Concurrent optical and magnetic stimulation therapy in patients with lower extremity hard-to-heal wounds

Objective: The treatment of patients with hard-to-heal wounds represents a major multidisciplinary challenge. Therefore, the development and clinical validation of new technologies remains extremely important. The novel application of concurrent optical and magnetic stimulation (COMS) offers a promising noninvasive approach to support physiological wound healing processes, especially in hard-to-heal wounds.
Method: In a multicentre, prospective, comparative, clinical trial, patients with hard-to-heal wounds on lower extremities of different aetiologies were treated with COMS as an adjunct to standard of care (SOC). The primary endpoint was safety; secondary endpoints were wound healing, pain and wound-specific quality of life (Wound-QoL).
Results: A total of 40 patients were enrolled in this study (intention to treat population (ITTP), n=40). Of these patients, 37 were included in the analysis of the primary endpoint (primary endpoint population, (PEP), n=37). A further subgroup of 30 patients was included in the analysis of the secondary endpoint (secondary endpoint population (SEP), n=30). Finally, the SEP was stratified regarding patients' responsiveness to SOC in an SOC non-responder subgroup (NRSG), n=21, and in an SOC responder subgroup (RSG), n=9. A total of 102 adverse events (AEs) were recorded, of which 96% were 'mild' or 'moderate', and 91% were either a singular or transient event. Only 11 AEs were serious and associated with inpatient treatments unrelated to the studied intervention. In the NRSG, reductions in wound size were found to be statistically significant within the different study periods. Additionally, an acceleration of the healing rate was detected between the baseline and the first four weeks of COMS treatment (p=0.041). The rate of near-complete and complete wound closure in the SEP after 12 weeks were 60% and 43%, respectively. Pain reduction across the treatment group was statistically significant (p≤0.002 for both the SEP and NRSG). The Wound-QoL score improved by 24% during the study (p=0.001).
Conclusion: In this study, COMS treatment for patients with hard-to-heal wounds on lower extremities was a safe and effective novel treatment option, especially for patients who did not respond to SOC.
Declaration of interest: The sponsor of the study was Piomic Medical AG, Switzerland. FR-J has received financial support for lectures, consultations and/or studies from the following companies: Coloplast, Lohmann&Rauscher and Urgo. JT has received financial support for lectures, consultations and/or studies from the following companies: Publicare, Coloplast, Smith+Nephew, Urgo and Piomic Medical. GL declares that there are no conflicts of interest. CB has received financial support for lectures, consultations and/or studies from the following companies: Piomic Medical. UB declares that there are no conflicts of interest. JD has received financial support for lectures, consultations and/or studies from the following companies: 3M, Coloplast, ConvaTec, Draco, Engelhardt, PAUL HARTMANN, Infectopharm, KCI, Lohmann&Rauscher, Mölnlycke, Piomic Medical, SastoMed, Uluru and Urgo.

advanced wound care • chronic • COMS • concurrent optical and magnetic stimulation • hard-to-heal • lower extremity wounds • quality of life • standard of care • wound • wound care • wound dressing • wound healing • Wound-QoL

The treatment and associated economical burden of hard-to-heal wounds represent a major challenge for modern healthcare systems around the globe.[1,2] Common causes of impaired wound healing of the lower legs are chronic venous insufficiency (CVI) and peripheral arterial disease (PAD), or a combination of both.[3] Adequate diagnosis and therapy of the underlying causes are key aspects for treatment.[4] In addition, topical treatment approaches need to be considered, as wound healing can stall in the inflammatory or proliferative phase.[5] New technologies which address the processes of modulating inflammation and tissue perfusion are thus a promising step forward in enabling the transition to successful wound healing.[6–11] The concurrent optical and magnetic stimulation (COMS) system incorporates the technologies of pulsed modulated electromagnetic fields and photon emission which is then locally applied to the wound area with the aim of accelerating wound tissue repair (Fig 1).[12,13]

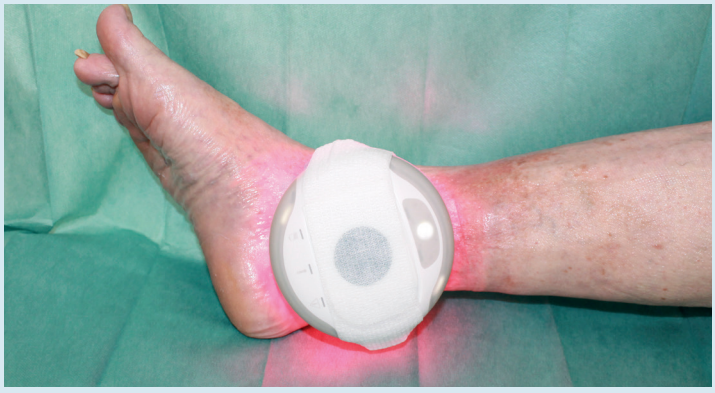
Magnetic stimulation

Endogenous electric signals have been reported as essential to driving tissue regeneration and wound healing.[12] A short-circuit of the transepithelial electrical potential (TEP) induced by a disrupted epithelium was reported to be an essential physical cue required to induce wound healing.[13] The electrical field, sensed by cells in the local vicinity, induces biological responses,

Finja Reinboldt-Jockenhöfer,[1] MD, Dr. med.; **Jürg Traber**,[2] MD, Dr. med.; **Georg Liesch**,[3] MD, Dr. med.; **Christiane Bittner**,[4] MD, Dr. med.; **Ulf Benecke**,[5] MD, Dr. med.; **Joachim Dissemond**,[1] MD, Professor, Dr. med.*
***Corresponding author email:** joachim.dissemond@uk-essen.de
1 Department of Dermatology, Venereology and Allergology, University Hospital, Essen, Germany. **2** Venenklinik Bellevue, Kreuzlingen, Switzerland. **3** Spital Männedorf, Männedorf, Switzerland. **4** Kantonsspital Nidwalden, Stans, Switzerland. **5** Kantonsspital St. Gallen, Switzerland.

which occur at small differences in electrical potential (0.1–0.2mV) in <15 minutes.[14] The risk of reduced transepithelial potential and, consequently, of impaired wound healing guiding currents is high in lower extremity hard-to-heal wounds, which are characterised by poor microcirculatory perfusion.[15] Re-induction of these vital electrical currents in compromised tissue can be achieved by externally applying electromagnetic fields with time-varying characteristics that exert a force on charged particles.[16] These electromagnetic fields in the COMS device are produced by a coil that emits pulsed modulated electromagnetic fields in the extremely low frequency (ELF) range of the electromagnetic spectrum. The signal is emitted in an asymmetrical trapezoidal shape at 20Hz, with an increasing peak field strength of up to 1.6mT (16 Gauss), at the treatment location, for a duration of 16 minutes per session.

