

Clinical Evidence for the Efficacy of the B-Cure Laser Device

Written by Lilach Gavish, PhD

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Overview

Low level laser therapy (LLLT), also called photobiomodulation is a non-thermal irradiation in the red to near infrared range of the electromagnetic spectrum (1,2). The LLLT photonic energy is absorbed in the mitochondria, boosting the cell energy and reducing oxidative stress (3,4). This low risk, non-invasive technology is widely used at clinics and for home-use (5) for pain reduction (6), acceleration of wound healing (7), and for treating a variety of inflammatory related conditions (8).

The B-Cure laser is a portal, non-invasive, LLLT device, that is sold over the counter without a physician's prescription in Israel, Europe, Canada, and Asia for the management of acute and chronic pain, as well as acceleration of wound healing. The device is a pulsed near infrared 808nm Ga-Al-As (Gallium-Aluminium-Arsenide) diode laser, with 250mW peak power at 15KHz, emitting fluence of 1.1J/cm² per minute over an area of 4.5 X 1 cm². These energetic parameters comply with the current recommendations of the World Association for Laser Therapy (WALT) for near infrared laser photobiomodulation (9).



This document contains a summary of the clinical evidence of the effectiveness of the B-Cure laser device for reduction of pain and acceleration of wound healing. To date, the safety and efficacy of the device was evaluated in 5 prospective single or double-blind randomized sham-controlled clinical trials (results and significance detailed in Table 1 on page 11), a prospective open-label study (results detailed in Table 2 on page 12), and several clinical experiences (case series and case reports, detailed in Table 3 on page 13). All these studies were performed by clinicians, who received devices for the purpose of the study, but were not paid by the company. The clinical trials with the B-Cure Laser were highlighted in 2 recent systematic reviews related to the therapeutic efficacy of home-use photobiomodulation devices in home-use (10) and photobiomodulation devices in oral health (11) emphasizing the unique contribution of the B-Cure laser device to the acceptance of photobiomodulation as a treatment modality. Additional important data originates from a post-marketing B-cure customer survey conducted and analysed by 3rd parties and a list of links to video testimonials by physicians and patients that have used or are still using the device.

The evidence is organized by clinical application with a short relevant explanation about the rationale for LLLT use for the specific indication. A tabulated summary of the studies can be found at the end of the document.

Abbreviations: LLLT=Low level laser therapy; TMD=temporomandibular joint disorders; DFU=diabetic foot ulcer; VAS=visual analogue scale; WALT=World Association of Laser Therapy

Temporomandibular joint Disorders

Background

The temporomandibular joint connects the jaw to the skull and along with its attached muscles, allows movements needed for speaking, chewing, and making facial expressions. Temporomandibular joint disorders (TMD) are common and associated with pain and functional disturbances, and can arise from distinct reasons including problem with the position of the articulating disc itself, degenerative joint disease, and increased muscle tension (12).

Can LLLT benefit TMD?

Two systematic reviews published in 2019 concluded that LLLT can be beneficial for treatment of TMD (11,13). LLLT was found to reduce palpation tenderness and improve microcirculation of tense muscles, thus leading to pain relief and increase of the maximum mouth opening in patients with acute and chronic TMD. The best results were reported after application of near infrared lasers with 100-500 mW power on the joint and tender points.

Clinical Evidence for the Efficacy of B-Cure for the Treatment of TMD

B-Cure Laser was evaluated for the treatment of TMD in two separate prospective blinded randomized sham-controlled clinical trials in Sapienza University in Rome and in University of Parma, Italy (14,15). The results support safety and effectiveness of the **B-Cure Laser in reducing of TMD related pain.**

