Influence of placebo effects on quality of life and wound healing in patients with chronic venous leg ulcers

Finja Jockenhöfer¹, Christopher Knust¹, Sven Benson², Manfred Schedlowski²³, Joachim Dissemond¹

(¹) Department of Dermatology, Venereology and Allergology, University Medical Center, Essen, Germany
(²) Institute of Medical Psychology and Behavioral Immunobiology, University Medical Center, Essen, Germany
(³) Department of Clinical Neuroscience, Osher Center for Integrative Medicine Karolinska Institutet, Stockholm, Sweden

Summary

Introduction: Placebo effects are used in the treatment of various medical conditions. To date, there is little scientific data in this regard as it relates to skin diseases in general and hardly any data with respect to wound healing in particular.

Material and methods: In a prospective randomized controlled trial, patients with chronic venous leg ulcers were observed for a period of 14 weeks. The objective was to investigate whether raising patients’ expectations with regard to a novel wound treatment might have an effect on wound healing processes as well as wound-related quality of life, anxiety, depression and pain.

Results: Overall, 20 patients were included in the trial. They were stratified based on gender and randomized to either the intervention (IG) or the control group (CG). In both groups, the wound area decreased significantly over the course of the observation period. Unlike patients in the CG, those in the IG experienced significant improvement in wound-related quality of life (wound-QoL) in terms of both the overall score and the various subscales. Neither group showed significant changes with respect to pain, anxiety and depression.

Conclusions: Our study is the first to show that – merely by raising patients’ expectations for a novel treatment – placebo effects can significantly improve quality of life in patients with chronic venous leg ulcers. In the future, our findings should be integrated into the development of treatment concepts for patients with chronic wounds and should be investigated in larger cohorts.

Introduction

By definition, a chronic wound is a skin defect that involves at least the upper dermis (ulceration) and that either persists for at least eight weeks or is associated with an underlying chronic disease that causes its persistence [1]. The most common causes of chronic wounds include vascular disorders such as chronic venous insufficiency and peripheral artery disease, followed by diabetic foot ulcers and decubitus ulcers. Less common causes are vasculitides, infectious diseases, and pyoderma pressure ulcer gangrenosum [2]. The mainstay of the treatment strategy is to diagnose any potential cause(s) resulting in impaired wound healing so as to be able to initiate causal treatment whenever possible. This should be accompanied by modern, stage-adjusted moist wound therapy that includes proper exudate management. Given that such treatment frequently requires a prolonged period of time and given the chronic, sometimes recurrent clinical course, patients may be exposed to considerable physical and psycho-emotional stress. Similar to other chronic diseases, every certified outpatient wound care center should therefore assess patients’ quality of life using a specific questionnaire in order to detect potential psycho-emotional stress in a timely fashion and to be able to intervene accordingly.
Clinical experience and experimental data have shown that wound healing processes may be adversely affected by psychological factors such as psychosocial stress [3, 4]. On the other hand, empirical data obtained from placebo research has revealed that psychological factors may also have positive effects on clinical symptoms [5–7]. To date, placebo responses have been described for various diseases, affecting and augmenting the effects of pharmacological and other medical interventions [6, 7]. The underlying neuropsychological and neurobiological mechanisms include cognitive processes such as the formation of positive treatment-related expectations, associative learning processes such as classic conditioning, as well as social factors such as the quality of the physician-patient relationship [6–8]. Although placebo responses have been shown to be clinically beneficial and have been included in S3 guideline recommendations for the management of acute pain [9], there have been only few studies investigating placebo responses in the context of dermatological diseases [10]. In patients with dust mite allergy, allergic symptoms can be significantly reduced by placebo interventions, in particular by associative learning processes [5, 11–13]. Placebo responses in patients with pruritus have been studied comparatively well [14]. Meta-analyses have revealed significant improvement of chronic pruritus in individuals with atopic dermatitis, psoriasis and idiopathic urticaria, as well as in patients who had been randomized to the placebo arms of various randomized controlled trials (RCTs) [15].

To date, there have been hardly any systematic studies investigating the significance of placebo effects on wound healing. Against this background, the objective of the present prospective randomized controlled pilot study was to investigate whether additional use of a placebo intervention might improve wound healing as well as patient-reported outcomes (PROs).

**Patients and methods**

In this prospective randomized controlled pilot study, we examined patients with chronic venous leg ulcers treated at the certified wound care clinic of the Department of Dermatology at the University Medical Center in Essen, Germany.

