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Observational Study to Assesses the Efficacy and Safety of Microcurrent Therapy with a Portable Device in Patients Suffering from Chronic Back Pain, Skeletal System Pain, Fibromyalgia, Migraine or Depression

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Purpose: In Germany, there are several microcurrent medical devices that are certified for the treatment of patients suffering from one of the indications chronic back pain, skeletal system pain, fibromyalgia, migraine or depression. While certification is based on controlled, randomized clinical trials, evidence of efficacy and safety under real-world conditions is limited to very few observational studies. To fill this gap, this study was conducted.

Patients and Methods: Fifty patients per indication already using the investigational device before study entry were included and followed for a total 6 months. Each participant used the Healy in an individualized schedule to optimize the treatment of his/her special indication. This means that each participant performed on average 1–2 microcurrent applications per day for 20 to 30 minutes each. In all indications, the improvement of health-related quality of life was assessed by the SF-36 questionnaire and other validated indication specific surveys.

Results: In all indications, the improvement of health-related quality of life as assessed by the SF-36 questionnaire was statistically highly significant and clinically relevant. These findings were supported by more specific outcome measures applied in each indication. Only four adverse events related to the application of microcurrent occurred during the trial.

Conclusion: Microcurrent therapy has been demonstrated to be efficient and safe under real-world conditions for the treatment of each of the conditions for which the device is certified.

Keywords: microcurrent therapy, pain, anxiety, sleep disturbances

Introduction

Microcurrent therapy, also known as microcurrent electrical neuromuscular stimulation (MENS), involves the application of low-level electrical currents to specific areas of the body for therapeutic purposes. It has a history that spans several decades.

In the 19th century, scientists such as Luigi Galvani and Alessandro Volta made significant discoveries in the field of bioelectricity.¹ They found that low-level electric currents can trigger muscle contractions in animals and proved that electric currents exist in living organisms.

In the late 19th and early 20th centuries, electrotherapy became a popular medical treatment for various conditions.² Devices such as the faradic battery, which produced electrical currents for therapeutic use, were developed and used by physicians.

Based on animal experiments and clinical investigations in the second half of the 20th century, the neurophysiological mechanisms of microcurrent therapy were elucidated in more detail.²

In the 1970s, Dr. Thomas Wing, an American physician, developed the concept of microcurrent therapy.³ He discovered that extremely low-level electrical currents, in the range of millionths of an ampere (microamperes), could effectively treat pain and promote healing in tissues.

Over the years, researchers and practitioners made significant advancements in microcurrent therapy. They developed more sophisticated devices that can deliver precise and controlled microcurrents to target specific tissues and conditions.

In the 1990s, the United States Food and Drug Administration (FDA) approved microcurrent devices for the treatment of various medical conditions, including pain management, wound healing and muscle rehabilitation.

Carolyn McMakin⁴ provided an in-depth understanding of the FSM (Frequency Specific Microcurrent) technique and its applications. Her work has also significantly contributed to the education and training of healthcare professionals in the field of microcurrent therapy.

In recent years, there has been an increase in the availability of microcurrent devices for home use. These portable devices allow individuals to self-administer microcurrent therapy for pain relief and other therapeutic purposes.

The exact mode of action of microcurrent therapy is not yet fully understood, and research in this area is still ongoing. Several theories have been proposed to explain how microcurrent therapy may exert its therapeutic effects on the organism:

ATP Production: Microcurrent therapy may enhance the production of adenosine triphosphate (ATP) within the cells.^{5,6} ATP is the energy currency of the body, and increased ATP levels can promote cellular metabolism and facilitate tissue repair processes.

Cellular Communication and Signaling: Microcurrents applied to the body may stimulate cell-to-cell communication and enhance intercellular signaling.^{7,8} This can influence various physiological processes, including pain modulation, inflammation reduction and tissue regeneration.

Electrochemical Effects: The electrical currents delivered during microcurrent therapy can alter the electrochemical environment in the tissues.^{9,10} This can affect ion exchange, pH levels and cell membrane potential, leading to changes in cellular activity and function.

Blood Flow and Circulation: Microcurrent therapy has been suggested to enhance blood flow and microcirculation in the treated area.^{11,12} Improved circulation can promote the delivery of oxygen, nutrients and immune cells to the tissues, supporting healing and reducing inflammation.

Neurological Effects: Microcurrents may have direct effects on the nervous system, influencing nerve conduction, reducing pain signals and promoting neuromuscular function.^{13,14} This can be beneficial in pain management and muscle rehabilitation.

Modulation of Cellular Processes: Microcurrent therapy may modulate various cellular processes, such as protein synthesis,^{15,16} gene expression¹⁷ and enzymatic activity.¹⁸ These effects can contribute to tissue repair, regeneration and modulation of inflammatory responses.

It is important to note that the exact mode of action may vary depending on the specific condition being treated and the parameters of the microcurrent therapy applied, such as frequency, waveform and intensity. Additionally, different mechanisms may work synergistically to produce the therapeutic effects observed in microcurrent therapy.

Several microcurrent devices similar to the Healy device have successfully been used in clinical trials to demonstrate the efficacy and safety of microcurrent therapies for different indications:

Pain Management: Numerous studies have investigated the use of microcurrent therapy for pain management.^{18–57} Research has shown positive results in various conditions, such as fibromyalgia, osteoarthritis, skeletal system pain and postoperative pain.

Anxiety and Depression: Microcurrent therapy has been studied as a non-invasive treatment option for anxiety and depression.^{58–78} Clinical trials have demonstrated benefits in reducing symptoms and improving overall mood.

Insomnia and Sleep Disorders: Some research has explored the use of microcurrent therapy for sleep disorders and insomnia.^{79,80} Studies have shown improvements in sleep quality and duration.

The Healy device has the same clinical, technical and biological properties as the devices used in these studies and is CE marked since 2017.

In this study, the Healy device was used solely within its approved intended use, including the following indications: chronic back pain, skeletal system pain, fibromyalgia, migraine and depression, anxiety and associated sleep disorders.

