offerings, and influence quality performance measures.<sup>1</sup>

Chronic or hard-to-heal wounds can be defined as wounds that have not reduced in size by 40% to 50% within 1 month after onset.<sup>2,3</sup> Chronic wounds affect over 10.5 million Medicare beneficiaries in the U.S. alone, representing a significant burden to the healthcare system.<sup>4</sup> Chronic non-healing wounds also take a significant toll on all aspects of patients' lives. Living with a chronic wound can be demanding and restrictive. Daily routines become dictated by clinic appointments, tests, and bandage changes—all taking many hours over the weeks of therapy.

Indirect consequences of living with a chronic wound such as pain, exudate, and odor often contribute to social isolation. Research has shown that chronic wound patients limit social interactions and experience impairments in all aspects of social interactions.<sup>5</sup> Social isolation can contribute to depression, anxiety and sleep disturbances, compounding the impact on quality of life. Additionally, many patients are unable to participate in the activities they love. Limited ability to engage in physical activities that help them cope can increase stress and even escalate pain.<sup>6</sup>

In fact, studies have reported that pain associated with chronic wounds is one of the symptoms that patients find particularly distressing.<sup>7</sup> Chronic wounds cause decreased functional ability and quality of life (QOL) for 1% to 3% of individuals 60 years and older.<sup>8</sup> QOL was a predictor of major amputation and death for patients who experienced all or some of the QOL deficits (mobility restrictions, self-care deficits, inability to perform usual activities, pain, and discomfort).<sup>9</sup>

The healing process for a chronic wound can take 6 to 8 months or longer; some patients live with their wounds for 15 years or more.

The prevalence of pain with chronic wounds is 48% to 81%, with 19% to 46% of patients reporting moderate to severe pain.<sup>8</sup> Wound pain can be classified as nociceptive or neuropathic, with differing characteristics for each.<sup>7</sup>

Nociceptive pain is the normal physiological response to a painful stimulus and serves as a biologic function

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## New Concepts and Studies

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to warn of injury.<sup>8</sup> Nociceptive pain usually presents as aching, throbbing, gnawing, and tender symptoms.<sup>7,8</sup>

Neuropathic pain is caused by dysfunction or damage in the nervous system, causing signals to travel in abnormal pathways<sup>10</sup> and can be described as burning, stinging, shooting, stabbing, cramp, and numbness.<sup>7,8</sup>

In addition to injury-associated pain, chronic wounds are characterized by endogenous inflammatory mechanisms that lower the threshold of peripheral nociceptor stimulation, which in turn intensifies pain levels.<sup>10</sup> Combined with the added problems that ischemic nerve injury may take time to resolve and ischemic wounds are higher risk to develop infection and subsequent infection-related pain, this causes a vicious cycle of ongoing pain as summarized in Figure 1.

