Pain Medicine, 22(1), 2021, 118–130
doi: 10.1093/pm/pnaa329
Advance Access Publication Date: 6 November 2020
Original Research Article

Green Light Exposure Improves Pain and Quality of Life in Fibromyalgia Patients: A Preliminary One-Way Crossover Clinical Trial

Laurent Martin, PhD,* Frank Porreca, PhD,*,† Elizabeth I. Mata, BS,‖ Michelle Salloum, MD,‖ Vasudha Goel, MD, Pooja Gunnala, BS,* Wiliam D.S. Killgore, PhD,‡ Sejal Jain, MD,§ Felesia N. Jones-MacFarland, MD,§ Rajesh Khanna, PhD,*,†, ¶ Amol Patwardhan, MD, PhD,*,† and Mohab M. Ibrahim, MD, PhD*,†**

*Departments of Pharmacology; †Anesthesiology; ‡Psychiatry; §Neurology; ¶Graduate Interdisciplinary Program in Neuroscience; ‖College of Medicine, University of Arizona, Tucson, Arizona; **Department of Anesthesiology, University of Minnesota, Minneapolis, Minnesota, USA

Correspondence to: Mohab M. Ibrahim, MD, PhD, Department of Anesthesiology, College of Medicine, University of Arizona, Tucson, AZ 85724. USA. Tel: (520) 626-7195; Fax: (520) 626-6066; E-mail: mibrahim@anesth.arizona.edu.

Funding sources: This study was funded by support from National Center for Complementary and Integrative Health R01AT009716, the Comprehensive Chronic Pain and Addiction Center-University of Arizona, and the University of Arizona CHiLLi initiative.

Conflicts of interest: Drs. Ibrahim and Khanna have a patent pending through the University of Arizona for the use of green light therapy for the management of chronic pain. All other authors have no conflict of interest to report. None of the authors of the manuscript received any remuneration or any reimbursement or honorarium in any other manner. The authors are not affiliated with any vendor or pharmaceutical company associated with this study.

Trial registration: ClinicalTrials.gov Id: NCT03677206.

Abstract

Objective. Fibromyalgia is a functional pain disorder in which patients suffer from widespread pain and poor quality of life. Fibromyalgia pain and its impact on quality of life are not effectively managed with current therapeutics. Previously, in a preclinical rat study, we demonstrated that exposure to green light-emitting diodes (GLED) for 8 hours/day for 5 days resulted in antinociception and reversal of thermal and mechanical hypersensitivity associated with models of injury-related pain. Given the safety of GLED and the ease of its use, our objective is to administer GLED as a potential therapy to patients with fibromyalgia. **Design**. One-way crossover clinical trial. **Setting**. United States. **Method**. We enrolled 21 adult patients with fibromyalgia recruited from the University of Arizona chronic pain clinic who were initially exposed to white light-emitting diodes and then were crossed over to GLED for 1 to 2 hours daily for 10 weeks. Data were collected by using paper surveys. **Results**. When patients were exposed to GLED, but not white light-emitting diodes, they reported a significant reduction in average pain intensity on the 10-point numeric pain scale. Secondary outcomes were assessed by using the EQ-5D-5L survey, Short-Form McGill Pain Questionnaire, and Fibromyalgia Impact Questionnaire and were also significantly improved in patients exposed to GLED. GLED therapy was not associated with any measured side effects in these patients. **Conclusion**. Although the mechanism by which GLED elicits pain reduction is currently being studied, these results supporting its efficacy and safety merit a larger clinical trial.

Key Words: Fibromyalgia; Complementary Therapy; Green Light; EQ-5D-5L

Introduction

Fibromyalgia is a clinical syndrome in which patients experience widespread pain, loss of energy, and possible cognitive or psychiatric dysfunction [1]. In the United States, the prevalence of fibromyalgia is 2% to 3%, and it is considered to be one of the common causes of chronic pain in women between the ages of 20 and 55 years [2, 3]. For reasons that are still unclear, women are more predisposed to fibromyalgia; six to nine patients out of 10 are females [4, 5]. Because the etiology of fibromyalgia is not clearly known [6, 7], treatments focus on symptom management. There are several classes of medications that may be used to reduce fibromyalgia symptoms. These include tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, and anticonvulsants. Randomized clinical trials have demonstrated that 25% to 45% of patients obtained relief with tricyclic antidepressants [8–10]. Serotonin–norepinephrine reuptake inhibitors are also used. A meta-analysis of six randomized clinical trials involving more than 2,200 patients showed that 60 mg/day of duloxetine reduced pain by 30% to 50% in the patient population [11]. A randomized clinical trial combining pregabalin and duloxetine provided better pain control than monotherapy for fibromyalgia patients. Patients usually respond better when both pharmacological and nonpharmacological modalities are used in a multidisciplinary fashion [12].

The side effects associated with some of the current pharmacological therapies for fibromyalgia may be severe enough to force some patients to abandon them [13]. For example, duloxetine is associated with hyperhidrosis, somnolence, diarrhea, insomnia, fatigue, dizziness, constipation, headache, dry mouth, and nausea to different extents in individual patients [14]. Physical therapy may offer benefit for some fibromyalgia patients [15–17]. However, adherence to physical therapy is dependent on the patient's ability to tolerate the therapy and willingness to participate. Additionally, patients with more severe symptoms of fibromyalgia typically have lower levels of aerobic fitness [18]. Thus, the addition of complementary and nonpharmacological means to manage fibromyalgia may provide better pain control and improve patients' quality of life.

Light therapy has been used for the treatment of several medical conditions, including sleep disorders [19], depression [19], circadian deregulation [20], wound healing [21], and back pain [22] in young and elderly populations. Most recently, green light exposure was found to treat actinic keratosis with less pain than seen with red light exposure [23]. Additionally, there is some evidence that being present in environments that are rich in the color green (e.g., forest bathing) can decrease pain and have other health benefits [24]. In conditions of central sensitization, such as migraine [25], some research groups also reported benefits from exposure to green light [26]. Therefore, colored light may have many biological functions with minimal side effects. Harnessing the biological effects of colored light may be a relatively safe method to complement our management of hard-to-manage conditions, such as fibromyalgia.

We recently reported anti- and pronociceptive effects associated with exposure to green and red light, respectively, in rats [27, 28]. Rats exposed to green light-emitting diodes (GLED) of 525 nm with intensity ranging from 4 to 100 lux for 8 hours/day developed antinociception and anti-allodynia in animal models of nociception and neuropathic pain, respectively, which was mediated through the visual system [27]. Few studies have investigated possible effects of light therapy on pain.

Given the low risk potential for side effects associated with low-intensity GLED exposure, we tested the primary hypothesis that, among patients diagnosed with fibromyalgia who failed traditional therapy, exposure to GLED would decrease their pain. Additionally, we tested the hypothesis that exposing patients with fibromyalgia to GLED would improve their functionality and their ability to fall and stay asleep as secondary outcomes. Here, we report the results of our study with a one-way crossover approach of patients with fibromyalgia exposed to GLED.

Methods

Study Design

This is a one-way crossover clinical trial. This article adheres to the applicable Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) guidelines.

Setting

The patients were recruited mostly from the University of Arizona/Banner Medical Center (Tucson, Arizona) chronic pain clinic between August 2016 and October 2019. Recruitment was done by word of mouth at the chronic pain clinic by fellowship-trained pain physicians. These are patients with chronic pain who have been known to the recruiting physicians for months to years.

Inclusion/Exclusion Criteria

Inclusion Criteria

1. Eighteen years or older and can speak and understand English.
2. Meets the diagnostic criteria for fibromyalgia according to the 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria [29]
3. Average numeric pain score of 5 out of 10 or greater over the 10 weeks prior to enrolling in the study and failure of medical therapy to control the pain.

Exclusion Criteria

1. Serious mental illness, defined as distortions of perception, delusions, hallucinations, and unusual behaviors resulting in loss of contact with reality. This was assessed during the screening interview. Patients with psychiatric disorders had their medical records reviewed to ensure they were not diagnosed with serious mental illness.
2. History of color blindness or uncorrected cataracts.
3. Subjects receiving remuneration for their medical conditions.