Fig 1. Concurrent optical and magnetic stimulation therapy in a patient with a hard-to-heal wound on the lower extremity (picture taken at Venenklinik Bellevue, Kreuzlingen, Switzerland)



Optical stimulation

In living organisms, the absorption of photonic energy by molecules with photoreceptive properties can trigger biological responses necessary for wound healing.[17,18] Photobiomodulation within tissues can occur at wavelengths in the far-red to near-infrared spectral range (600–1000nm), the so-called bio-optical window, where the photonic energy can reach deeper into the tissue and is not reflected at the surface.[19]

The most prominent target for biomodulative action is the enzyme cytochrome C oxidase in the inner mitochondrial membrane.[20] The haemoprotein which contains two iron ions (haem a and haem a3) and two copper centres (CuA and CuB) at its catalytic cleft is known to absorb light in the far-red and near-infrared spectral range, in a redox state-dependent course.[21] Simultaneous application of these wavelengths can therefore be more effective than either one applied alone.[22] Exposure to light in the absorption spectrum of 660–840nm induces nitric oxide (NO) photo dissociation which, among other factors, is a potent mediator for vasodilation.[23]

The optical stimulation component of the COMS device is designed to emit light by two types of light-emitting diodes (LEDs) in the wavelengths of 660nm (far-red) and 830nm (near-infrared). The optical signal is pulsed at 1kHz with a maximum pulse width of 0.3ms. The device emits a pulse peak power of 25mW/cm^2, at an average power output of 5mW/cm^2 at the treatment area.

Concurrent optical and magnetic stimulation

The concurrent application of both technologies is intended to facilitate the dynamic and synergistic processes of wound healing. The anti-inflammatory action attributed to magnetic stimulation (MS) originates from a shift in the cytokine profile, which drives the process through the pro-inflammatory state towards its resolution.[24–28] Triggering the process of neoangiogenesis and tissue perfusion is critical for effective regeneration of wounded skin. The support of coordinated proliferative behaviour through optical stimulation (OS) augments the tissue's regenerative capacity to restore functional integrity in the dermal layers of mammalian skin.[29–31] In addition, the facilitation of collagen deposition and reorganisation through OS during the subsequent remodelling phase is crucial to the biomechanical strength of scar tissue, for cell-to-cell adhesion and for communication within the newly formed tissue.[32,33]

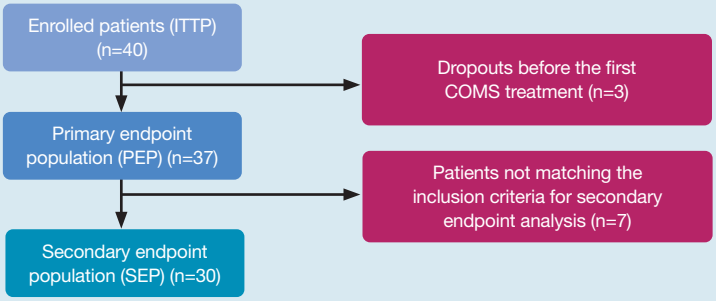
These new technologies do not replace standard of care (SOC) measures; however, they represent a promising intervention in expediting wound healing. It can therefore be stated that OS and MS have significant, scientifically proven, positive effects on almost all phases of tissue repair. While MS is associated with immunomodulatory action[34] and stimulation of tissue perfusion,[35] OS induces cell proliferation[36] and connective tissue remodelling.[37] The aim of this prospective clinical study was to assess the primary safety outcomes of the concurrent application of these technologies in wound healing while measuring improvements in wound healing, pain and quality of life (QoL) as secondary outcomes.

Methods

This clinical investigation was planned as a multicentre, prospective, comparative, clinical study. The study was approved by the Ethics Committee Ostschweiz, Swissmedic reference number 2017-MD-0008 (ClinicalTrials.gov Identifier: NCT03112395) according to the requirements of the International Conference on Harmonisation Good Clinical Practices (ICH GCP) guidelines, based on the ethical principles of the Declaration of Helsinki.

Patients were recruited from four centres in Switzerland (Venenklinik Bellvue AG, Kreuzlingen; Kantonsspital Nidwalden, Stans; Spital Männedorf; Kantonsspital St. Gallen) over a period of 32 months. In consultation with the regulatory authorities, patients were recruited for the study using the following inclusion criteria:

Fig 2. CONSORT diagram. ITTP—intention to treat population; COMS—concurrent optical and magnetic stimulation



- Age: minimum 18 years old, maximum 90 years old
- Aetiology: venous, arterial or mixed leg ulcers
- Wound duration: at least four weeks
- Wound area: minimum 1cm^2, maximum 50cm^2
- No changes of treatment of causal therapy of underlying disease planned.

Exclusion criteria were:

- Pregnant women
- Known or suspected non-compliance/adherence
- Addiction such as drug or alcohol misuse
- Participation in another study with investigational treatment(s) within the 30 days preceding and during the present study
- Enrolment of the investigator, his/her family members, employees and other dependent persons
- Patients with active medical devices, such as pacemakers and defibrillators, infusion devices and insulin pumps, metallic implants or endoprosthesis at the extremity of concern, placed below the hip
- Life-threatening condition
- Immunosuppressive after organ transplant or chemotherapeutic treatment within 30 days before the start of the study.

All patients provided written informed consent to participate in the study, and this included the use of the photograph.

For the data analysis, patients were stratified into subgroups according to the specific endpoints to be analysed (Fig 2):

- Intention to treat population (ITTP): defined as all patients who were enrolled in the study
- Primary endpoint population (PEP): a subpopulation of the ITTP, defined as all patients who received at least one treatment with the investigational product and was used to assess the primary safety outcome
- Secondary endpoint population (SEP): defined as all patients who completed at least 18 COMS treatments. This group was further divided into:
  - SOC non-responder subgroup (NRSG): defined as patients with low healing prospects (<30% reduction of wound area in the SOC baseline phase)
  - SOC responder subgroup (RSG): defined as patients showing substantial healing solely from improved compliance with SOC (>30% reduction of wound area in the baseline phase).

This division in subgroups was applied to specifically select therapy-refractory, hard-to-heal wounds which did not demonstrate significant wound healing within 30 days, based on the recommendations of the European Wound Management Association (EWMA)[38] as well as the US Food and Drug Administration (FDA) Guidance for industry.[39]

Treatment and wound healing progress

In this study, wound healing progress during the SOC treatment was assessed over a period of four weeks to provide a comparative control phase before the interventional treatment started (baseline phase: weeks –4–0). Wound healing progress was then observed for eight weeks of SOC plus COMS treatment (treatment phase: weeks 0–8). Additionally, wound healing progression after termination of the interventional treatment was observed for a further four weeks (follow-up phase: weeks 8–12). The treatment regimen for SOC remained similar in all phases of the trial and was performed on average 2–3 times per week (Fig 3).

SOC was aligned with guidelines of the Swiss Association for Wound Care (SAWC), but was individualised as deemed necessary by the treating physicians. It included: wound cleansing; debridement; exudate management; maintenance of a physiologically moist wound environment; and management of infection and inflammation. No other advanced wound care products were allowed to be used during the study period. Measures to address the underlying vascular aetiology, such as compression therapy, were considered as SOC, and were continuously assessed throughout the study period.

The COMS treatment was added as an adjunctive treatment to SOC for eight weeks and was administered 2–3 times per week for 16 minutes at each application. The treatment took place during standard patient visits, after cleansing and debridement of the wound under examination. The therapy was applied over the wound through a single-use disposable barrier to avoid patient cross-contamination and infection. Each patient was treated with the same treatment frequency, the same treatment duration and the same dosage.

Primary endpoint

The primary endpoint of the study was safety. The incidence, severity, time of occurrence, type and causality of adverse events (AE) during SOC (baseline and follow-up phase) were compared with those of the COMS treatment phase. AEs were coded using the MedDRA (English Version 23.0) coding dictionary and analysed through an independent medical advisor along predetermined criteria for severity and duration. An autocorrelation analysis (Ljung–Box test) was performed to detect whether the treatment-related AEs were independently distributed or whether they exhibited a serial correlation over the course of the study.