An observational period of 6 months and a total study population of 250 participants (50 participants per indication) were assumed to be sufficient to achieve reliable results concerning the treatment's efficacy and safety. Because this was an observational trial designed to collect data on normal use of the Healy device, participants were asked to use the device according to their needs and indications.

Materials and Methods

Design

The study was a monocentric observational post market follow-up study with a treatment duration of six months, with measurement points at the beginning (V1), after 28 days (V2), after 3 months (V3) and at the end of the study after 6 months (V4). A study protocol was established before recruitment began. Participants were recruited via an existing network of persons interested in this type of treatment and suffering from one of the approved indications (chronic back pain, skeletal system pain, fibromyalgia, migraine and depression, anxiety and associated sleep disorders). The confirmation of the diagnosis (indication) was diligently carried out by the therapist through a pre-screening, following the rules of the professional code of conduct for non-medical practitioners (BoH). Because of the corona virus situation at baseline, all study visits were conducted remotely.

Written informed consent was obtained from participants before undertaking the screening and baseline assessments. The trial received research ethics committee approval from the International Medical & Dental Ethics Commission (IMDEC) prior to including the first participant into the study (Ethics committee approval reference No. 2021/117).

This study was conducted according to the principles outlined in the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.⁸¹

Participants

All participants were already using the investigational microcurrent device for at least three months at the time of study entry for the treatment of one of the five indications mentioned above. They gave written informed consent to participate prior to any study-related procedure. Volunteers were excluded if they were younger than 18, older than 70 years, pregnant, had a pacemaker or any other electronic or metallic device at or near the place of application on the body, open wounds, scar tissue or insensitivity or radiation therapy near the place of application, or a history of epilepsy.

Treatment Device

For application of individualized frequency modulated microcurrent applications, the investigational device (Healy device) was to be attached to the body via adhesive electrodes, ear clips or bracelet electrodes and cables on various places depending on the program and objective (see [Figure 1](#), Healy application for chronic back pain).

Healy uses frequencies from 0.1 Hz to 1 MHz. It applies an electrical current between 0 μ A and 4000 μ A. The maximum applied voltage is 10 V.

Treatments Administered

Each participant used the Healy in an individualized schedule to optimize the treatment of his/her special indication. This means that each participant performed on average 1–2 microcurrent applications per day for 20 to 60 minutes each. The frequency pattern of these applications was designed by experienced therapists, not involved in any study-specific procedures.

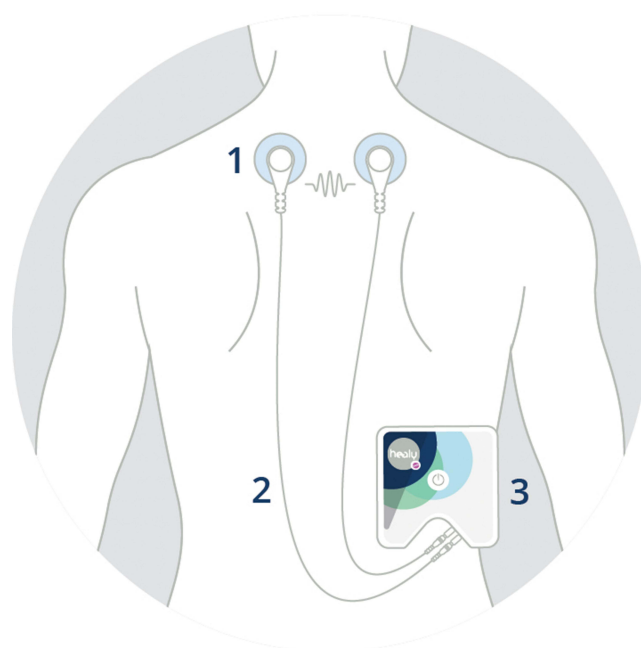


Figure 1 Example of the application of the investigational medical product (Healy device); 1: Adhesive electrodes, 2: Cables, 3: Healy device.

Outcome Measurements

SF 36

Scoring the SF 36-Item Health Survey is a two-step process. First, pre-coded numeric values are recoded according to the scoring key.^{82–84} All items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a scale from 0 to 100, so that the lowest and highest possible scores are 0 and 100, respectively. The score indicates the percentage of the total possible score. In step 2, the items in the same scale are averaged to create the 8 scale scores. Items in which one or more answers are left blank (missing data) are not considered when calculating the scale scores. Thus, the scale scores represent the average for all items in the scale that the respondent answered.

After the eight scale scores are calculated, a z-score is determined for each by subtracting the scale mean of a sample of the US general population from an individual's scale score and then dividing by the standard deviation from the US general population. Each of the eight z-scores is then multiplied by the corresponding factor scoring coefficient for the scale.^{85,86} There are two different sets of factor-scoring coefficients, one for the physical component summary (PCS) and another for the mental component summary (MCS). The products of the z-scores and factor scoring coefficients for the PCS are then summed together and a similar calculation is performed for the MCS. Each resulting sum is multiplied by 10 and added to 50 to linearly transform the PCS or MCS to the T-score metric, which has a mean of 50 and a standard deviation of 10 for the US general population.

Pain Assessment Score (Valid for Chronic Back Pain and Skeletal System Pain)

Pain Scores were assessed by three 10-point Likert scales (average pain, maximal pain, current pain).^{87,88} The assessment is carried out by the patients themselves. Pain scores were evaluated at each study visit starting with the baseline visit according to the following verbal descriptive endpoints of the scale:

0 = no pain at all; 10 = unbearable pain

Severity of Migraine Assessment (MiDAS; Only Valid for the Indication “Migraine”)

The severity of migraine was assessed by use of the Migraine Disability Assessment (MiDAS) questionnaire. The MiDAS Questionnaire was developed to assess headache-related disability with the aim of improving migraine care.^{89–91} Headache sufferers answer five questions, scoring the number of days, in the past 3 months of activity limitations due to migraine. All assessments were carried out by the patient using various questionnaires. Scores were evaluated at each study visit starting with the baseline visit.

Mental Illness Assessment (Valid for Indications “Fibromyalgia” and “Depression” Only)

In terms of mental illness, several rating scales were used. All assessments were carried out by the patient using various questionnaires. Scores were evaluated at each study visit starting with the baseline visit.

