





Case Report: Green Light Exposure Relieves Chronic Headache Pain in a Colorblind Patient

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ABSTRACT: Patients with chronic headaches sometimes prefer non-pharmacological methods for pain management. We have shown previously that green light exposure (GLED, Green Light Emitting Diode) reversed thermal hyperalgesia and mechanical allodynia in a rat model of neuropathic pain. This effect is mediated through the visual system. Moreover, we recently showed that GLED was effective in decreasing the severity of headache pain and the number of headache-days per month in migraine patients. The visual system is comprised of image-forming and non-image-forming pathways; however, the contribution of different photosensitive cells to the effect of GLED is not yet known. Here, we report a 66-year-old man with headaches attributed to other disorders of homeostasis and color blindness who was recruited in the GLED study. The subject, diagnosed with protanomaly, cannot differentiate green, yellow, orange, and red colors. After completing the GLED exposure protocol, the subject noted significant decreases in headache pain intensity without reduction in the number of headache-days per month. The subject also reported improvement in the quality of his sleep. These findings suggest that green light therapy mediates the decrease of the headache pain intensity through non-image-forming intrinsically photosensitive retinal ganglion cells. However, the subject did not report a change in the frequency of his headaches, suggesting the involvement of cones in reduction of headache frequency by GLED. This is the first case reported of a colorblind man with chronic headache using GLED to manage his headache pain and may increase our understanding of the contribution of different photosensitive cells in mediating the pain-relieving effects of GLED.

KEYWORDS: Phototherapy, green light, analgesia, colorblind, headaches attributed to other disorders of homeostasis

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Introduction

Chronic daily headache (CDH) is an umbrella term that describes several types of medical conditions that result in daily headaches. It is a debilitating medical condition affecting about 4% of the world population with women more predisposed than men.¹ It is defined as experiencing 15 or more headache-days per month.¹ Recently, there has been interests in understanding the role of the visual system in modulating headaches. For example, when the red spectrum is filtered out using a thin film filter placed on spectacles, patients with migraine reported decreased photophobia and a reduction in scores on the Headache Impact Test-6 (HIT-6) survey, suggesting improvement of their overall headache symptoms.² In a different study, nearly 20% of patients with active migraine attacks reported that exposure to green light reduced the intensity of their migraine headache.³ To investigate the potential for green light exposure (GLED) as a chronic pain therapy, we initially characterized its pain-modulating effects in rats. GLED reversed the thermal hyperalgesia and mechanical allodynia in

neuropathic pain models and reduced pain sensitivity from thermal acute noxious stimuli.⁴ We further assessed the potential of GLED in the clinical setting, in which GLED improved symptoms for patients with fibromyalgia and migraine.^{5,6} In migraine patients, GLED decreased the number of headache-days/months and the intensity of their migraine headaches. However, the underlying mechanisms of this light therapy remain undefined; although we demonstrated the requirement of the visual system, identifying the photoreceptive cells involved in the process is of great interest, as it will unveil the potential brain pathways required for GLED-induced antinociception.

There are 3 photosensitive cell types in the mammalian retina: rods, cones, and intrinsically photosensitive retinal ganglion cells (ipRGCs). ipRGCs are known to participate in the regulation of non-image-forming functions, from circadian entrainment to mood.⁷ There is a significant difference in the composition of rods and cones between rats and humans⁸; therefore, the effects of the GLED may be mediated, in part, by ipRGCs whose spectral sensitivity and functions are conserved across mammals.^{9,10} However, we were unable to assess this

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theory because none of the patients recruited in our previous study had any vision pathology. Recently, we recruited to the GLED clinical study a 66-year-old man with CDH who is colorblind, unable to discriminate among green, yellow, orange, and red colors. Our primary outcome was the change in the number of headache-days/month. The secondary outcome assessed changes in the intensity of the headaches using the numerical pain scale, decrease in HIT-6 survey score, improvement in the quality of life using the EQ-5D-5L survey, improvement in short-form McGill pain questionnaire (SFMPQ), improvement in the Pittsburgh Sleep Quality Index (PSQI), and analgesic medication reduction.