Light-Emitting Diodes

All visible spectrum light-emitting diode (LED) flex strips were purchased from ledsupply.com (vendor, Vermont, USA). The green LEDs were #LS-AC60-6-GR (525-nm wavelength [i.e., green], 8 watts, 120 volts, 120-degree beam angle), and the white LEDs were #LS-AC60-66-WH (9.6 watts, 120 volts, 120-degree beam angle). A lux meter (HDE, Allentown, Pennsylvania, USA) was used to determine the illuminance and luminous emittance of the LED strips. The LED strips were not manufactured as medical devices.

Light Exposure Protocol

Our study was inspired by the positive results obtained with GLED therapy in animals in different preclinical pain models [27, 28], as well as by the noninvasive nature of green light. Given the severity of the recruited patients' fibromyalgia pain, in spite of previous therapeutics, and given the lack of side effects seen in animals exposed to GLED, the patients consented to undergo the GLED therapy after Institutional Review Board approval was obtained from the University of Arizona. The present study used a one-way crossover design. Patients with fibromyalgia were assigned to the white LEDs (WLED; control) first and then crossed over to the GLED therapy. To minimize bias, the patients were not told about the positive effects of GLED on animals.

The patients were initially provided with a WLED strip that was 2 meters long. We used electrical tape to cover some light bulbs to achieve light intensity of 4 and 100 lux measured at approximately 1 and 2 meters, respectively, from a lux meter. Patients were free to change the distance of the light source between 1 and 2 meters from their eyes to find the intensity that best suited them. To achieve this intensity, we covered two of every three light bulbs across the whole 2-meter strip. The patients were instructed to take the LED strip home and use it in a dark room with no other source of light except the light strip we provided for a minimum of 1 hour every day, with the option to increase the exposure time to 2 hours daily for 10 weeks. The patients were instructed not to fall asleep while undergoing the light therapy. We encouraged the patients to participate in activities that did not require an additional source of light, such as writing, reading, listening to music, etc. We discouraged the patients from engaging in any activity that could introduce another source of light, such as watching television or using devices with screens, such as computers, tablets, or mobile phones. We provided the patients with several paper surveys to document the primary and secondary outcomes.

After WLED exposure for a minimum of 1 hour and a maximum of 2 hours daily for 10 weeks with a minimum intensity of 4 lux and maximum of 100 lux, the patients were crossed over to the GLED after a 2-week "washout" period. The patients were provided with GLED of 525-nm wavelength, with similar exposure parameters as the WLED. The patients were asked to eliminate other sources of extraneous light (no use of televisions, computers, or smartphones; curtains drawn and existing room lights turned off). The patients were encouraged to keep their eyes open, to blink at a normal rate, and not to stare directly at the light source. The patients were encouraged to engage in any activity while undergoing the GLED therapy, such as reading or listening to music, and avoid falling asleep. The patients were allowed to continue their current medical therapy as recommended by their treating physicians. They were also allowed to start any new medications as recommended by their treating physicians. Patients were instructed to document all medications used for their pain. The patients self-reported the data every 2 weeks while undergoing the study to minimize the chances of recall bias. Figure 1 represents the study design.

Surveys for Data Collections

The patients were provided with six paper surveys to fill out. The recruiting physicians explained the surveys to the recruited patients to minimize errors in filling them out. This was done on the day of recruitment. The first survey documented the number of hours per day patients were exposed to the LED strips. The second survey documented their daily analgesic(s) requirement. The third survey, the validated EQ-5D-5L, was designed to evaluate a global quality of life of patients with pain [30]. The fourth survey was a modified follow-up pain clinic survey from the University of Arizona pain clinic to document the patients' average numeric pain scale (NPS) and the percent improvement of their fibromyalgia pain averaged at the end of every 2 weeks for 10 weeks. The fifth survey was the validated Short-Form McGill Pain Questionnaire (SF MPQ) [31]. The sixth survey was the validated Fibromyalgia Impact Questionnaire (FIQ) [32]. The patients were contacted at least once every 2 to 3 weeks to answer any questions they may have had. Additionally, they had unlimited access to the research staff and were able to contact the staff with any question at any time. At the end of the 10 weeks, patients returned all the surveys, and the data were entered into a database for analysis.

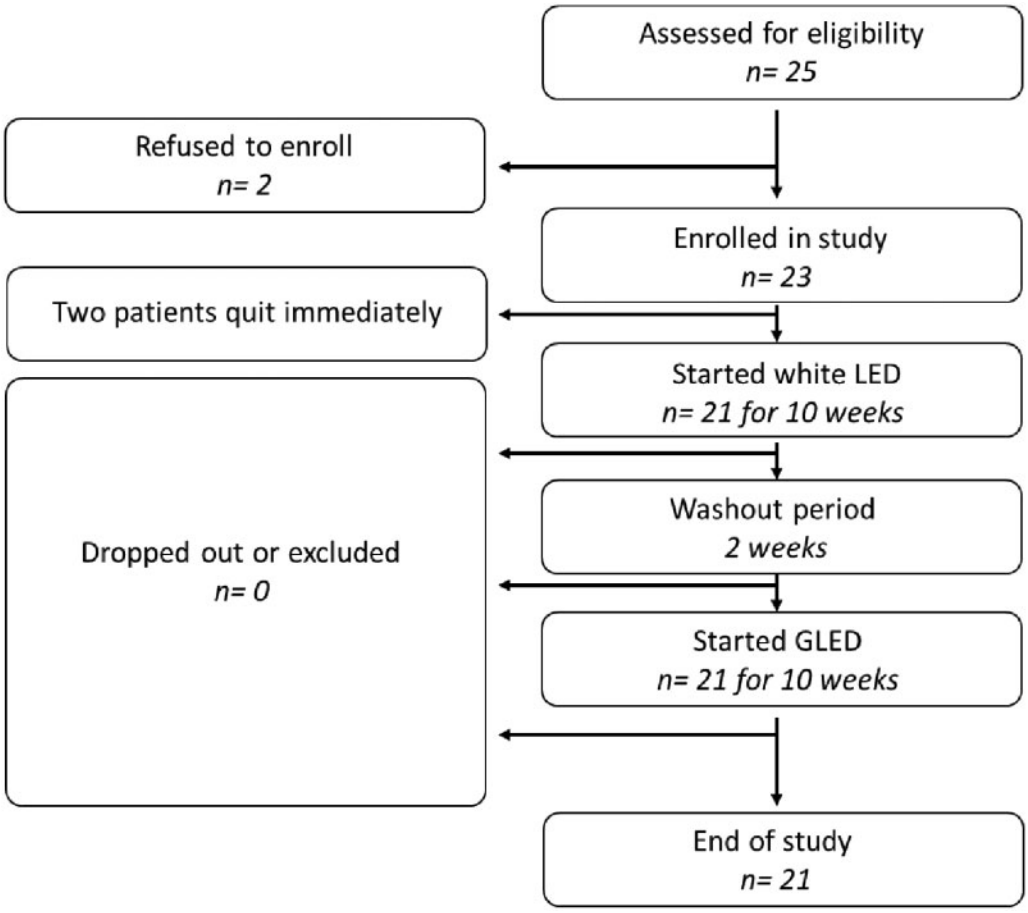

Figure 1. Study design: one-way crossover clinical trial. Twenty-five patients with fibromyalgia were screened for the study, and two patients refused to enroll. Twenty-three patients were assigned to the control WLED group first. Two patients withdrew immediately from the study because of lack of effect or inability to secure the time needed to conduct the study. Analysis did not include these two patients. After 10 weeks of daily WLED, all of the 21 patients who finished the WLED treatment underwent a 2-week washout period and were then crossed over to the GLED treatment.

