Shining a green light on pain management

- Since the 1980s light therapy has been used to treat seasonal affective disorder and now its application expands to sleep disorders, pain, and depression, among others.
- In first-of-their-kind studies, Dr Laurent Martin and Dr Mohab M Ibrahim at the University of Arizona College of Medicine, USA show green light can reduce headaches and pain in patients with migraines and fibromyalgia, respectively.
- Green light therapy seems to work by stimulating the body's natural pain relief system – the opioid system – while also acting on brain regions in the descending pain pathway.
- Pending larger studies, it is hoped that such a non-pharmacological option with less side effects may help address the unmet clinical need for effective pain management.

Worldwide, chronic pain is common and for many sufferers, current medications are not fully effective. Such medications can have side effects including addictive or tolerance susceptibilities as well as physical effects like gastrointestinal disturbances, among others. Non-pharmacological options with fewer side effects are highly sought after. Addressing this unmet clinical need is Dr Laurent Martin and Professor Mohab Ibrahim, researchers at the University of Arizona College of Medicine. Their work on innovative pain management techniques focuses on photoneuromodulation which is the application of specific wavelengths of light to the visual system to activate neurones. For over seven years, efforts have focused on studying green light emitting diodes (GLED) and has both raised awareness of and strengthened the evidence for using green light to manage chronic pain.

Light at the end of the tunnel

Shown to be therapeutic in several medical conditions, light therapy is believed to work through our visual and/or integumentary systems (the outer most layer like our skin, nails, hair). The varying wavelengths of light produce assorted colours. Infra-red light's longer wavelengths are able to penetrate skin and tissues, while green light with a shorter wavelength of 525nm cannot penetrate the skin but instead acts on the retina of the eye to exert its effects. Environmental sources of green light like forest bathing can have positive health benefits and reduce pain prompting investigation into the mechanism of such effects.

The ancient Chinese philosopher Lao Tzu famously said, 'The journey of a thousand miles begins with a single step.' As is the case with many research journeys, the story of GLED started with one key study. This study by Ibrahim in animal models described the effects of GLED on the sensory and neurological pain pathways and suggested a role for natural pain relief – the opioid system. This set the scene for exploration in humans and in 2021, the team published their results from two first-of-their-kind studies.

One study looked at if white light emitting diodes (WLED) and GLED could help prevent migraines in sufferers who were not responding to their current therapies. Migraines are headaches often accompanied by sensitivity to light and sounds and affect just under 15% of people worldwide. The 29 migraine patients were initially exposed to one to two hours of WLED for 10 weeks followed by two weeks of no light exposure, and finally ten weeks exposure to GLED. GLED not only reduced the number of headache days per month by about 60% compared to before therapy, but also lessened headache intensity.

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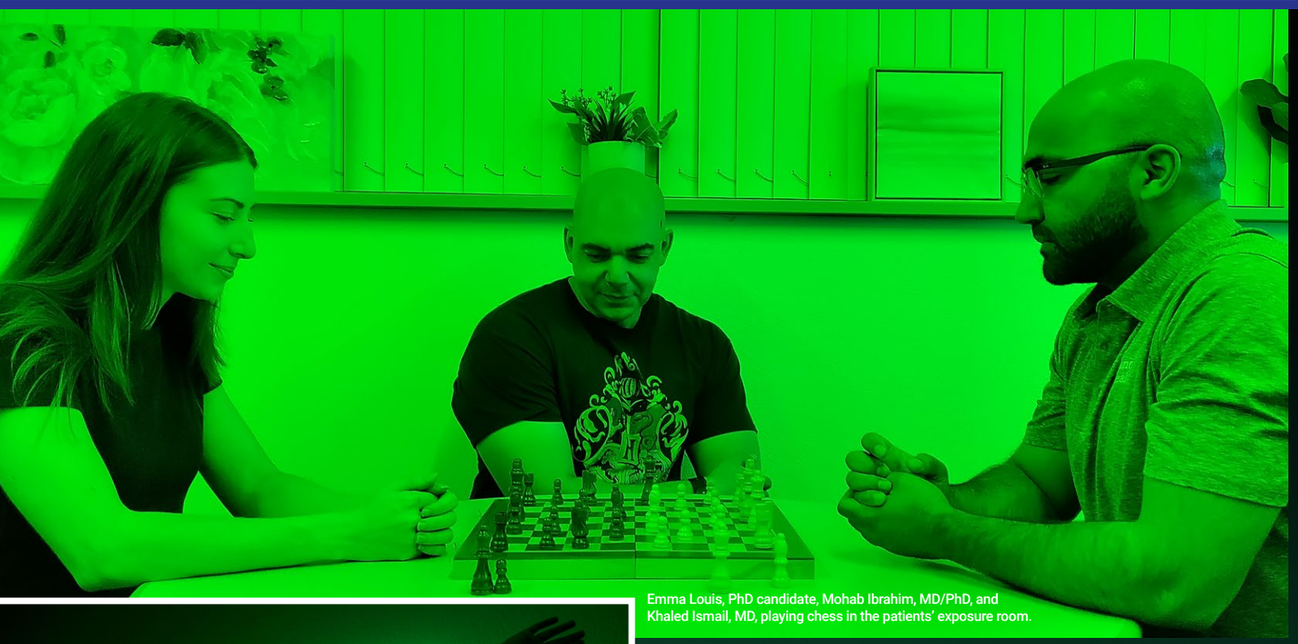

Emma Louis, PhD candidate, Mohab Ibrahim, MD/PhD, and Khaled Ismail, MD, playing chess in the patients' exposure room.