Case Presentation

Patient demographic details and medical history

The subject is a 66-year-old white man, married, non-smoker, with no family history of chronic headaches secondary to headaches attributed to other disorders of homeostasis according to the International Classification of Headache Disorders, third edition.¹¹ He has a history of protanomaly, resulting in his inability to distinguish between green, yellow, orange, red, and brown colors, and started experiencing headaches attributed to other disorders of homeostasis in 2003. He was diagnosed with polycythemia vera in 2004 which is managed with hydroxyurea. His medical history includes hypertension, hyperlipidemia, and depression, conditions for which he takes amlodipine (10 mg once, every night), atorvastatin (10 mg once daily), telmisartan-hydrochlorothiazide (88-12.5 mg once daily), bupropion (150 mg once daily), and hydroxyurea 500 mg (total 4500 mg/week). The subject's past surgical history referenced an appendectomy at age 14.

Symptoms and signs

The subject describes the headache as always being present in both of the temple areas with a severity that waxes and wanes throughout the day. The headache pain is mostly "achy" in nature. The subject is unable to identify any factors which reduce his headache pain. Loud noises aggravate his headache pain. He denies any visual changes or nausea with his headaches and was never diagnosed with migraines. He was initially started on hydrocodone and transdermal fentanyl patches to control his headache pain (he cannot recall the doses). He stopped all opioids about 6 years before trial initiation and started taking 2 tablets a day of over-the-counter combination medication containing acetaminophen 250 mg, aspirin 250 mg, and caffeine 65 mg/tablet. The subject also started taking 1 mL a day of sublingual CBD oil (8000 mg of hemp oil extract/mL) 3 to 4 years ago. An MRI of the brain done in 2016 was unremarkable. The subject contacted the pain clinic at the University of Arizona-Banner Medical Center to inquire about the green light study after he heard about the study on National Public Radio. The subject started the trial on March 11th, 2021. He completed the study on May 20th, 2021.

Intervention

We implemented the same protocol used in our prior study.⁶ In short, after providing written consent, the subject was provided with a green (525 nm) light-emitting diode (GLED) strip that was approximately 2 m long. Black electrical tape sequentially covered 2 diodes for every 1 diode uncovered for the length of the light-emitting diode (LED) strip to achieve a light intensity between 4 and 100 lx (2 and 73 cd/m²) measured at approximately 2 and 1 m from a luxmeter, respectively. The subject was instructed to keep the GLED strips within his field of vision while staying awake during the therapy and was free to change the distance of the light source between 1 and 2 m from his eyes. The GLED was to be used in a dark room in his house for 2 hours/day for 10 weeks, and the subject was encouraged to participate in activities that did not require external light sources such as listening to music or exercising. Activities such as reading were also allowed as long as there was no additional light from other sources such as a lamp or an electronic device. We asked the subject to undergo the GLED therapy at the same time every day all at once. He was encouraged to blink at a normal rate and not to stare directly at the light strips.

Outcomes

The primary outcome was the number of headache-days/month, recorded using a daily migraine headache diary. We defined a headache day as a day with moderate to severe headache pain that lasted for at least 4 hours. The secondary outcomes of this study included measures of headache quality, quality of life, and sleep quality. These outcomes included: (1) Subjective reduction in the numerical pain score (NPS, range 0-10, where 0 is no pain and 10 is the worst possible pain) of the intensity of the headache, (2) headache impact, as measured by the HIT-6 questionnaire (scale 36-78, where 36 = No impact from migraine, 78 = worst possible impact from migraine,¹² (3) quality of life, discomfort, anxiety, as measured by the validated EQ-5D-5L questionnaire (index scale 0-1 where 0 = worst quality of life, 1 = best quality of life), designed to evaluate a global quality of life of patients with pain,¹³ (4) perceived decrease in intensity, frequency, duration of the headache episodes, ability to perform work and daily activity, using a modified University of Arizona pain clinic follow-up questionnaire,⁶ (5) sleep quality, using Pittsburgh Sleep Quality Index (PSQI, range from 0 to 21 and a score >5 is considered as a significant sleep disturbance),¹⁴ and (6) reduction of pain medications, through a survey documenting their daily analgesic(s).