Secondary endpoints

The secondary endpoints of this study were focused on

efficacy. The change of wound area and volume, pain level and QoL were analysed over the course of the different study phases. Silhouette Star (ARANZ Medical, New Zealand) hardware and Silhouette connect v3.21.0 (Build 154) software were used to measure wound size and volume. In order to ascertain the change in wound healing rate over time, a linear mixed model (LMM) analysis was performed on the SEP and NRSG subgroups. Here, the changes in wound area measurements were compared at five equidistant analysis timepoints (at 28 days apart) appropriate for direct testing and comparison. The timepoints were chosen at the beginning and end of the SOC baseline (weeks –4 and 0), the beginning, middle and end of the SOC/COMS treatment period (weeks 0, 4 and 8) as well as the beginning and end of the follow-up phase (weeks 8 and 12).

Additionally, the rate of near-complete and complete wound closure, defined as a total wound area reduction of 90% and 100%, respectively, were assessed. Kaplan–Meier survival analysis was performed to analyse the proportion of wounds achieving complete and near-complete closure during the 12 weeks after COMS treatment initiation, considering the latest timepoint of the closure event.

Pain was assessed using the visual analogue scale (VAS).[40] The change in VAS score of the SEP from the baseline (week –4) to follow-up (week 12), as well as the first SOC/COMS treatment (week 0) to the study close out visit (week 12) were analysed. The significance of the changes in VAS responses were tested using the paired samples t-test. Wound-specific QoL was quantified using the validated Wound-QoL questionnaire.[41] In terms of content, these items were assigned to the areas of physical, psychological and everyday aspects of QoL impairment. Health-related QoL was assessed at baseline and study close and analysed to determine the change in Wound-QoL in the SEP over the study period. The significance of the changes were compared in all three dimensions, as well as the overall Wound QoL score using the paired samples t-test.

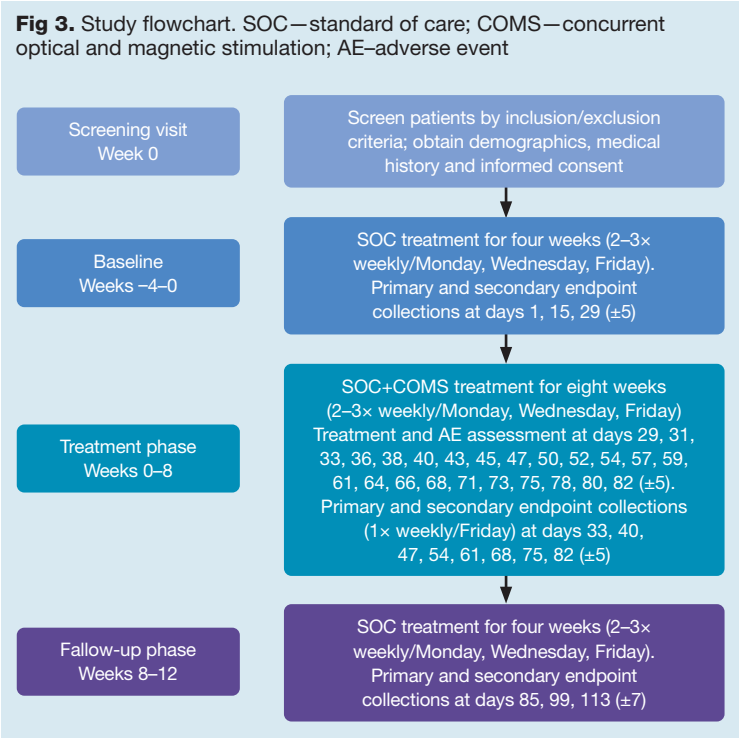


Fig 3. Study flowchart. SOC—standard of care; COMS—concurrent optical and magnetic stimulation; AE–adverse event

Statistical analysis

A statistical data analysis was performed for the different endpoints. Descriptive statistics were used to summarise demographic characteristics of the study

Table 1. Characteristics of the patient sample population for ITTP, PEP and SEP

By population (descriptive)	ITTP	PEP	SEP
Sample size, valid n	40	37	30
Sex, n (%)			
Male	22 (55.0)	22 (59.5)	17 (56.7)
Female	18 (45.0)	15 (40.5)	13 (43.3)
Age, years, mean±SD (median)	72.3±11.0 (72.0)	72.2±11.4 (72.0)	72.5±11.7 (72.5)
Height, cm, mean±SD (median)	171.2±11.0 (171.5)	171.9±11.1 (174.0)	170.5±10.5 (173.5)
Weight, kg, mean±SD (median)	82.2±21.4 (80.0)	84.7±20.2 (82.0)	83.6±21.3 (81.0)
BMI, kg/m^2, mean±SD (median)	27.9±6.1 (28.3)	28.6±5.8 (29.0)	28.7±6.4 (29.1)
Duration between wound onset and screening week 4, days, mean±SD (median)	366.9±717.1 (169.0)	373.5±735.0 (169.0)	333.3±658.0 (155.5)
Wound area at screening week 4, cm^2, mean±SD (median)	7.94±7.59 (5.46)	8.31±7.71 (5.52)	9.89±7.71 (7.65)
Wound area at baseline week 0, cm^2, mean±SD (median)	7.70±7.56 (5.65)	8.05±7.69 (5.80)	9.68±7.65 (7.20)

ITTP—intention to treat population; PEP—primary endpoint population; SEP—secondary endpoint population; SD—standard deviation; BMI—body mass index

Fig 4. Ljung–Box test for autocorrelation of all adverse events (AEs) to study visits. Relationship of AEs to study visits. The Ljung–Box test suggests there was no autocorrelation for AEs over the course of the study periods. SOC—standard of care; COMS—concurrent optical and magnetic stimulation

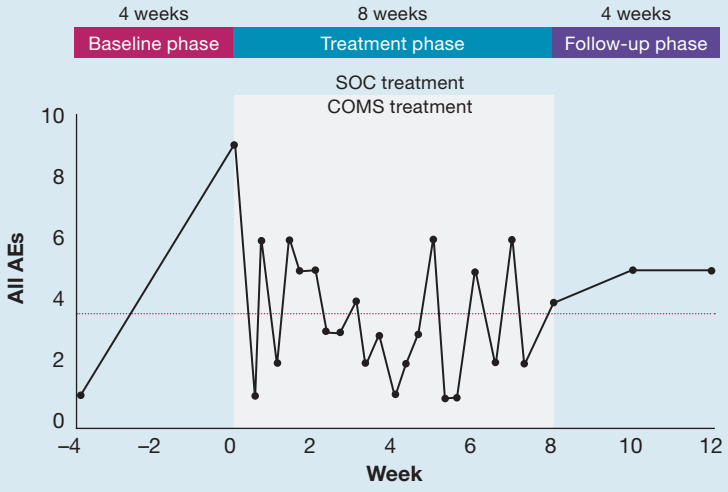
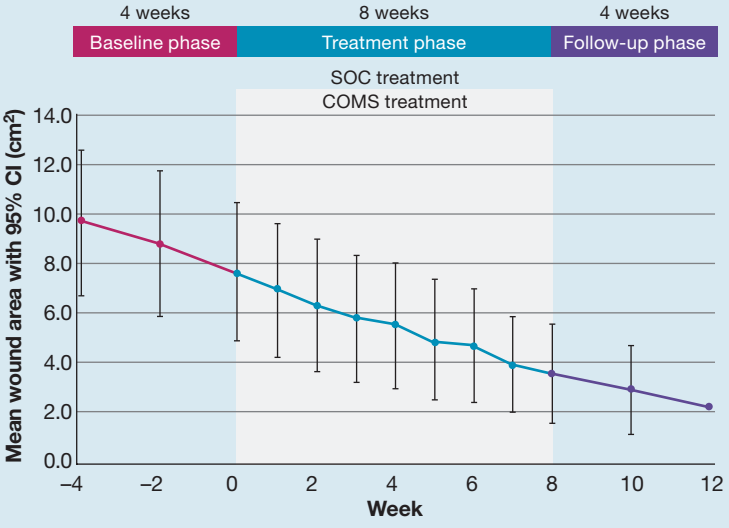