Fornaini et al (15) evaluated the efficacy of self-treatment at home with the B-Cure laser for TMD. Twenty-four patients (Age 17– 64 years; M:F 5:19) with mono- or bi-lateral TMD were randomly assigned to daily LLLT treatments for 2 weeks (808 nm, 16.5J/cm²) or sham device. The patient performed the self-treatment at home for 15 minutes extra-orally on the cutaneous zone corresponding to the TMJ. Subjective pain level was recorded by visual analogue scale (VAS [0=no pain to 100=unbearable pain]) at baseline, 1, and 2 weeks after the last treatment. It was found that the treatments with the B-Cure laser resulted in significant pain relief compared to baseline and to the sham irradiation at both follow ups (the change in pain level by VAS after 1 week, mean±SD: B-Cure laser 2.7±0.9 [48% reduction compared to baseline] vs Sham 0.4±1.0 [8%], p<0.0001). No adverse effects were reported. These results were published in the peer-reviewed journal *Laser Therapy* in 2015 (15).

Del Vecchio et al (16) compared the effect of LLLT to those of treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and compared both to sham treatment. In this study 90 consecutive patients (Age 18-73 years; M:F 12:78) affected by TMD for more than 6 months were randomly assigned to one of 3 groups: (A) n=29, LLLT twice a day for 1 week (808 nm, 16.5J/cm²); (B) n=28, Sham LLLT for 1 week; (C) n=29, 2 five days of nimesulide (100 mg daily), interspersed with one 5-day cycle of cyclobenzaprine hydrochloride (10 mg daily). The authors reported that the pain reducing effect of the B-Cure laser was comparable to that of NSAIDs and both were superior to sham irradiation (Change in pain from baseline by VAS: LLLT 3.5±2.2; NSAIDs 3.7±2.0; Sham 2.2±1.7, p=0.01). No adverse effects were reported. These results were published in the peer-reviewed journal *Cranio* in 2019 (16).

Oral Mucositis

Background

Oral Mucositis is a common painful and debilitating side effect of cancer chemotherapy and radiotherapy protocols, as well as dental procedures and other pathologies. It is characterized by erythema, ulceration, and pain, thus frequently impairing the ability for food intake, and potentially preventing the patient from receiving the full cancer treatment (17).

Can LLLT benefit Oral Mucositis?

LLLT was found to be effective for the treatment of patients with oral mucositis based on its ability to accelerate wound healing, reducing inflammation, and increasing cell metabolism (18). Indeed, both the UK National Institute for Health and Care Excellence (NICE), and the Multinational Association of Supportive Care in Cancer, and the International Society of Oral Oncology (MASCC/ISOO) recommended LLLT as a favorable intervention for prevention of oral mucositis (19,20).

Clinical Evidence for the Efficacy of B-Cure for the Treatment of Oral Mucositis

B-Cure Laser was evaluated for the prevention and treatment of peri-implant oral mucositis in a prospective blinded randomized sham-controlled clinical trial in Perm, Russia. In addition, descriptive clinical data of patients with oral mucositis treated with the B-Cure Laser was gathered at the Scarborough Health Network clinics in Toronto, Canada and reported in a case series. Based on the results reported in these studies, it can be concluded that the **B-Cure Laser may be self-applied for prevention and treatment of oral mucositis and for prevention of pain and edema related to oral surgery.**

Gileva et al (21) evaluated the efficacy of B-Cure laser for prevention and treatment of Peri-Implant oral mucositis. Thirty patients with partial edentulism (Age: 28-57; M:F 13:17) that were planned to undergo dental implantation were assigned to active or sham LLLT. The treatment was applied extra-orally on the cutaneous zone corresponding to the dental implantation installation location - twice prior to the procedure at the dental office, and 2-3 times a day after the procedure (8 minutes per application) for 7-10 days at home. Compared to sham irradiated controls, patients from the active group were found to have significantly reduced frequency and intensity of pain in the first days after the installation of endosseous implants ($p < 0.01$), and a reduced frequency, duration, and intensity of local edema-inflammation in peri-implantation area and edema of soft tissues. In addition, although most patients in the sham group developed clinically functional and aesthetic disorders, associated with limitation of mouth opening throughout the surgical stage of dental implantation, patients from the active group did not present with any limitations. These results were reported in the proceedings of the conference Physics of Cancer: Interdisciplinary Problems and Clinical Applications, Perm, Russia (21).