Based on a recent study performed by the RKI in Germany,⁹² the Patient Health Questionnaire (PHQ 9)⁹³ is a suitable instrument to assess the severity of depression symptoms.

It consists of 9 questions measuring the frequencies of depression-related complaints during the previous 14 days by use of a 4-point Likert scale:

Not at all, On single days, On more than half of the days, On almost every day.

Anxiety Assessment (Valid Only for the Indications Fibromyalgia and Depression)

Anxiety is measured according to GAD-7 anxiety severity.^{94,95} Scores are dependent on frequency of symptoms (0: not at all / 1: several days / 2: more than half the days / 3: nearly every day).

Sleep Quality (Valid for Indications “Fibromyalgia” and “Depression” Only)

Insomnia severity was measured according to Insomnia Severity Index (ISI), based on 7-point questionnaire.^{96,97} Total score categories are defined as follows.

- 0–7 no clinically significant insomnia
- 8–14 subthreshold insomnia
- 15–21 clinical insomnia (moderate severity)
- 22–28 clinical insomnia (severe)

Statistics

Efficacy Analysis

All efficacy variables were listed by subject. Data was summarized by treatment group. N, Mean, Standard Deviation, Minimum and Maximum were used to summarize continuous efficacy variables, whereas number and percent were used to summarize categorical efficacy variables.

All analyses of the continuous efficacy variables (eg, pain score) were performed as analysis of variance for repeated measurements. In case Mauchly tests for sphericity yielded departure from sphericity, Greenhouse-Geisser and Huynh-Feldt corrections were performed. All indications were tested at the two-sided 5% significance level.

To confirm test results in case of severe deviations from sphericity, additional non-parametric tests (Friedman test) were performed.

For group comparison of total effect sizes (differences between final and baseline values), covariance analysis was performed with baseline adjustments.

Safety Analysis

All newly occurring diseases and deterioration of existing diseases were recorded as adverse events. All adverse events were listed by study participants as recorded and as coded according to the ICD-10 classification. Incidences of Adverse Events (AEs) per organ class and group and incidences of AEs assessed as potentially induced by the study procedure were listed and compared with incidence rates in comparable populations.

Results

Demographics

The first screening was performed in June 2021, the first subject was included (date of IC signature) on 30th June 2021. Screening was completed in August 2022; the last subject was included on 11th August 2022. The last patient completed the clinical part of the study (last patient out) on Jan 13, 2023.

Of the 317 potential participants screened for study participation, 256 persons signed the informed consent form and were included into one of the five indication groups. Seven of these included participants terminated the study prior to

performing any study-related procedure (no survey completed, no study visit performed), resulting in 249 participants with study-related data.

Five participants terminated the study prematurely between visit 1 and visit 4, resulting in 244 study completers. Forty-eight participants were diagnosed with chronic back pain or migraine, respectively, 49 with skeletal system pain and fibromyalgia and 50 with depression, anxiety and associated sleep disorder.

Two hundred and twenty female patients and 29 male patients were included in the study. Two hundred and forty-seven patients were Caucasians, 2 Asians. The average age of the complete full analysis set was 51.3 years, average height was 1694 cm, average weight 73.3 kg (Table 1).

Table 1 Summary of Demographic Data, All Study Participants and Participants Suffering from the Different Indications, Mean Values and Standard Deviation in Brackets. Second Line Minimum and Maximum

Complete Population	Female	Male	Total
Participants	220	29	249
Ethnicity Caucasian	218	29	247
Asian	2	0	2
Age [years]	51.33 (8.90)	50.65 (9.51)	51.25 (8.95)
	23–68	35–68	23–68
Weight [kg]	72.07 (16.93)	82.72 (8.93)	73.31 (16.55)
	47–153	65–110	47–153
Height [cm]	168.00 (6.12)	179.97 (5.85)	169.39 (7.19)
	150–187	169–192	150–192
Chronic back Pain			
Participants	38	11	49
Age [years]	53.42 (8.53)	49.45 (8.54)	52.53 (8.69)
	34–68	41–62	34–68
Weight [kg]	73.05 (14.80)	81.27 (10.48)	74.90 (14.52)
	52–120	65–110	52–120
Height [cm]	167.68 (4.44)	180.45 (6.08)	170.55 (7.14)
	159–176	169–191	159–191
Skeletal system pain			
Participants	43	7	50
Age [years]	54.95 (7.96)	59.71 (5.95)	55.62 (7.89)
	31–68	49–68	31–68
Weight [kg]	78.70 (22.22)	79.00 (4.90)	78.74 (20.68)
	49–153	72–85	49–153
Height [cm]	169.33 (6.68)	177.00 (3.30)	170.40 (6.86)
	158–185	175–182	158–185

(Continued)

Table 1 (Continued).

Fibromyalgia			
Participants	50	1	51
Age [years]	53.45 (6.93)	38.00 (0)	53.14 (7.20)
	36–67	38	36–67
Weight [kg]	73.94 (17.16)	79.00 (0)	74.04 (17.00)
	47–120	79	47–120
Height [cm]	167.14 (6.55)	180.00 (3.30)	167.40 (6.73)
	150–187	180	150–187
Migraine			
Participants	45	4	49
Age [years]	46.27 (8.55)	46.25 (8.47)	46.27 (8.54)
	23–67	37–57	23–67
Weight [kg]	67.44 (12.60)	90.00 (5.10)	69.25 (13.64)
	51–112	84–98	51–112
Height [cm]	168.20 (6.90)	182.25 (3.90)	169.35 (7.73)
	154–186	176–186	154–186
Depression			
Participants	44	6	50
Age [years]	48.84 (9.23)	47.33 (7.11)	48.66 (9.02)
	26–63	41–56	26–63
Weight [kg]	67.41 (12.77)	85.50 (7.78)	69.58 (13.62)
	49–100	80–100	49–100
Height [cm]	167.73 (5.19)	181.00 (7.35)	169.32 (6.99)
	158–180	172–192	158–192

Abbreviations: kg, kilogram, cm, centimeter.

