Pilot Study

# Green Light-Based Analgesia – Novel Nonpharmacological Approach to Fibromyalgia Pain: A Pilot Study

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**Background:** There continues to be significant reliance on pharmacological modalities for the management of chronic pain, with a particular focus on opioid analgesics as a singular option for pain management. Fibromyalgia is a prototypical central pain disorder, which is often used as a model to study chronic pain disorders. It has an estimated prevalence of approximately 1.1% to 5.4% in the general population. The widespread use of opioids in patients with fibromyalgia has been well demonstrated in several health claims database studies, with rates of use ranging from 11.3% to 69%. Minimizing opioid exposures reduces misuse risk, but requires adequate opioid-sparing multimodal analgesic strategies, particularly nonopioid analgesic adjuncts, to ensure effective treatment of pain, particularly high-impact pain. We chose fibromyalgia as our study population. Given that it is a disordered sensory processing condition, it may be particularly amenable to the beneficial effects of green-light therapy.

**Objectives:** Most studies have evaluated exposure to light-emitting diode lights as a mode of green-light delivery; our study used green-light filtering eyeglasses, which would allow the wearer to move about with minimal interference.

**Design:** We conducted a randomized controlled trial to test the feasibility of green-light filtering eyeglasses in the treatment of chronic pain.

**Setting:** This study was conducted at Duke University Health System.

**Methods:** We recruited and randomized adult patients with a known diagnosis of fibromyalgia patients and excluded patients who were unable to wear eyeglasses for at least 4 hours per day or were colorblind according to the Ishihara Colorblindness Test. Patients were assigned to 1 of 3 arms: clear eyeglasses (control), green eyeglasses, or blue eyeglasses. We initially recruited 45 patients and randomly assigned 15 patients per group.

**Results:** To evaluate clinical significance, we determined the rate of ≥ 10% decline in oral morphine equivalents and found that 33%, 11%, and 8% of the green, blue, and clear eyeglass groups, respectively, achieved this clinically meaningful outcome.

**Limitations:** This study was powered to detect feasibility of the intervention, rather than conclusive analgesic effects.

**Conclusions:** Our study demonstrated the feasibility of this treatment approach and study design and supports a future study to determine the efficacy of green light-based analgesia on opioid use, pain, and anxiety. While the reduction of opioid use was not of statistical significance, we believe it to be of clinical significance as there was no increase of patient-reported pain. This warrants further investigation in a large-scale trial of the use of green-light filtration of ambient light to mitigate opioid use and possible mediation of psychological impacts of pain with the use of green-lensed eyeglasses.

**Key words:** Chronic pain, fibromyalgia, pain, pain management, green light, green-light filtering eyeglasses, green-light analgesia, chronic pain management

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There continues to be significant reliance on pharmacological modalities for the management of chronic pain, with a particular focus on opioid analgesics as a singular option for pain management. This is a leading cause of the prescription opioid epidemic, which has had devastating impacts on our population (1,2). Fibromyalgia is a prototypical central pain disorder, which is often used as a model to study chronic pain disorders. The widespread use of opioids in patients with fibromyalgia has been well demonstrated in several health claims database studies, with rates of use ranging from 11.3% to 69%. The continued large-scale use of opioids in this population persists in spite of evidence suggesting lack of efficacy and concern for side effects (3).

Minimizing opioid exposures reduce misuse risk (4), but requires adequate opioid-sparing multimodal analgesic strategies to ensure effective treatment of pain, particularly high-impact pain (5). In practice, this manifests as polypharmacy. Nonopioid medications commonly hold their own abuse potential and side-effect profile (6,7), which may limit their use. Non-pharmacologic options have long been shown to offer benefits in patients with fibromyalgia; however, these continue to be limited in use or difficult to integrate into routine self-care (8-10). A broadly effective and easily implemented nonpharmacological analgesic approach would be of considerable value.

Concentrated exposure to the visual light spectrum can be obtained by filtering specific wavelengths in or out, resulting in desired narrow spectrum exposure to patients. Green light has been studied in nonvisual responses. Exposure to green light of the cone photoreceptors in the eye alters melatonin production to stimulate energy and alertness and results in resetting the circadian rhythm as an example of a nonvisual response (11,24). Green light alters serotonin levels and stimulates the endogenous opioid system with an increase in enkephalins (12). Cleymaet et al (12) have recently elaborated on the relationship between endogenous opioid signaling and exposure to green light.