Raizman et al (22) treated 3 patients with oral mucositis (WHO grade ≥ 3) of which 2 were related to cancer treatment and one to Steven Johnston Syndrome (SJS). The patients self-applied the treatment daily extra-orally, intraorally, and over the cervical lymph nodes. All 3 patients experienced a rapid pain relief resulting in a reduction in WHO grade manifested in the return of the ability to eat after 1-2 treatments. One patient that had to halt chemotherapy regimen in view of the oral mucositis, resumed chemotherapy after 1 laser treatment. This case series was presented at the 2019 EWMA conference (22).

Diabetic Foot Ulcers

Background

Diabetic foot ulcer (DFU) is a common complication of diabetes that may lead to limb amputation. The standard-of-care protocols are not always sufficient to prevent DFU deterioration, particularly in complicated diabetic patients with co-morbidities.

Can LLLT benefit Diabetic Foot Ulcers?

Two recent systematic reviews of randomized controlled studies evaluating LLLT for treatment of DFUs reported an overall positive result with no associated adverse events (23,24). The authors of the reviews concluded that this technology has significant potential to become a portable, minimally invasive, easy-to-use, and cost-effective modality for treatment of DFU (20). Additional supportive evidence was reported in two reviews of non-controlled studies, case series, and case reports (25,26).

Clinical Evidence for the Efficacy of B-Cure for the Treatment of Diabetic Foot Ulcers

B-Cure Laser was evaluated for the treatment of diabetic foot ulcers in a prospective double blinded randomized sham-controlled clinical trial at Hadassah Medical Center in Jerusalem, Israel. In addition, clinical experiences collected in several different centers in Israel and Canada were gathered to develop an optimal protocol for the treatment of DFU as well as to determine the time to closure of DFU following treatment with B-Cure Laser. The results reported here suggest that **treatment with B-Cure Laser at home as an adjunct treatment to standard care, is a valuable tool for acceleration of DFUs even for frail patients with severe diabetic foot ulcers and co-morbidities. Healing time is dependent on the initial wound size.**

At this time, 2 double-blind sham controlled clinical studies are conducted in Israel (NCT03687320) and Canada (NCT03687580). The results from these studies are expected to be reported towards mid-2021.

Haze et al (27) evaluated the safety and efficacy of the B-Cure Laser for treatment of diabetic foot ulcers. Nineteen patients (Age=55-88 years, M:F 14:7) with various degrees of renal failure and deep DFUs, most (17 of 19) with involvement of bone (Wagner-Meggitt grade III), sized 3-37.5cm² were assigned to sham or active laser treatment. The treatment was applied at home by a care giver for 8 minutes per application in up to 7 locations for the entire wound. Significant wound size reduction in laser treated group compared to sham was found (%change in wound size from baseline: active 97% vs sham 57%, p=0.033) with, 7 of 10 active patients but only 1 of 9 sham patients having >90% wound closure by the end of the study (p=0.019). No device related adverse device effects were observed.

Raizman et al (28-30) treated 4 cases of diabetic leg/foot ulcers (Age=67-84 years, all male). **The treatment was self-applied by the patients** at the clinic or at home. All wounds closed within 1-3 weeks with no reported adverse events. Patients found routine easy to follow and painless, and in wounds that involved pain reported pain reduction after 1-3 treatments. Based on the clinician's previous experience with these patients, self-applied LLLT as an adjunct therapy, led to accelerated healing and rapid pain alleviation compared to standard care alone. As part of this clinical experience, an optimal protocol for B-Cure Laser self-applied treatment of DFUs was developed. The protocol includes a recommendation of differential time of treatment over the open wound, wound margins,

surrounding lymph nodes, and over arterial blood supply to the foot in cases of weak blood supply.