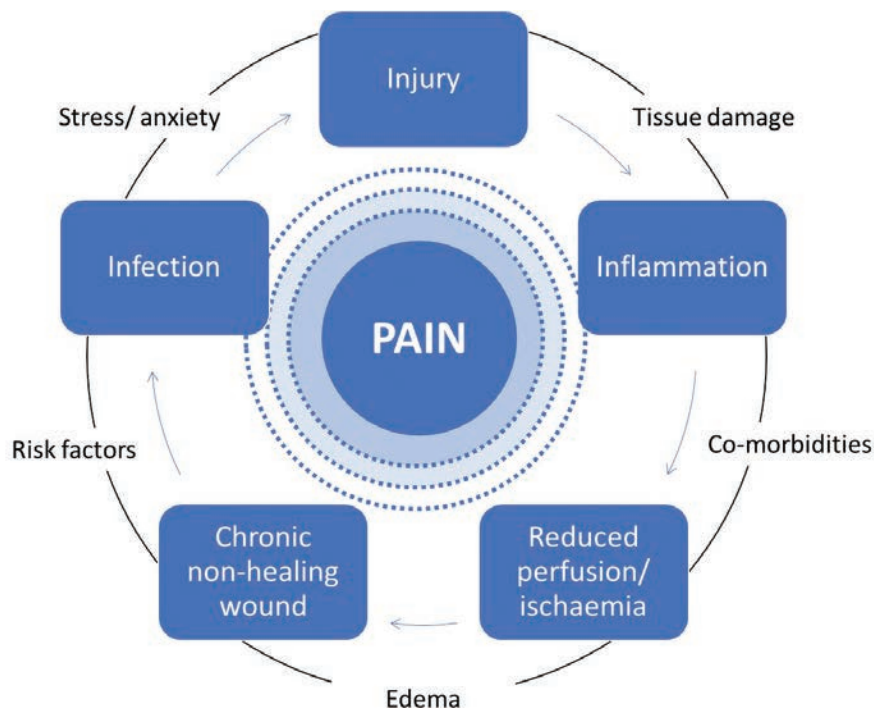


Figure 1: Cycle of pain in chronic wounds

### Pitfalls in Pain Management

Effective pain management can improve patient QOL and reduce resource consumption related to global care management.<sup>11</sup> The World Health Organization (WHO) Analgesic Dosing Ladder, originally developed for cancer patients, is frequently applied for effective wound pain management.<sup>7</sup> This ladder employs a three-step system to recommend increasingly potent treatments based on increasing pain severity scoring, as detailed in Figure 2.

### The Alarming Rise in Opioid Use

Opioid use is rising alarmingly with prescriptions in the United States increasing 272% from 76 million in 1991 to 207 million in 2013.<sup>13</sup> Furthermore, concurrent issues with opioid overuse, misuse, and addiction are much more prevalent.<sup>14,15</sup> In the United States, there were

142,557 opioid-involved overdose emergency room visits between July 2016 and September 2017, and over 60,000 opioid-related deaths in 2017.<sup>13</sup>

Drug overdose-related deaths escalated in the U.S. during the first year of the COVID-19 pandemic, noting a 30.6% increase in the first 12 months. This phenomenon was seen widespread across the country with as many as 47 states logging statistically significant increases in drug-related overdose deaths from 2019-2020.<sup>13</sup> To date, opioid addiction remains at epidemic levels in the U.S. and worldwide. The United States accounts for 80% of all opioid consumption in the world.

Opioids are still commonly prescribed for moderate to severe and persistent chronic pain in wound care,<sup>7</sup> even though opioids are known to have risks such as dependence and overdose. In 2022, the CDC published updated guidelines for prescribing opioids for pain control with the goal of equitable, safe, and effective individual pain management.<sup>16</sup> The consensus document recommends the judicious use of opioid use based on risk analysis after failure of a comprehensive non-opioid based treatment plan.<sup>16</sup>

Not only are opioids addictive with potentially serious complications, but this class of drugs can also have a negative impact on tissue

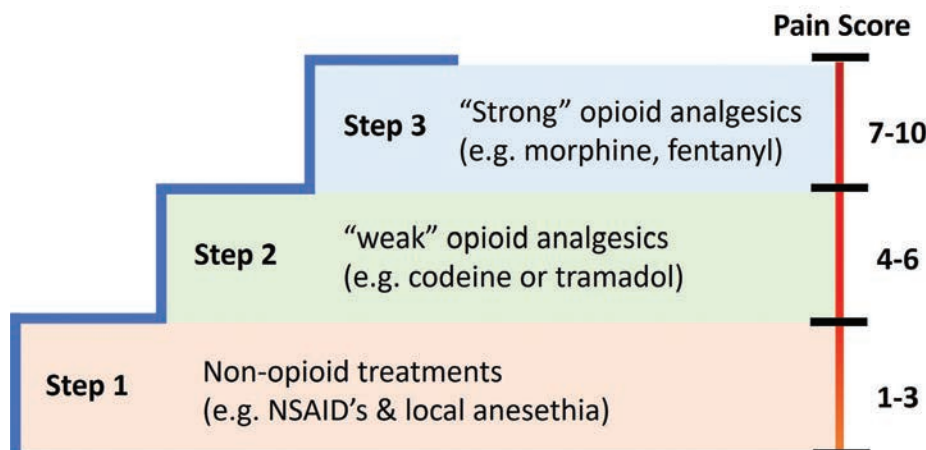


Figure 2: The WHO ladder of pain management. Modified from<sup>12</sup>.