**Inclusion and exclusion criteria**

Inclusion criteria were a minimum disease duration of eight weeks, an ankle-brachial pressure index (ABPI) of ≥ 0.8, patient age between 18 and 90 years, pain level of at least two on a numeric rating scale (NRS: 0 = no pain to 10 = most severe pain imaginable) as determined after getting up in the morning, no need for specific wound therapy (for example, vacuum-assisted therapy, surgical intervention), and willingness to participate in the study.

Excluded were patients with acute, superinfected, highly exudative wounds or with wounds at sites other than the lower legs, individuals with known contact sensitization to any of the ingredients contained in the hydrogel to be applied, those with a history of depression and other psychiatric disorders, as well as patients who had undergone any venous or wound procedure within six months prior to enrollment or who were about to undergo such a procedure in the near future.

**Study design**

Over an observation period of 14 weeks, we examined whether raising patients’ expectations with regard to a “novel, highly effective wound treatment” could affect wound healing processes and wound-related quality of life (primary endpoints) as well as anxiety, depression, and pain (secondary endpoints) (see below). Patients were consecutively randomized to either study arm (male/female ratio in both groups: 1 : 1).

The treating physician informed the intervention group (IG) in a standardized manner that the agent to be applied to the wound was a special novel drug that had positive effects on wound healing and pain. The agent was also visually marked. In addition, IG patients were seen three times by one of the principal investigators of the study (V0 baseline visit; V3 after 6 weeks; and V6 after 12 weeks) who again focused their attention on the “novel agent that potentially had positive effects on wound healing”. Similar to the IG, treatment of the control group (CG) was provided on a regular basis and documented in an equally detailed manner. In actuality, both groups received modern moist wound therapy using an identical wound gel (Suprasorb G, manufactured by Lohmann & Rauscher, Neuwied, Germany). Subjects randomized to the CG were informed about this circumstance. In addition, patients in both groups were provided individual treatment on an as-needed basis, including debridement, wound dressings and compression therapy. Any dressing materials that had previously been used by the patients (non-adhesive wound contact layers, various secondary dressings based on a patient’s individual amount of wound exudate, and compression therapy using short-stretch bandages, ulcer stocking systems, or adaptive systems) were maintained throughout the study; no changes were made either before or during the intervention.

All patient data were digitalized and pseudonymized. The study was approved by the Ethics Commission of the Medical Faculty of the University of Duisburg-Essen (14-5745-BO).

**Primary and secondary endpoints**

All outcome parameters were assessed prior to treatment (V0) as well as after the 14-week intervention period (V7).
Additional (exploratory) assessment was performed after six weeks of treatment (V3). Primary endpoints included reduction in wound area and changes in wound-related quality of life, which were determined at baseline (V0) as well as after six (V3) and 14 (V7) weeks. The wound area was measured using a three-dimensional camera system (Silhouette®, ARANZ Medical, Christchurch, New Zealand). Wound-related quality of life was assessed with a validated questionnaire (wound-QoL) [16]. Based on a Likert scale, the questionnaire includes 17 items that refer to the seven days preceding the assessment. Individual item scores are added up to obtain an overall score and divided into subscales in terms of physical, psychological, and everyday quality of life. The lower the scores, the better the quality of life.

Secondary endpoints included the levels of anxiety, depression and pain as determined by validated scores. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) [17]. The questionnaire includes seven Likert items each for assessing clinically relevant symptoms of anxiety and depression. Higher scores indicate more severe symptoms. Using a pain diary [18], average pain levels during the day and during dressing changes were assessed using a numerical scale from 0 (no pain) to 10 (most severe pain imaginable).

### Statistical analysis

Given the small cohort size, all analyses were conducted using non-parametric methods, as they are less susceptible to bias. Changes in dependent variables (primary and secondary outcomes) between treatment initiation (baseline, V0) and the end of the 14-week intervention period (V7) were analyzed by Wilcoxon test for both the IG and the CG. In addition, the two groups were compared using Mann-Whitney U tests, both at baseline and after the intervention period. Moreover, exploratory analysis of any changes from V0 until the second visit after six weeks (V3) was done by Wilcoxon test. Unless stated otherwise, all data are presented as median values (25th/75th percentile). Data were analyzed with SPSS (22.9, SPSS Inc., Chicago, IL, USA); a p-value < 0.05 was considered to be significant.