Differences concerning the demographic data between the indication groups are small, with participants in the skeletal system pain group being slightly older (on average 55.62 years) and participants in the Migraine group being slightly younger (on average 46.27 years) than the total participants' average age.

Previous and Concomitant Diseases and Previous and Concomitant Therapies

Three hundred and eighty previous relevant diseases were reported in 165 patients.

Most prominent are diseases of the musculoskeletal system and connective tissue (116), endocrine, nutritional and metabolic diseases (59), diseases of the nervous system (38) and diseases of the circulatory system (36).

None of the recorded previous diseases fulfilled any of the exclusion criteria.

Three hundred and eighty-one previous and concomitant treatments were reported in 125 patients. All pharmacological treatments were coded according to the WHO drug dictionary, all non-pharmacological treatment were classified as “non-pharmacological”.

The most prominent medications were for diseases of the musculoskeletal system (64), alimentary tract and metabolism (53), respiratory system (41), treatments for diseases of the nervous system (41) and various others (51).

Beside these, 21 non-pharmacological treatments were reported, these are physiotherapy (8), orthopedic surgeries (3), rehabilitation facility stays (3), psychotherapy (2), hearing aids (1), acupuncture (1), ultrasound therapy (1), dental treatment (1), laser eye treatment (1).

None of the recorded previous treatments fulfilled any of the exclusion criteria.

Primary Endpoint: Quality of Life Assessment by SF-36 Questionnaire (All Indication Groups)

In all indication groups, the SF-36 total score steadily increased (Figure 2a). Repeated-measures ANOVA yielded highly significant results for both the overall time effect and the time effects within each individual indication group after Greenhouse-Geisser or Huynh-Feldt corrections for deviation from sphericity (Table 2). These results could be confirmed by non-parametric Friedman rank sum tests which were performed additionally because of departure from sphericity.

The highest daily increase (slope of the curve) could be found in all groups except the migraine group between the initial and the second study visit, whereas for migraine the highest improvement rate occurred between study days 28 and 84.

Group differences are due to the low baseline scores of the fibromyalgia (50) and depression (59) groups, in the other groups, the baseline value is about 65 scoring points.

The highest overall increases in SF-36 score occurred in the fibromyalgia and depression group (20 scoring points), whereas in the other groups the scores increased by about 12 points.

Group differences are caused due to differences in baseline values; after adjustment for baseline score, no significant differences could be detected (ANCOVA for group differences in final score with baseline adjustment, $Df = 4$, $F = 1.342$, $p = 0.2548$).

When separating the SF-36 score into a physical and a mental component, both scores increased steadily during the study (Figure 2b and c). For all but the mental component in the chronic back pain group, these increases are statistically significant (Table 2).

For the physical component, significant group differences (group effect of repeated-measure ANOVA with Greenhouse-Geisser correction for departure from sphericity; $DF = 4;241$, $F = 10.78$, $p < 2e-16$) were mainly due to the comparable lower increase in the depression group (about 4 scoring points) in comparison to the other groups (7–8 scoring points).

For the mental component, the situation is reversed; here significant group effects (group effect of repeated measure ANOVA with Greenhouse-Geisser correction for departure from sphericity; $DF = 4;241$, $F = 16.87$, $p < 2e-16$) are mainly due to the much higher increase in the depression group (about 16 scoring points), whereas the increases in the other groups were between about 3 (chronic back pain) and 9 scoring points (fibromyalgia).

The relative partitioning of both components mirrors its importance in the different indications: For the indication group with pain-related issues (back and skeletal system pain), the improvement of the physical component was dominant, whereas in the depression group the effect of the mental component is prevailing. In fibromyalgia and migraine both components improved to almost the same extent.

The increase in total score (12–20 scoring points) is at least twice as high as the minimal clinically important differences as limit to indicate clinical relevance; these are 5 scoring points.⁹⁸ For the physical component scale, in all indication groups but the depression group, the increase of the score (about 7 points) is higher than the mentioned limit for clinical relevance (4); for the mentioned component the fibromyalgia group (about 9) and the depression group (15), the increase was above the limit for clinical relevance (3.2).

Secondary Endpoints

In each of the five indications additionally to the generic SF-36 instrument at least one more specific assessment instrument was used for efficacy assessment. For chronic back pain (Figure 3a) and skeletal system pain (Figure 3b) a standardized pain