Outcome Measures

The primary outcome measure was the reduction in the average intensity of fibromyalgia pain, as measured by the NPS. Secondary outcome measures included a decrease in the frequency of pain episodes, a decrease in the duration of pain episodes, an improvement in the ability to fall asleep and stay sleep, an improvement in the ability to perform work and daily activity, an improvement in quality of life, an improvement in the SF MPQ, an improvement in the FIQ, an improvement in the EQ-5D-5L survey, and a reduction in pain medications, as reported by the provided surveys.

Study Approval

This study has been conducted according to Declaration of Helsinki principles. All study subjects provided written, informed consent before enrolling, and the study was approved by the University of Arizona Institutional Review Board. We recruited 21 patients meeting the American College of Rheumatology criteria for fibromyalgia (20 females and one male) for the study. All patients failed traditional therapies for fibromyalgia. This study is registered with clinicaltrials.gov under NCT03677206.

Statistical Analysis

All returned survey data were analyzed. If a survey was not completed, or if the answer was not legible and we were not able to contact the patient for clarification, we excluded that survey from analysis. Applying these criteria, we were not able to analyze three GLED SF MPQs and one WLED SF MPQ, three GLED FIQs and two WLED FIQs, four GLED EQ-5D-5L surveys and two WLED EQ-5D-5L surveys. If a patient did not have one of the parameters affected by fibromyalgia, we asked the patient to write "not applicable" (N/A) next to it, and we did not include this particular parameter in the analysis. For example, if the patient had no problem going to work secondary to his/her fibromyalgia, the patient would mark "N/A" next to the question inquiring about improvement of "ability to work." To analyze our results, we chose to use rank tests, as the data corresponded to qualitative ordinal data. We used Mann-Whitney tests to determine statistical significances

comparing groups that were not paired. For paired groups (before and after), we used Wilcoxon matched-pairs signed rank tests. Statistical significance was considered when the P value was measured at 0.05 or less. We used GraphPad Prizm 8 for statistical analysis.

Results

Patient Demographics and Baseline Pain Data

The average age (± standard error of the mean [SEM]) of the patients at the time of recruitment was 53.25 ± 2.9 years (range: 26 to 75 years). Although males can experience fibromyalgia, females have a greater prevalence of fibromyalgia [33, 34]. With the exception of one male patient, all recruited patients were females. This predominance of female patients in the study was unintentional. Table 1 illustrates the demographics of the recruited patients.

Patient Recruitment

We screened 25 patients with fibromyalgia for the study. Two patients refused to enroll. We recruited 23 patients with fibromyalgia into the study. All patients were enrolled in the WLED group first (control). One patient withdrew from the study because of lack of effect. Another patient withdrew immediately because of inability to secure the time needed to conduct the study. These two patients were excluded from analysis. All of the 21 patients who finished the WLED treatment were crossed over into the GLED treatment (Figure 1).

The patients were not monetarily compensated.

Exposure Time

On average, patients used the WLED for 1.6 ± 0.02 (SEM) hours/day, as assessed by self-report. Patients used the GLED for 1.45 ± 0.02 (SEM) hours/day. On average, patients remained in the WLED group for an average of 7 weeks before crossing over to the GLED group. When patients were asked about the reason for early termination, they reported the lack of effect to be the reason for early termination of the WLED exposure. No side effects or intolerability issues were cited. Patients remained in the GLED group for 9.37 ± 0.3 (SEM) weeks of the 10 weeks.

Table 1. The demographics and initial pain score of the recruited patients with fibromyalgia

Demographics	
Average age, years	53.25 ± 2.9
Female, %	95%
Male, %	5%
Caucasians, %	71%
Hispanics, %	29%
Average pain score (0–10)	8.7 ± 0.24

Data are presented as percent or average ± SEM.

Table 2. NPS scores before and after WLED or GLED exposure

NPS	Initial value ± SEM	Final value ± SEM	n	P value	Significance
WLED	8.71 ± 0.24	8.14 ± 0.40	21	0.14	
GLED	8.38 ± 0.27	4.86 ± 0.44	21	<0.0001	***

Data are presented as average ± SEM.

WLED exposure did not produce a statistically significant reduction in NPS scores (scale 0–10). GLED exposure produced a statistically significant reduction in the NPS scores (Wilcoxon matched-pairs signed rank test, $***P < 0.001$).

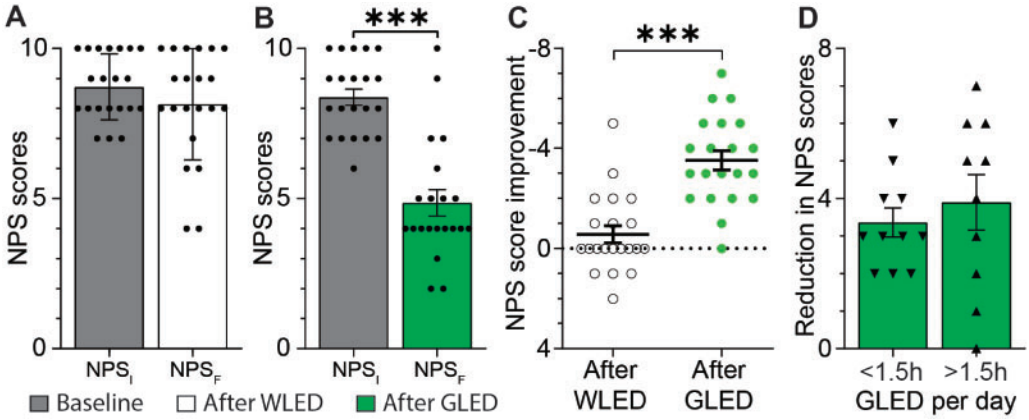

Figure 2. Pain score evaluation before and after WLED and GLED exposure. **(A)** WLED exposure did not significantly change the pain intensity baseline represented by bar on the left hand side of panel A for patients with fibromyalgia evaluated with the NPS (n = 21), and **(B)** GLED exposure statistically decreased the baseline represented by bar on the left hand side of panel B pain intensity for patients with fibromyalgia evaluated with the NPS (n = 21, Wilcoxon matched-pairs signed rank test, $***P < 0.001$). NPS_I = initial NPS; NPS_F = final NPS. **(C)** Results represent NPS score improvement in both WLED and GLED groups. Values correspond to the initial score subtracted from the final score. Patients exposed to GLED reported significantly higher NPS pain reduction than patients exposed to WLED (n = 21, Mann-Whitney test, $***P < 0.001$). **(D)** Patients exposed to GLED for greater than 1.5 hours/day (>1.5 h/day) reported slightly higher, but not statistically significant, NPS pain reduction than that of patients exposed to GLED for less than 1.5 hours/day (<1.5 h/day) (n = 10–11, Mann-Whitney test, $P = 0.4750$).

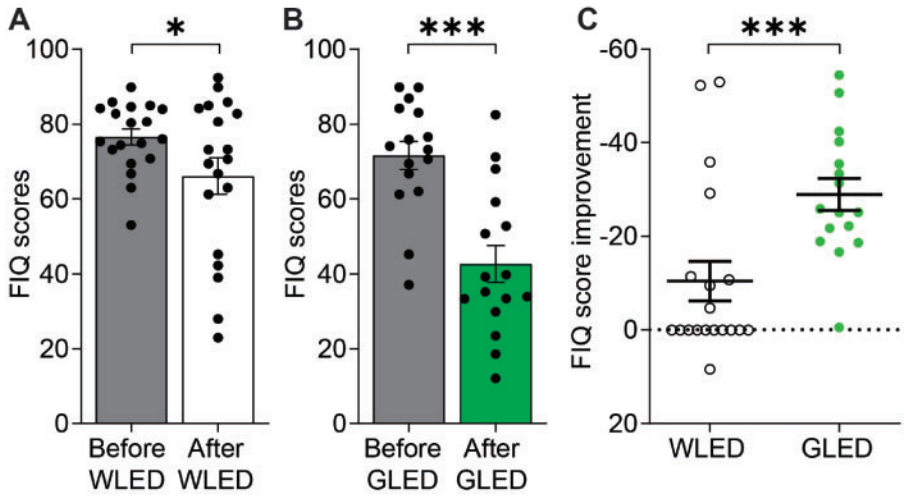

Figure 3. FIQ scores before and after WLED or GLED exposure. **(A)** WLED exposure produced a small but statistically significant reduction in FIQ. **(B)** GLED exposure produced a statistically significant larger reduction in the FIQ (scale 0–100, where 0 = no impact from fibromyalgia, and 100 = worst possible impact from fibromyalgia). Data are presented as average ± SEM (n [WLED] = 19, n [GLED] = 16, Wilcoxon matched-pairs signed rank test, $*P < 0.05$, $***P < 0.001$). **(C)** Results represent FIQ score improvement in both WLED and GLED groups. Values correspond to the initial score subtracted from the final score. Patients exposed to GLED reported significantly higher FIQ score improvement than did patients exposed to WLED (n [WLED] = 19, n [GLED] = 16, Mann-Whitney test, $***P < 0.001$).