Photoneuromodulation is the application of specific wavelengths of light to the visual system to activate neurones.

Now, collaboration and joined-up thinking is needed to take this forward, discover the true potential of this non-pharmacological therapy, and then raise awareness of this therapeutic alternative.

also lessened headache intensity as well as improving patient's quality of life in terms of sleep quality and work productivity. This small-scale study laid the foundation for future larger studies.

Since then, a recent real-life study by Lipton and colleagues of almost 700 patients used a lamp to deliver a narrow band of green light (around 525nm) during acute migraine episodes. Headaches improved in about 55% of migraine attacks with sensitivity to light and anxiety reducing too, thereby strengthening the therapeutic evidence for GLED treatment. The second study from Martin and Ibrahim's lab focused on fibromyalgia – one of the most common reasons for chronic pain in early- to middle-aged women. In addition, a lack of energy and sometimes cognitive and psychiatric dysfunction add to the symptoms of unknown cause. In a study design like their migraine research, 21 patients with fibromyalgia whose current therapy was not controlling the pain trialled WLED and GLED as therapies. This novel proof-of-concept study demonstrated the ability of GLED to reduce fibromyalgia pain intensity and improve quality of life.

But how does it work?

These proof-of-concept studies did not divulge the underlying mechanisms at play. However, another research group from China, Tang and colleagues, explained the mechanisms of how green light relieves pain in animal models. Their study confirmed the visual system is indeed involved and that green light activates cone neurones in the eye, causing knock-on effects in specific regions of the descending pain pathway that work to increase the inhibitory signals and effectively reduce pain. More specifically, their study suggests involvement of the naturally produced opioids, enkephalin (ENK) and proenkephalin (PENK) in the descending pain pathway to bring about pain relief.

Following promising results, Martin and Ibrahim have since focused their efforts on exploring mechanisms of post-surgical pain relief using GLED in animal models. The duo's recent animal model suggests GLED acts on several systems to relieve this type of pain. One way is by increasing naturally produced opioid levels, the other is by decreasing the receptors needed for pain transmission; finally, the last is regulating inflammation. However, the researchers say all these systems interconnect and affect each other to alleviate pain. Evidence is also emerging from other researchers for the added benefit of psychotherapy sessions done under green light for general anxiety disorder compared to standard room lighting.

Stronger together

With pre-clinical and small-scale human studies laying the foundations, research is progressing into larger studies of alternative design in a bid to further strengthen the evidence for GLED in chronic pain conditions. Work in this field is gaining traction with several studies and publications in the last few years. Now, collaboration and joined-up thinking is needed to take this forward, discover the true potential of this non-pharmacological therapy, and then raise awareness of this therapeutic alternative.

Details

Dr Laurent Martin

Dr Mohab Ibrahim

Laurent Martin
e: laurentmartin@arizona.edu
w: pharmacology.arizona.edu/person/laurent-f-martin
www.linkedin.com/in/laurent-martin-phd-97290095

Mohab Ibrahim
e: mibrahim@anesth.arizona.edu
w: anesth.medicine.arizona.edu/profile/mohab-m-ibrahim-phd-md

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University of Arizona – Department of Anesthesiology

Bio

Drs Martin and Ibrahim are an assistant professor and a professor, respectively, at the University of Arizona Health Sciences Comprehensive Center for Pain & Addiction and College of Medicine – Tucson. Their research focuses on innovative pain management techniques, including green light therapy. Their lab bridges fundamental science and clinical applications to develop nonpharmacological treatments for chronic pain.

Further reading

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Competing interest statement

Dr Ibrahim is a member of Luxxon Therapeutics LLC, which aims to bring GLED therapy to chronic pain patients.

Personal response

What led you to study non-pharmacological treatments for chronic pain and light therapy in particular?

As the United States grapples with an opioid epidemic, there is an increasing demand from chronic pain patients for non-pharmacological and safer therapies. Over the past two decades, research has demonstrated that neurones in the retina are connected to brain regions involved in pain modulation, such as the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM). We hypothesised that by using specific wavelengths of light, we could 'trick' these retinal neurones into modulating the activity of these brain areas. This led us to discover that different wavelengths (colours) of light have distinct effects on pain, either increasing or decreasing pain sensitivity depending on the wavelength.

Can you explain a bit more about the practical aspects of using GLED-how is this set up and what does the patient do during exposure?

Our migraine and fibromyalgia patients were exposed to an LED light strip for one to two hours a day in a closed room, eliminating any additional light sources. They were free to engage in any activities that did not involve screens (cell phones, tablets, computers, etc). Many patients chose to read, while others opted to perform household chores.

Are there any things that have surprised you during this project?

The most surprising thing was the long-lasting effects of the therapy. Even days after stopping light treatment, patients still benefited from its effects. We also observed this phenomenon in our preclinical models of pain. This led us to think that the therapy affected 'brain plasticity', or how the brain adapts to the environment.

What are the main challenges researchers like yourself face in moving this work forward?

One of the biggest challenges we faced in recent years was scepticism within the scientific community. However, this began to shift as multiple teams worldwide successfully replicated our results. Now, the greatest challenge lies in making this therapy accessible to patients.