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repair in wounds. Narcotic pain medications can reduce immune system activation, decrease endothelial proliferation, impact tissue oxygenation, alter fibroblast recruitment, and impact keratinocyte function.<sup>17</sup>

Interruptions in any one of these physiological functions can interfere with the wound repair process phases, thus causing improper or impaired wound healing and chronic non-healing wounds. These risks, combined with reports that certain pain such as ischemic pain can be refractory to NSAID and opioid treatment, highlight the unmet clinical need for alternative interventions to aid both pain management and healing in wounds.<sup>18</sup>

## Topical Oxygen Therapy

Following injury, poor blood circulation, edema, injured microcirculation, and contraction of vessels in traumatized tissue limit oxygen distribution to a wound, thereby reducing the wound's capacity to heal.<sup>19,20</sup> Wound repair and tissue regeneration is heavily reliant on the presence of adequate oxygen levels within the injured tissues with essential roles in multiple wound



Figure 3: The continuous topical oxygen therapy device (cTOT), NATROX® O2

**Pain is often an indication that the underlying pathophysiology of the chronic wound has not been identified or treated effectively.**

healing processes including oxidative killing of bacteria, cellular signaling and proliferation, collagen deposition, and angiogenesis.<sup>20,21</sup>

Despite a critical need for oxygen, levels are frequently insufficient in patients with chronic wounds due to a variety of systemic disease states causing poor circulation, inactivation of growth factors, and cellular senescence. Low levels of oxygen in the wounded tissues will prolong healing and cause physical symptoms such as wound pain.

The use of supplemental oxygen for wound healing can be traced back to the 1960s.<sup>22</sup> Nevertheless, the evidence supporting the utility of topical oxygen therapy in

wound management has continued to mount in recent years. In February of 2022, the American Diabetes Association published a clinical compendium concluding that the “evidence supporting topical oxygen’s efficacy in healing chronic DFUs can no longer be disputed.”<sup>23</sup>

Similarly, the 2023 consensus document published by the International Working Group of the Diabetic Foot (IWGDF) made the recommendation to consider adjunctive topical oxygen therapy for the treatment of hard-to-heal DFUs.<sup>24</sup> These international guidelines reflect the results of published randomized clinical trials (RCTs), meta-analyses, and systemic reviews with statistically significant improvements in outcomes for chronic wound patients treated with topical oxygen therapy.<sup>25-32</sup>

## Topical Oxygen Therapy and Pain Management

Pain is often an indication that the underlying pathophysiology of the chronic wound has not been identified or treated effectively. Untreated pain can contribute to lack of patient compliance or adherence to treatment regimens and prolong healing. Chronic wound pain is multifactorial. Tissue damage, nerve injury, blood vessel dysfunction, ischemia, bacterial contamination, and infection can all be contributing elements. Different pain characteristics have been associated with various wound etiologies (Table 1).

Management of wound pain requires a multifaceted approach. It is imperative to determine the underlying etiology and pathology causing the pain to break the cycle.<sup>7</sup> Wound healing often stalls in the inflammatory phase, causing the wound to become non-healing or chronic. Physiological features of chronic wounds such as high metabolic activity in the tissues, edema, poor microcirculation, diffusion constraints, and O<sub>2</sub> consumption by bacteria affect tissue oxygenation.

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TABLE 1

## Pain Characteristics Associated with Different Chronic Wounds<sup>33-35</sup>

Wound Type	Pain Description
Venous Leg Ulcer	Aching, heaviness
Arterial Ulcer	Cramping or spasms with activity
Pressure Injury	Inflammatory or irritation from pressure and friction
Diabetic Ulcer	Burning, tingling, shooting, and or stabbing (continuous or intermittent)



Additionally, physical damage due to extensive tissue injuries disrupts the microvasculature and reduces tissue oxygenation.<sup>36</sup> Moreover, the requirement for oxygen is three times greater in wounded tissues than in intact tissue.<sup>37</sup> Tissue hypoxia can cause pain, decrease tissue repair and regeneration, and increase infection rates. Worsening or a change in the quality of pain may be a signal of wound deterioration or infection.<sup>38</sup>

Leukocyte production and function is compromised in low oxygen environments, allowing bacteria to persist and invade the wound environment and causing infection.<sup>39</sup> The presence of bacteria in a wound, particularly if multiplying rapidly due to an infection, cause additional drain on local oxygen availability. Thus, higher O<sub>2</sub> levels are required to reverse local hypoxia in wounded tissues and facilitate the host response to wound infection, and aid antibiotic effectiveness and wound progression through the healing cascade.<sup>20,36,40</sup>