Surveys

The surveys used in this study are the same as described previously.⁶ Briefly, the subject was asked to fill out several paper surveys to document changes in his headache. The first survey (Time Log) documented the number of hours/day of exposure to the GLED strips. The second survey was a migraine daily

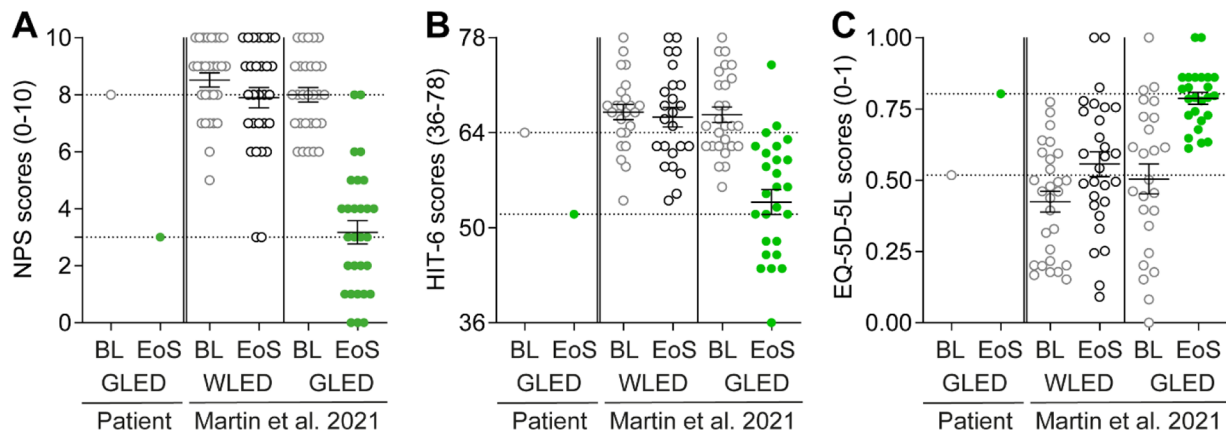


Figure 1. Colorblind patient response to green light exposure is similar to normal vision migraine patients. (A) After 10 weeks of exposure to green light (GLED), the colorblind patient reported improvements between baseline (BL) and end-of-study (EoS) in pain intensity, as measured by the numerical pain scale (NPS). Score improvements were also observed in the (B) Headache Impact Test (HIT-6), as well as the (C) EQ-5D-5L test, which measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Results from Martin et al. 2021 are presented as historical controls for points of reference: migraine patients were exposed for 10 weeks to white light emitting diodes (WLED) or GLED.

diary documenting headache-days/month (primary outcome). The third survey was a modified University of Arizona pain clinic follow-up questionnaire documenting the headache NPS and the subject's perceived change in the duration and frequency of headache episodes, improvement of the ability to fall and stay asleep, ability to perform work, and daily activity. The fourth survey was the Headache Impact Test (HIT-6) Questionnaire, a reliable and validated tool for measuring the impact of headaches on daily life in migraine and headache sufferers.¹² The fifth survey was the 5-level version of the EuroQol 5-dimensional survey (EQ-5D-5L) to evaluate the global quality of life of subjects in pain.¹³ The sixth survey was the Short-Form McGill Pain Questionnaire (SFMPQ), which allows individuals to provide a good description of the quality and intensity of pain that they are experiencing.¹⁵ The seventh survey was the Pittsburgh Sleep Quality Index (PSQI), a self-reported, validated questionnaire designed to measure retrospective sleep quality and disturbance. The eighth survey (Daily Medications) documented their daily analgesic(s). The subject was contacted once every 3 to 4 weeks by a research team member. At the end of the 10 weeks, the subject returned all the surveys. Any data not reported by the subject was not included for analysis.

Ethics approval and consent to participate

This study has been conducted according to the Declaration of Helsinki principles. The study subject provided written informed consent prior to enrolling and the study was approved by the University of Arizona Institutional Review Board (IRB). This study is registered with clinicaltrials.gov under NCT03677206.