Table 3. FIQ results before and after WLED or GLED exposure

FIQ	Initial value ± SEM	Final value ± SEM	n	*P* value	Significance
WLED	76.53 ± 2.11	66.1 ± 4.84	19	0.012	*
GLED	71.62 ± 3.74	42.7 ± 4.9	16	<0.0001	***

Data are presented as average ± SEM.

WLED exposure produced a small but statistically significant reduction in FIQ. GLED exposure produced a statistically significant larger reduction in the FIQ (scale 0–100, where 0 = no impact from fibromyalgia, and 100 = worst possible impact from fibromyalgia) (Wilcoxon matched-pairs signed rank test, $*P < 0.05$, $***P < 0.001$).

Primary Outcome

Pain intensity was measured with the average NPS (averaged every 2 weeks). WLED exposure had no significant effect on pain intensity for patients with fibromyalgia. Their NPS pain intensity was 8.7 ± 0.2 (SEM) (range from 7 to 10) and 8.1 ± 0.4 (SEM) (range from 4 to 10) before and after exposure to WLED light, respectively (Figure 2A **and** Table 2). Patients were then crossed over to the GLED treatment after a 2-week washout period and were instructed to follow the same exposure parameters. They reported a statistically significant reduction in their average NPS pain intensity, from 8.4 ± 0.3 (SEM) (range from 6 to 10) to 4.9 ± 0.4 (SEM) (range from 2 to 10) (Figure 2B and Table 2). When NPS score improvements in the WLED and GLED groups were compared, patients who were exposed to GLED presented a reduction in their NPS score of 3.5 ± 0.4 (SEM) versus a reduction of 0.6 ± 0.3 (SEM) for patients exposed to WLED (Figure 2C). Patients with an average exposure to GLED of 1.5 hours/day or less reported a reduction of 3.4 ± 0.4 (SEM) points (i.e., improvement) in the NPS score. Patients who were exposed to GLED for an average of 1.5 hours/day or more reported a reduction of 3.90 ± 0.7 (SEM) points in their NPS score ($P = 0.4750$) (Figure 2D).

We also compared the degree of pain reduction after exposure to GLED between premenopausal and postmenopausal patients (data not shown). In premenopausal patients, GLED decreased the NPS by 4.25 ± 1 (SEM) points. In postmenopausal patients, GLED decreased the NPS by 3.76 ± 0.44 (SEM) points. No statistically significant difference was noted between the pre- and postmenopausal patients' responses to GLED.

Secondary Outcomes

Although the reduction in pain intensity was encouraging, it is also important to evaluate the potential effects of GLED exposure on quality-of-life measures. We used the FIQ to assess the effects of WLED and GLED exposure on the health status of patients with fibromyalgia. Patients reported a small but statistically significant improvement in the FIQ score after exposure to WLED (Figure 3A and Table 3). GLED exposure, on the other hand, produced a significantly greater improvement of the FIQ score than did WLED exposure. (Figure 3B and C and Table 3).

We also asked the patients to subjectively evaluate their pain frequency; duration of pain episodes; ability to fall asleep, stay asleep, work, exercise, and do household chores; and their overall quality of life. WLED exposure did not significantly improve the evaluated parameters in patients with fibromyalgia (Figure 4 and Table 4). GLED exposure, on the other hand,

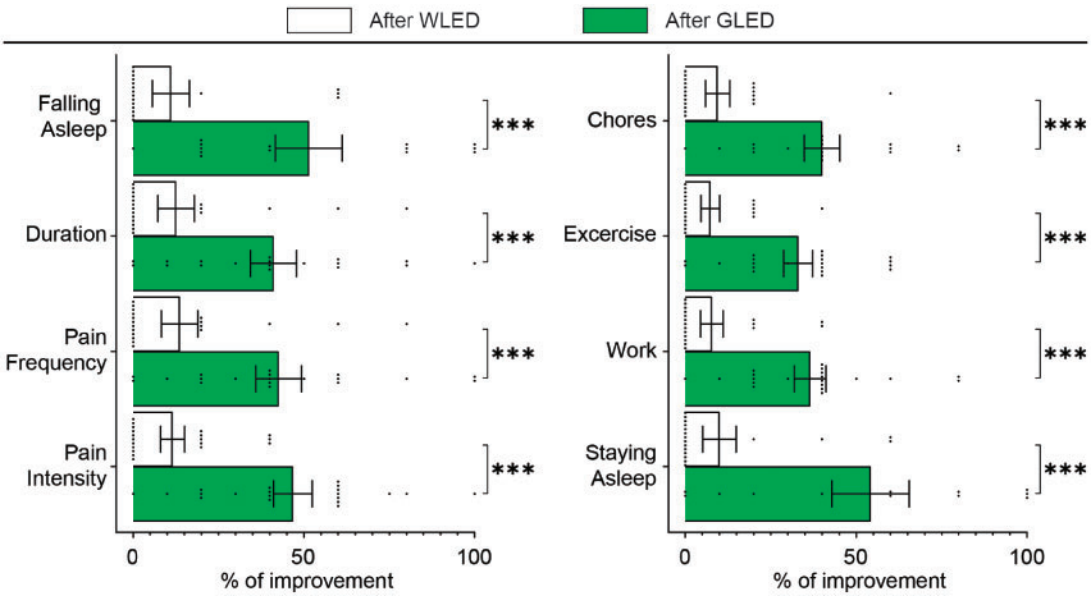

Figure 4. Patients' subjective improvement of several criteria after WLED or GLED exposure. WLED exposure produced minimal improvement in several parameters for patients with fibromyalgia, whereas GLED exposure produced significant improvement in all parameters. Data are presented as average ± SEM (n [WLED] = 18–19, n [GLED] = 12–21, Mann-Whitney test, ***$P < 0.001$).

Table 4. Improvement of different quality of life criteria after WLED or GLED exposure

Function	% Improvement ± SEM (WLED)	n_{WLED}	% Improvement ± SEM (GLED)	n_{GLED}	*P* value	Significance
Pain intensity	11.6 ± 3.53	19	42.5 ± 5.81	21	<0.0001	***
Pain frequency	13.7 ± 5.31	19	42.6 ± 6.70	19	0.0006	***
Pain duration	12.6 ± 5.34	19	41.1 ± 6.76	18	0.0007	***
Ability to fall asleep	11.1 ± 5.41	18	51.4 ± 9.77	14	0.0001	***
Ability to stay asleep	10.0 ± 4.91	18	54.1 ± 11.31	12	0.0004	***
Ability to work	7.7 ± 3.29	18	36.5 ± 4.60	20	<0.0001	***
Ability to exercise	7.39 ± 2.74	19	33.0 ± 4.24	20	<0.0001	***
Ability to perform chores	9.47 ± 3.54	19	40.0 ± 5.18	18	<0.0001	***

Data are presented as average ± SEM.

WLED exposure produced a minimal improvement in several parameters in patients with fibromyalgia. The following criteria were evaluated after completion of WLED therapy as compared with baseline (n = 19): percent improvement of pain intensity, pain frequency, pain duration, ability to fall asleep, ability to stay asleep, ability to work, ability to exercise, and ability to do chores. GLED exposure produced a significant improvement in all measured parameters in patients with fibromyalgia (n = 19).