In a recently published manuscript by Jebiril and colleagues,<sup>41</sup> the utilization of topical oxygen to treat chronic venous leg ulcers contributed to a 76% reduction in substantial pain in the study cohort. This 20-patient retrospective pilot study also reported that 69% of patients stopped opioid use while 53% had complete resolution of all pain symptoms.<sup>41</sup> While the exact mechanism of action is not yet understood, this initial trial illustrates the potential of topical oxygen therapy as a treatment option to support not only wound healing, but chronic wound pain management.

## Wound Progression and Pain Management with Topical Oxygen Therapy: Case Example

The author has been using the NATROX® O<sub>2</sub> (Figure 3), Inotec AMD, Cambridge UK) continuous topical oxygen therapy (cTOT) in her clinical practice for the past 4 years. The NATROX O<sub>2</sub> device is FDA-cleared, compact, and battery-operated. The oxygen generator delivers 98% pure, humidified continuous oxygen 24/7 to the wound through a tube connected to an oxygen delivery system. The device is lightweight, portable, discreet, easy to use, and importantly allows patients to maintain mobility during treatment.

cTOT has been validated as a low-risk, adjunctive therapy for wound management in a variety of chronic wound types and across a wide range of care settings. Herein, we will provide a patient case report il-

lustrating the utility of NATROX O<sub>2</sub> cTOT to successfully treat a painful, non-healing venous leg ulcer.

### History

A 77-year-old female patient with a history of venous insufficiency, varicose veins, hypertension, and degenerative joint disease presented to the outpatient wound clinic with a non-healing wound of 2 months duration. The patient had originally hit her leg on a car door causing a small laceration that continued to deteriorate over the last 6 weeks. The patient had been seen by her primary care physician for this complaint without much success.

### Initial Presentation

The wound base was covered with adherent slough and the wound area was measured at 3.06 cm<sup>2</sup> (Figure 4a). She related that her pain was 10 out of 10 on the visual analog scale.

After a complete patient and wound assessment was performed, the diagnosis of a non-healing venous leg ulcer was made and a treatment regimen consisting of wound debridement, NATROX O<sub>2</sub>, alginate, and multi-layer compression bandaging was initiated.

The patient was seen weekly in the wound clinic for evaluation. By week 2, the base of the wound was beefy and granular, the wound dimensions had reduced to 1.77 cm<sup>2</sup> and the patient's pain had dropped to 3 on a 10-point scale (Figure 4b).

The treatment plan, including continuation of NATROX O<sub>2</sub> therapy, was adhered to. By week three the patient was completely pain-free and the wound continued to progress on a healing trajectory (Figure 4c). By week 5, the wound had reached complete closure with 100% epithelial tissue and no associated pain (Figure 4d).

### Conclusion

Improving the patient journey and increasing QOL for patients suffering from chronic wounds is vital. PROMs, PREMs, and QOL data have given way to the concept of patient-centered care. Individualized care delivery and its application to wound management is becoming increasingly important to payers, facilities, and caregivers. At its core, individualized care focuses on addressing specific goals and addressing adverse factors affecting patients with wounds to promote their overall wellbeing.

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Figure 4a: Wound at initial presentation



Figure 4b: Wound at 2 weeks



Figure 4c: Wound at 3 weeks



Figure 4d: Wound at 5 weeks



Treatment plans and applied therapies must remain flexible and encompass the needs of the individual patient, diverting from a one-size fits all care regimen, with different underlying problems and care needs. Adequate pain management is an essential part of this journey and can help improve patient compliance with treatment plans.

Reversal of hypoxic conditions in any non-healing wound can support faster healing by supporting increased demand for oxygen tissue repair and the immune response and to minimize barriers to healing such as

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inflammation, infection, and biofilm—thus breaking the cycle of non-healing and wound pain. NATROX O2 cTOT is an option that supports wound healing and pain management and is well tolerated, easy to use, and readily adopted by patients, thus increasing patient quality of life.