Ibrahim et al (13), in preclinical studies, have shown that green light elicits a strong antinociceptive response in rats. They proposed the antinociceptive effects of green light were from reversal of tactile and thermal hypersensitivity, while the antiallodynic and antihyperalgesic effects were due to decreased calcium influx via the N-type calcium channel. The rats, who were fitted with green contacts that permit light transmission in the green part of the visual spectrum, developed antinociception when exposed to ambient light. The effect of green light on the endogenous opioid system appears to play a key role in antinociception, antiallodynia, and antihyperalgesia. They demonstrated green-light phototherapy's ability to reverse reduced sensory thresholds in a model of neuropathic pain, supporting its use as a possible novel, nonpharmacological approach in managing chronic pain. The antinociceptive effects of green-light therapy also involves the modulation of descending pain-control mechanisms, which results in changes in the signaling and proteomes at the spinal cord level.

In order to explore the use of green light in pain conditions further, we conducted a National Institutes of Health-funded trial, evaluating the impact of green light on pain, opioid use, and anxiety in patients with fibromyalgia. We chose fibromyalgia as our study population. Given that it is a disordered sensory processing condition, it may be particularly amenable to the beneficial effects of green-light therapy. Most studies have evaluated exposure to light-emitting diode lights as a mode of green-light delivery; however, our study used green-light filtering eyeglasses, which would allow the wearer to move about with minimal interference.

## Methods

After obtaining Institutional Review Board (IRB) approval (IRB 102106), we recruited adult patients with a known diagnosis of fibromyalgia patients at Duke University Health System taking opioids from August 2019 through December 2020 (i.e., 17 months, including a 3-month COVID-19 suspension). We excluded patients who were unable to wear eyeglasses for at least 4 hours per day or were colorblind according to the Ishihara Colorblindness Test (14).

Following enrollment and consent, we randomized patients to 1 of 3 arms: clear eyeglasses (control), green eyeglasses, or blue eyeglasses. Randomization was determined by computer processing and given to the study personnel as enrollment occurred. The blue eyeglasses were included as a second intervention of colored light, which allowed us to evaluate the impact of colored light vs clear light, and to determine the extent to which the effects observed in any group were unique to a specific color. Patients were instructed to wear their study eyeglasses for at least 4 hours per day for 2 weeks while awake and record the times they wore their eyeglasses to measure compliance. Adverse events were tracked via follow-up calls and in-person study visits during the study period. We administered

the Patient-Reported Outcome Measurement System-Profile 57 (PROMIS-57) Profile just before randomization (baseline [BL]) and again after 1 and 2 weeks of study participation (15). The PROMIS-57 Profile is a detailed, standardized battery of PROMIS measures covering anxiety, depression, fatigue, pain intensity, pain interference, physical function, sleep disturbance, and ability to participate in social roles and activities. Daily opioid use (documented in oral morphine equivalents [OME]) and pain scores were recorded for each patient at BL, week 1, and week 2.

The primary aim of this study was to evaluate feasibility, as measured by completion and compliance rates, monitor adverse event rates, and generate preliminary efficacy estimates for future studies. The primary efficacy outcome for this study was the achievement of significant reduction of opioid use after 2 weeks of intervention. Given the potential for high rates of no change in opioid use, and the interest in clinically significant reductions of opioid use, we defined the primary outcome as a binary variable. The clinically significant reduction was determined to be at least a 10% reduction in opioid use after 2 weeks of intervention, based on current guidelines for active opioid taper aim to reduce opioid dose by 10% to 20% every week (16,17). Secondary outcomes include change in opioid use as a numeric value, patient-reported pain scores, and PROMIS scores. Pain scores were evaluated on a numerical scale (0-10) and anxiety was reported as part of the PROMIS-57 survey. We also investigated rates of decline in patient-reported pain and PROMIS scores.