Results

This case report only references results from 1 colorblind subject; therefore, previous results from our article reporting the impact of GLED exposure in migraine patients were included as historical controls.⁶ These results are presented only as reference

points of the overall analgesic effect of GLED in a previous cohort of 29 patients with episodic or chronic migraines.

Throughout the 10-week GLED exposure period, the subject underwent 2 hours of GLED exposure per day for 70 days. The exposures primarily occurred between the hours of 9:00 AM and 3:00 PM.

Primary outcome

The subject reported 27 days of headache per month prior to starting the GLED trial. At the end of the GLED trial, the subject did not experience any reduction in the frequency of his headaches.

Secondary outcomes

NPS. The subject reported a significant reduction in the severity of his headache pain. His average headache pain decreased from 6/10 prior to treatment to 3/10 after treatment. His worst headache pain level decreased from 8/10 prior to treatment to 3/10 after treatment (Figure 1A).

HIT-6. The subject reported a reduction of the HIT-6 score from 64 to 52 (Figure 1B).

EQ-5D-5L. The subject reported improvement in the EQ-5D-5L score from 0.513 to 0.803 and an overall increase in the subject's own perception of his quality of life from 60 to 70 (Figure 1C).

SFMPQ. The subject reported improvement in the areas he initially identified as problematic (Table 1).

Modified University of Arizona pain clinic follow-up questionnaire. The subject reported perceived improvement in all the measured parameters. He reported a perceived pain intensity reduction of 40% (Figure 2).

Table 1. Short-form McGill Pain Questionnaire (SFMPQ) score improvements after GLED exposure in a colorblind subject.

SHORT-FORM MCGILL PAIN QUESTIONNAIRE	COLORBLIND SUBJECT		MARTIN ET AL. <i>CEPHALALGIA</i> , 2021	
	IMPROVEMENT (END OF STUDY—BASELINE)		IMPROVEMENT (END OF STUDY—BASELINE)	
	GLED		WLED	GLED
Throbbing	0		0.2963 ± 0.2605	-1.167 ± 0.2142
Shooting	-1		0.1111 ± 0.1797	-1.042 ± 0.229
Stabbing	0		-0.1481 ± 0.1158	-0.7917 ± 0.2251
Sharp	-1		-0.2593 ± 0.1144	-1.042 ± 0.2126
Cramping	0		0.03704 ± 0.1554	-0.5417 ± 0.1994
Gnawing	0		0 ± 0.1194	-0.25 ± 0.1621
Burning	0		-0.1852 ± 0.1773	-0.875 ± 0.2025
Aching	-2		0.07407 ± 0.1682	-1.167 ± 0.1966
Heavy	-2		0.1111 ± 0.1797	-0.9167 ± 0.2548
Tender	-1		-0.1111 ± 0.1343	-0.875 ± 0.2112
Splitting	-2		-0.3704 ± 0.17	-1.000 ± 0.2482
Tiring	-2		-0.03704 ± 0.1359	-1.667 ± 0.2225
Sickening	0		-0.1852 ± 0.1605	-1.167 ± 0.2802
Fearful	-2		-0.07407 ± 0.1595	-0.5 ± 0.1806
Punishing	-1		-0.1111 ± 0.1541	-1.083 ± 0.2325

A colorblind subject with headaches attributed to other disorders of homeostasis reported improvements in SFMPQ parameters after being exposed to green light (GLED). Results from Martin et al. (2021) are presented as historical controls for points of reference: migraine patients were exposed for 10 weeks to white light-emitting diodes (WLED) or GLED.

PSQI. The subject reported improvement in his sleep quality. His PSQI scores decreased from 10 to 5. Additionally, the time required to fall asleep decreased from 30 to 15 minutes (Table 2).

Daily medication. There was no change in the subject's use of daily analgesic medications.