### Results

#### Patient characteristics

Overall, 20 patients with chronic venous leg ulcers were enrolled in the study; they were stratified based on gender and randomized to either the IG or the CG. For all participating patients, complete data was available for every visit. There were no dropouts. The median age was 61.5 years (37–79 years). At baseline, there were no significant differences between both patient groups as regards age, wound area, quality of life (Wound-QoL), anxiety and depression scores (HADS), as well as average pain levels during the day and during dressing changes (Table 1). Given the stratified recruitment, gender distribution was identical (n = 5 male/female, each).

#### Wound area

The wound area was determined at V0 (baseline), V3 (after 6 weeks) and V7 (after 14 weeks). The change in wound area from the beginning of the study (V0) to the final visit after 14 weeks (V7) was used as primary endpoint. In both groups, the median wound area decreased significantly over the observation period (CG: U = –2.19, p = 0.028; IG: U = –2.50, p = 0.016).

### Table 1 Comparison of patient characteristics at baseline.

|                      | Control group (n = 10) | Intervention group (n = 10) | U value* | P value* |
|----------------------|------------------------|----------------------------|----------|----------|
| Age (median)         | 60.5 (57.0/69.5)       | 64.0 (59.0/76.3)           | U = –0.80 | 0.44     |
| Gender (m/f)         | 5/5                    | 5/5                        | ./       | ./       |
| Wound area (cm²) (median) | 12.9 (1.28/35.68)   | 11.6 (3.25/28.23)          | U = –0.11 | 0.91     |
| Wound-QoL            | 23.5 (8.5/45.5)        | 24.5 (18.5/325)            | U = –0.11 | 0.91     |
| HADS anxiety         | 5.5 (2.0/10.3)         | 5.5 (2.0/8.0)              | U = –0.04 | 0.97     |
| HADS depression      | 5.0 (2.8/11.3)         | 5.0 (3.0/8.3)              | U = –0.32 | 0.83     |
| Average pain levels during the day | 1.4 (0/4.8)         | 2.4 (0.7/3.5)              | U = –0.69 | 0.49     |
| Pain during dressing changes | 0.5 (0/4.6)         | 2.2 (0.7/4.7)              | U = –0.73 | 0.48     |

Abbr.: Wound-QoL, wound-related quality of life; HADS, Hospital Anxiety and Depression Scale.
Values are presented as median values (25th/75th percentile).
*Group comparisons were done by Mann-Whitney U test.
Table 2 Primary and secondary endpoints.

| Endpoint                              | Baseline          | Post intervention | U value* | P value** |
|---------------------------------------|-------------------|------------------|----------|-----------|
| Wound area (cm²)                      | CG                | 12.9 (1.28/35.68) | 8.8 (1.53/30.48) | U = –2.19 | 0.028     |
|                                       | IG                | 11.6 (3.25/28.23) | 5.15 (2.55/10.68) | U = –2.50 | 0.012     |
| Wound-QoL, overall score              | CG                | 23.5 (8.5/45.5)  | 21.0 (11.5/36.3) | U = –1.34 | 0.175     |
|                                       | IG                | 24.5 (18.5/32.5) | 16.0 (7.3/23.5)  | U = –2.53 | 0.012     |
| Wound-QoL, physical subscale          | CG                | 6.5 (1.0/11.5)   | 6.0 (1.0/8.8)    | U = –0.12 | 0.905     |
|                                       | IG                | 5.5 (4.0/9.0)    | 3.5 (1.8/5.0)    | U = –2.21 | 0.027     |
| Wound-QoL, psychological subscale     | CG                | 7.0 (1.0/14.0)   | 5.0 (2.3/13.0)   | U = –1.13 | 0.258     |
|                                       | IG                | 9.5 (3.8/15.3)   | 5.0 (2.8/10.8)   | U = –2.20 | 0.028     |
| Wound-QoL, everyday-life subscale     | CG                | 7.5 (4.0/18.0)   | 8.0 (4.8/13.8)   | U = –0.88 | 0.380     |
|                                       | IG                | 7.5 (3.8/13.3)   | 6.0 (1.8/9.3)    | U = –2.38 | 0.018     |
| HADS anxiety                          | CG                | 5.5 (2.0/10.3)   | 4.5 (1.8/9.8)    | U = –0.63 | 0.527     |
|                                       | IG                | 5.5 (2.0/8.0)    | 5.5 (1.5/9.0)    | U = –0.78 | 0.473     |
| HADS depression                       | CG                | 5.0 (2.8/11.3)   | 4.5 (2.0/9.0)    | U = –1.36 | 0.172     |
|                                       | IG                | 5.0 (3.0/8.3)    | 4.0 (1.8/9.5)    | U = –0.01 | 0.990     |
| Average pain levels during the day    | CG                | 1.4 (0/4.8)      | 0.4 (0/3.9)      | U = –0.31 | 0.753     |
|                                       | IG                | 2.4 (0.7/3.5)    | 2.1 (0.4/4.7)    | U = –0.14 | 0.889     |
| Pain during dressing changes          | CG                | 0.5 (0/4.6)      | 0.3 (0/2.3)      | U = –0.31 | 0.753     |
|                                       | IG                | 2.2 (0.7/4.7)    | 1.7 (0/3.3)      | U = –1.68 | 0.093     |