Applying the above protocol to 12 patients (Age 53-92, M:F 9:4) in outpatient clinics of 5 different medical centers in Israel, information of DFU closure timing following treatment with B-Cure laser was collected and confirmed by the treating physicians. See example of DFU from this analysis in Figure 1 below. None of the wounds treated with B-Cure Laser increased in size during the treatment time and neither the patients nor the treating physician reported any device-related adverse events. Using Kaplan Meier survival analysis, and stratifying by wound size, the median time to achieve complete wound closure in wounds $<6\text{cm}^2$ at baseline was 8 weeks with a mean time of 7.6 weeks [95% CI= 4.7-10.5] whereas larger wounds had a much longer median time of 21 weeks with a mean healing time of 16.4 [10.4-22.5] weeks ($p=0.023$ by Log-Rank test).

Merigo et al (31) used the B-Cure Laser to treat an 84-year-old woman, with diabetes type 2 and related co-morbidities for 3 painful diabetic ulcers on her right leg. The patient self-treated her leg twice daily in 15-minute sessions for 1 month. After the first week, the 2 smaller ulcers closed, and 3 weeks later the larger ulcer closed, as well.



Figure 1: Diabetic Foot Ulcer Treated with the B-Cure Laser

Patient (male, 68-years-old, diabetes type 2) with a large diabetic foot ulcer on the dorsal aspect of the foot that was not healing for 1 year. Patient self-applied B-Cure Laser treatment at home daily. Note accelerated healing following 4 weeks of treatment. Ulcer was still closed at 21 weeks.

Post-Surgical Wounds

Background

Surgical incisions are often accompanied with inflammation, edema, and pain, that if left untreated can lead to post-surgical side effects such as dehiscence and necrosis. Spine surgeries often involve laminectomy, which is the removal of the posterior part of the vertebra ('lamina') to create space and expose the spinal canal thereby relieving pressure on the spinal cord or nerves (32). This procedure is frequently accompanied by formation of an epidural scar that may result in pain and physical impairment.

Can LLLT prevent post-surgical side effects?

LLLT was shown to accelerate wound healing in various wound types, including surgical wounds (7) thereby facilitating cicatration and reducing the amount of post-surgical analgesics required. Pre-conditioning the surgical site with LLLT was also shown to be beneficial - using a skin flap rat model, Martignago et al (30) found that LLLT pre-conditioning resulted in improved skin flap viability, increased angiogenesis, and growth factor secretion.

Clinical Evidence for the Efficacy of B-Cure for prevention of post-surgical side effects

B-Cure Laser was evaluated for prevention of laminectomy related side effects in a prospective single blinded randomized sham-controlled clinical trial at Sao Paulo Hospital, Nove de Julho University, Brazil. Clinical experiences from treatments of various post-surgical wounds using the B-Cure Laser were also reported. These results suggest that **B-Cure Laser may be used for prevention and treatment of post-surgical side effects.**

Holanda et al (33) evaluated the safety and efficacy of the B-Cure laser for prevention of post-laminectomy complications in a prospective randomized controlled study. Forty-six patients (Age=40-80 years, M:F 23:23) were assigned to sham or active laser treatment during spine surgery. The treatment protocol included 1' irradiation over the laminectomy site, 1 minute over the subcutaneous tissue, and 2 minutes over the wound. Significant pain relief and accelerated healing compared to controls were observed in the LLLT treated group due to more rapid resolution of acute inflammation and earlier initiation of proliferation as suggested by CRF and CK measurements respectively. The authors concluded that a short application of B-Cure Laser during laminectomy stimulated better wound healing, reduced inflammation in the wound, decreased drainage output and assisted in postoperative analgesia in spinal surgery as compared to non-treated controls. These results were reported as a PhD dissertation and presented at the 2014 ASLMS conference.