Fig 5. Secondary endpoint population (SEP) (n=30) mean wound area (cm^2). Mean wound area by visit with 95% confidence interval (CI). No significant acceleration of wound healing could be observed in the SEP as a proportion of patients already exhibit substantial healing solely from improved compliance with standard of care (SOC). COMS—concurrent optical and magnetic stimulation; CI—confidence interval



population and to perform survival analysis using the Kaplan–Meier method. For categorically scaled variables, the absolute and relative frequencies were reported. For continuously scaled variables the mean, standard deviation (SD), median, minimum and maximum were reported. The relationship of AEs to study visits was analysed by using the Ljung–Box test for autocorrelation. The significance of the changes in wound area were tested using the paired samples t-test. A p-value of <0.05 was considered statistically significant.

Results

A total of 40 patients were recruited to the study. However, one patient enrolled in the study was a screening error and had no defined aetiology. Of these, 20 (51.3%) patients had venous leg ulcers, seven (17.9%) had arterial leg ulcers, nine (23.1%) had mixed leg ulcers and three (7.7%) had diabetic foot ulcers (DFUs). Wound size in the ITTP ranged from 0.1–29.6cm^2 (mean: 7.9cm^2, median: 5.5cm^2). There was a broad distribution of ulcer locations within the different subgroups (calf, ankle, malleolus, plantar, toe). There were no relevant differences between the analysed populations with regards to the collected demographic data (Table 1).

Primary endpoint population

Of the total ITTP (n=40), three (7.5%) patients dropped out of the study before receiving any COMS treatment, either due to a screening error or lack of patient adherence. Therefore, 37 (92.5%) patients (female: n=15 (40.5%), male: n=22 (59.5%), age: 32–90 years, mean: 72.2 years, median: 72.0 years) received between one and 24 COMS treatments over a period of eight weeks.

During the investigation 29 (78.4%) patients experienced 102 AEs. Almost half (48.6%) of the PEP experienced ≤1 AEs throughout the study. AEs were to a large extent mild or moderate (96%) and either a singular or transient event (91%). Altogether, 54% of the AEs resolved without intervention. In addition, half of the AEs (51%) were expected, namely, a temporary modified pain perception. As a known side-effect related to the onset and phase transition of hard-to-heal wounds towards healing, this modulated pain perception was expected.

Overall, 45 (44.1%) of the AEs were considered 'causally', 'probably' or 'possibly' related to the COMS treatment. Of these, 32 (71.1%) occurred before treatment and 13 (28.9%) immediately after treatment. Of the unexpected AEs, only a small proportion (8%) were rated as 'possibly' related to the investigational treatment. There was no noticeable relationship between the AEs and study visits throughout the whole of the study period, confirming that the COMS treatment did not result in an increased number of AEs (autocorrelation coefficient –0.11–0.06, p=0.620 to p=0.935, Fig 4).

There were 11 AEs (10.8%) that required inpatient treatment and were categorised as serious adverse events (SAE). The reasons for hospitalisation in five patients were related to known complications of the underlying disease being treated, consequently they were credibly assessed as unrelated to the COMS treatment. A further five patients with SAEs were hospitalised due to cardiovascular incidents related to their general state of health, while another SAE occurred due to an accident (rip fracture) and was assessed as 'very likely' not related to the investigational treatment.

Secondary endpoint population

A total of seven patients were excluded from the secondary endpoint analysis due to a failure to meet the

eligibility criteria for the SEP. The analysis required a wound area >1cm^2 in order to reliably detect changes over the course of the study. Of the seven patients excluded, three were classified as DFUs. Therefore, the SEP resulted in n=30 patients (female: n=13 (43.3%), male: n=17 (56.7%), age: 32–90 years, mean and median: 72.5 years) of whom 21 (70.0%) patients were part of the NRSG and nine (30.0%) patients part of the RSG.

Mean ulcer duration between onset and screening for the NRSG and RSG subgroups (Table 2) was 417.9 days and 136.0 days, respectively (median: 199.0 days for NRSG and 91.0 days for RSG).

In the SEP group, no visible effects of the COMS treatment on wound healing were observed when analysing the change in wound area over time, as a proportion of patients in the RSG already showed substantial healing during the baseline phase because of improved adherence with SOC (Fig 5). After the initial four weeks of SOC, the wound area in the NRSG reduced by approximately 10%, while in the RSG it reduced by 65%. The mean wound area in the NRSG was approximately four times that of the RSG at the time of COMS treatment initiation, namely 9.99±7.30cm^2 versus 2.41±2.64cm^2, respectively.

In the NRSG subgroup, a decrease in wound area was present in all different study phases, with an acceleration of the healing rate after initiation of the COMS treatment (Fig 6). The mean difference in wound size reduction was 0.91cm^2 during the baseline phase, increasing to 2.21cm^2 (weeks 0–4, p=0.002) and 2.60cm^2 (weeks 4–8, p=0.006) during the COMS treatment phase (Table 3). The healing rates during the COMS treatment increased 2.43-fold in the initial treatment phase (weeks 0–4) and 2.85-fold in the second treatment phase (weeks 4–8), when compared with the initial SOC phase (baseline). In the follow-up phase, the healing rate remained approximately twice as high (–1.84cm^2, p=0.001) when compared with the baseline phase, which raised the possibility of a residual beneficial effect of the COMS treatment. The acceleration of the healing rate between the baseline and the first four weeks of the COMS treatment (p=0.041) was remarkable, considering the low wound healing progress during the baseline phase, as well as the prolonged wound duration in the NRSG (Table 4).

The Kaplan–Meier survival analysis of the SEP (Fig 7) showed that COMS-treated patients reached a 60% rate of near-complete wound closure (>90% area reduction) and a 43% rate of complete wound closure (100% area reduction) at week 12. Wound volume measurements were excluded after initial analysis due to lack of quality of the respective data.

The reduction in pain (VAS scoring) in the SEP after completion of the COMS treatment was impressive (p<0.001). In the NRSG, the reduction in pain was noticed for both the treatment and follow-up phases (p=0.001 and p=0.002, respectively). In the RSG, there was only a clear reduction (p=0.013) from the baseline phase, but not for the treatment phase (p=0.054) as a high proportion of wounds were by then already closed due to substantial healing in the SOC phase (Table 5).