***$P < 0.001$.

produced significant improvement in all measured parameters (Figure 4 and Table 4). Patient health status was evaluated through the EQ-5D-5L questionnaire (Figure 5). Both WLED and GLED exposure produced a statistically significant improvement in patients' quality of life as assessed with the EQ-5D-5L surveys (Figure 5A and B and Table 5), but GLED exposure was responsible for a significantly greater improvement than was WLED (Figure 5C). When the patients reported their perception of their own health, both WLED and GLED improved this parameter (Figure 5D and E and Table 5), and no significant differences were noted between the two groups (Figure 5F).

SF MPQ results demonstrated minor, but statistically significant, changes from baseline in 6 of the 15 descriptive pain measures, including the "throbbing," "tender," "sickening," "shooting," "aching," and "stabbing" components of their pain (Figure 6 and Table 6). On the other hand, SF MPQ analysis demonstrated statistically significant improvements from baseline in 12 of the 15 descriptive pain measures. Indeed, patients exposed to GLED showed improvements in all the sensory and affective components, except in the "fearful" aspect (Figure 7 and Table 7).

Assessing the reduction in pain medication secondary to GLED was challenging. Patients were on

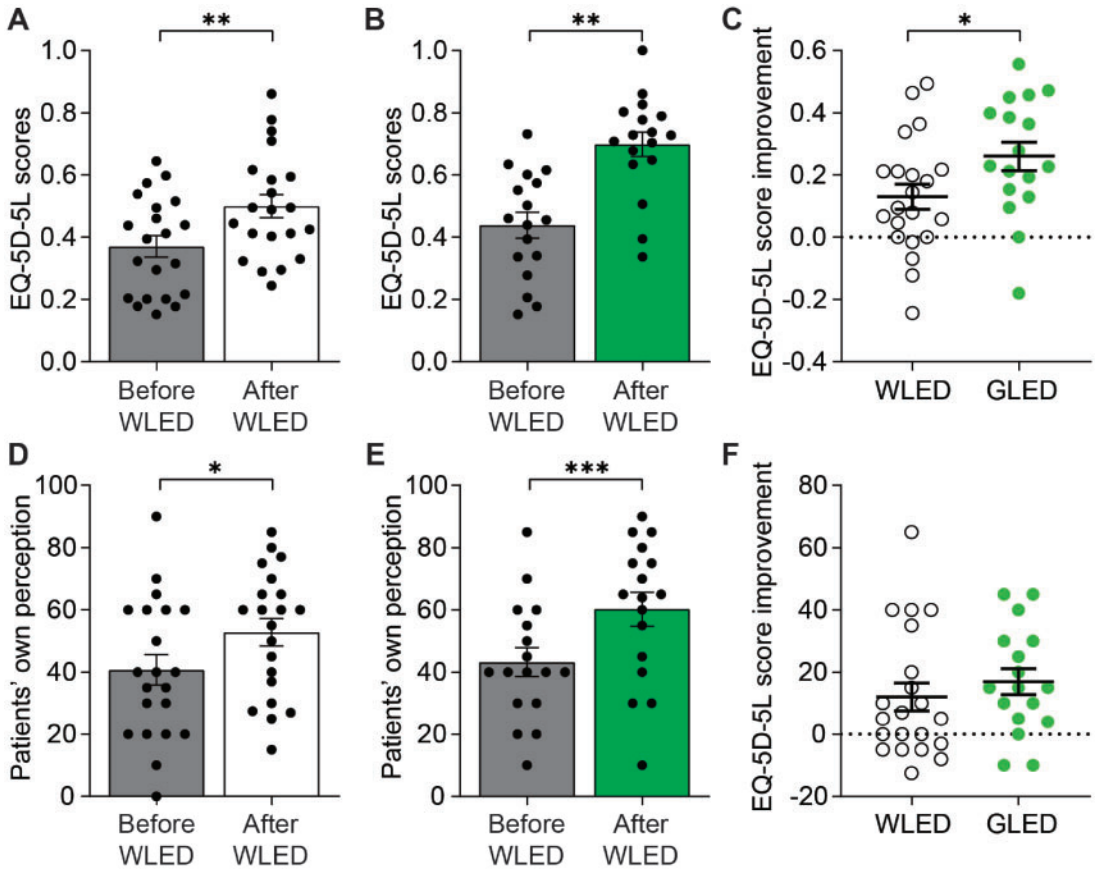

Figure 5. Quality of life and patients' perception of their own health after WLED or GLED exposure. **(A)** WLED exposure produced a small but statistically significant improvement in the quality of life and patients' perception of their own health as measured by the EQ-5D-5L survey (n = 20, Wilcoxon matched-pairs signed rank test, $*P < 0.05$). **(B)** GLED exposure produced greater and statistically significant improvement in the quality of life and the patients' perception of their own health as measured by the EQ-5D-5L survey (n = 17, Wilcoxon matched-pairs signed rank test, $**P < 0.01$). **(C)** Results represent EQ-5D-5L score improvement in both WLED and GLED groups. Values correspond to the initial score subtracted from the final score. Patients exposed to GLED reported significantly higher EQ-5D-5L scores than did patients exposed to WLED (n [WLED] = 21, n [GLED] = 17, Mann-Whitney test, $*P < 0.05$). **(D)** WLED exposure produced a small but statistically significant improvement of the quality of life and patients' perception of their own health as measured by the EQ 5 D-5L survey (n = 21, Wilcoxon matched-pairs signed rank test, $*P < 0.05$). **(E)** GLED exposure also produced a significant improvement of the quality of life and the patients' perception of their own health as measured by the EQ 5 D-5L survey (n = 17, Wilcoxon matched-pairs signed rank test, $***P < 0.001$). **(F)** Results represent patients' own perception of improvement in both the WLED and GLED groups, as reported in the EQ-5D-5L. Values correspond to the initial score subtracted from the final score. Patients exposed to GLED did not report a significantly higher improvement in their perception of their own health (n [WLED] = 21, n [GLED] = 17, Mann-Whitney test, $P = 0.2275$). Data are presented as average ± SEM.

Table 5. EQ-5D-EL survey evaluation after WLED or GLED exposure

EQ-5D-5L	Initial value ± SEM	Final value ± SEM	N	P value	Significance
WLED					
Index (0-1)	0.37 ± 0.03	0.50 ± 0.04	21	0.0061	**
Health Perception (0-100)	40.7 ± 4.89	52.8 ± 4.41	21	0.017	*
GLED					
Index (0-1)	0.44 ± 0.04	0.70 ± 0.04	17	0.0002	***
Health Perception (0-100)	43.2 ± 4.62	60.2 ± 5.46	17	0.001	***

Data are presented as average ± SEM.

WLED exposure produced a statistically significant improvement in the EQ-5D-5L index. Index scale was 0–1, where 0 = worst quality of life, and 1 = best quality of life. WLED also produced a small significant improvement in the patients' own perceived health according to the EQ-5D-5L survey (health perception scale 0–100, where 0 = worst imagined health, and 100 = best imagined health; n = 21, Wilcoxon matched-pairs signed rank test, $*P < 0.05$, $**P < 0.01$). GLED exposure produced a statistically significant improvement in the EQ-5D-5L index and the patients' own perceived health according to the EQ-5D-5L survey (n = 17, Wilcoxon matched-pairs signed rank test, $***P < 0.001$).