### Statistical Analysis

Patient and surgical characteristics were described by treatment group via means (standard deviation) or median (Q1, Q3) for numeric variables and count (%) for categorical variables. We performed an overall comparison across the 3 groups, as well as pairwise comparisons of the colored eyeglassed group to the control group via appropriate parametric or nonparametric tests. If numeric factors failed the Shapiro-Wilks normality test, nonparametric tests (i.e., Wilcoxon rank sum or Kruskal-Wallis) were used, and if a categorical factor had low expected cell counts, the Fisher's exact test was used.

Rates of completion and reported adverse events were summarized and compared between groups with the chi-square or Fisher's exact test. The comparison of achievement of a ≥ 10% decrease in OME consumption was analyzed via the chi-square test and logistic regression. For the secondary outcomes of numeric change in OME consumption, pain score, and PROMIS score, we compared groups using the Wilcoxon rank sum test and linear regression analysis. For the binary outcome of decline in pain or PROMIS scores, we used the chi-square test and logistic regression.

Study sample size was based on the Viechtbauer et al (18) method for detection of adverse events in pilot studies. Based on the formula in the paper, a study of 45 chronic pain patients will provide approximately 80% confidence in detecting issues with a 5% probability of occurrence. Hence we enrolled and randomized a minimum of 15 patients per treatment group.

## Results

We initially recruited 45 patients and randomly assigned 15 patients per group. Of these 30 (67%) completed the study, with the highest loss to follow-up rate in the clear eyeglasses control group (20% in green, 33% in blue, and 47% in the clear eyeglasses group). Patient retention was impacted significantly by COVID-19 in the earlier part of the year, and reports of headaches in the blue and clear eyeglasses groups lead to patient withdrawal (1 blue, 2 clear). Given the high rate of attrition in the clear eyeglasses control group, we enrolled an additional 4 patients to treat with clear eyeglasses, all of whom completed the study, to provide sufficient control patients for comparison. This resulted in an analysis set of 34 patients, of which 31 (91%) patients identified as women, with an average age of 57 ± 10. Patient BL factors were similar across the 3 groups (Table 1).

There were a total of 9 adverse events among the 49 enrolled patients (2 blue, 6 clear, 1 green, $P = 0.15$), and 3 patients withdrew due to adverse events. Eight out of the 9 events were headaches and one patient was hospitalized for a nonstudy-related event. Seven of the headaches were considered study-related; none of which were considered severe. The one headache that was not considered study-related was in the green group.

To evaluate clinical significance, we determined the rate of ≥ 10% decline in OME and found that 33%, 11%, and 8% of the green, blue, and clear eyeglass groups, respectively, achieved this clinically meaningful outcome ($P = 0.23$, Fig. 1). A logistic regression analysis indicated a trend toward the difference between green and clear eyeglass groups, with the odds of achieving a ≥ 10% decline in OME for the green group estimated to be 5.5 times higher than that for the clear group (95%

Table 1. *Demographic and BL characteristics by group.*

| | Blue (n = 10) | Clear (n = 12) | Green (n = 12) | *P* value |
|---|---|---|---|---|
| Race | | | | 0.418[1] |
| White or Caucasian | 7 (70.0%) | 7 (58.3%) | 5 (41.7%) | |
| Black or African American | 3 (30.0%) | 4 (33.3%) | 4 (33.3%) | |
| More Than One Race | 0 (0.0%) | 1 (8.3%) | 3 (25.0%) | |
| Age | 53.0 (46.0, 64.0) | 58.0 (51.0, 67.0) | 57.5 (51.5, 64.0) | 0.773[2] |
| Gender (Female) | 9 (90.0%) | 10 (83.3%) | 12 (100.0%) | 0.351[1] |
| OME at Consent | 51.3 (16.0, 80.0) | 55.0 (17.5, 81.2) | 37.5 (25.0, 74.0) | 0.938[2] |
| BL Pain Score | 8.0 (7, 8) | 7.0 (5.5, 8) | 7.0 (6, 8) | 0.457[2] |
| BL PROMIS | | | | |
| Physical Function | 4.5 (3, 5) | 4.0 (3, 4) | 3.5 (3, 4.5) | 0.649[2] |
| Anxiety | 18.5 (14, 24) | 19.5 (14, 21.5) | 22.0 (18, 28) | 0.236[2] |
| Depression | 14.0 (10, 22) | 14.5 (10.5, 19.5) | 15.0 (11, 22.5) | 0.818[2] |
| Fatigue | 32.0 (28, 35) | 30.5 (26.5, 35.5) | 32.0 (28.5, 37.5) | 0.632[2] |
| Sleep | 27.0 (22, 31) | 26.0 (22.5, 33) | 30.0 (24.5, 38.5) | 0.356[2] |
| Activities | 19.5 (15, 24) | 19.0 (15, 25) | 17.0 (8, 24) | 0.561[2] |
| Pain | 31.5 (30, 37) | 32.0 (28.5, 34) | 32.5 (26.5, 39.5) | 0.822[2] |