Table 2. Time between wound onset and screening by populations (NRSG, n=21; RSG, n=9). The NRSG seemed to have a longer time between wound onset and screening when compared with the RSG

	SEP	
	NRSG (n=21)	RSG (n=9)
Duration between wound onset and screening week 4, days		
Mean	417.9	136.0
Standard deviation	771.7	134.1
Median	199.0	91.0
25th percentile	91.0	50.0
75th percentile	400.0	128.0
Minimum	33	33
Maximum	3630	418

SEP—secondary endpoint population; NRSG—non-responder subgroup; RSG—responder subgroup

The overall Wound-QoL score for the SEP improved by 24% during the whole of the study period (p=0.001), and improved scores were also observed for both the NRSG and RSG (p=0.036 and p=0.008, respectively; Table 6).

Discussion

The treatment of patients with hard-to-heal wounds remains a major multidisciplinary challenge.[42,43] In particular, these protracted, therapy-refractory wounds, which do not demonstrate any significant wound healing within 30 days, place a physical, psychological and economic burden on all involved, including patients and healthcare systems.[44]

In recent years, a number of new treatment options for patients with hard-to-heal wounds have come to the market.[45] Unfortunately, the underlying scientific evidence regarding these new medical devices and treatments is often insufficient to objectively assess their real benefits in wound healing. The assessment of safety and efficacy should be an obligatory prerequisite for clinical use and, optimally, for the reimbursement of the therapy; however, this is not always the case.

The clinical trial reported in this paper is, to the authors' knowledge, the first to investigate the clinical effects of COMS technology in a single device in patients with hard-to-heal leg ulcers of different aetiologies. In terms of safety, no relevant issues were found with regard to clinical implementation. The general pattern of AEs observed during the investigation was mild, transient and of spontaneous resolution. The majority of the AEs (n=89; 87.3%) were reported at the patient visit prior to the start of COMS treatment. The autocorrelation coefficient showed no autocorrelation for AEs over the course of the study, indicating that the COMS treatment did not lead to an elevated incidence of AEs.

Table 3. Mean difference with 95% CI of change in wound area between treatment periods (baseline (weeks −4–0), treatment (weeks 0–8) and follow-up (weeks 8–12), NRSG (n=21)). Wound healing rates in the NRSG increased by a factor of 2.5–3 after initiation of the COMS treatment

				95%CI for difference	
Week	versus Week	Mean difference, cm^2	p-value	Lower bound	Upper bound
−4	0	−0.91	0.045	−0.02	−1.80
0	4	−2.21	0.002	−0.95	−3.48
4	8	−2.60	0.006	−0.84	−4.35
8	12	−1.84	0.001	−0.80	−2.87

CI—confidence interval; NRSG—non-responder subgroup; COMS—concurrent optical and magnetic stimulation

Table 4. Mean difference with 95% CI of change in wound area from SOC treatment (baseline) by analysis period. Acceleration of the healing rate between the baseline and the first four weeks of COMS treatment (p=0.041)

					95%CI for difference	
Period	versus Period	Mean change, cm^2	SE	p-value	Lower bound	Upper bound
Baseline (w4—w0)	w0—w4	1.31	0.60	0.041	0.06	2.55
	w4—w8	1.69	1.06	0.127	−0.53	3.90
	w8—w12	0.93	0.81	0.268	−0.77	2.63

CI—confidence interval; SOC—standard of care; COMS—concurrent optical and magnetic stimulation; w—week; SE—standard error

Table 5. VAS score (weeks −4, 0 and 12) and paired samples t-test for difference in VAS score (weeks −4–12 and weeks 0–12) for the NRSG and RSG. The lowered pain scores by VAS after the course of the treatment suggested that COMS treatment contributed to reducing pain

				Paired samples t-test for difference	
	Mean VAS week −4	Mean VAS week 0	Mean VAS week 12	VAS week −4– VAS week 12	VAS week 0– VAS week 12
NRSG	3.38	3.00	1.14	t=3.54 (p=0.002)	t=4.09 (p=0.001)
RSG	3.78	2.00	0.44	t=3.16 (p=0.013)	t=2.26 (p=0.054)

VAS—visual analogue scale; NRSG—non-responder subgroup; RSG—responder subgroup; COMS—concurrent optical and magnetic stimulation

Table 6. Wound-QoL score (weeks −4 and 12) and paired samples t-test for difference in Wound-QoL (weeks −4–12) for the NRSG and RSG. Both groups demonstrated improved Wound-QoL at the end of the investigation

	Mean QoL week −4	Mean QoL week 12	Paired samples t-test for difference QoL week −4–QoL week 12
NRSG	2.45	1.97	t=2.25 (p=0.036)
RSG	2.25	1.41	t=3.47 (p=0.008)

QoL—quality of life; NRSG—non-responder subgroup; RSG—responder subgroup

Pain is one of most limiting factors for patients with hard-to-heal leg ulcers with respect to their QoL in everyday life.[40] Therefore, capturing and analysing patient-reported outcomes (PRO) has become an indispensable quality marker of wound healthcare, and for the selection and evaluation of treatment plans.[46] Improvements in patient-relevant benefits, such as reduction in pain and improvements in health-related QoL, are considered major criteria of therapeutic success since complete wound closure cannot always be achieved, especially in patients with hard-to-heal wounds.[47]

Over the course of the study period, sensation of pain decreased consistently and the Wound-QoL assessment showed improvement in all three analysed dimensions (body, psyche and everyday life), further validating the effectiveness of the investigational treatment. For the NRSG in particular, the VAS pain scores were significantly lower after the treatment course than at baseline (NRSG: p=0.001; RSG: p=0.054). This suggests that the COMS treatment did not cause additional pain or disproportionate discomfort, but instead may have contributed to minimising existing pain due to the

onset of the healing process. These results are in line with previous findings on the analgesic properties of MS or OS in other indications, suggesting that COMS treatment actively supports pain modulation through immunomodulatory effects, and electrophysiological inhibition of proinflammatory and noxious stimuli.[48–51]

If confirmed, this effect could contribute to reducing analgesic medication and its side-effects, thus allowing patients to participate more effectively in work and daily life. While the data did not show a significant acceleration in wound healing in the SEP when directly comparing the baseline and treatment phases, it must be noted that this overall analysis was based on a relatively heterogeneous population and some patients had already shown substantial healing during the SOC baseline phase. This was expected as patients responding to SOC often experience an initial fast decrease of the mean wound area during the initial SOC treatment followed by a stagnation (Fig 6).

In order to take account of this aspect, the present study was designed to stratify the SEP according to the predetermined criteria of EWMA[38] and the FDA[39] regarding responsiveness to SOC (NRSG/RSG subgroups) and future healing prospects. However, other potential beneficial effects of the COMS therapy in patients already demonstrating substantial healing may not have been detected with the current study design and through the measurements in changes of wound area over time. Therefore, additional endpoints, such as quality in scar tissue formation, wound reoccurrence and time to wound closure, should be included in future, similar clinical investigations.

The statistical analysis showed that the stratification successfully selected patients who did not respond to SOC (NRSG) and whose wounds could be categorised as therapy-refractory or hard-to-heal. These patients benefited in a statistically significant manner from the COMS treatment. The mean wound healing rate increased by a factor of 2.43–2.85 after the initiation of the investigational treatment in this group. The wound healing rates during the follow-up phase demonstrated that the beneficial effect continued to persist once the COMS treatment was stopped. This suggests a carry-over effect of the COMS treatment once the cycle of stagnant wound healing was broken. This persistent beneficial treatment effect fits well into a phase-adapted individual wound-healing concept.