Abbr.: CG, control group; IG, intervention group; wound-QoL, wound-related quality of life; HADS, Hospital Anxiety and Depression Scale.
Values are presented as median values (25th/75th percentile).
*Comparisons of baseline and post-intervention values in both groups were performed by Wilcoxon tests. Significant changes are shown in bold font.

There were no significant group differences in median wound area both at baseline (U = –0.11, p = 0.91) and after the intervention (U = –0.61, p = 0.58) (Table 2). Exploratory analysis at V3 revealed a significant decrease in wound area in the IG after only six weeks (U = –2.50, p = 0.012), a finding that was not observed in the CG (U = –0.14, p = 0.89). To rule out potential bias, the analysis was repeated after excluding two CG patients with a wound area > 40 cm². However, the results remained the same.

Wound-related quality of life (wound-QoL)

Another primary endpoint analyzed in both groups referred to the change in wound-related quality of life. Patients in the IG showed a significant improvement in quality of life after the intervention, as determined by the overall wound-QoL score (U = –2.53, p = 0.012) (Figure 1, Table 2). This effect was observed in all three wound-QoL subscales: physical (U = –2.21, p = 0.027), psychological (U = –2.20, p = 0.028) and everyday (U = –2.38, p = 0.018) quality of life (Table 2). By contrast, patients in the CG experienced no significant changes in quality of life, neither in the overall wound-QoL score nor in the various subscales (all p > 0.26) (Figure 1, Table 2). Direct comparison revealed no significant differences between the groups at V0 and V7. At six weeks (V3), neither group showed any significant changes. The results were the same after two CG patients with a wound area > 40 cm² had been excluded.

Secondary endpoints

Secondary endpoints included parameters such as anxiety and depression (HADS) as well as average pain levels during the day and during dressing changes. Specifically, we analyzed whether there were any changes from baseline to the post-intervention period. Neither group showed significant changes in this regard (Table 2).
Discussion

With the introduction of randomized controlled trials in the 1950s, medical researchers became increasingly interested in the potential effects of placebo interventions. In this context, the placebo effect is frequently considered a confounding factor that renders it difficult for investigators to accurately assess the effectiveness of pharmacological and non-pharmacological treatments. Placebos are an indispensable component of clinical drug trials in which they are used to treat a CG for comparison purposes; the premise is that placebos elicit neither pharmacological nor any other specific therapeutic effects. Still, it is not uncommon for some control subjects to show effects that are usually achievable only with a specific drug. Given that a placebo is a substance without pharmacologic activity, it remains to be explained in what way placebo treatments cause said effects [6]. Studies in this regard have revealed that placebo effects are predominantly controlled by cognitive processes, such as expectations, and associative learning processes. It has been shown that the mere expectation of a study subject to receive (or to no longer receive) a strong pain medication significantly enhances (or neutralizes) the analgesic effects of the opiates given. Conditioned pharmacological responses that may develop even without the patient’s specific expectation have been detected in various systems of the body, including the pain sensory system, the motor system, the immune system, and the autonomic nervous system [7]. Neuroscience studies conducted over the past three decades have clearly demonstrated that placebo-related neuropsychological phenomena may change overall treatment outcomes. Clinical trials have shown placebo treatment to be able to reduce disease symptoms and to positively affect the healing process. Even open-label placebo use (thus, the mere expectation) has been demonstrated to substantially reduced the severity of symptoms in patients with irritable bowel syndrome compared with an untreated CG [19]. However, the exact significance of expectations/associative learning processes for placebo effects relating to different physiological systems remains to be elucidated. The most extensive neuroscientific data in terms of placebo responses exists for placebo analgesia. Using central nervous system imaging, various studies have shown that reduced pain perception is associated with activation of the descending pain-inhibitory system, thus resulting in reduced activity of the (classic) pain-processing areas of the brain. Activation of regions that are similar to the pain-inhibitory system has also been demonstrated for placebo responses related to emotions. It remains unclear to what extent various regions of the brain contribute in the same or in different ways to placebo effects involving other physiological systems [20].