Discussion

Here, we report that GLED exposure improved chronic headache pain in a subject with protanomaly. More specifically, the subject experienced improvements in headache pain intensity, overall quality of life, and perceived headache frequency. These results are similar to what was previously observed in our larger clinical study on GLED exposure in normal vision migraine patients, in which patients reported a 60% reduction in headache frequency as well as improvement in NPS, HIT-6, EQ-5D-5L, SFMPQ, and PSQI scores.⁶ Though quality-of-life parameters were all improved in this subject, the degree of improvement due to GLED was not as pronounced as observed in normal vision migraine subjects.⁶ Although the subject perceived improvements in headache frequency, there was no

actual change in headache frequency documented in the subject's daily migraine diary.

Importantly, we must note that normal color processing involves cone photoreceptors, retinal ganglion cells, relay neurons in the lateral geniculate nucleus, the primary (V1) and secondary (V2) visual cortices, and parts of the inferior temporal lobe (V4). Red-green and blue-yellow signals arriving in V1 are known to activate double-opponent neurons whose role is to compare color signals they receive from cone-opponent neurons across visual space. V1 double-opponent cells establish the neural basis of color contrast and constancy. In V1, color encoding cells project to distinct stripes in V2 that in turn convey color signals to the inferior and posterior inferior temporal cortex, where the human brain generates the perception of millions of different colors.¹⁶ Thus, functional deficits in the lateral geniculate nucleus or the visual cortices could affect the protanomaly. Notably, the visual system has been shown to affect pain.¹⁷ Intrinsically photosensitive retinal ganglion cells (ipRGCs) can activate GABAergic neurons in the ventral lateral geniculate nucleus (vLGN), ultimately inhibiting GABAergic neurons in the pain-modulating periaqueductal gray which is sufficient to