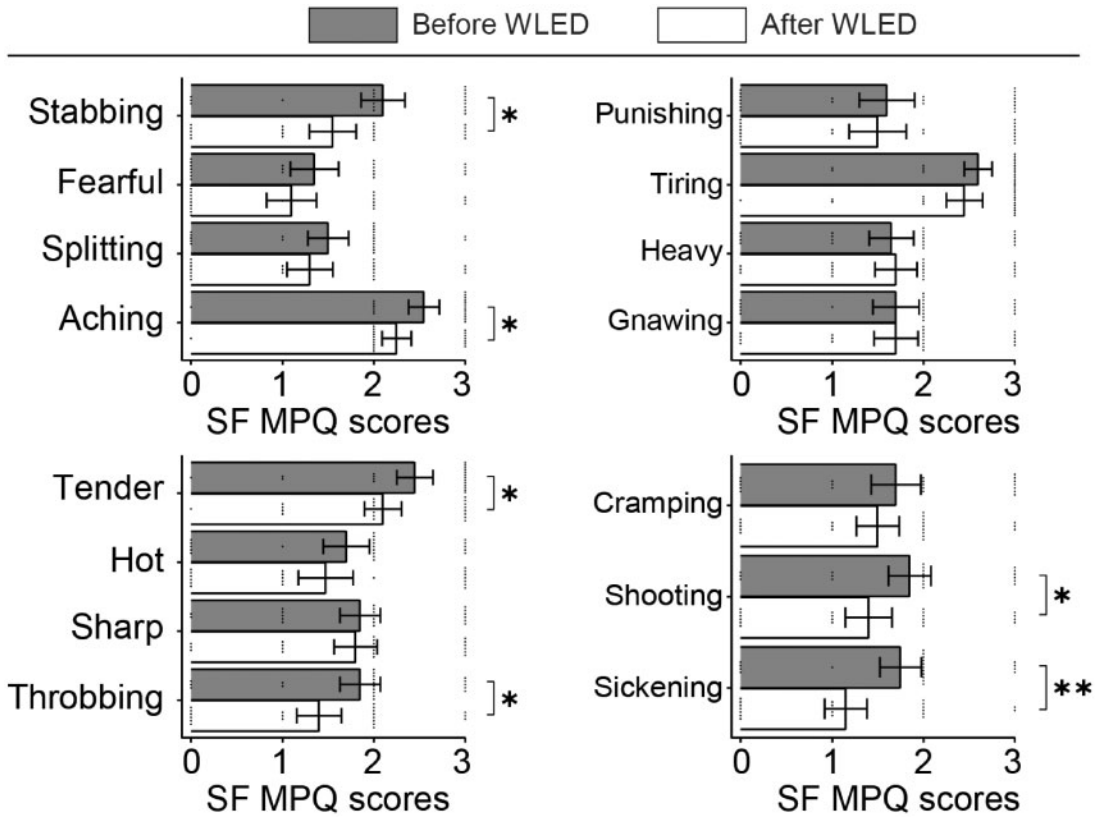

Figure 6. SF MPQ scores before and after WLED exposure in patients with fibromyalgia. WLED exposure significantly decreased 6 of the 15 baseline values for patients with fibromyalgia in the SF MPQ. Data are presented as average ± SEM (n = 20, Wilcoxon matched-pairs signed rank test, $*P < 0.05$, $**P < 0.01$).

Table 6. SF MPQ scores before and after WLED exposure

Descriptive	Initial score (0–3) ± SEM	Final score (0–3) ± SEM	n	*P* value	Significance
Throbbing	1.85 ± 0.22	1.40 ± 0.24	20	0.047	*
Sharp	1.85 ± 0.22	1.80 ± 0.24	20	>0.999	
Hot	1.70 ± 0.25	1.47 ± 0.30	20	0.41	
Tender	2.45 ± 0.19	2.10 ± 0.20	20	0.0016	*
Sickening	1.75 ± 0.22	1.15 ± 0.23	20	0.0054	**
Shooting	1.85 ± 0.23	1.40 ± 0.25	20	0.035	*
Cramping	1.70 ± 0.27	1.50 ± 0.24	20	0.36	
Aching	2.55 ± 0.17	2.25 ± 0.16	20	0.031	*
Splitting	1.50 ± 0.22	1.30 ± 0.25	20	0.37	
Fearful	1.35 ± 0.26	1.10 ± 0.27	20	0.31	
Stabbing	2.10 ± 0.24	1.55 ± 0.26	20	0.032	*
Gnawing	1.70 ± 0.25	1.70 ± 0.24	20	>0.999	
Heavy	1.65 ± 0.24	1.70 ± 0.23	20	0.97	
Tiring	2.60 ± 0.15	2.45 ± 0.20	20	0.25	
Punishing	1.60 ± 0.30	1.50 ± 0.31	20	0.77	

Data are presented as average ± SEM.

WLED exposure produced some improvement for some of the components of the SF MPQ., (n = 20, Wilcoxon matched-pairs signed rank test, $*P < 0.05$, $** P < 0.01$).

pharmacologically different classes of medication as they began the studies. For example, some patients with comorbid arthritis were on nonsteroidal anti-inflammatory drugs, whereas others were taking muscle relaxants on an as-needed basis. Therefore, we were not able to average and compare pain medication reduction in these patients. However, 11 patients self-reported that they had reduced their habitual pain

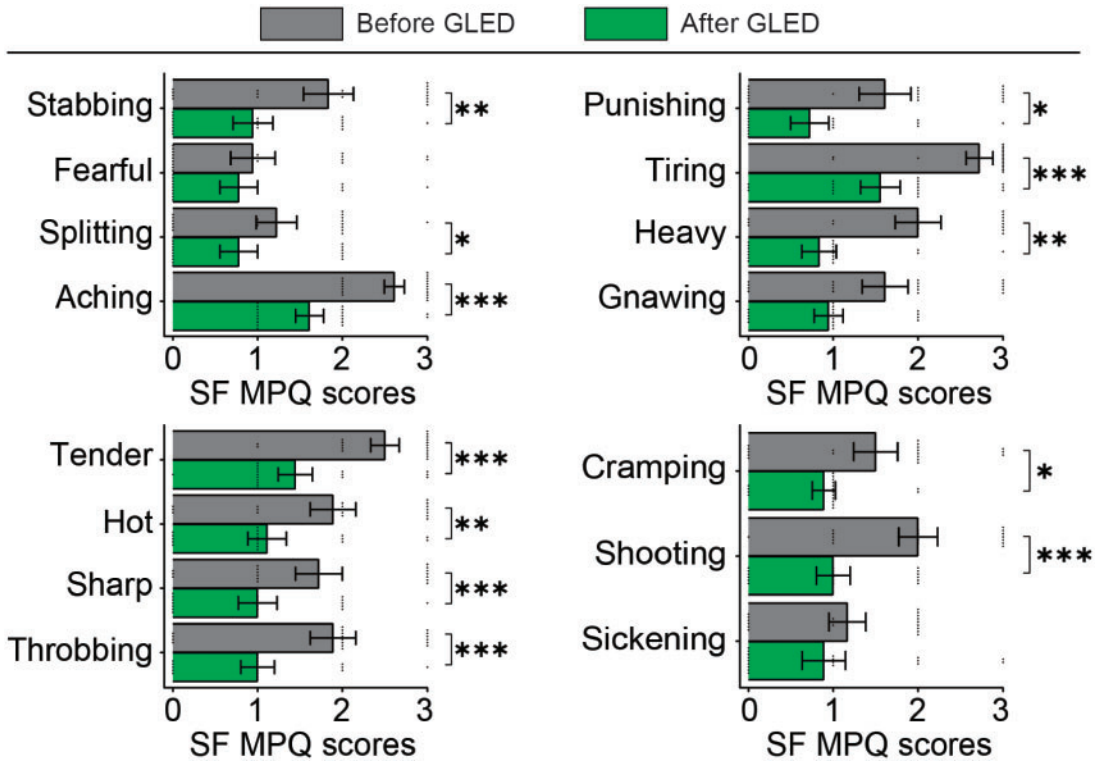

Figure 7. SF MPQ scores before and after GLED exposure in patients with fibromyalgia. GLED exposure significantly decreased 12 of the 15 baseline values for patients with fibromyalgia in the SF MPQ. For each parameter, the top bar represents the Before GLED value while the bottom bar represent the After GLED value. Data are presented as average ± SEM (n = 18, Wilcoxon matched-pairs signed rank test, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$).

