Complementary Therapies in Medicine 41 (2018) A1–A6

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Editorial

"Let there be light." Research on phototherapy, light therapy, and photobiomodulation for healing – Alternative therapy becomes mainstream

In the Judeo-Christian tradition, light was the first creation. Light therapy or heliotherapy has been used since ancient times for healing. For example, prior to the advent of antimicrobial therapies, one of the mainstays of treatment for infectious respiratory diseases such as tuberculosis was increased exposure to sunlight provided in sanatoria.[1] One hundred years ago, visionaries such as Edgar Cayce and Rudolph Steiner predicted that in the future vibrational healing from color and light would revolutionize medicine.[2,3] But for most of the intervening years, as biochemistry dominated conventional therapeutics, the idea of light as therapy was, with few exceptions, generally considered radically alternative and antiquated. Since then, the field has grown exponentially, spawning a confusing array of terminology. (Table 1).

1. Visible light

In 1903, Danish Nobel laureate Niels Finsen described the use of red light to prevent suppuration and scarring in patients with smallpox, and later used ultraviolet light to treat pulmonary tuberculosis, Lupus vulgaris, and rickets.[5] In the 1950′s nurses observed that infants whose cribs were located near windows were less likely to have jaundice than infants whose cribs were farther from windows.[6,7] Within 20 years, phototherapy was widely adopted as a standard treatment for neonatal jaundice due to high levels of unconjugated bilirubin, and research established that the wavelengths of 480–500 nm (blue-green) were most effective in helping convert bilirubin to more readily excreted isomers of bilirubin.[8] These light waves are longer than ultraviolet rays, and do not increase the risk of later skin damage or skin cancer.

Three wavelengths of light in the visible and near-visible range are commonly used in low intensities (e.g., light-emitting diode, LED, lights) to treat dermatologic conditions: blue (415 nm), red (633 nm), and near infra-red (830 nm). Blue light is used to treat acne because it produces a strong photoactivation of endogenous porphyrin chromophores.[9] Red LEDs have been used to promote post-surgical wound healing after blepharoplasty and laser resurfacing; red LEDs are also used to treat psoriasis and to reduce wrinkles in aging skin.[9,10]

Bright light therapy has become a common complementary therapy to treat both seasonal and non-seasonal affective disorder in adults and children[11–13]; in fact, there is emerging evidence that individuals who use indoor tanning beds may do so not only for esthetic reasons, but also as a form of "self-medication" for mood disorders.[14] Furthermore, ever since a photoreceptor with a highest sensitivity to 470–490 nm (blue) light was discovered, there have been controversies about whether these wavelengths alone are better than or equivalent to full spectrum white light.[13] On the other hand, some researchers are investigating the benefits of red and infrared light alone on mood and cognitive function.[15] Substantial research questions remain about the mechanisms by which light affects mood (e.g., is it something other than effects on melatonin production?), and the optimal wavelengths or combination of wavelengths, intensities, and duration of treatments that promote optimal mood, memory, and other affective and cognitive function. Excessive exposure to blue light has been linked to insomnia leading to widespread recommendations to avoid blue-light emitting electric screens (or block them with amber glasses) before bed.[16]

With photodynamic therapy (PDT), light is used to activate a light-sensitive compound to promote a therapeutic effect. For example, in dermatology, phototherapy with red, green, or blue LEDs has been used to activate 5-aminolevulinic acid (5-ALA), leading to release of cytotoxic free radicals and cell death; this is one approach to treating squamous cell carcinoma in situ and actinic keratoses.[9] Photodynamic therapy is a rapidly growing field of oncology, joining chemotherapy, hormonal and immunologic therapies, surgery, and radiation therapy as a highly specific approach to localized tumor treatment.[17–21]

In addition to phototherapy for jaundice and bright light therapy for mood problems, an increasing number of medical applications have emerged for non-visible forms of light. Of sunlight reaching the earth, approximately 54% is infrared (30% is near infrared), 44% is visible light and 2%–3% is ultraviolet radiation (Table 2).

In the highly acclaimed novel, "All the light we cannot see," Anthony Doerr describes the lives of a blind Parisian girl and a German orphan boy whose lives are brought together by the invisible light of radio waves during World War II. As Doerr's novel reminds us, visible light (wavelengths of approximately 400–700 nanometers, nm) comprises only a small part of the electromagnetic spectrum (which range from extremely short gamma rays and X-rays to long radio waves).

2. Ultraviolet light, slightly shorter wavelengths than visible light

Ultraviolet wavelengths of 290–315 nm are absorbed by dermal 7-dehydrocholesterol, converting it into pre-vitamin D3, which in turn isomerizes in vitamin D3, supporting the immune system and reducing the risk of rickets, infectious diseases, diabetes, hypertension, and cancer.[22] In addition to promoting the production of vitamin D, ultraviolet light (405 nm) can be used to disinfect or sterilize surfaces, air, and water, e.g., eliminating Pseudomonas aeruginosa from water taps.[23,24] Ultraviolet (UV) light disinfects (kills germs) by damaging DNA, creating difficult to repair thymine dimers.