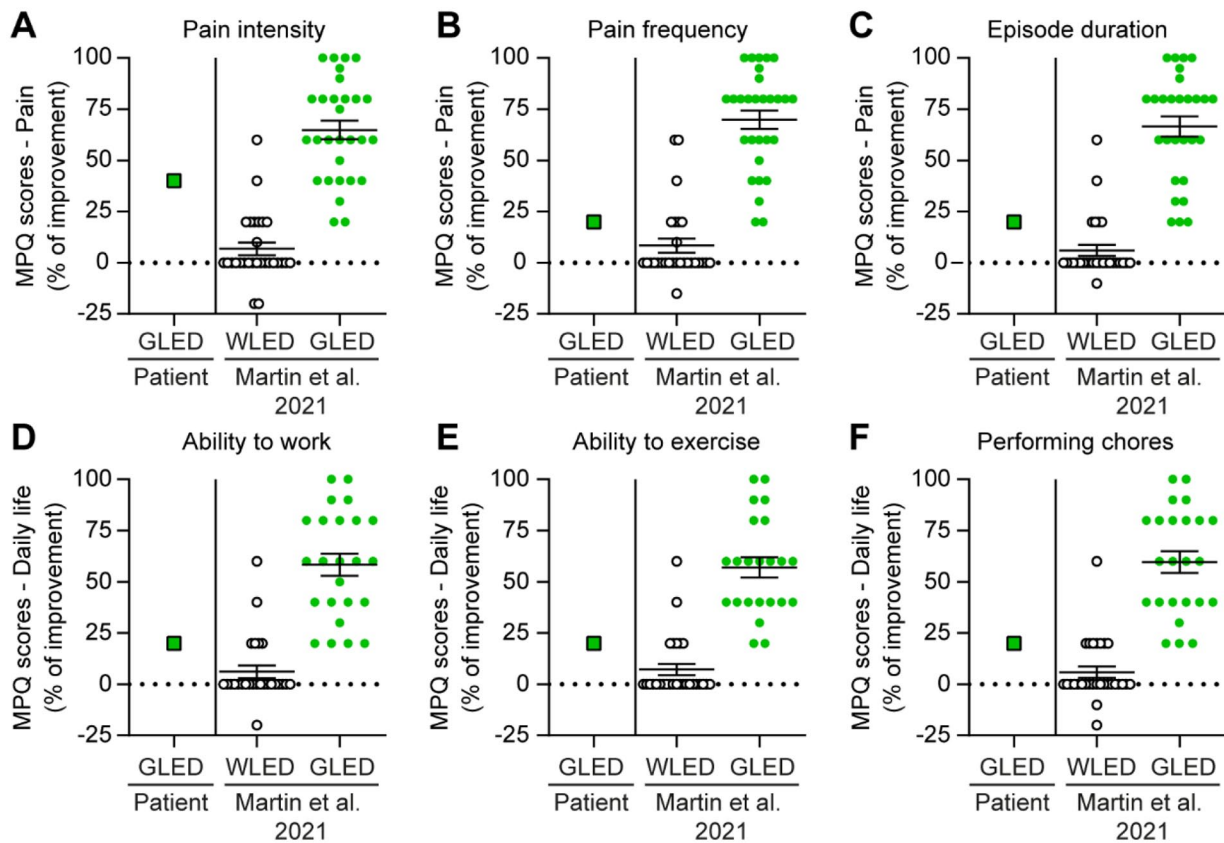


Figure 2. GLED slightly improved the colorblind patient's quality of life parameters reported using the modified pain clinic questionnaire (MPQ). The following criteria were evaluated: perceived percent improvement of (A) headache pain intensity, (B) frequency, (C) duration, (D) ability to work, (E) exercise, and (F) performing chores after completion of GLED therapy. GLED exposure demonstrated improvements in all measured parameters but was less pronounced when compared to the normal vision patients. Results from Martin et al. 2021 are presented as historical controls for points of reference: migraine patients were exposed for 10 weeks to white light emitting diodes (WLED) or GLED.

Table 2. Pittsburgh Sleep Quality Index (PSQI) index score improvements after GLED exposure in a colorblind subject.

PITTSBURGH SLEEP QUALITY INDEX	SUBJECT—GLED	
	BASELINE	70 DAYS OF EXPOSURE
Falling asleep (min)	30	15
Hours of sleep	7.5	9
Hours in bed	9	9.5
PSQI score	10	5

After 10 weeks of exposure to GLED, a colorblind subject with headaches attributed to other disorders of homeostasis reported improvements in his sleep quality as reported by the PSQI questionnaire.

suppress nocifensive behaviors.¹⁸ Establishing the exact pathways through which GLED modulates pain will require ultimately further studies, as GLED-induced analgesia could also rely on the modulation of the different visual cortices.

Previous animal and human studies^{3-6,19} reported by multiple groups have confirmed the analgesic effect of GLED exposure. A cone-driven retinal pathway for migraine photophobia has been reported, in which 20% of patients exposed to green light experienced reduced pain intensity.³ These results suggest

the importance of retinal cones in headache pain modulation by light. The importance of non-image-forming contributions to headache pain modulation by light was also suggested due to the exacerbation of migraine headache photophobia in blind patients without functioning rods or cones.²⁰ In agreement with animal studies,⁴ these studies highlight the importance of the visual system in GLED-induced analgesia. Pharmacologic studies in animals have also shown that the endogenous opioid system and central areas of pain modulation (ie, rostral ventromedial medulla) are important in GLED-induced analgesia.⁴ However, the exact link between the visual system and central pain modulation areas has not yet been elucidated.

GLED improving chronic headache pain in this subject with protanomaly gives rise to 2 hypotheses for the contribution of the visual system to GLED-induced analgesia. Protanomaly is characterized by the presence of S-, M-, and L-cones (blue, green, red, respectively) but with impaired functioning such that there is a shift in the spectral sensitivity of L-cones toward the M-cones peak sensitivity.²¹ Previous studies have shown that activation of M-cones (green) and L-cones (red) elicit different effects—green light exposure decreases pain,^{4-6,22} while red light exposure increases pain.^{3,23} One possible hypothesis of GLED-induced analgesia is that it

is dependent on M-cone photoreception. However, due to the spectral shift of L-cone sensitivity in this protanomalous subject, L-cones could also be activated by GLED. Therefore, the activation of both M-cones (antinociceptive) and L-cones (pronociceptive) in this subject could explain the less pronounced improvements in quality-of-life parameters and the reduced intensity of headache pain without a change in headache frequency. Furthermore, we posit that the activation of only M-cones in normal vision patients and the activation of both M-cones and L-cones in this protanomalous subject could provide an explanation for the differences in response to GLED in these 2 patient populations.