To date, there have been only few systematic reports addressing the correlation between placebo effects and wound healing. In a 2015 study of our working group, Cesko et al. examined whether the mere expectation of being treated with a wound healing agent would speed up the healing process. Included were 22 healthy men who were subjected to ablative laser treatment to create an acute wound. The study revealed no significant intrindividual or interindividual differences with respect to wound healing [21]. In this context, it was suggested that acute wounds usually have hardly any impact on the quality of life of otherwise healthy individuals. This prompted us to initiate a pilot RCT to systematically investigate whether placebo effects may have an impact on wound healing and quality of life in patients with chronic wounds.

The occurrence of placebo effects is characterized by great interindividual variation, as evidenced by the varying degrees of individual placebo responses. While some subjects respond well to placebo interventions and thus show pronounced placebo responses (responders), others do not respond at all to these interventions (non-responders). In this context, current research focuses on potential predictor variables in particular. Factors thought to be associated with placebo responses and thus to have a predictive value include psychological, neuroendocrine, and genetic factors.
Other patient-related psychological variables such as anxiety, degree of depression and optimism also seem to explain some of the variation in placebo responses. Individual brain anatomy, too, might affect the ability to respond to placebo interventions [22].

Given the way we randomized our patients, the gender and age distribution in both groups was readily comparable in the present study; so was the type of wounds, which was intended to minimize any interindividual differences (Table 1). The mean age of our patients (7th decade) was similar to cohorts in other studies of individuals with venous leg ulcers [23]. Neither were there any major discrepancies in median baseline wound areas (Table 1). Large differences in this regard may be a potential cause of bias, given that small initial wounds tend to heal better [24]. Earlier studies investigating placebo interventions (placebo acupuncture, placebo surgery) showed that – merely due to the expectation of receiving an intervention – PROs in the placebo group, in terms of pain and quality of life in particular, were not inferior to those in the IG [25, 26]. As regards the secondary endpoints (average pain levels during the day and during dressing changes, anxiety and depression), there was no evidence of significant changes in either group (Table 2) between baseline and the post-intervention period. This may indicate that the effects of the intervention had more specific impact on the wound and wound-related quality of life than at patients’ psychological burden. The lack of effect on pain levels may seem surprising. However, with an average pain level during the day of 1.4 in the IG and 2.4 in the CG (Tables 1, 2) on an 11-point NRS, pain levels in this study were comparatively low overall. This suggests a kind of “floor effect” that prevents the intervention from significantly reducing the scores any further. It is also conceivable that – unlike disorders associated with chronic pain – placebo interventions may have less of an impact on pain in patients with chronic venous leg ulcers. Potential effects on psychological burden and pain levels associated with chronic venous leg ulcers should be investigated in future studies with sufficient statistical “power”. Subsequent studies should be conducted to assess the stability of these effects over a longer follow-up period. Furthermore, patients with other types of chronic wounds should be included to verify the general validity of our findings.

The “sham intervention” used in the present study yielded positive effects on the primary endpoints in terms of PROs. Both groups showed a significant reduction in median wound area (Table 2). Interestingly, patients in the IG experienced a significant reduction in wound area already after six weeks, which was not observed in the CG. However, these effects are most likely due to the complex wound therapy the patients received and must be distinguished from any expectation-induced effects. Patients in the IG experienced significant improvement in wound-related quality of life (the most important PRO) at the end of the intervention period, both in terms of the overall wound-QoL score and in the subscales. By contrast, no significant change in quality of life was observed in the CG.

A recent review article that included 18 moderate-to-high quality studies (out of 5,168 publications) of patients with chronic diseases revealed that a positive or negative attitude of SOs (significant others, i.e., partners, family members, relatives, and friends) towards work participation has corresponding effects on these patients. If – as in our study – there is an increase in quality of life, the interaction with SOs may become easier, thus facilitating patients’ integration into everyday (work) life [27]. Even though in our cohort (mean age in the 7th decade) reintegration into professional life may not play a major role, integration into everyday life as a result of improved quality of life is a fundamental aspect of patients’ well-being.