[1]Chi-square. [2]Kruskal Wallis
Abbreviations: OME, oral morphine equivalents; BL, baseline.

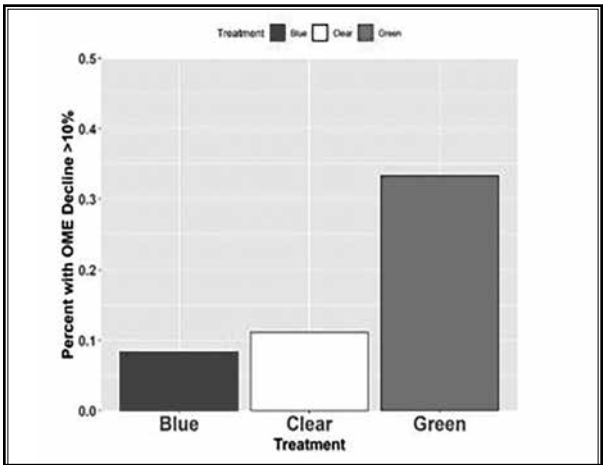


Fig. 1. *Percent of patients with > 10% decline in opioid use after 2 weeks, by group.*

confidence interval [CI] [0.66, 119]; *P* = 0.159), and this trending difference remained when we adjusted for age in the model. There was no evidence of a difference for the blue group compared to the clear group (odds ratio [OR] [95% CI] 1.38 [0.05, 38.41]; *P* = 0.662). In our secondary analysis, we found no difference in the 2-week numeric change in opioid dose between the treatment groups, and in all 3 groups the median change was 0 units (*P* = 0.60). The blue and clear groups' upper and lower quartiles were also found to be zero change; however, the 25th percentile for the green group was a 17.5 OME decline.

For our secondary outcome of pain score change, we observed median [Q1, Q3] values of -0.5 (-1, 0) in the blue group, 0 (-1, 0) in the clear group, and -1 (-1, 0) in the green group, which corresponded to a *P* value of 0.62. A linear regression analysis for pain score change estimated mean difference (95% CI) of -0.10 (-1.25, 1.06) for the green and clear groups (*P* = 0.86), and 0.22 (-1.0, 1.4) for the blue and clear groups (*P* = 0.71). The rate of decline in pain score was 67%, 50%, and 45% for the green, blue, and clear eyeglasses groups (*P* = 0.56), and the logistic regression did not indicate a significant difference in pain score decline between green and clear (OR [95% CI] 2.40 [0.44, 12.98]; *P* = 0.31) or between blue and clear (OR [95% CI] 1.20 [0.22, 6.68]; *P* = 0.84).

For another of our secondary outcomes, the PROMIS scores, we observed a promising signal in the anxiety domain. The green eyeglasses group was the only group with a majority of patients having a decline in anxiety score (medians of -3, 3.5, and 2 in the green, blue, and clear groups, respectively [*P* = 0.11]), and there was a significant difference in the fear question, in particular (*P* = 0.03). Linear regression analysis for change in anxiety domain score indicated that the

decline in anxiety score for the green group was 4.2 points greater than that for the clear group (95% CI [-9.8, 1.4]; $P = 0.138$) (Fig. 2). There was no evidence of a difference between the anxiety domain scores for the blue group compared to the clear group (mean difference [95% CI] 1.5 [-4.3, 7.4]; $P = 0.601$). The rate of decline in anxiety was 75%, 30%, and 33% for the green, blue, and clear eyeglasses groups, respectively ($P = 0.054$), and the logistic regression indicated that patients in the green eyeglasses group had significantly higher odds of anxiety score reduction than those in the clear group (OR [95% CI] 6.00 [1.02, 35.37]; $P = 0.048$), but those in the blue eyeglasses group did not (OR [95% CI] 0.86 [0.14, 5.23]; $P = 0.87$).