Another hypothesis of the visual system's contribution to GLED-induced analgesia may lie in ipRGCs. ipRGCs are classically involved in circadian rhythm entrainment and have been implicated in the mechanism of GLED-induced analgesia due to the effects that its inputs have on central pain modulation areas.²² A clinical observation that supports this hypothesis is the improvement in sleep quality in both normal vision migraine patients and this subject after GLED exposure.^{5,6} Chronic pain is correlated with sleep quality.²⁴ Therefore, GLED-induced analgesia may in part be a result of GLED-induced sleep improvement. Interestingly, GLED has been demonstrated to produce rapid sleep induction in mice, and this effect was shown to be dependent on melanopsin, the photopigment specific to ipRGCs, and its functions.²⁵ The ipRGC hypothesis could explain the improved sleep quality (and, therefore, headache pain) observed in both normal vision patients and this subject.

Significant sleep improvements after GLED exposure were reported in our previous study on normal vision migraine patients, where most patients initiated daily GLED exposure prior to sleeping at night.⁶ Patients were instructed to refrain from participating in activities that required external light sources (ie, screens/monitors) during GLED exposure. Since the correlation between pre-sleep blue light exposure from electronic screens and poor sleep quality has been well-documented,^{26,27} it was suggested that the improvements in sleep quality after GLED exposure were due to the reduction of blue light exposure prior to sleep. However, the subject here performed daily GLED exposure between the hours of 9:00 AM and 3:00 PM; yet he also reported improvements in sleep quality. This suggests that GLED exposure itself has a modulatory effect on sleep that is separate from the avoidance of electronic screens before sleeping at night.

Another notable factor potentially affecting the results of this report is the subject's preconceived notion of GLED's effects. The subject inquired about joining the GLED clinical study after hearing of the initial positive outcomes of the study on National Public Radio. It is reasonable to consider that the subject's positive expectations of GLED exposure partially contributed to the improvements in pain and quality of life measures. To rule out this limitation, exposure to different

color wavelengths will be required in further studies involving colorblind patients.

To summarize, this pain-relieving effect of GLED observed in a colorblind subject provides insights into the different subtypes of photoreceptive cells that can modulate pain sensitivity. This pivotal observation will undoubtedly impact the design of future studies assessing the benefits of light therapy across multiple conditions. Furthermore, these results reveal the strong potential of GLED-induced analgesia, even in visually impaired patients.

Limitations of the Study

This case report possesses limitations due to constraints on research design and methodology. These factors may impact the findings of our study and must be reported. First, the subject contacted the clinic with expectations that GLED will alleviate his headache. Second, self-reported improvement through questionnaires may induce bias in the reported results; the subject could expect sleep improvement as he is asked to fill a sleep improvement questionnaire. It is also important to notice that regardless of the positive effects of GLED exposure, the patient did not report any modifications to his analgesic medication. Daily habits could explain this observation, but GLED's potential effects on medication intake will require a throughout analysis in more patients and should be included in future clinical trials. Additionally, while we assumed that the subject's headache may be secondary to headaches attributed to other disorders of homeostasis given his history of polycythemia vera, it is also possible that his headaches are secondary to medication overuse headache. Finally, this case report does not include a color electroretinography analysis. This technique would have permitted us to confirm or refute the assumption that the patient does not have normally functioning retinal cones that are sensitive to the green light. More knowledge about the functionality of the subject's retinal cones would have provided insights into the potential involvement of visual cortices. All these limitations are of crucial interest as they will allow the accurate design of future studies involving more patients. The purpose of this case report is to present potential hypotheses on how GLED could modulate neuronal functions, hypotheses that require further studies.

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Author Contributions


Conceptualization, M.M.I., A.P.; Methodology, M.M.I., A.P.; Investigation and data analysis, M.M.I., L.F.M., K.C.; Writing—Original Draft, M.M.I., L.F.M., K.C., H.C.;

Writing—Review & Editing, M.M.I., A.P., L.F.M., K.C., H.C.; Funding Acquisition, M.M.I., A.P.; Supervision, M.M.I., A.P.

Data Availability Statement


The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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