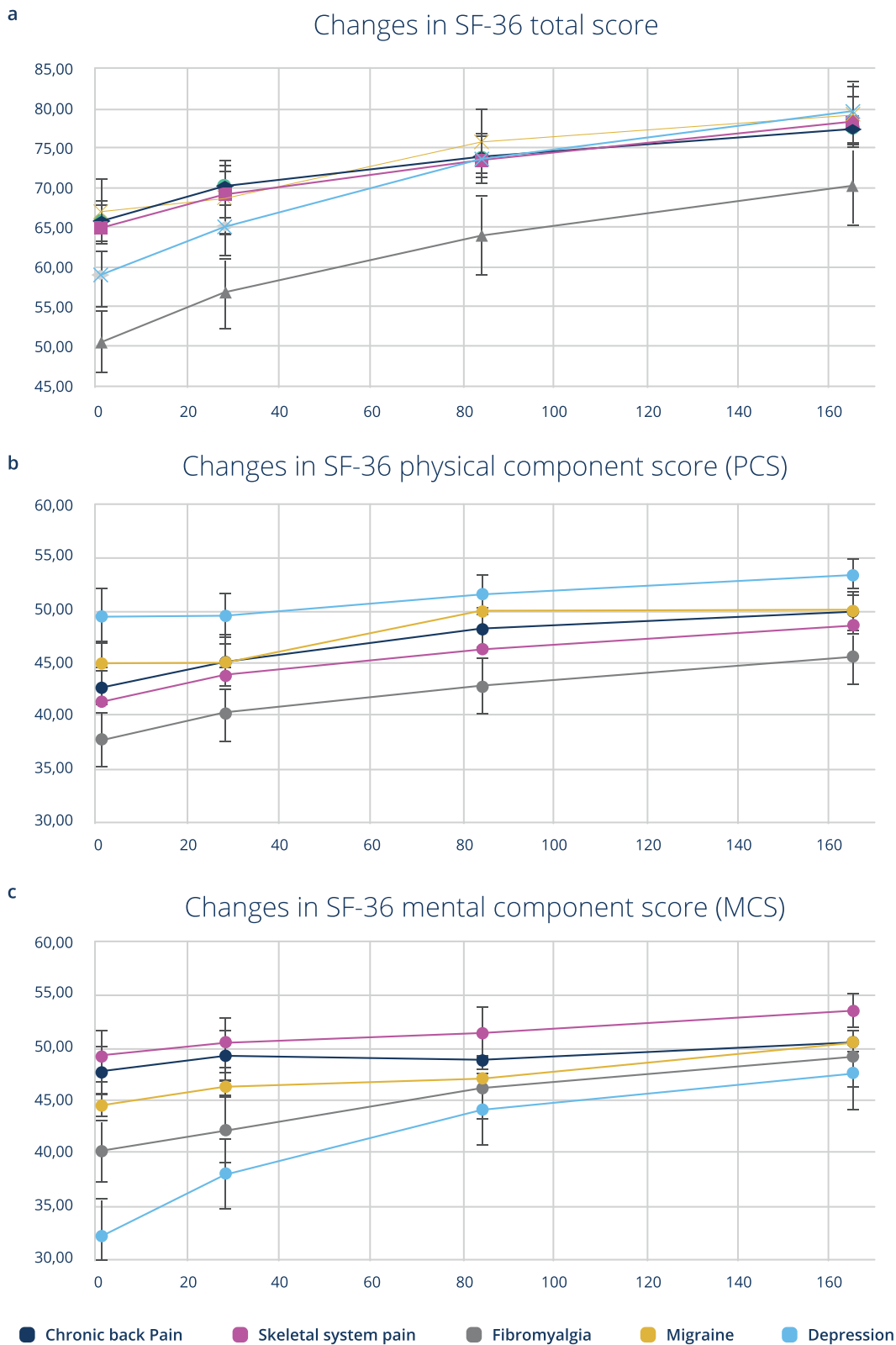


Figure 2 Temporal changes in quality of life as assessed by the patients; x-axis study day, y-axis SF-36 score; Mean values and 95% confidence interval in SF-36 total scores (a), physical component score (b) and mental component score (c).

Table 2 Results of Repeated Measurement ANOVA and Friedman Test of SF-36 Scores and Physical and Mental Components. Clinically Significant Results ($P < 0.05$) are Indicated in Bold

Parameter/Group	DF/Den DF	(Corrected ¹) F	Pr(>F)	Friedman Chi-Squared	Df	Friedman p value
Total Score						
All indications	3/720	106.38 ¹	<2e-16	262.21	3	<2.2e-16
Chronic back pain	3/141	9.67 ¹	0.000045111	32.319	3	0.0000004482
Skeletal system pain	3/147	9.49 ¹	0.000003415	38.903	3	0.0000000182
Fibromyalgia	3/141	46.488	<2.2e-16	69.539	3	5.359e-15
Migraine	3/144	12.125 ¹	0.0000000535	42.636	3	0.00000002941
Depression...	3/147	47.679	<2.2e-16	91.272	3	<2.2e-16
Physical Component Score						
All indications	3/735	61.61 ¹	<2.2e-16	169.47	3	1.66e-16
Chronic back pain	3/141	17.09 ¹	0.00000001269	42.908	3	0.00000002574
Skeletal system pain	3/147	8.99 ¹	0.000005854	38.241	3	0.00000002513
Fibromyalgia	3/144	23.239	2.51e-12	53.229	3	1.639e-11
Migraine	3/144	8.620 ¹	0.00001361	27.123	3	0.00000555
Depression...	3/147	6.26 ¹	0.0002411	21.192	3	0.00009604
Mental Component Score						
All indications	3/735	43.13 ¹	<2.2e-16	129.07	3	2.2e-16
Chronic back pain	3/141	0.90 ¹	0.2381 (ns)	7.334	3	0.06198 (n.s.)
Skeletal system pain	3/147	2.279 ¹	0.04659	9.0361	3	0.02881
Fibromyalgia	3/144	12.718 ¹	0.0000001453	37.09	3	0.00000004404
Migraine	3/144	6.8642 ¹	0.0002355	28.5	3	0.000002852
Depression...	3/147	57.561 ¹	<2.2e-16	83.328	3	2.2e-16

Notes: 1F value after Greenhouse-Geisser or Huynh-Feldt correction; in each case the correction method was deployed, which is delivering the most conservative results.
Abbreviation: ns, not significant.

assessment instrument was used, for fibromyalgia (Figure 3c) and depression (Figure 3d) anxiety severity was measured by use of GAD7, insomnia severity by use of ISI and for severity of depression the PHQ9 instrument was used. Migraine severity was assessed by the MiDAS questionnaire in the respective indication group (Figure 3e).

In both pain groups, the chronic back pain and the skeletal system pain group, pain intensity dropped steadily from moderate intensity (>4) at baseline by almost 2 scoring points. Final values are within the range of mild intensity. This effect is statistically highly significant (Table 3) and clinically relevant.^{99,100}

For anxiety severity (GAD-7),^{101,102} severity of depression symptoms (PHQ-9)^{101,103} and insomnia severity (ISI)^{96,104} the decline in scores during the study is both highly significant (Table 3) and clinically relevant in the fibromyalgia and the depression group.

In the migraine group, no relevant changes in total MiDAS score, consisting of 5 categories asking for days of impairment during the previous three months, could be detected during the study.^{105,106} The indicated number of days of impairments declined marginally from visit 1 to visit 2, remains unchanged up to visit 3 and then slightly increased again. These changes were statistically not significant ($p = 0.5777$ for repeated measure ANOVA after Greenhouse-Geisser correction; 14.2.4).