The proportion of ulcers reaching a (near-)complete wound closure after 12 weeks' follow-up, in the COMS/SOC treatment phase, were 60% and 43%, respectively, in the SEP. Clinical trials of other advanced wound care products, such as cold atmospheric plasma, extracorporeal shockwave therapy or oxygen wound therapy, report comparable rates of wound closure for their treatment group.[6–11] The COMS treatment compared well with the above-mentioned counterparts and seemed to be at least as effective as these alternative treatment methods, and therefore capable of being a valuable addition to improving wound healing, especially for patients who do not show significant improvement with SOC. The device's simple, user-friendly design allows for use in both ambulatory and homecare settings, and should give it an advantage over other treatment modalities. The implementation in the homecare setting is especially appealing because these hard-to-heal wounds not only pose a particular challenge for patients and therapists, but also have severe economic implications to healthcare systems,

Fig 6. Subgroup analysis mean wound area (cm^2). Mean wound area by visit with 95% confidence interval (CI) for the standard of care (SOC) non-responder group (NRSG, n=21) and responder group (RSG, n=9). The wound healing rate of the NRSG population increased by a factor of 2.5–3 and persisted even after the concurrent optical and magnetic stimulation (COMS) treatment was stopped, suggesting a beneficial carry-over effect

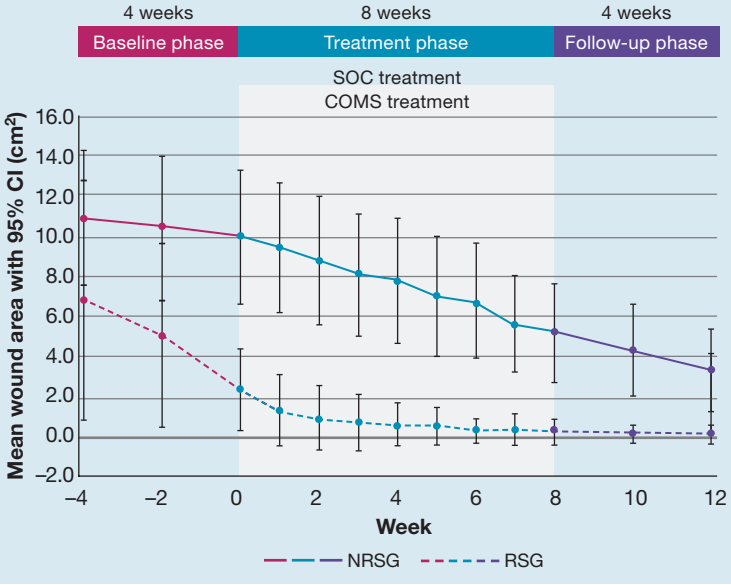
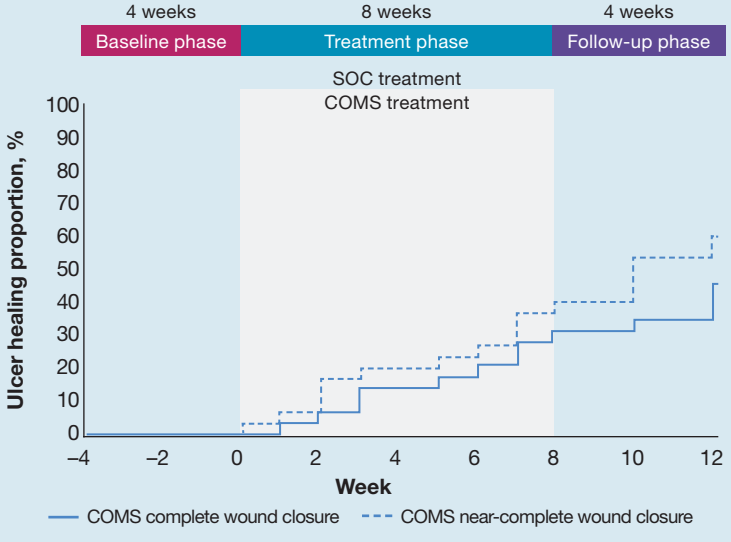


Fig 7. Kaplan–Meier curve for complete and near-complete wound closure over 12 weeks after therapy initiation in the secondary endpoint population (SEP, n=30). SOC—standard of care; COMS—concurrent optical and magnetic stimulation



patients and society as a whole.[44]

The differences between healing and hard-to-heal wounds have long been the subject of research. While not all involved processes are fully understood, it is now known that there are many differences in, for example, matrix metalloproteinases, growth factors, pH or macrophage activity between healing and hard-to-heal wounds.[52–54] Although no direct measurements were made on the wounds included in this study, it may be that the wounds that did not respond to SOC have a special microenvironment that is particularly receptive to COMS therapy. Considering the electrophysiological environment of these wounds, an essential electrical cue for efficient tissue regeneration seems to be missing.[55] The 'skin battery' effect, induced through the electric field of transepidermal potential, is diminished and, thus, the skin presents lower electric field gradients when compared with acute wounds.[56] It is assumed that cellular sensing mechanisms of electric fields are mediated through the two poles of a cell, parallel to the electric field lines.[57,58] Therefore, reinduction of these electric currents at compromised wound edges can be a valuable cue to promote mobilisation of fibroblasts and keratinocytes, leading to augmented re-epithelialisation and, therefore, to support wound healing.[14,59,60] However, for a more detailed analysis, further studies are necessary to better understand wound healing at the molecular level.

In this study, COMS treatment seemed to be equally effective for the different investigated wound aetiologies. Future investigations should focus on other types of hard-to-heal wounds, such as diabetic foot and pressure ulcers, in order to confirm that the beneficial effects can be transferred to other hard-to-heal wound indications.

Limitations

We are fully aware that the considered sample size and the absence of a control group can be seen as limitations of this study. A larger, blinded and randomised controlled trial (RCT) with different treatment arms is required to validate any advantages of COMS therapy over SOC. Additionally, the SOC was aligned with the guidelines of the SAWC; however, protocols were not standardised between the different study centres involved. Each patient was treated with the standard practice and materials in the respective centres. Future clinical investigations should aim to clearly articulate standardised wound care protocols to evaluate, initiate and perform treatment in a more standardised and systematic way.

The inclusion and exclusion criteria selected a specific population of patients. Nonetheless, because of the less stringent exclusion criteria when compared with many RCTs, the study aimed to assess efficacy outcomes in a patient population more prone to reflect real-world clinical practice.

Conclusions

The data from this prospective clinical trial demonstrated that COMS was a safe and effective new treatment option for patients with hard-to-heal wounds on lower extremities. It was particularly beneficial for patients who did not respond to SOC and its possible post-application beneficial effect was also noted.

In this study, the COMS therapy significantly reduced the time to wound closure for hard-to-heal wounds when compared with SOC alone, and could therefore lead to substantial savings in healthcare time and costs. In addition to its clinical effectiveness, it can enable patient self-management and hasten the timely transfer of patients with persistently high-cost conditions towards a more cost-effective treatment setting.