Raizman et al (28-30) applied B-Cure laser treatment on a series of post-surgical wounds including 3 abdominal wounds, a post-surgical seroma with 4.5cm tunnel after breast cancer removal, and post-surgical large dehiscence wounds following treatment of compound fracture with planned amputation. The abdominal wounds achieved complete epithelialization after 5-6 treatments at the clinic over a period of 9-21 days. The seroma wound closed after 8 weeks of treatment at the clinic and at home. In view of the unexpected accelerated healing of the dehiscence wounds, the surgeon decided to forgo amputation and performed instead muscle flap surgery on 1 side and a skin graft on the other. The results of these clinical experiences were presented at the ASLMS 2019, EWMA 2019, and Wound Canada 2019 conferences.

Musculoskeletal Conditions

Background

Musculoskeletal conditions affect the muscles, bones, joints and associated tissues such as ligaments and tendons. They are typically characterized by pain and limitations in mobility, dexterity and functional ability, reducing people's ability to work and participate in social roles with associated impacts on mental wellbeing. The most common and disabling musculoskeletal conditions are osteoarthritis, back and neck pain, fractures associated with bone fragility, injuries and systemic inflammatory conditions such as rheumatoid arthritis (34).

Can LLLT reduce musculoskeletal pain?

The World Association for Laser Therapy (WALT) has issued recommendations for energy related parameters for the treatment of specific musculoskeletal pain indications (9). These recommendations are currently considered the gold standard and include recommendations of energy per point of treatment, total energy dose per session, and minimal energy dose per point.

Several systematic reviews have demonstrated that LLLT is beneficial for reduction of musculoskeletal pain, including the review by Chow et al in the Lancet journal for neck pain (35), Huang et al and Glazov et al (36,37) for non-specific back pain, and recently Stausholm et al for pain related to knee osteoarthritis (38).

Clinical Evidence for the Efficacy of B-Cure for reducing musculoskeletal pain

B-cure devices comply with the WALT guidelines for beneficial effects of near infrared (780-860 nm) lasers.

The efficacy of B-Cure laser for reduction musculoskeletal related pain was evaluated in a prospective open-label study of athletes with knee osteoarthritis and by a real-life post-marketing telephone survey of customer experience and satisfaction. The results reported here suggest that the **treatment with B-cure laser results in safe and effective pain relief related to musculoskeletal pain and that this effect is unrelated to age or sex.**

Kruglova et al (39) evaluated the clinical effectiveness of the B-Cure Laser in a prospective open-label study in a population of high-performance athletes for improvement of symptoms and reduction of pain related to osteoarthritis of the knee. Twenty professional adult athletes (football, rugby, wrestling, basketball) with osteoarthritis of the knee joint were included in this study. The treatment protocol included daily self-treatments over the knee joint of 8 minutes per pain point, 6 days a week for 2 weeks. Evaluations included pain level by VAS and evaluation of flexibility and movement coordination of the affected limb. At the end of the treatment a significant pain reduction was observed in all athletes (Pain by VAS, mean±SD: Baseline - 83±5; Week 1 - 45±1; Week 2 - 5±1) as well as an improvement in support function of the affected limb. No adverse events were noticed. Note that a natural reduction in pain over time was also expected and may have contributed to the pain reduction.

According to the sales department, the vast majority of the B-Cure Laser customers buy the device to treat musculoskeletal related pain. In order to evaluate the real-life experience of B-Cure Laser customers, a phone survey was conducted by Geocartography Knowledge Group that specializes in customer surveys. A database of 10,000 coded numbers representing patients that purchased the device at least 3 months prior to the survey, was