As patient perspectives on wound care treatments will increasingly impact utilization, the use of novel and innovative therapies such as cTOT will continue to impact care algorithms. The need for additional studies to determine the exact mechanism of action and the application to a larger cohort of patients does exist, but early clinical reports are promising. **PM**

### References

- Weldring, T. & Smith, S. M. S. Article Commentary: Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). *Health Serv Insights* 6, HSI.S11093 (2013).
- Atkin, L., et al. Implementing TIMERS: the race against hard-to-heal wounds. *J Wound Care* 28, S1–S50 (2019).
- Kyaw, B. M., et al. Need for improved definition of “chronic wounds” in clinical studies. *Acta Dermato-Venereologica* vol. 98 157–158 Preprint at <https://doi.org/10.2340/00015555-2786> (2018).
- Carter, M. J., et al. Chronic wound prevalence and the associated cost of treatment in Medicare beneficiaries: changes between 2014 and 2019. *J Med Econ* 26, 894–901 (2023).
- Klein, T. M., et al. Social participation of people with chronic wounds: A systematic review. *Int Wound J* 18, 287–311 (2021).
- Ribu, L. & Wahl, A. Living with diabetic foot ulcers: a life of fear, restrictions, and pain. *Ostomy Wound Manage* 50, 57–67 (2004).
- Price, P., et al. Managing painful chronic wounds: the Wound Pain Management Model. *Int Wound J* (2007) doi:10.1111/j.1742-481X.2007.00311.x.
- Newbern, S. Identifying Pain and Effects on Quality of Life from Chronic Wounds Secondary to Lower-Extremity Vascular Disease: An Integrative Review. *Adv Skin Wound Care* 31, 102–108 (2018).
- Siersma, V., et al. Health-Related Quality of Life Predicts Major Amputation and Death, but Not Healing, in People With Diabetes Presenting With Foot Ulcers: The Eurodiale Study. *Diabetes Care* 37, 694–700 (2014).

- Bechert, K. & Abraham, S. E. Pain Management and Wound Care. *Journal of the American College of Certified Wound Specialists* vol. 1 65–71 Preprint at <https://doi.org/10.1016/j.jcws.2008.12.001> (2009).

- Franks, P. J., Barker, J., Laeuchli, S., Med, Priv.-D. & Mosti, G. Chief of Dermatologic Surgery, President of the European Wound Management Association (EWMA). [www.markallengroup.com](http://www.markallengroup.com) (2016).

- Anekar, A. A., Hendrix, J. M. & Cascella, M. WHO Analgesic Ladder. (2023).

- National Center for Drug Abuse Statistics (NCDAS). [DrugAbuseStatistics.org](http://DrugAbuseStatistics.org).

- Mclellan, A. T. Substance misuse and substance use disorders: Why do they matter in healthcare? *Trans Am Clin Climatol Assoc* 128, (2017).

- Alghnam, S. & Castillo, R. Traumatic injuries and persistent opioid use in the USA: Findings from a nationally representative survey. *Injury Prevention* 23, 87–92 (2017).

- Dowell, D., Ragan, K. R., Jones, C. M., Baldwin, G. T. & Chou, R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain—United States, 2022. *MMWR. Recommendations and Reports* 71, 1–95 (2022).

- Shanmugam, V. K., Couch, K. S., McNish, S. & Amdur, R. L. Relationship between opioid treatment and rate of healing in chronic wounds. *Wound Repair and Regeneration* 25, 120–130 (2017).

- Kogure, T., et al. Ischemic Ulcer Pain Is Both Nociceptive and Neuropathic Pain Based on a Discriminant Function Analysis Using the McGill Pain Questionnaire. *J Pain Palliat Care Pharmacother* 31, 98–104 (2017).

- Gottrup, F. Physiology and measurement of tissue perfusion. *Ann Chir Gynaecol* 83, 183–9 (1994).

- Frykberg, R., et al. Use of Topical Oxygen Therapy in hard to heal wounds. *J Wound Care* In press, (2023).

- Rodriguez, P. G., Felix, F. N., Woodley, D. T. & Shim, E. K. The Role of Oxygen in Wound Healing: A Review of the Literature. *Dermatologic Surgery* 34, 1159–1169 (2008).