Although these findings need additional confirmation in larger patient populations, COMS therapy can already be considered a promising and innovative therapeutic option in the treatment of patients with hard-to-heal wounds of various aetiologies. JWC

References

1 Lal BK. Venous ulcers of the lower extremity: definition, epidemiology, and economic and social burdens. Semin Vasc Surg 2015; 28(1):3–5. https://doi.org/10.1053/j.semvascsurg.2015.05.002

2 Goh OQ, Ganesan G, Graves N et al. Incidence of chronic wounds in Singapore, a multiethnic Asian country, between 2000 and 2017: a retrospective cohort study using a nationwide claims database. BMJ Open 2020; 10(9):e039411. https://doi.org/10.1136/bmjopen-2020-039411

3 Körber A, Klode J, Al-Benna S et al. Etiology of chronic leg ulcers in 31,619 patients in Germany analyzed by an expert survey. J Dtsch Dermatol Ges 2011; 9(2):116–121. https://doi.org/10.1111/j.1610-0387.2010.07535.x

4 Dissemond J. ABCDE rule in the diagnosis of chronic wounds. J Dtsch Dermatol Ges 2017; 15(7):732–733. https://doi.org/10.1111/ddg.13273

5 Dissemond J, Assenheimer B, Engels P et al. M.O.I.S.T. – a concept for the topical treatment of chronic wounds. J Dtsch Dermatol Ges 2017; 15(4):443–445. https://doi.org/10.1111/ddg.13215

6 Arensbergerova M, Engels P, Gkalpakiotis S et al. [Topical hemoglobin promotes wound healing of patients with venous leg ulcers]. Hautarzt 2013; 64(3):180–186. https://doi.org/10.1007/s00105-012-2528-3

7 Moelleken M, Jockenhöfer F, Wiegand C et al. Pilot study on the influence of cold atmospheric plasma on bacterial contamination and healing tendency of chronic wounds. J Dtsch Dermatol Ges 2020; 18(10):1094–1101. https://doi.org/10.1111/ddg.14294

8 von Beckerath O, Zapenko A, Dissemond J, Kröger K; Initiative Chronische Wunden (ICW) e.V. Ten-year analyses of the German DRG data about negative pressure wound therapy. Int Wound J 2017; 14(3):501–507. https://doi.org/10.1111/iwj.12635

9 Gottrup F, Dissemond J, Baines C et al. Use of oxygen therapies in wound healing. J Wound Care 2017; 26(Suppl 5):S1–S43. https://doi.org/10.12968/jowc.2017.26.Sup5.S1

10 Dissemond J, Augustin M, Dietlein M et al. Efficacy of MMP-inhibiting wound dressings in the treatment of chronic wounds: a systematic review. J Wound Care 2020; 29(2):102–118. https://doi.org/10.12968/jowc.2020.29.2.102

11 Cooper B, Bachoo P. Extracorporeal shock wave therapy for the healing and management of venous leg ulcers. Cochrane Database Syst Rev 2018; 2018(6):CD011842. https://doi.org/10.1002/14651858.CD011842.pub2

12 Zhao M, Penninger J, Isseroff RR. Electrical activation of wound-healing pathways. Adv Skin Wound Care 2010; 1:567–573

13 Messerli MA, Graham DM. Extracellular electrical fields direct wound healing and regeneration. Biol Bull 2011; 221(1):79–92. https://doi.org/10.1086/BBLv221n1p79

14 Wang ET, Zhao M. Regulation of tissue repair and regeneration by electric fields. Chin J Traumatol 2010; 13(1):55–61

15 Reid B, Zhao M. The electrical response to injury: molecular mechanisms and wound healing. Adv Wound Care 2014; 3(2):184–201. https://doi.org/10.1089/wound.2013.0442

16 Panagopoulos DJ, Karabarbounis A, Margaritis LH. Mechanism for action of electromagnetic fields on cells. Biochem Biophys Res Commun 2002; 298(1):95–102. https://doi.org/10.1016/S0006-291X(02)02393-8

17 Anders JJ, Lanzafame RJ, Arany PR. Low-level light/laser therapy versus photobiomodulation therapy. Photomed Laser Surg 2015; 33(4):183–184. https://doi.org/10.1089/pho.2015.9848