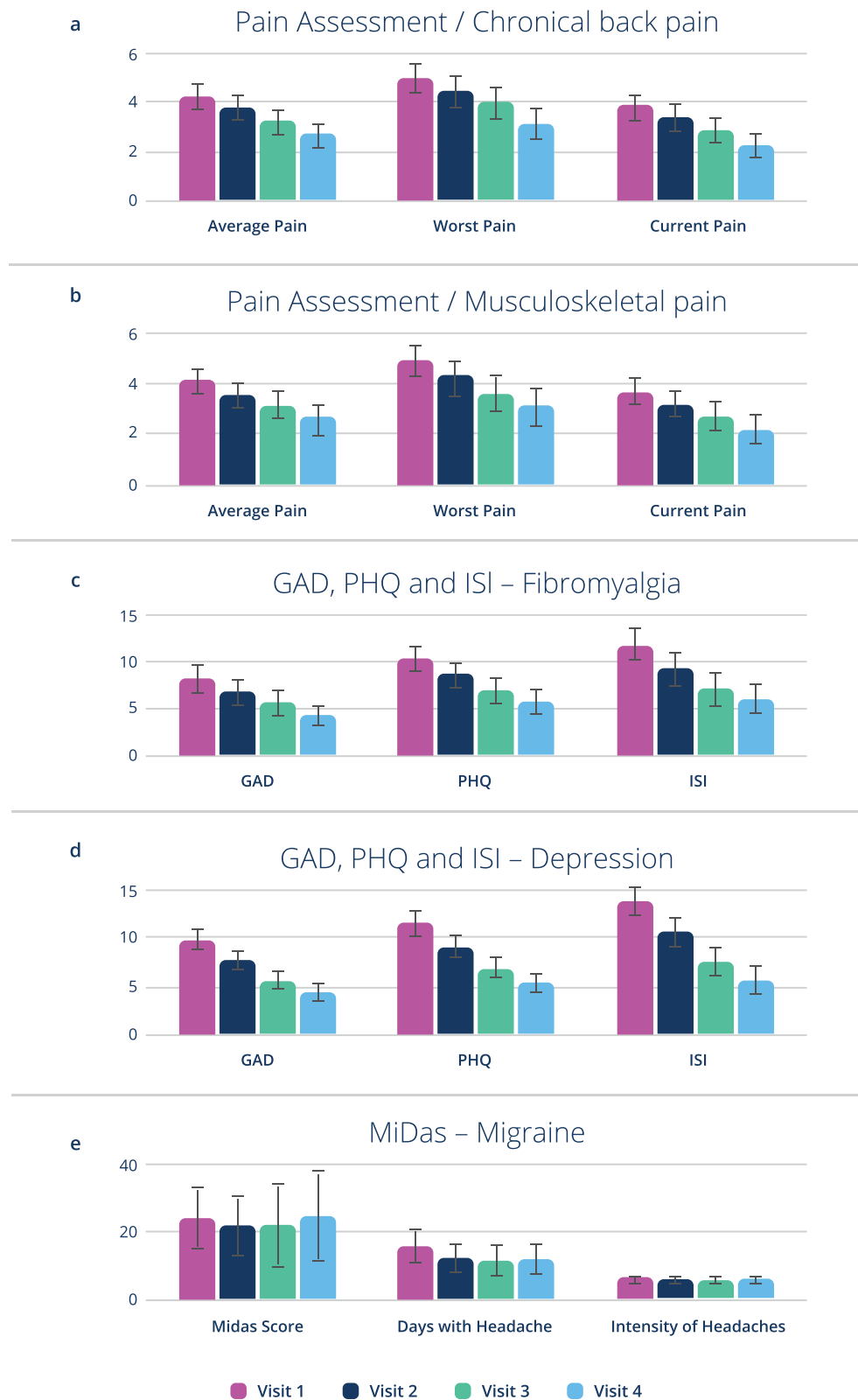


Figure 3 Changes in secondary endpoint variables during the study: Pain Assessment Score for chronic back pain (a) and skeletal system pain group (b); Mental Illness Assessment (PHQ 9), Anxiety assessment (GAD-7), Sleep quality (ISI) valid for indications fibromyalgia (c) and depression (d) only; MiDas in the migraine group (e) only; Mean values and 95% confidence interval.

Table 3 Results of Repeated Measurement ANOVA and Friedman Test of Secondary Endpoints, Pain Assessment Score for the Chronic Back Pain and Skeletal System Pain Group, Generalized Anxiety Disorder (GAD-7), Patient Health Questionnaire for the Assessment of Depression Severity (PHQ-9) and Insomnia Severity Index (ISI) for Fibromyalgia- and Depression Groups and Migraine Disability Assessment Score (MiDAS) for the Migraine Group. Clinically Significant Results ($P < 0.05$) are Indicated in Bold

Parameter/Group	DF/Den DF	(Corrected ¹) F	Pr (>F)	Friedman Chi-Squared	Df	Friedman p value
Pain Assessment score / Chronic back pain						
Average pain	3/138	18.445	4.042e-10	37.860	3	0.0000003027
Maximum pain	3/138	16.574	0.00000002973	34.102	3	0.0000001885
Current pain	3/141	13.504 ¹	0.0000001086	29.166	3	0.000002066
Pain Assessment score / Skeletal system pain						
Average pain	3/141	10.86 ¹	0.00000118	45.418	3	7.542e-10
Maximum pain	3/141	8.629 ¹	0.00001717	28.578	3	0.000002747
Current pain	3/141	146.29 ¹	0.000001047	50.500	3	6.252e-11
Generalized Anxiety Disorder (GAD), Patient Health Questionnaire-9 (PHQ) and the Insomnia Severity Index (ISI) / Fibromyalgia						
GAD-7	3/147	13.551 ¹	0.0000005076	47.59	3	2.603e-10
PHQ-9	3/147	19.016 ¹	1.444e-10	57.847	3	1.695e-12
ISI	3/147	15.514 ¹	0.00000001206	40.137	3	0.00000009966
Generalized Anxiety Disorder (GAD), Patient Health Questionnaire-9 (PHQ) and the Insomnia Severity Index (ISI) / Depression						
GAD-7	3/147	37.001 ¹	<2.2e-16	80.744	3	<2.2e-16
PHQ-9	3/147	37.901	<2.2e-16	75.058	3	3.522e-16
ISI	3/147	40.392 ¹	<2.2e-16	80.489	3	<2.2e-16
Migraine Disability Assessment Score (MiDAS) / Migraine						
MiDAS Score	3/138	0.216 ¹	0.5777 (n.s)	9.6042	3	0.02225
Days with Migraine	3/138	3.416 ¹	0.004284	12.542	3	0.005739
Pain Intensity	3/138	1.952 ¹	0.04061	11.27	3	0.01035

Notes: 1: F value after Greenhouse-Geisser or Huynh-Feldt correction; in each case the correction method was deployed, which is delivering the most conservative results (highest correction factor).