prepared with the intention to survey a sample of n=300. It was found that two thirds (67%) of the customers that answered the survey were over 55 years old, which is 3 folds more than the percentage of this age group in the general population. The distribution by sex (56% males) was similar to the general population (49.5% males) (Israel central bureau of statistics, 2013). The customers were evenly distributed according to their income level. Overall, 70% of the customers reported that they were satisfied with the treatment (19% very satisfied, 27% satisfied, 24% slightly satisfied). Subjective pain level was quantified using the numerical rating scale (NRS) where 0 was “no pain” and 10 was “intolerable pain. Of the customers surveyed, 177 considered themselves as suffering intolerable pain (defined here as pain NRS=8-10) before beginning the treatment but only 69 considered themselves in this category after treatment (reduction of 61%, $p<0.0001$ by chi square). The major pain for which the customers reported using the device were knee pain (34%), low back pain (15%), and upper back and neck pain (11%). Using ANOVA adjusted for age, sex and initial pain level, it was demonstrated that there was no significant difference between the knees, lower back, upper back, or other regions regarding satisfaction level ($p=0.69$) or change in pain level ($p=0.12$). None of the customers reported experiencing adverse events.

Oral Neuronal Disorders

Background

Nerve-related complications following oral and dental surgery can be categorized into: anaesthesia (no sensory modalities), paraesthesia (abnormal sensation like tingling, whether spontaneous or evoked), hypoesthesia (diminished sensitivity), and hyperaesthesia (increased sensitivity). These typically occur as a result of damage to the inferior alveolar nerve and usually recover within 4 - 8 weeks after surgery. However, some injuries may be permanent and last longer than 6 months. Treatment may include drugs, surgery, and LLLT (40).

Can LLLT improve oral neuronal disorders?

LLLT has been used intensively in the dental field for a variety of indications including prevention and treatment of neuronal disorders as reviewed by Ross et al (41). Regenerative effects following a biostimulatory dose of LLLT at the site of injury modulates secretion of neurotropic factors which increase the amount of nerve sprouts (42). Thus, LLLT results in a significant acceleration in the time course and magnitude of neurosensory recovery (43).

Clinical Evidence for the Efficacy of B-Cure for improving oral neuronal disorders

The efficacy of B-Cure laser for prevention of iatrogenic oral neuronal disorders was reported in the double blind RCT of patients undergoing dental implantation. In addition, a clinical experience using the B-Cure Laser for the treatment of cases with established oral neuronal disorders was also reported. The results reported here suggest that **B-Cure Laser can prevent oral neuronal disorders following dental implantation and can accelerate healing of pre-existing disorders.**

In addition to evaluating the effect of B-Cure laser for prevention and treatment of peri-Implant oral mucositis Gileva et al (21) also evaluated the efficacy of B-Cure Laser in prevention of expected iatrogenic oral neuronal disorders related to dental implantation

procedure. Thirty patients with partial edentulism (Age: 28-57; M:F 13:17) that were planned to undergo dental implantation were assigned to active or sham LLLT. See treatment specification in the mucositis section. The sham treated patients developed lower jaw transient sensory-paresthetic symptom in 20% of the cases. It was manifested by paresthesia of the chin, including 6.7% of observations in combination with the typical neurological pain, radiating in the course of the inferior alveolar nerve. None of the B-Cure Laser treated patients experienced any of these neuronal disorders.

Merigo et al (44) reported 3 cases (Age 55–63; M:F 1:2) of post-surgical anesthesia/paresthesia of the left lower lip, right lower lip, or lower cheek associated with surgical anesthesia, osteonecrosis (related to bisphosphonates), or implant surgery, respectively. The latter case not responding to pharmacological treatment. The treatment protocol included 1-2 daily 15-min self-treatments over the lower lip, chin, and mental foramen for 1-3 weeks. Complete resolution of symptoms was observed. No adverse events were reported.