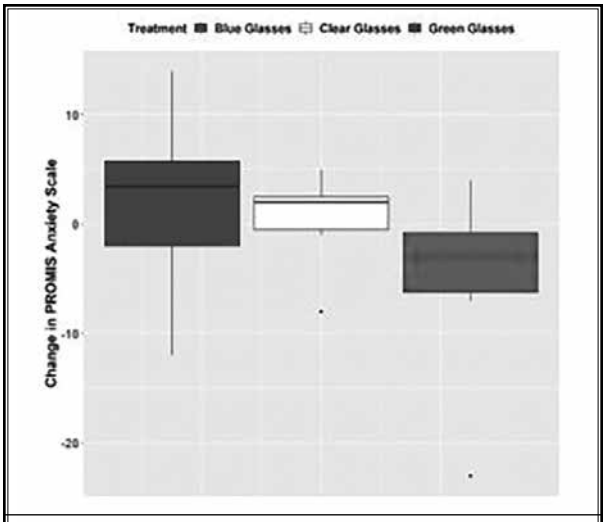


Fig. 2. *Change in anxiety scores at 2 weeks, by group.*

## Discussion

Our pilot study produced multiple key findings regarding study feasibility and design that will guide future studies. We identified a lack of evidence for continued study of blue eyeglasses, headaches as a primary driver for study attrition, and a need for extending the study period to observe longer term changes in this chronic-pain patient population. We observed a trend toward higher odds of achieving a ≥ 10% reduction in daily opioid requirements in patients who wore green-light filtering eyeglasses compared to clear-light filtering eyeglasses, and that the odds of a decrease in anxiety score was significantly higher for patients randomized to green vs clear eyeglasses, but pain scores remained similar in the green and clear eyeglasses groups. The ability to reduce opioid use in the chronic pain population without increasing reported pain would have immense impact on managing this pain.

### Exposure to Green Light-Based Analgesia Reduces Opioid Requirements

The complex pain experience of those suffering from fibromyalgia results in chronic use of pain medications, of which opioids are a part. In fact, over 60% of patients diagnosed with fibromyalgia are prescribed long-term opioids (3,19). Further, fibromyalgia is diagnosed predominately in women (20,21), and opioid medications are prescribed to women considerably more often than men (22). These compounding factors create a population of patients who are at high risk for opioid side effects and misuse. This risk can be minimized by decreasing opioid exposure, which can only be accomplished with a balanced multimodal approach to their pain management. The use of multimodal therapy, which includes the use of opioids, opioid-sparing medications, and nonpharmacological therapies, is essential for a responsive treatment of pain (5). Pharmacological options for pain management have narrow therapeutic benefit and significant side effects and risks.

Recent clinical studies (12,13,23), including our own, support the findings of the preclinical studies described above, which demonstrate the beneficial effects of green light-based analgesia for chronic pain management. Martin et al (24), in a one-way crossover clinical trial in fibromyalgia patients, reported a 60% reduction in pain and an almost 50% reduction in daily morphine milligram equivalent use. A study, evaluating headache frequency and quality of life in migraine patients exposed to green light, has shown that patients saw their BL pain scores (8-10) prior to green-light exposure, reduce to 2.8. These patients also demonstrated over 40% reduction in opioid use (24,25).

### Green Light Therapy Improves Patient-Reported Measures of Anxiety and Pain

Psychological comorbidities often coexist in chronic pain conditions, like fibromyalgia, such as anxiety which is reported in up to 85% of fibromyalgia patients (26,27). Anxiety, especially fear-based anxiety, has been linked to higher opioid use (28). Colasanti et al (28) have demonstrated these effects in both animal and human models, where endogenous opioids, particularly enkephalins, are stimulated to mitigate anxiety and fear.

Krebs et al (29) in the Strategies for Prescribing Analgesics Comparative Effectiveness randomized

clinical trial involving 240 patients with osteoarthritis pain or chronic back pain found no difference in pain-related function in patients treated with opioids compared to nonopioid medications. While they also found most other health-related quality-of-life measures did not differ between the 2 groups, only anxiety symptoms were statistically better in the opioid group. These findings were consistent with Sullivan et al (30) on the role of the endogenous opioid system, particularly enkephalins in stress and emotional suffering, resulting in the increased use of opioids due to underlying anxiety.