Abbreviation: ns, not significant.

Numbers of days with headache declined slightly during the first study period and thereafter stayed almost constant until study completion. The decline in the first study period was statistically significant ($p = 0.004$).

For pain intensity, a slight, but significant decline by only 0.7 assessment points could be observed ($p = 0.04$), mainly in the first 3 study months (up to visit 3).

Safety Evaluation

In total, 246 adverse events occurred in 161 participants of the safety data set (256 participants who signed the informed consent form).

Most frequent AEs were related to COVID-19 (88), the respiratory system (54), the musculoskeletal system and connective tissue (23) and diseases of the digestive system.

A listing of the frequency of AEs per ICD10 class is given in [Table 4](#).

Seventeen adverse events occurred after the person signed the informed consent form but prior to Visit 1.

Table 4 Adverse Events According to ICD-10 Class Assignment in Descending Order According to the Frequencies

Frequency	ICD-10 Class	ICD-10
88	COVID-19 in the patient's own history	U08
54	Diseases of the respiratory system	J
23	Diseases of the musculoskeletal system and connective tissue	M
15	Diseases of the digestive system	K
11	Injuries to unspecified parts of the trunk, extremities, or other body regions, burns - (7) Complications of surgery and medical treatment, not elsewhere classified - vaccination side effect - (4)	T
10	Diseases of the nervous system	G
9	Certain infectious and parasitic diseases	A
7	Diseases of the urogenital system	N
6	Viral infections	B
5	Symptoms and abnormal clinical and laboratory findings not elsewhere classified	R
4	Neoplasms	C
4	Diseases of the eye and eye appendages	H
3	Diseases of the blood and blood-forming organs and certain disorders involving the immune system	D
2	Mental and behavioral disorders	F
2	Diseases of the skin and subcutaneous tissue	L
2	Diseases of the circulatory system	I
1	Congenital malformations, deformities and chromosomal anomalies	Q
1	Persons using the health care system for the purpose of specific measures and medical care	Z

All these pre-study AEs were assessed as being not related to the Healy device electrostimulation.

In total 230 adverse events occurred during the study, after visit 1.

In total 12 serious adverse events (SAEs) occurred in 12 different participants during the study (Table 5). All were resolved during the study. The severity of these SAEs was assessed as being “mild” in 2 cases, “moderate” in 2 cases and “severe” in 8 cases. For all events, at least one treatment was applied. None of the SAEs was related to the application of electrostimulation by the Healy device. The intensity of most AEs was assessed as mild (199), 22 were assessed as being of moderate intensity, 9 AEs were severe.

Two hundred and twenty-six AEs were assessed as being not related to the Healy electrostimulation; 4 AEs as related to the electrostimulation with the Healy device.

The average incidence of AEs is slightly higher than the average incidence of diseases within a comparable population of persons not suffering from chronic diseases in Germany during the COVID-19 pandemic.¹⁰⁷

Four adverse events in total, all non-serious, were assessed to be related to the Healy device. In 2 cases, the electrostimulation induced additional pain of mild intensity, the other 2 events were adverse skin reactions. The respective conditions are mentioned in the current Healy Instructions for Use as potential side effects of Healy electrostimulation. In 2 of the 4 cases, the respective AEs are the cause of premature study termination.

Discussion

For all indications, most commonly fibromyalgia, the baseline values of the SF-36 scores are below the average values of a comparable population collected in a large survey in Germany.¹⁰⁶ This, along with the fact that values increased most

Table 5 Serious Adverse Events per Patient

SIC/ Pat#	As Reported by the Investigator	As Coded	ICD- 10	Start Date	Resolution Date	Intensity	Relation to Device	Treatment
1	Cervical cancer	Cervical Cancer	C53	03.12.2021	03.03.2023	Severe	No	Yes
7	Lymphoedema leg right	Erysipelas	A46	25.08.2021	30.09.2021	Mild	No	Yes
10	White skin cancer on left nostril	Skin cancer	C44	20.10.2021	27.09.2022	Severe	No	Yes
30	Ovariectomy right;	Ovarian Cyst	D27	26.02.2022	27.02.2022	Severe	No	Yes
51	Surgery of the left breast	Breast correction after cancer	Z41	23.11.2021	27.11.2021	Severe	No	Yes
58	Nasal surgery: 3 days in hospital	Breathing difficulties	Q30	10.02.2022	13.02.2022	Severe	No	Yes
77	Nausea, diarrhea,	Gastro-intestinal infection	A09	16.11.2021	30.11.2021	Severe	No	Yes
118	Multiple sclerosis acute episode	Multiple sclerosis	G35	16.02.2022	30.04.2022	Severe	No	Yes
148	Palate seam dilation	Toothache/Tooth problems	K08	05.04.2022	10.04.2022	Severe	No	Yes
163	Covid positive, in hospital	COVID-19	U08	11.03.2022	21.03.2022	Mode- rate	No	Yes
171	Lid lifting both sides surgery,	Amblyopia	H53	03.05.2022	05.05.2022	Mild	No	Yes
194	Migraine	Headache/Migraine	G44	24.11.2022	24.11.2022	Mode- rate	No	Yes

during the first phase of the study, makes it clear that participants were using microcurrent therapy rather sub optimally before the study began. The consultation with the investigator at the beginning of the study, together with increased motivation, obviously leads to a better and possibly more frequent use of the investigated microcurrent therapy.