Testimonials

Below please find testimonial videos of doctors, physiotherapist, chiropractors, professional athletes, and private customers

Clinicians

1. Dr. David Ben Kiki, Chiropractor: <https://www.youtube.com/watch?v=khbhFk-vQio>
2. Jenine Saunders, Somatic Physiotherapy: https://www.youtube.com/watch?v=sJnd4E_58xo
3. Prof. Vatin: https://www.youtube.com/watch?v=PkDDVKpW_88&t=13s
4. Prof. Reiss: https://www.youtube.com/watch?v=at4MRUUIJuE&feature=emb_logo
5. Jess Amar, Osteopath: <https://www.youtube.com/watch?v=TpKdZMgpFXI>

Professional Athletes

6. Yarden Gerbi, Former World Champion, women judo: <https://www.youtube.com/watch?v=jVxAIP3gHvs>
7. Clarisse Agbngnenou, Four time World Champion, women judo: <https://www.youtube.com/watch?v=egGGafqaRJs>
8. Stefano Tacconi, Former Juventus Goalkeeper: <https://www.youtube.com/watch?v=HvyYnPbK7Z8>

Customers

9. Mabel Moskal: <https://www.youtube.com/watch?v=28ZPDA9Jckk&t=32s>
10. Karen Van Der Hayden: https://www.youtube.com/watch?v=pX_poT5M_mM
11. Jane Moskal: <https://www.youtube.com/watch?v=Pa9Z8ECcQnw>
12. Michael Dagostino: <https://www.youtube.com/watch?v=287sQBBAQWk>
13. Marlene Niks: https://www.youtube.com/watch?v=mUs4RVoO3oA&feature=emb_logo
14. Philip: Landa https://www.youtube.com/watch?v=v6Alw9QISFs&feature=emb_logo

Table 1: B-Cure Laser Randomized Controlled Studies

Indication	Author (year)	Study Design (Level of Evidence ^a)	Control /co-intervention	n	Study Population (Age range)	Treatment Protocol	Sites Treated	Results (significance)
TMD	Fornaini (2015) ⁽¹⁵⁾	DB-RCT (2)	Sham	24	Patients with TMD (17-64 yo)	At home, self-application, 15minX2 sides, dailyX2 weeks. Total 14 Tx	Extraoral, over Temporomandibular joint	Pain ↓ (p<0.0001)
TMD	Del Vecchio (2019) ⁽¹⁴⁾	DB-RCT (2)	Sham vs NSAIDs	90	Patients with TMD (18-73 yo)	<u>LLLT group</u> : At home, self-application, 8min, 2Tx/day X 7. Total 14 Tx <u>Drug group</u> : 5 day cycles: nimesulide; cyclobenzaprine hydrochloride; nimesulide	Extraoral, over Temporomandibular joint	Pain ↓ compared to sham (p<0.01) Pain reduction not different than drug group
Mucositis	Gileva (2017) ⁽²¹⁾	SB-RCT (2)	Sham	30	Patients undergoing dental implantation (28-57yo)	At clinic by dentist (preventive), then at home, self-application, 8min, 2Tx/day X 7-10 days. Total 15-21 Tx	Extraoral, over dental implantation location	Pain ↓ (p<0.01) inflammation ↓ No sensory disturbances
Post-operative wounds	Holanda (2014) ⁽³³⁾	SB-RCT (2)	Sham	46	Patients undergoing laminectomy (40-80 yo)	During surgery by clinician, 4 minutes: 1min laminectomy, 1min subcutaneous tissue, 2min surgical wound. Single treatment	Laminectomy, subcutaneous tissue, wound	Pain ↓ (p<0.001) Accelerated healing of surgical wound
DFU	Haze (2017) ⁽²⁷⁾	DB-RCT (2)	Sham / standard care	19	Patients with deep /large DFUs, most with osteomyelitis and severe co-morbidities (55-88yo)	At home, application by care giver, 8min per application, dailyX3 months. Total up to 90 Tx	Wound	Accelerated healing (p=0.033)

^aGrade according to the Oxford Centre for Evidence-based Medicine—Levels of Evidence; n=number of patients; TMD=temporomandibular disorder; DB=double blind; SB=single blind; RCT=randomized controlled trial; DFU=diabetic foot ulcer; min=minutes; Tx=treatments; yo=years old;

