**Opioid Sparing Potential of Light-Induced Analgesia: a Pilot Trial of a Novel, Non-Pharmacological Treatment for Pain**

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## Purpose of the study

This offers fascinating potential for use in opioid sparing multimodal analgesia while maintaining pain control, for which there is an urgent need. The green light effect is visually mediated. Further, the green-biased light spectrum involved can be obtained by filtering ambient light. Therefore, if such putative green light analgesia is possible in human populations, it would be inducible simply by using green lensed eyeglasses.

Our long-term goal is to test the efficacy of eyeglasses-based green light therapy as an analgesic adjunct. In particular, we aim to assess green light therapy's potential for broad adoption as an opioid sparing strategy while maintaining pain control. Reductions in opioid exposure are particularly important given links to opioid misuse risk. This aligns with national priorities aiming to identify interventions to prevent opioid misuse and abuse. The objective here, and the next step in pursuit of that goal, is to conduct a pilot trial testing clinical usage of green light therapy as an analgesic adjunct to opioid therapy. Our central hypothesis is that eyeglasses-based green light therapy will be well-tolerated and opioid sparing. The rationale for the proposed study is based on the published findings as described above. Namely, that green light visualization reduces pain responses. We expect that this effect will allow reduced opioid exposures in clinical care.

We will conduct the proposed pilot trial in both acute and chronic pain conditions.
Patients scheduled for thoracic surgery with anticipated post-operative opioid treatment (acute surgical pain) and patients with fibromyalgia currently treated with opioids (chronic pain) will be identified, enrolled, and randomized to one of three arms: 1. clear eyeglasses (control), 2. green eyeglasses or 3. blue glasses

## Design and Procedures

Trial Procedures – Acute Pain group:

Acute Pain group participants will be visited by study staff after their transfer to a floor unit (either normal care or step down; that is, after post-anesthesia care). Upon confirming their willingness participate, they will be randomized to receive either green, blue or clear glasses. Participants will be asked to wear their study glasses for at least 4 hours per day throughout their hospital stay and will be provided log books in which to record their glasses-wearing duration each day and any commentary they wish to share. During this visit, participants will also complete the PROMIS-57 Profile. The Patient-Reported Outcomes Measurement Information System (PROMIS) is a collection of patient-reported measures developed by an initiative of the National Institutes of Health as high-quality, well-validated, and standardized patient-reported outcomes measures across multiple domains. 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. On day of discharge or at 48 hours postoperative, whichever comes first, study

staff will again visit participants to collect the study glasses. Participants will again complete the PROMIS-57 Profile. During participants' inpatient stays, study staff will continue to coordinate with the primary care teams to monitor for any issues arising from the study or the use of the study glasses. Providers will be supplied with contact information to provide any feedback they wish to share.

For the postoperative patients in the study who are inpatient for the duration of the study, this is evaluated for them throughout their inpatient stay and the primary teams have the ability to address any sleep disturbance, mood change or change in the patients pain control per standard care. Should the providers caring for the patient or the patient themselves perceive the study intervention to be a significant contributor to the patients worsening condition, an adverse event will be recorded per the Data Safety Monitoring Plan and the patient will be withdrawn from the intervention/study.

Trial Procedures – Chronic Pain group:

Chronic Pain group participants will begin study procedures immediately following their enrollment. Participants will be randomized to receive either green, blue or clear glasses and will complete the PROMIS-57 Profile. Participants will be asked to wear their study glasses for at least 4 hours per day for a period of 2 weeks. Unlike the Acute Pain group in which pain will typically self-resolve with operative healing and the hospital stay provides a convenient and applicable treatment timeline, the appropriate duration of green light therapy for use in chronic pain states is unknown. Preclinical findings suggest the onset of analgesic effects after 3 days. However, such timelines rarely translate directly to human populations. Most pharmacological analgesics achieve effect onset within minutes to hours, although the analgesic effects of antidepressants upon chronic pain states (which may also involve modulation of descending pain control mechanisms) can require a week or longer to manifest. Here, we have chosen a moderate 2-week duration to allow for a range of times-to-onset. Participants will be provided log books in which to record their glasses-wearing duration, average pain, and opioid use each day. They will also be invited to include any commentary they wish to share.

For outpatients with fibromyalgia who are enrolled for 2 weeks all patients are administered the PROMIS-57 profile which evaluates the domains of sleep, mood and pain at enrollment, week 1 and at week 2 when the intervention ends. If there is any worsening of the patients condition in any of the domains, they will be offered immediate evaluation and management for the same. Should the providers caring for the patient or the patient themselves perceive the study intervention to be a significant contributor to the patients worsening condition, an adverse event will be recorded per the Data Safety Monitoring Plan and the patient will be withdrawn from the intervention/study.

All patients are provided with a phone number to call should they suffer from any side effects or worsening of their condition including any sleep disturbances.

Participants in this group will be asked to complete the PROMIS-57 Profile at the 1-week and 2-week time points. Two copies of the PROMIS-57 questionnaire will be given to the patient for completion at week 1 and week 2. A member of the study staff will call the patients at week 1 to

ensure completion of the questionnaire over the phone with the subjects. The week 2 questionnaire will be completed either over the phone (in the same way as week 1) or on site at the pain clinic. For patients completing the survey on site, the study staff will collect study materials (glasses and diary) at that visit. For patients completing the final study visit (week 2) over the phone, stamped and addressed shipping supplies will be provided to the patient for the return of the study materials (glasses and diary). Study staff will follow up with participants' pain providers to obtain any relevant feedback.