Ultraviolet light is hazardous not only to bacteria, but also to human eyes and skin. UV-A (320–400 nm) accounts for up to 95% of the UV radiation from the sun that reaches the earth; it contributes most to tanning, skin aging, and wrinkling, and may contribute to skin cancer.

https://doi.org/10.1016/j.ctim.2018.10.007

Available online 06 October 2018

Table 1
Common Terms in the Field of Light Therapies.

Term	Definition	Example
Biphasic dose response	Decreasing biological effect with higher doses (hormesis) often observed with low level light therapy	Low level light therapy with near infrared light for traumatic brain injury; fewer doses are sometimes more effective than more frequent doses
Far infrared light therapy (FILT)	15 micrometer – 1 mm	Sauna, Waon therapy
Gamma knife therapy	Use of focused gamma rays for surgical purposes	Stereotactic brain surgery for brain tumors
Heliotherapy	Exposure to sunshine, used in ancient healing practices to support overall well-being	Tuberculosis sanatoria
Infra-red Light Therapy (IRLT)	Infrared light applied for short time periods or in pulsations	Promote wound healing; decrease pain, edema
Infrared Neural Stimulation (INS)	IR pulsed radiation stimulates action potentials in various kinds of nerve cells	Wound healing; tissue regeneration
Infrared Pulsed Laser Device (IPLD)	Infrared light at 904 nm pulsed at 3 MHz	Age-related macular degeneration
LED	Light Emitting Diodes, low intensity light	Acne
Light Therapy	General term sometimes used the same as heliotherapy or phototherapy, usually using polychromatic or full spectrum light	Treat delayed sleep phase disorder, seasonal affective disorder, neonatal jaundice, several dermatologic disorders
Low level light therapy (LLLT) or Low Level Laser Therapy (LLLT) or Cold Laser or Soft Laser	Use of light at red and near infra-red wavelengths (600-1000 nm) at low power intensity (< 500mW) to modulate biological activity	Wound healing; neuroprotection for stroke, TBI, degenerative brain disorders
Photobiomodulation (PBM)	LLLT at red to near infrared frequencies using non-ionizing, non-thermal light sources including lasers, LEDs, and broad band light involving endogenous chromophores to elicit photophysical and photochemical effects [4]	Wound healing; skin rejuvenation; fibromyalgia
Photodynamic Therapy	Phototherapy used with light-sensitive compounds	Actinic keratosis Cancer treatment
Phototherapy	Blue or full spectrum light	Neonatal jaundice
Pulsed radio frequency energy	Radio frequencies	Deep heat to treat pain, edema, and promote wound healing
Radiation Therapy	Ionizing radiation damages DNA	Destruction of solid tumors
Ultraviolet light therapy	UV-A or UV-B light	Promote dermal vitamin D synthesis; bactericidal
Waon Therapy	Infrared sauna used to induce hyperthermia	Chronic heart failure, COPD by stimulating endothelial nitric oxide synthase protein and increasing parasympathetic nervous system activity

Table 2
Electromagnetic Spectrum and Therapeutic Uses.

Wave length	Type of EM Radiation	Therapy	Mechanism(s)
< 0.01 nm	Gamma	Gamma Knife for brain tumors	Tissue destruction
0.01 nm – 10 nm	X-ray	Radiation therapy for Solid tumors	Tissue destruction/burning
1 nm -400 nm	Ultraviolet	Vitamin D Disinfectant	Atopic dermatitis, acne, psoriasis, vitiligo
400 nm -500 nm	Violet -Blue Light	Phototherapy	Isomerization of bilirubin
510 nm – 640 nm	Green – Orange Light	Dermatologic and esthetic uses	Binds to photoacceptors in the dermis
650 nm – 700 nm	Red Light	Photobiomodulation	Reduce suppuration from small pox
700 nm – 3000 nm	Infra-red (near)	Photobiomodulation	Wound healing; stroke; TBI; degenerative brain disorders.
3 micrometers – 1mm	Infrared (medium -far)	Thermal infrared	Increase tissue temperature and circulation
1 mm – 30 cm	Microwaves	Diathermy	Used for thermal tissue ablation, e.g., diathermy
15 – 30 cm	Radar		Remote monitoring; monitoring movement
10 cm – 100 km	Radio/TV (UHF, VHF, FM)	Dentistry; Body contouring; keloid reduction; electrosurgery; wart removal	Wound healing; hemostastis; deep tissue heating