Pain shares similar biological mechanisms with anxiety (31). Anxiety is an important mediator in the cognitive constructs of catastrophizing, hypervigilance, and fear avoidance in the exacerbation of pain experiences. Anxiety has been implicated in the development of persistent pain states, especially during the postoperative period (32). Henry et al (33) describe evidence supporting the role of enkephalins in anxiety states and stress-induced analgesia.

Opioids are implicated in acute modulation of anxiety and anxiety-related brain response. In addition to pain relief, opioid benefits may relate to off-target effects, such as anxiety. For example, anxiety improved over 12 months in chronic pain patients randomized to opioid therapy (29). Randomization to opioid therapy, in patients with low back pain and osteoarthritis, produces long-term (i.e., 12-month) improvements in self-reported anxiety. Acute administration of opioids can acutely reduce anxiety and anxiety response in the amygdala. For example, reduced anxiety response in the amygdala and reduced self-reported anxiety occur after a single dose of heroin, an opioid agonist (34).

Many patients taking opioids for chronic pain are reluctant to decrease their regimen due to the fear of severe pain, and this fear-based anxiety can lead to the escalation of opioid use. In the chronic pain population, this anxiety may be elated by the opioids these patients take for their pain syndrome. In order to successfully decrease or eliminate opioid use in these patients, their anxiety must also be addressed. As noted above, a pharmacological regimen may cause adverse effects or drug interactions, which may cause harm to patients. Nonpharmacological interventions, especially one that also manages pain, would be ideal. Exposure to green light has been shown to increase enkephalin levels in spinal cord tissue samples after the therapy (13), supporting its feasibility as a anxiolytic. Our results demonstrated decreased anxiety in patients receiving green-light therapy, most notably in the fear-based anxiety. The decline in the anxiety score for the green group was estimated to be 4.2 points greater than that for the clear group (95% CI [-9.8, 1.4]; $P = 0.138$). This further supports the use of green light in decreasing anxiety, particularly fear-based anxiety, which may have contributed to the observed decrease in opioid use.

The results of our study yielded other key findings. First, the blue eyeglasses group had similar or worse results compared to the clear group for all outcomes, suggesting that the next phase of the study should focus on contrasting green and clear eyeglasses alone. Any benefit from the green group can be considered a benefit of wavelengths of light within the green spectrum, rather than total spectrum (i.e., clear) light. Second, certain patient groups may not be appropriate for treatment with light (i.e., those with a history of headaches). We did not see any study-related adverse events in the green eyeglasses group, suggesting the intervention is safe for this population. Further investigation should exclude patients with a preexisting diagnosis of headaches or migraines to ensure safety of patients within the control group. Third, during our 2-week follow-up window, many patients had no change in their OME or pain levels, indicating that a longer follow-up window and treatment exposure may be required to observe a difference in outcomes of interest.

## Limitations

One limitation of this study is the small sample size due to the pilot nature of this study. While we were able to see some trends within the data, a larger sample size would allow for more discernable differences between the groups. The primary purpose of this study was to assess feasibility and inform future study design and the observed sample was sufficient for that purpose. A second limitation of this study was the high rate of attrition, especially among the clear eyeglasses patients. While we believe some of the factors leading to attrition are time frame-specific (e.g., COVID-19), others such as the rate of headaches will inform the target population for future studies. Another limitation of this study is duration of the intervention period. Two weeks of intervention in patients with chronic pain and long-term opioid therapy may not be adequate time to see conclusive results. Further investigation should include longer duration of the intervention in this population.

## Conclusions

Our study demonstrated the feasibility of this treatment approach and study design and supports a future study to determine the efficacy of green light-based analgesia on opioid use, pain, and anxiety. While the reduction of opioid use was not of statistical significance, we believe it to be of clinical significance as there was no increase of patient-reported pain. This warrants further investigation in a large-scale trial of the use of green-light filtration of ambient light to mitigate opioid use and possible mediation of psychological impacts of pain with the use of green-lensed eyeglasses.

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