**Selection of Subjects**

Subjects will be identified through chart review using MaestroCare reports. Inclusion/exclusion criteria for the study will be:

Inclusion

1. Scheduled for thoracic surgery for which post-operative opioid PCA is anticipated (Acute Pain group) OR currently treated with opioid therapy for fibromyalgia (Chronic Pain group)
2. 18 years of age and older
3. Able to wear study eyeglasses for at least 4 hours per day
4. Agree to participate and provide written informed consent and HIPAA authorization

Exclusion:

1. Color blindness (patients will be administered a color blindness test online at **https://colormax.org/color-blind-test/**

**Recruitment and Compensation**

In identifying and approaching all patients, the study team will coordinate with the primary clinical team. If the eligible patient agrees to hear more about the study, a study team member will attend, explain the study in detail, and obtain written informed consent. For patients who participate in remote enrollment, written electronic consent forms will be provided to the patient via email through REDCap and patients will sign and submit the e-consent. Study staff will then print a copy of the signed e-consent for our records and a copy will be automatically sent to the study participant as well. We will use the Duke hosted REDCap platform for collecting eConsent.

**Study Interventions**

Patients scheduled for thoracic surgery with anticipated post-operative opioid treatment (acute surgical pain) and patients with fibromyalgia currently treated with opioids (chronic pain) will be identified, enrolled, and randomized to one of three arms: 1. clear eyeglasses (control), 2. green eyeglasses or 3. blue eyeglasses.

Patients are able to withdraw from the study at any time as is clearly stated in the consent: "You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first."

For the postoperative patients (acute pain) who are inpatients for the time they are enrolled in the study, they continue to have access to opioid medications and other pain medications to address their pain per their primary teams per standard care.

For the outpatients (chronic pain) with fibromyalgia who are enrolled in the study, should they suffer from worsening pain may withdraw from the study at any time as is clearly stated in the consent: "You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first."

Participants are provided with a phone number to contact should they suffer from any side effects or worsening of their condition at which point the y would immediately be evaluated and managed to address their symptoms.

The patients will be managed for their pain per standard of care with the regimen decided by their treating physician. The only intervention based on the study will be the introduction of the glasses which participants are required to wear for 4 hours during the day. There is NO change made to the patients pain management regimen, it is as per their primary treating physician.

This is not standardized in the 3 groups as we will be recording the medications used for pain and their utilization.

Patients will be exposed to ambient light, no standardized source of light. We will ask patients to document their 4 hours of usage of the glasses during each day for exact times worn and whether they were indoors or outdoors. In this pilot study we hope to understand patient usage patterns and compliance factors to inform a larger study in the future.

The eyeglasses which will be used for this study are commercially obtained from online vendors. They are then tested to ensure they meet the below requirements

**Eyeglasses**

Thanks to recent fashion trends and the dramatic expansion of e-commerce enabling low-cost niche manufacturing, a wide array of eyeglasses in varying styles and colors are now easily available. To identify eyeglasses for use in this trial, we purchased several different examples from a major online retailer. We screened these eyeglasses for perceived lens color (as some eyeglasses relied on reflective coating to appear green, but did not transmit perceptibly green light), fit (across various study personnel and colleagues), subjective build quality, aesthetic acceptability, and availability of matching clear-lensed versions for use as controls. The remaining eyeglasses were subjected to transmission spectroscopy across the 425nm to 700nm

visual spectrum. On the basis of these spectra, the eyeglasses with the most green-biased transmission will be chosen for use in this study.

The brand we have tested with spectroscopy which meet the above requirements (shown on mannequin below) are WearMe Pro - Colorful One Piece Transparent Round Super Retro Sunglasses: Green. The blue glasses were selected from the same manufacturer: WearMe Pro - Colorful One Piece Transparent Round Super Retro Sunglasses: Blue. These specific glasses have been chosen as they are registered with the FDA as a medical device; registration of these glasses can be found on the FDA website (fda.gov) under registered medical devices. (Full spectroscopy analysis for the glasses has been attached).

**Data Analysis and Statistical Considerations**

We calculate that a total enrollment of 120 participants will be sufficient to provide greater than 95% confidence in detecting issues with a 5% probability of occurrence. Divided evenly across Acute Pain and Chronic Pain groups (60 each) this sample will also provide approximately 80% confidence in detecting issues with a 5% probability of occurrence in only one group. This yields a 15 participant per condition (acute/chronic x green/clear/blue) sample size. Adding the blue glasses group to compare, continues to allow us a similar confidence in detecting issues with a 5% probability of occurrence in one group.

Interestingly, this chosen sample size also fulfills several other methods/guidelines for pilot trial sample sizes which range from 10 to 15 per condition. These methods have generally sought to power pilot trials to produce usable estimates of outcome measure values. While the appropriateness of such an approach is debated, it does suggest that our chosen sample size will be satisfactory to produce such estimates.