UV-B (290–320 nm) comprises much less of the sun's UV radiation, but it is more damaging, causing sunburns, and leading to skin cancer. Both types of UV radiation appear to contribute to age-related cataracts and macular degeneration, not through DNA damage, but by triggering a chain reaction leading to protein glycation.[25,26] UV radiation scatters at the skin surface and reaches only about 2–3 mm into the dermis, so its adverse effects appear mostly in the skin and eyes. There appears to be a greater risk of damage due to UV radiation in those whose diets are deficient in antioxidant compounds found in fruits, vegetables, and seeds (vitamins C and E, carotenoids, polyphenols, etc.).[27] This intersection of light and diet represents an important integrative health care research target: What combinations of dietary compounds and light exposures lead to optimal vitamin D levels without increasing the risk of skin cancer, cataracts, or macular degeneration?

Despite these risks, narrow band UV-B therapy has become a standard treatment for skin conditions such as psoriasis and vitiligo, even in an age of biological and chemical therapies[10,28]; for example, narrow band UV-B (311 nm) can be used safely to treat psoriasis, vitiligo, and eczema.[29,29] It works by suppressing Langerhans cells, cytokines, and adhesion molecules, and by selectively reducing T-lymphocytes.

3. The shortest wavelengths: gamma rays and X-rays

The shorter the light rays, the greater the potential of DNA damage and tissue destruction, which can cause disease or be used therapeutically. The shortest of these, gamma rays, are a form of penetrating ionizing radiation that typically arises from nuclear decay, nuclear fission, or nuclear fusion. However, the extremely short waves of gamma radiation can be harnessed as gamma knife surgery. Gamma "knife" surgery is not an actual knife, but rather a type of stereotactically-guided radio-surgical therapy used with fine precision to treat brain tumors and vascular abnormalities of the brain. Similarly, X-ray waves (0.01–10 nm) are longer than gamma waves but shorter than UV waves. They are best known medically for their use in imaging, with classical X-rays, X-ray crystallography, fluoroscopy, and CT scans. X-radiation can cause radiation burns, bone marrow suppression, and cancer, but therapeutically, it is used to treat several types of solid tumors. Both types of short light waves – gamma waves and X-rays – can cause substantial damage or provide powerful benefits depending on how they are used, but both have clearly moved from the realm of invisible mysterious energy to everyday conventional medical practice.

4. Slightly longer than visible light: infrared light, near infrared

Approximately half of the sunlight that reaches the earth is infrared radiation. Infrared radiation reaches deeper into the body than visible or ultraviolet light, penetrating 20–30 mm through a range of tissues; it may have effects even more deeply by triggering changes in circulating cytokines.[30] Far red and infrared low-level laser and LED therapy are used to promote wound healing and to treat several kinds of pain, including low back pain, osteoarthritis, tendinopathies, fibromyalgia, muscle fatigue, wounds, and temporomandibular joint disorder, as well as edema and inflammation, peripheral nerve injuries, plantar fasciitis, male infertility, and strokes.[31–38] Studies in rodent and monkey models of Parkinson's disease have shown that PBM enhances dopaminergic cell survival and recovery;[39–47] several small case series in humans support its benefits, despite the limited penetration of transcranial infrared light from the scalp to the brainstem, suggesting non-local mechanisms of effects.[48–50] LLLT applied to the forehead increases frontal cortical blood flow and metabolism, decreases inflammation, stimulates neurogenesis, and reduces depression scores among patients with major depressive disorder. [51–53] A meta-analysis of 11 clinical trials concluded that LLLT can be considered an effective therapy for breast cancer-related lymphedema.[54] A review of 28 randomized trials concluded that LLLT promoted statistically significant improvements in periodontitis, and it has become widely used in dentistry. [55] Several studies suggest LLLT can help frozen shoulder and rotator cuff injuries; [56,57] it has become a routine adjunct to physical therapy. A 2009 case series showed significant immediate benefits on pain and stiffness in adults with rheumatoid arthritis or ankylosing spondylitis treated with LLLT.[58] Additional case reports suggest safe improvements in executive function and memory in patients with chronic symptoms following traumatic brain injury (TBI). [59,60] In addition to TBI, other brain problems affected by LLLT or PBM include stroke, depression, and degenerative diseases such as Alzheimer's disease, dementia, and Parkinson's disease. [61–66] Since 1967, over 100 phase III randomized controlled trials and over 1000 laboratory studies have investigated the effects of LLLT [67]

Interestingly, LLLT does not exhibit a classical linear dose-response effect, but instead shows a biphasic dose response in which the lowest levels of light show no effect, but low levels of light (1 mW – 500 mW) have a much better effect on stimulating and repairing tissues than higher levels of light.[67] This example of hormesis or biphasic dose response is well recognized in LLLT and is widely used in conventional physical therapy applications, another shift from alternative to mainstream thinking.