Table 2: B-Cure Laser Open Label/Post marketing Studies

Indication	Author (year)	Study Design (Level of Evidence ^a)	n	Study Population (Age range)	Treatment Protocol	Sites Treated	Results
Musculo-skeletal	Kruglova (2015) ⁽³⁹⁾	Prospective, Open label (3)	20	Professional athletes with knee osteoarthritis (20-40yo)	Daily 8-minutes per pain point, 6 days a week for 2 weeks At home, self-application, 8min per pain point, daily X 2 weeks (6 days/week). Total 12 Tx	Pain points over knee	Pain↓
Musculo-skeletal	Geocartography Knowledge Group (2018)	Post-marketing cross sectional (2)	300	Customers with musculoskeletal pain that purchased the device > 3 months prior to the survey and were randomly selected from a database of 10,000 (67%>55yo; 56% males)	Varying: Most customers 15minX2-4 times a day	Areas of pain	Of the 300 customers, 19% were very satisfied, 27% satisfied, and 24% slightly satisfied (overall 70% satisfied). Moreover, following self-treatment with the B-Cure Laser at home there was a 61% reduction in the number of customers that reported feeling intolerable pain (before treatment n=177 vs after n=69)

^aGrade according to the Oxford Centre for Evidence-based Medicine—Levels of Evidence; n=number of patients; NA=not applicable; min=minutes; Tx=treatments; yo=years old

Table 3: B-Cure Laser Clinical Experiences - Case Series and Case Reports

Indication	Author (year)	Study Design (Level of Evidence ^a)	n	Study Population (Age range)	Treatment Protocol	Sites Treated	Results
Oral neuronal disorders	Merigo (2017) ⁽⁴⁴⁾	Case series (4)	3	Patients with iatrogenic post-surgical anesthesia / paresthesia of the lips/cheeks (55–63yo)	At home, self-application, 15min, 1-2 times daily X 1-3 weeks. Total 3-21 Tx	Areas of neuronal disorder	Complete resolution
Post-surgical wounds	Raizman (2019) ⁽²⁸⁻³⁰⁾	Case series (4)	5	Patients with abdominal wounds (n=3), seroma post breast cancer surgery with 4.5cm tunnel, large dehiscence wounds following treatment of compound fracture with planned amputation	At clinic and at home, self-application 0.5min open wound; 2.5min wound margins;	Wound and wound margin	Complete resolution. In case of large dehiscence wound, accelerated healing preventing amputation
Mucositis	Raizman (2019) ⁽²²⁾	Case series (4)	3	Patients with oral mucositis (WHO grade ≥3) related to cancer therapy (n=2) and Steven Johnston Syndrome (n=1)	At clinic, self-application, daily until resolve:	Extra-orally, intraorally, and over the cervical lymph nodes	Pain ↓ WHO grade ↓ Could eat and resume chemotherapy
DFU	Raizman (2019) ⁽²⁸⁻³⁰⁾	Case series (4)	4	Patients with DFU and comorbidities (67-84yo)	At home, self-application, 0.5min open wound; 2.5min wound margins; 1min lymph, daily until closure 1-3 weeks	Wound, wound margin and related lymph nodes	Wound closure
DFU	Gavish (2018)	Analysis of Case series (4)	12	Patients with DFU from 5 medical centers.	See Raizman DFU protocol.	Wound, margins, lymph nodes	Time to closure: median=11 weeks, mean time=12.4 weeks [95%CI: 8.0, 16.8]
DFU	Merigo (2019)	Case report (4)	1	Patient with DFU and comorbidities (84yo)	At home self-application, 15min, daily, 1 months	Wound	Wound closure

^aGrade according to the Oxford Centre for Evidence-based Medicine—Levels of Evidence; n=number of patients; NA=not applicable; min=minutes; Tx=treatments; yo=years old; DFU=diabetic foot ulcer

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