Table 7. SF MPQ scores before and after GLED exposure

Descriptive	Initial score (0–3) ± SEM	Final score (0–3) ± SEM	n	*P* value	Significance
Throbbing	1.88 ± 0.27	1.00 ± 0.20	18	0.0005	***
Sharp	1.72 ± 0.28	1.00 ± 0.23	18	0.0005	***
Hot	1.89 ± 0.27	1.11 ± 0.23	18	0.0078	**
Tender	2.50 ± 0.17	1.44 ± 0.20	18	0.0001	***
Sickening	1.17 ± 0.22	0.89 ± 0.25	18	0.3438	
Shooting	2.00 ± 0.23	1.00 ± 0.20	18	0.0002	***
Cramping	1.50 ± 0.26	0.89 ± 0.14	18	0.0225	*
Aching	2.61 ± 0.12	1.61 ± 0.16	18	<0.0001	***
Splitting	1.22 ± 0.24	0.78 ± 0.24	18	0.0313	*
Fearful	0.94 ± 0.26	0.78 ± 0.22	18	0.6152	
Stabbing	1.83 ± 0.29	0.94 ± 0.23	18	0.0039	**
Gnawing	1.61 ± 0.27	0.94 ± 0.17	18	0.0549	
Heavy	2.00 ± 0.27	0.83 ± 0.20	18	0.0022	**
Tiring	2.72 ± 0.16	1.56 ± 0.23	18	0.0003	***
Punishing	1.61 ± 0.30	0.72 ± 0.23	18	0.0146	*

Data are presented as average ± SEM.

GLED exposure significantly improved 12 of the 15 components of the SF MPQ (n = 18, Wilcoxon matched-pairs signed rank test, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$).

medications (including opioids) while being exposed to GLED.

Adverse Events

No adverse events were reported or noticed in any of the participants secondary to either WLED or GLED exposure.

Discussion

This study investigated the use of GLED as a nonpharmacological approach to managing fibromyalgia pain. To our knowledge, this one-way crossover design efficacy-study clinical trial is the first description of a successful implementation of GLED exposure as a therapy to

manage fibromyalgia pain without any reported side effects. The patients enrolled in this study reported significant reduction in their overall average pain intensity, frequency, and duration after GLED treatment relative to the WLED control condition. Patients who were exposed to GLED for an average of 1.5 hours/day or more reported slightly greater pain reduction than those who were exposed to GLED for an average of less than 1.5 hours/day. However, although there was a trend toward having greater NPS pain reduction with longer exposure to GLED, that difference was not significantly different. Additionally, the menopausal state of patients did not affect their responses to GLED. The patients' ability to fall asleep, remain asleep, and perform chores also improved with GLED exposure. Although it has long been established that pain and sleep are intimately related [35, 36], whether GLED improved pain, which then led to an improvement in sleep, or vice versa could not be determined in the present study. Light therapy can affect sleep; it has been previously documented that blue light suppresses melatonin release and delays the onset of sleep [37, 38]. Therefore, it is possible that GLED therapy may have independently improved both sleep and pain by the same or different mechanisms. The potential effects of GLED on sleep in animals is currently being investigated in our laboratory.

The recruited patients reported significant improvement not only in terms of their pain scores, but also with regard to their perception of their overall health as measured by the EQ-5D-5L survey after exposure to GLED. This is possibly secondary to improvements in pain and sleep. Depression is comorbid with both sleep disorders and chronic pain [39]. It is also possible that GLED therapy may have simply elevated patients' "mood," leading to a more positive perception of their own health. GLED also resulted in statistically significant improvement in 12 of the 15 components of the SF MPQ, as well as the FIQ. WLED produced some improvements in six components of the SF MPQ and FIQ, but these improvements were less robust than those seen with GLED.

For 11 of the recruited patients, GLED was associated with a self-reported reduction in pain medication, but this effect was not consistently observed. The pain medications included opioids, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, acetaminophen, and membrane stabilizers (gabapentin and pregabalin). Given that we took into consideration only pain medications that were used on a daily basis, and appreciating that patients may use pain medications for the management of transient unrelated pain, it was difficult to draw a conclusion about the reduction in pain medications after GLED therapy. However, there was a nonsignificant trend toward a decreased need for pain medications. It is also possible that patients were reluctant to decrease their pain medications in the time given to gather the data during this study, despite improvement in their pain, because some of these medications require careful titration by the prescribing physicians. For example, abrupt cessation of gabapentin may result in seizures [40] and catatonia [41]. Therefore, patients are typically advised to contact their physicians before decreasing gabapentin [42]. A longer follow-up is needed to better evaluate the effect of GLED on the likelihood of reducing the amount of pain medication.

Other studies have shown that different light wavelengths may influence the perception of pain. Hoggan et al. recruited patients with chronic migraine and then asked them to wear special filter glasses that block out certain color wavelengths during all waking hours for 2 weeks, followed by completing the Headache Impact Test survey to evaluate the intensity and the effect of the migraine pain on their daily activities. That study reported that blocking either red or blue light by using glasses coated with thin filters lowered the intensity of pain experienced by migraine patients [43]. Although the Hoggan et al. study focused on blocking a specific wavelength in the red spectrum, it is important to note that the glasses allowed the green wavelength to pass through relatively unimpeded. It is possible that the effects reported by this group were attributable not only to blocking of red and blue light but also to relatively sustained exposure to green light. Noseda and colleagues investigated the effects of several visible wavelengths on patients with acute migraine attack. They noticed that patients with acute migraine had increased photophobia when exposed to different wavelengths, but the color with the least photophobia was green. Additionally, they noted that about 20% of the patients in their green light group reported improved migraine pain intensity by about 15% during an acute migraine attack [26]. Our results are in agreement with both of these studies and also support a possible beneficial role of green light in the treatment of migraine.

Some limitations of our study should be noted. This study was designed as a proof-of-concept investigation. We assessed 25 fibromyalgia patients and were able to recruit 21 patients. All our analyzed patients were females, except for one male patient. Therefore, the effects of GLED or the extent of pain reduction cannot be generalized to males at this time. In our studies in animals, however, both male and female rats responded to GLED [27], suggesting that males are likely to respond in a similar manner. In animal studies, we have shown that the effect of GLED was mediated through the visual system. In humans, we assumed that the effect was through the visual system, but we did not investigate that assumption in the present study. Future studies of GLED in humans will focus on the role played by the visual system. Another limitation to the study was the inability to fully assess the effect of GLED on pain medication use. Although some patients reported a decrease in their requirement for pain medications, it was not possible to reach any conclusion because of variability in the classes and doses of

medications. Another limitation is that we have not investigated the mechanisms of action of the GLED in humans. Our published work in animals suggests the possibility of increased spinal cord enkephalins after GLED exposure. However, there are likely other mechanisms of action that could drive the observed effects in humans. For example, patients with fibromyalgia have been reported to have increased inflammatory cytokines [44–46] that might be modulated by GLED exposure. Such possibilities will be explored in future studies.

In terms of compliance, we were not able to independently verify the length of exposure time except through the written time log survey. Future studies will use electronic devices with time stamps to verify the time and length of light exposure. Additionally, future studies will use electronic methods rather than paper surveys for documentation by patients. Finally, this was a one-way crossover trial. There were two main reasons to decide on such a design. First, an accurate washout period for the effect of GLED was not known in humans. Therefore, it was more practical to start the exposure with the control condition (white light exposure) given that we assumed it had no significant effect on the primary outcome. Second, given the fact that the recruited patients with fibromyalgia had very limited treatment options by the time they were recruited, we tested our hypothesis with a simple trial design that was less burdensome to the patient in case of a negative trial. Had we exposed the patients to GLED light first and they experienced pain relief with GLED, it would have been difficult to convince the patients to abandon a therapy that worked and try the control condition (WLED). Such a design would have decreased compliance among patients. However, the patients were not aware of which was the control light and which was the treatment light. Furthermore, patients did not communicate with one another, as the recruitment was done with patients individually. These measures were designed to minimize bias among patients. Future experiments will use a randomized clinical trial design with possible crossover from control to treatment.