During the first month of study, SF-36 scores as measure for the health-related quality of life initially increased sharply. After the first 2 visits, this increase flattened out, but continued until the end of the study. At this time, for all subclasses except fibromyalgia, the level of a healthy comparison population was reached,¹⁰⁸ whereas for fibromyalgia, the final values were slightly lower.

The same pattern as described for SF-36 was also detected for pain assessment in the chronic back pain and skeletal system pain group, for Generalized Anxiety Disorder (GAD), Patient Health Questionnaire (PHQ) and Insomnia Severity Index (ISI) in the fibromyalgia and depression group. After a large improvement, scores in these cases continued to decline to a lesser extent during the initial phase of the study (up to the second visit) until the conclusion of the study.

This is clear evidence of the effectiveness of the therapy under investigation. The low baseline values and the gradual improvements in the first 4 study weeks may indicate that optimization of the Instructions for Use and better support channels are required to safeguard the optimal use of the device, also under non-study conditions.

Except for the MiDAS score for all parameters measured during the study, almost the same pattern of score improvement could be detected: Starting from baseline values within a range indicating at least moderate impairment,¹⁰⁹ the levels improved markedly until study completion. At the end of the study, the respective levels were within the range of a comparable healthy population (for SF-36) or improved by at least one degree in severity, eg, from moderate impairments to mild impairments for GAD in the fibromyalgia and depression group. These effects are clinically significant, and the changes are evidently above the levels for Minimum Clinically Important Differences (MCID, for values and sources see Table 6).

Table 6 Minimum Clinically Important Differences as Mentioned in Scientific Publications

Instrument	Minimum Clinically Important Differences (Scoring Points)	Reference Number
SF-36	5.0 10.0	[98] [110]
Pain Assessment Score	0.8–2.0 1.5–1.8	[99] [100]
GAD-7	3.3 4.0	[101] [102]
PHQ-9	3.7 3.0	[101] [103]
ISI	8.4 6.0	[96] [104]
MIDAS	4.5 5	[105] [106]

The Minimum Clinically Important Difference (MCID) represents the smallest improvement considered worthwhile by a patient. This concept is offered as the new standard for determining effectiveness of a given treatment and describing patient satisfaction in reference to that treatment.¹¹¹ The patient-centered approach of MCID has some shortcomings in terms of methods of determination, but is still a standardized measure of therapy success.

For the MIDAS total score, no improvements could be detected within the complete study. This may be caused by the fact that this instrument refers to changes within a 3-months period, resulting in some overlapping and in some difficulties in reporting reliable values.

Despite this methodical issue, for the migraine group a positive effect could be detected as well, as assessed by the SF-36 instruments and the additional MIDAS questions asking for days with headache (improvement by 4 days per period) and intensity of headache (improvement by 0.7 scoring points).

Cohen's approach^{112,113} to determine the effect size calculates the ratio of the difference between the group means and the value dispersion. Values less than 0.5 are considered small (unhedged) effects. Values between 0.5 and 0.8 are considered medium and values greater than 0.8 are considered strong effects. According to this classification, there are strong effects for the changes in all parameters in this observational study, except for MIDAS, as further evidence of the effectiveness of Healy electrostimulation. For MIDAS, the values are in the range of unhedged effects. It is possible that for this instrument neither the number of participants nor the length of the observational period was sufficient to detect any positive effects. The other potential explanation is that microcurrent may have a strong positive effect on the general health status in patients suffering from migraine, but the direct effect on the symptoms of the disease itself is weak.

In randomized blinded clinical trials, microcurrent therapy was only considered effective when its effect was better than the placebo response triggered by a sham treatment. Nevertheless, in patient care, effective treatment is unavoidably delivered with additional placebo response. This is also applicable in this observational study. Given that the beneficial effects of the placebo effect are often clinically significant, especially in chronic pain,^{14,114} assessing the overall treatment effect that includes placebo response is important in optimizing patient care.

To assess the effect of concomitant therapies on study outcome parameters, analyses of the complete populations were compared with results excluding all participants applying any therapy potentially having a positive effect on study outcome. Twenty participants in total were excluded in the secondary analysis set due to this assessment.

The comparisons of the two analyses were performed for all parameters and yielded only marginal differences for the two populations (<3%).

This study was performed in participants already using the Healy device and having a positive attitude concerning its effectiveness. This has to be taken into account, when generalizing the study results. The effectiveness and effect sizes within this group may be higher than in a comparable group, having no experiences in microcurrent applications.

In total, 230 adverse events occurred during the study. This could be interpreted as an average incidence of about 1.8 events per participant per year. In comparison to the average sick days per year in the German adult population (1.1 sick days per year in 2021 and 2022),^{107,108} this seems to be quite high. But the difference could be easily explained by the fact that the average age of the study population is higher than the mean of the employed population. Additionally, all participants in the study were suffering from at least one chronic condition. Both factors (higher age and chronic diseases) are increasing the incidence of diseases in comparison with younger healthy persons.

Four adverse events of mild intensity were related with the application of electrostimulation. The corresponding complaints (pain twice, skin reactions twice) are already listed in the Healy Instructions for Use as possible side effects. Considering that the 250 study participants have used the investigational microcurrent device at least once per day for 6 months, the incidence rate of side effects in this study is very low (1 case per 10.000 applications). This underpins that microcurrent electrostimulation is safe and well tolerated by its users.

Conclusion

For all parameters except one, the improvements between study entry (V1) and study completion (V4) are both significant and clinically relevant. Being aware and taking into consideration that the mode of action of microcurrent electrostimulation therapy is not fully understood, this observational study clearly demonstrated its effectiveness and safety.

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Mrs. Annemarie Blam contributed as investigator in the study; she performed the remote study visits with the participants and verified the inclusion/exclusion criteria. Mrs. Stephanie Reddig drafted some essential study documents, performed the submission to the ethics committee and contributed to data management activities. Mr. Georg Salcher reviewed the first draft version of this report.

Disclosure

PM is an employee of Healy GmbH, the sponsor of the study. WW received consulting fees from Healy GmbH. The authors report no other conflicts of interest in this work.

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