- Mutluoglu, M., Cakkalkurt, A., Uzun, G. & Aktas, S. Topical Oxygen for Chronic Wounds: A PRO/CON Debate. *Journal of the American College of Clinical Wound Specialists* 5, 61–65 (2013).

- Boulton, A. J. M., et al. New evidence based therapies for complex diabetic foot wounds. *America Diabetes Association* (2022).

- Chen, P., et al. IWGDF Guidelines on interventions to enhance healing of foot ulcers in people with diabetes. [www.iwgdfguidelines.org](http://www.iwgdfguidelines.org) (2023).

- Serena, T. E., et al. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. *J Wound Care* 30, 7–14 (2021).

- Al-Jalodi, O., Kupcella, M., Breisinger, K. & Serena, T. E. A multicenter clinical trial evaluating the durability of diabetic foot ulcer healing in ulcers treated with topical oxygen and standard of care versus standard of care alone 1 year post healing. *Int Wound J* 19, 1838–1842 (2022).

- Kaufman, H., et al. Topical oxygen therapy used to improve wound healing in a large retrospective study of wounds of mixed aetiology. *Wounds International* 12, 63–68 (2021).

- Carter, M. J., et al. Efficacy of Topical Wound Oxygen Therapy in Healing Chronic Diabetic Foot Ulcers: Systematic Review and Meta-Analysis. *Adv Wound Care (New Rochelle)* 12, 177–186 (2023).

- Sun, X. K., Li, R., Yang, X. L. & Yuan, L. Efficacy and safety of topical oxygen therapy for diabetic foot ulcers: An updated systematic review and meta-analysis. *Int Wound J* 19, 2200–2209 (2022).

- Sethi, A., Khambhayta, Y. & Vas, P. Topical oxygen therapy for healing diabetic foot ulcers: A systematic review and meta-analysis of randomised control trials. *Health Sciences Review* 3, 100028 (2022).

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<sup>31</sup> Thanigaimani, S., Singh, T. & Golledge, J. Topical oxygen therapy for diabetes-related foot ulcers: A systematic review and meta-analysis. *Diabetic Medicine* 38, (2021).

<sup>32</sup> Connaghan, F., Avsar, P., Patton, D., O'Connor, T. & Moore, Z. Impact of topical oxygen therapy on diabetic foot ulcer healing rates: a systematic review. *J Wound Care* 30, 823–829 (2021).

<sup>33</sup> Barron, G. S., Jacob, S. E. & Kirsner, R. S. Dermatologic Complications of Chronic Venous Disease: Medical Management and Beyond. *Ann Vasc Surg* 21, 652–662 (2007).

<sup>34</sup> Briggs, M. & Closs, S. J. Patients' perceptions of the impact of treatments and products on their experience of leg ulcer pain. *J Wound Care* 15, 333–337 (2006).

<sup>35</sup> Buttker, J. Identifying the Charcot Foot. *Adv Skin Wound Care* 19, 189–191 (2006).

<sup>36</sup> Troitzsch, D., Vogt, S., Abdul-Khaliq, H. & Moosdorf, R. Muscle Tissue Oxygen Tension and Oxidative Metabolism during Ischemia and Reperfusion. *Journal of Surgical Research* 128, 9–14 (2005).

<sup>37</sup> Castilla, D. M., Liu, Z.-J. & Velazquez, O. C. Oxygen: Implications for Wound Healing. *Adv Wound Care (New Rochelle)* 1, 225–230 (2012).

<sup>38</sup> Swanson, T., et al. IWII Wound Infection in Clinical Practice consensus document: 2022 update. *J Wound Care* 31, S10–S21 (2022).

<sup>39</sup> Gottrup, F., et al. Use of oxygen therapies in wound healing. *J Wound Care* 26, S1–S42 (2017).

<sup>40</sup> Jensen, P. Ø., et al. Improving antibiotic treatment of bacterial biofilm by hyperbaric oxygen therapy: Not just hot air. *Biofilm* 1, 100008 (2019).

<sup>41</sup> Jebiril, W., Physician, I., Nowak, M., Bachar-Wikstrom, E. & Wikstrom, J. D. Topical oxygen treatment relieves pain from hard-to-heal leg ulcers and improves healing: a case series. (2022).



emerging biotech companies and has been integral in collaborating on innovative research protocols.

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helping patients with wounds regain their lives.

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