Conclusions

Scientific clinical studies on placebo responses have shown that the mechanisms controlling these responses may be specifically used to optimize the effectiveness of pharmacological interventions as well as other medical treatments. To date, there have been no clinical trials investigating the effects placebo interventions have on wound healing. Our study is the first to demonstrate that the mere expectation of receiving an intervention significantly improves wound-related quality of life in patients with chronic venous leg ulcers. In the future, these findings should be integrated not only into training and CME curricula for health care professionals but also in the care of patients with chronic wounds in order to improve their quality of life. In particular, this relates to interpersonal interactions and discussions between patients and health care providers.

References

1. Dissemond J, Bültemann A, Gerber V et al. Definitionen für die Wundbehandlung. Hautarzt 2016; 67: 265–6.
2. Dissemond J, Körber A, Grabbe S. Differentialdiagnosen des Ulcus cruris. J Dtsch Dermatol Ges 2006; 4: 627–34.
3. Kiecolt-Glaser JK, Marucha PT, Malarkey WB et al. Slowing of wound healing by psychological stress. Lancet 1995; 346(8984): 1194–6.
Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol 2005; 5(3): 243–51.

Ader R, Mercurio MG, Walton J et al. Conditioned pharmacotherapeutic effects: a preliminary study. Psychosom Med 2010; 72(2): 192–7.

Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? Nat Rev Drug Discov 2013; 12: 191–204.

Schedlowski M, Enck P, Rief W, Bingel U. Neuro-bio-behavioral mechanisms of placebo and nocebo responses: Implications for clinical trials and clinical practice. Pharmacol Rev 2015; 67: 697–730.

Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. Nat Rev Neurosci 2015; 16: 403–18.

Klinger R. The potential of the analgetic placebo effect — S3-guideline recommendation on the clinical use for acute and perioperative pain management. Anesthesiol Intensivmed Notfallmed Schmerzther 2010; 45: 22–9.

Evers AW. Using the placebo effect: how expectations and learned immune function can optimize dermatological treatments. Exp Dermatol 2017; 26: 18–21.

Goebel MU, Meykadeh N, Kou W et al. Behavioral conditioning of antihistamine effects in patients with allergic rhinitis. Psychother Psychosom 2008; 77(4): 227–34.

Vits S, Cesko E, Benson S et al. Cognitive factors mediate placebo responses in patients with house dust mite allergy. PLoS One 2013; 8(11): e79576.

Hadamitzky M, Sondermann W, Benson S, Schedlowski M. Placebo effects in the immune system. In: Colloca L (ed.). Neurobiology of the placebo effect. Int Rev Neurobiol 2018; 138: 39–59.

Sölle A, Bartholomäus T, Worm M, Klinger R. How to psychologically minimize scratching impulses benefits of placebo effects on itching using classical conditioning and expectancy. Z Psychol 2014; 222(3): 140–7.

vonLaahrhoven AIL, van der Smaan-Mauriks IM, Donders ART et al. Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. J Invest Dermatol 2015; 135: 1234–43.

Blome C, Baade K, Debus E et al. The “Wound-Qol”: a short questionnaire measuring quality of life in patients with chronic wounds based on three established disease-specific instruments. Wound Repair Regen 2014; 22(4): 504–14.

Herrmann-Lingen C, Buss U, Snaith R. Hospital anxiety and depression scale – German Version. Huber Verlag, Bern 2005.

Larbig W, Fallert B, de Maddalena H. Tumorschmerz: Interdisziplinäre Therapiekonzepte. 2. Auflage, Schattauer Verlag, 2002: 186–7.

Kaptchuk TJ, Kelley JM, Conboy LA et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ 2008; 336: 999–1003.

Petrie KJ, Rief W. Psychobiological mechanisms of placebo and nocebo effects: Pathways to improve treatments and reduce side effects. Annu Rev Psychol 2019; 70: 599–625.

Walterburn J, Vedhara K, Hankins M et al. Psychological stress and wound healing in humans: a systematic review and meta-analysis. J Psychosom Res 2009; 67: 253–71.

Vits S, Dissemond J, Schadendorf D et al. Expectation-induced placebo responses fail to accelerate wound healing in healthy volunteers: results from a prospective controlled experimental trial. Int Wound J 2015; 12: 664–8.

Margolis DJ, Berlin JA, Strom BL. Which venous leg ulcers will heal with limb bandages? Am J Med 2000; 109: 9–15.

Moseley JB, O’Malley K, Petersen NJ et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002; 347(2): 81–8.

Snippen NC, de Vries HJ, van der Burg-Vermeulen SJ et al. Influence of significant others on work participation of individuals with chronic diseases: a systematic review. BMJ Open 2019; 9(1): 021742.