Conclusion

GLED may be a safe and affordable method to manage fibromyalgia. We did not observe side effects in animal studies or in reports from our patients. The observed safety and efficacy, coupled with the simplicity of this method, merit further investigation and the design of a randomized clinical trial to fully investigate the role of GLED for fibromyalgia and possibly other chronic pain conditions.

Acknowledgments

The authors thank Ms. Vangie Steinbrenner for her valuable assistance with obtaining the Institutional Review Board approval for this study. We also thank Debbie Schaab, RN, for her tireless efforts to follow up with patients and her overall help with this study.

References

1. Bennett RM. Clinical manifestations and diagnosis of fibromyalgia. Rheum Dis Clin North Am 2009;35(2):215–32.
2. Goldenberg DL. Fibromyalgia syndrome: An emerging but controversial condition. JAMA 2014;311(15):1570.
3. Goldenberg DL. Fibromyalgia syndrome a decade later: What have we learned? Arch Intern Med 1999;159(8):777–85.
4. Vincent A, Lahr BD, Wolfe F, et al. Prevalence of fibromyalgia: A population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. Arthritis Care Res (Hoboken) 2013;65(5):786–92.
5. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33(2):160–72.
6. Bradley LA. Pathophysiology of fibromyalgia. Am J Med 2009;122(12):S22–30.
7. Jahan F, Nanji K, Qidwai W, Qasim R. Fibromyalgia syndrome: An overview of pathophysiology, diagnosis and management. Oman Med J 2012;27(3):192–5.
8. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis Rheum 1986;29(11):1371–7.
9. Carette S, McCain GA, Bell DA, Fam AG. Evaluation of amitriptyline in primary fibrositis. A double-blind, placebo-controlled study. Arthritis Rheum 1986;29(5):655–9.
10. Carette S, Bell MJ, Reynolds WJ, et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. Arthritis Rheum 1994;37(1):32–40.
11. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev 2014;1:CD007115.
12. Hassett AL, Gevirtz RN. Nonpharmacologic treatment for fibromyalgia: Patient education, cognitive-behavioral therapy, relaxation techniques, and complementary and alternative medicine. Rheum Dis Clin N Am 2009;35(2):393–407.
13. Hauser W, Walitt B, Fitzcharles MA, Sommer C. Review of pharmacological therapies in fibromyalgia syndrome. Arthritis Res Ther 2014;16(1):201.
14. Brunton S, Wang F, Edwards SB, et al. Profile of adverse events with duloxetine treatment: A pooled analysis of placebo-controlled studies. Drug Saf 2010;33(5):393–407.
15. Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev 2013;(12):CD010884.
16. Bidonde J, Busch AJ, Webber SC, et al. Aquatic exercise training for fibromyalgia. Cochrane Database Syst Rev 2014;(10):CD011336.
17. Hauser W, Klose P, Langhorst J, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: A systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther 2010;12(3):R79.
18. Sanudo B, Galiano D. Using cardiovascular parameters and symptom severity to prescribe physical activity in women with fibromyalgia. Clin Exp Rheumatol 2009;27(5 Suppl 56):S62–6.
19. Eastman CI, Young MA, Fogg LF, Liu L, Meaden PM. Bright light treatment of winter depression: A placebo-controlled trial. Arch Gen Psychiatry 1998;55(10):883–9.

20. Leichtfried V, Matteucci Gothe R, Kantner-Rumplmair W, et al. Short-term effects of bright light therapy in adults with chronic nonspecific back pain: A randomized controlled trial. Pain Med 2014;15(12):2003–12.
21. Andrade FdS, Clark RM, Ferreira ML. Effects of low-level laser therapy on wound healing. Rev Col Bras Cir 2014;41(2):129–33.
22. Hsieh RL, Lee WC. Short-term therapeutic effects of 890-nanometer light therapy for chronic low back pain: A double-blind randomized placebo-controlled study. Lasers Med Sci 2014;29 (2):671–9.
23. Osiecka BJ, Nockowski P, Szepietowski JC. Treatment of actinic keratosis with photodynamic therapy using red or green light: A comparative study. Acta Derm Venereol 2018;98(7):689–93.
24. Hansen MM, Jones R, Tocchini K. *Shinrin-yoku* (forest bathing) and nature therapy: A state-of-the-art review. Int J Environ Res Public Health 2017;14(8):851.
25. de Tommaso M, Sciruicchio V. Migraine and central sensitization: Clinical features, main comorbidities and therapeutic perspectives. Curr Rheumatol Rev 2016;12(2):113–26.
26. Noseda R, Bernstein CA, Nir RR, et al. Migraine photophobia originating in cone-driven retinal pathways. Brain 2016;139 (7):1971–86.
27. Ibrahim MM, Patwardhan A, Gilbraith KB, et al. Long-lasting antinociceptive effects of green light in acute and chronic pain in rats. Pain 2017;158(2):347–60.
28. Khanna R, Patwardhan A, Yang X, et al. Development and characterization of an injury-free model of functional pain in rats by exposure to red light. J Pain 2019;20(11):1293–306.
29. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016;46(3):319–29.
30. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727–36.
31. Melzack R. The Short-Form McGill Pain Questionnaire. Pain 1987;30(2):191–7.
32. Burckhardt CS, Clark SR, Bennett RM. The Fibromyalgia Impact Questionnaire: Development and validation. J Rheumatol 1991;18(5):728–33.
33. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: Updated statistics from government health surveillance studies. Headache 2015;55(1):21–34.
34. Jones GT, Atzeni F, Beasley M, et al. The prevalence of fibromyalgia in the general population: A comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis Rheumatol 2015;67(2):568–75.
35. Cheatle MD, Foster S, Pinkett A, Lesneski M, Qu D, Dhingra L. Assessing and managing sleep disturbance in patients with chronic pain. Sleep Med Clin 2016;11(4):531–41.
36. Yang CP, Wang SJ. Sleep in patients with chronic migraine. Curr Pain Headache Rep 2017;21(9):39.
37. Brainard GC, Hanifin JP, Greeson JM, et al. Action spectrum for melatonin regulation in humans: Evidence for a novel circadian photoreceptor. J Neurosci 2001;21(16):6405–12.
38. Esaki Y, Kitajima T, Ito Y, et al. Wearing blue light-blocking glasses in the evening advances circadian rhythms in the patients with delayed sleep phase disorder: An open-label trial. Chronobiol Int 2016;33(8):1037–44.
39. Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: Research findings and theoretical considerations. Psychosom Med 2002;64(5):773–86.
40. Barrueto F, Jr., Green J, Howland MA, Hoffman RS, Nelson LS. Gabapentin withdrawal presenting as status epilepticus. J Toxicol Clin Toxicol 2002;40(7):925–8.
41. Rosebush PI, MacQueen GM, Mazurek MF. Catatonia following gabapentin withdrawal. J Clin Psychopharmacol 1999;19(2):188–9.
42. Norton JW. Gabapentin withdrawal syndrome. Clin Neuropharmacol 2001;24(4):245–6.
43. Hoggan RN, Subhash A, Blair S, et al. Thin-film optical notch filter spectacle coatings for the treatment of migraine and photophobia. J Clin Neurosci 2016;28:71–6.
44. Ernberg M, Christidis N, Ghafouri B, et al. Plasma cytokine levels in fibromyalgia and their response to 15 weeks of progressive resistance exercise or relaxation therapy. Mediators Inflamm 2018;2018:1–14.
45. Rodriguez-Pinto I, Agmon-Levin N, Howard A, Shoenfeld Y. Fibromyalgia and cytokines. Immunol Lett 2014;161(2):200–3.
46. Ross RL, Jones KD, Bennett RM, et al. Preliminary evidence of increased pain and elevated cytokines in fibromyalgia patients with defective growth hormone response to exercise. Open Immunol J 2010;3(1):9–18.