18 Mignon C, Botchkareva NV, Uzunbajakava NE, Tobin DJ. Photobiomodulation devices for hair regrowth and wound healing: a therapy full of promise but a literature full of confusion. Exp Dermatol 2016; 25(10):745–749. https://doi.org/10.1111/exd.13035
19 Schindl A, Schindl M, Pernerstorfer-Schön H, Schindl L. Low intensity laser therapy in wound healing. a review with special respect to diabetic angiopathies. Acta Chirurgica Austriaca 2001; 33(3):132–137. https://doi.org/10.1046/j.1563-2563.2001.01067.x
20 Karu TI, Kolyakov SF. Exact action spectra for cellular responses relevant to phototherapy. Photomed Laser Surg 2005; 23(4):355–361. https://doi.org/10.1089/pho.2005.23.355
21 Farivar S, Malekshahabi T, Shiari R. Biological effects of low level laser therapy. J Lasers Med Sci 2014; 5(2):58–62
22 Kuffler DP. Photobiomodulation in promoting wound healing: a review. Regen Med 2016; 11(1):107–122. https://doi.org/10.2217/rme.15.82
23 Keszler A, Lindemer B, Hogg N et al. Wavelength-dependence of vasodilation and NO release from S-nitrosothiols and dinitrosyl iron complexes by far red/near infrared light. Arch Biochem Biophys 2018; 649:47–52. https://doi.org/10.1016/j.abb.2018.05.006
24 Liburdy RP, Callahan DE, Harland J et al. Experimental evidence for 60 Hz magnetic fields operating through the signal transduction cascade: effects on calcium influx and c-MYC mRNA induction. FEBS Lett 1993; 334(3):301–308. https://doi.org/10.1016/0014-5793(93)80699-u
25 Löschinger M, Thumm S, Hämmerle H et al. Induction of intracellular calcium oscillations in human skin fibroblast populations by sinusoidal extremely low-frequency magnetic fields (20 Hz, 8 mT) is dependent on the differentiation state of the single cell. Radiat Res 1999; 151(2):195–200. https://doi.org/10.2307/3579770
26 Mattsson MO, Lindström E, Still M et al. [Ca2+](i) rise in Jurkat E6-1 cell lines from different sources as a response to 50 Hz magnetic field exposure as a reproducible effect and independent of poly-L-lysine treatment. Cell Biol Int 2001; 25(9):901–907. https://doi.org/10.1006/cbir.2001.0774
27 Hoare JI, Rajnicek AM, McCaig CD et al. Electric fields are novel determinants of human macrophage functions. J Leukoc Biol 2016; 99(6):1141–1151. https://doi.org/10.1189/jlb.3A0815-390R
28 Fivenson DP, Faria DT, Nickoloff BJ et al. Chemokine and inflammatory cytokine changes during chronic wound healing. Wound Repair Regen 1997; 5(4):310–322. https://doi.org/10.1046/j.1524-475X.1997.50405.x
29 Chiarotto GB, Neves LM, Esquisatto MA et al. Effects of laser irradiation (670-nm InGaP and 830-nm GaAlAs) on burn of second-degree in rats. Lasers Med Sci 2014; 29(5):1685–1693. https://doi.org/10.1007/s10103-014-1573-9
30 Catarino HR, de Godoy NP, Scharlack NK et al. InGaP 670-nm laser therapy combined with a hydroalcoholic extract of Solidago chilensis Meyen in burn injuries. Lasers Med Sci 2015; 30(3):1069–1079. https://doi.org/10.1007/s10103-014-1707-0
31 Maligieri LA, Neves LM, de Morais DT et al. Differing energy densities with laser 670 nm InGaP controls inflammation and collagen reorganization in burns. Burns 2017; 43(7):1524–1531. https://doi.org/10.1016/j.burns.2017.04.008
32 Belli M, Fernandes CR, Neves LM et al. Application of 670 nm InGaP laser and microcurrent favors the healing of second-degree burns in Wistar rats. Laser Phys 2015; 25(2):025602. https://doi.org/10.1088/1054-660X/25/2/025602
33 de Medeiros ML, Araújo-Filho I, da Silva EM et al. Effect of low-level laser therapy on angiogenesis and matrix metalloproteinase-2 immunoexpression in wound repair. Lasers Med Sci 2017; 32(1):35–43. https://doi.org/10.1007/s10103-016-2080-y
34 Lee YJ, Hyung KE, Yoo JS et al. Effects of exposure to extremely low-frequency electromagnetic fields on the differentiation of Th17 T cells and regulatory T cells. Gen Physiol Biophys 2016; 35(04):487–495. https://doi.org/10.4149/gpb_2016011
35 Li F, Yuan Y, Guo Y et al. Pulsed magnetic field accelerate proliferation and migration of cardiac microvascular endothelial cells. Bioelectromagnetics 2015; 36(1):1–9. https://doi.org/10.1002/bem.21875
36 Jere SW, Houreld NN, Abrahamse H. Photobiomodulation at 660 nm stimulates proliferation and migration of diabetic wounded cells via the expression of epidermal growth factor and the JAK/STAT pathway. J Photochem Photobiol B 2018; 179:74–83. https://doi.org/10.1016/j.jphotobiol.2017.12.026
37 Ayuk SM, Abrahamse H, Houreld NN. Photobiomodulation alters matrix protein activity in stressed fibroblast cells in vitro. J Biophotonics 2018; 11(3):e201700127. https://doi.org/10.1002/jbio.201700127
38 Price P, Gottrup F, Abel M. EWMA study recommendations: For clinical investigations in leg ulcers and wound care. J Wound Care 2014; 23(Suppl 5):S1–S36. https://doi.org/10.12968/jowc.2014.23.Sup5c.S1
39 FDA Wound Healing Clinical Focus Group. Guidance for industry: Chronic cutaneous ulcer and burn wounds-developing products for treatment. Wound Repair Regen 2001; 9(4):258–268. https://doi.org/10.1046/j.1524-475X.2001.00258.x
40 Leren L, Johansen E, Eide H et al. Pain in persons with chronic venous leg ulcers: a systematic review and meta-analysis. Int Wound J 2020; 17(2):466–484. https://doi.org/10.1111/iwj.13296
41 Augustin M, Conde Montero E, Zander N et al. Validity and feasibility of the wound-QoL questionnaire on health-related quality of life in chronic wounds. Wound Repair Regen 2017; 25(5):852–857. https://doi.org/10.1111/wrr.12583
42 Dissemond J. Modern management of chronic wounds. Hautarzt 2021; 72(8):733–744. https://doi.org/10.1007/s00105-021-04858-6
43 Shaydakov ME, Ting W, Sadek M et al.; American Venous Forum Research Committee. Review of the current evidence for topical treatment for venous leg ulcers. J Vasc Surg Venous Lymphat Disord. Forthcoming 2022; 10(1):241–247.e15. https://doi.org/10.1016/j.jvsv.2021.06.010
44 Boersema GC, Smart H, Giaquinto-Cilliers MG et al. Management of nonhealable and maintenance wounds: a systematic integrative review and referral pathway. Adv Skin Wound Care 2021; 34(1):11–22. https://doi.org/10.1097/01.ASW.0000722740.93179.9f
45 Lindholm C, Searle R. Wound management for the 21st century: combining effectiveness and efficiency. Int Wound J 2016; 13(Suppl 2):5–15. https://doi.org/10.1111/iwj.12623
46 Augustin M, Blome C, Goepel L et al. Patient-reported outcomes as diagnostic tools and clues in chronic wounds: considerations for practice. Wound Medicine 2015; 8:6–14. https://doi.org/10.1016/j.wndm.2015.03.009
47 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 2018; 31(3):102–108. https://doi.org/10.1097/01.ASW.0000530069.82749.e5
48 Kingsley JD, Demchak T, Mathis R. Low-level laser therapy as a treatment for chronic pain. Front Physiol 2014; 5:306. https://doi.org/10.3389/fphys.2014.00306
49 Cotler HB, Chow RT, Hamblin MR, Carroll J. The use of low level laser therapy (LLLT) for musculoskeletal pain. MOJ Orthop Rheumatol 2015; 2(5):00068. https://doi.org/10.15406/mojor.2015.02.00068
50 Yang X, He H, Ye W et al. Effects of pulsed electromagnetic field therapy on pain, stiffness, physical function, and quality of life in patients with osteoarthritis: a systematic review and meta-analysis of randomized placebo-controlled trials. Phys Ther 2020; 100(7):1118–1131. https://doi.org/10.1093/ptj/pzaa054
51 Andrade R, Duarte H, Pereira R et al. Pulsed electromagnetic field therapy effectiveness in low back pain: a systematic review of randomized controlled trials. Porto Biomedical Journal 2016; 1(5):156–163. https://doi.org/10.1016/j.pbj.2016.09.001
52 Willenborg S, Eming SA. Cellular networks in wound healing. Science 2018; 362(6417):891–892. https://doi.org/10.1126/science.aav5542
53 Tardáguila-García A, García-Morales E, García-Alamino JM et al. Metalloproteinases in chronic and acute wounds: a systematic review and meta-analysis. Wound Repair Regen 2019; 27(4):415–420. https://doi.org/10.1111/wrr.12717
54 Schultz GS, Wysocki A. Interactions between extracellular matrix and growth factors in wound healing. Wound Repair Regen 2009; 17(2):153–162. https://doi.org/10.1111/j.1524-475X.2009.00466.x
55 Clausen T, Van Hardeveld C, Everts ME. Significance of cation transport in control of energy metabolism and thermogenesis. Physiol Rev 1991; 71(3):733–774. https://doi.org/10.1152/physrev.1991.71.3.733
56 Foulds IS, Barker AT. Human skin battery potentials and their possible role in wound healing. Br J Dermatol 1983; 109(5):515–522. https://doi.org/10.1111/j.1365-2133.1983.tb07673.x
57 Nishimura KY, Isseroff RR, Nuccitelli R. Human keratinocytes migrate to the negative pole in direct current electric fields comparable to those measured in mammalian wounds. J Cell Sci 1996; 109(1):199–207. https://doi.org/10.1242/jcs.109.1.199
58 Funk RH, Monsees TK. Effects of electromagnetic fields on cells: physiological and therapeutical approaches and molecular mechanisms of interaction: a review. Cells Tissues Organs 2006; 182(2):59–78. https://doi.org/10.1159/000093061
59 Sheridan DM, Rivkah Isseroff R, Nuccitelli R. Imposition of a physiologic DC electric field alters the migratory response of human keratinocytes on extracellular matrix molecules. J Invest Dermatol 1996; 106(4):642–646. https://doi.org/10.1111/1523-1747.ep12345456
60 Balakatounis KC, Angoules AG. Low-intensity electrical stimulation in wound healing: review of the efficacy of externally applied currents resembling the current of injury. Eplasty 2008; 8:e28

Reflective questions

- What additions to standard of care treatment regimens are required to enable efficient treatment of hard-to-heal wounds?
- What technologies are needed to allow the transfer of patient care from inpatient to post-acute settings, such as home care?
- What makes an advanced wound care treatment predestined for use not only by health professionals, but also by trained patients or carers?