5. Far infrared

Physical therapists use far infrared (FIR) therapy to help patients with a variety of problems, e.g., cardiovascular disease, diabetes, and chronic kidney disease.[68] FIR enables energy to reach 2–3 cm below the skin's surface without excessively heating the skin above 40 °C. FIR is usually administered by an emitter 20 cm above the skin's surface or via dry sauna therapy. FIR produces both thermal and non-thermal effects including increased arterial blood flow, improved circulation and endothelial function, lowered blood pressure, and reduced fatigue and pain.[68] One month of daily FIR sauna therapy has been shown to upregulate endothelial nitric oxide synthase and nitric oxide production as well as augment angiogenesis.[69,70] For example, Waon therapy, a Japanese version of FIR sauna therapy, provided daily for six weeks to patients with peripheral arterial disease led to improved 6 min walking distance, mobilization of endothelial progenitor cells, and improved blood flow in the legs.[71] In patients with Type 2 Diabetes Mellitus (T2DM), repeated dry sauna therapy with FIR was associated with significant reductions in urinary markers of oxidative stress;[72,73] even limited FIR treatment aimed at the legs or feet alone was associated with normalized blood sugar levels, lower cortisol levels, and improved insulin sensitivity.[74] For patients with chronic kidney disease dependent on hemodialysis, FIR therapy can improve blood flow in and patency of AV grafts.[75] In addition, FIR therapy has been effective for patients with chronic pain, phantom limb pain, chronic fatigue, fibromyalgia, insomnia, and athletes with muscle damage from over-exercise.[68]

6. Microwaves

Microwaves are used to ablate tissue thermally. Another name for microwave treatment is dielectric heating or diathermy. Diathermy is used to treat large tumors, e.g., liver, lung, or prostate tumors. Microwaves can also be used surgically to coagulate bleeding in the liver or spleen.

7. Radio waves

Pulsed radio frequency energy (PRFE) is used in the palliative treatment of pain and edema and to promote wound healing. In a 2012 meta-analysis of 25 controlled trials involving over 1300 patients, Guo and colleagues concluded that there were statistically significant improvements in pain, edema, and wound-healing applications with PRFE treatments.[76]

8. How does light affect human biology? Photobiology

The biological effects of light therapy imply a conversion of luminous energy to metabolic energy, followed by modulation of cell functioning. Light must first reach the target tissue. Shorter wavelengths in the blue and ultraviolet spectrum are scattered in the superficial skin and absorbed by hemoglobin and melanin, and they are less able to reach deeper tissues than red and near infrared wavelengths. High energy, short wavelength energy, such as gamma rays or lasers release a great deal of energy, resulting in heating and tissue destruction. Furthermore, wavelengths in the ultraviolet spectrum can cause DNA damage. In contrast, low level light therapy does not cause heating or tissue destruction.

Biological systems contain both specialized, photoreceptor, and nonspecialized, photoacceptor, molecules that can absorb and respond to light. The specialized photoreceptor molecules include the opsins (responding to red, green, and blue wavelengths) of the eye as well as pinopsin in the pineal gland (which responds to blue light at 470 nm). The more numerous non-specialized molecules that can be affected by light are called photoacceptors. Photoacceptor molecules, found in nearly all living cells, are able to absorb light and thereby change cell functioning.[77] The form of the photoacceptor molecule that absorbs light is called a chromophore. Chromophores typically absorb very specific wavelengths of light and reflect others, e.g., chlorophyll has peaks of absorption at 430 nm (blue) and 662 nm (red) and reflects green light.

Chromophores are usually organic cofactors or metal ions in a protein structure and contain electrons that can be excited from a ground to an excited state, leading to a change in the molecule's conformation, which in turn affects molecular function and cellular metabolism.[77] For example, phototherapy leads to isomerization of bilirubin into a more easily excreted form. Chromophores almost always

Table 3
Mechanisms by which Light Affects Biological Systems.

Mechanism	Examples
Chromophore excitation	1 Bilirubin isomerization from blue light, making it more readily excreted 2 Cytochrome C oxidase excited by red/near infrared facilitates electron transport and ATP production 3 NO release leads to vasodilation
DNA damage, killing rapidly dividing cells	1 Radiation therapy for cancer 2 Gamma knife therapy
Heating intracellular water	1 Infrared radiation absorbed by water heats it, affecting temperature-gated calcium ion channels 2 Calcium channels open, leading to secondary signaling
Indirect effects	1 Release of circulating cytokines and antioxidants 2 Activation of immune cells or stem cells 3 Triggering of superficial cortical cells in the brain that send electro-chemical signals to deeper structures

ATP; adenosine triphosphate.

occur as either: a) conjugated pi electron systems (e.g. molecules like flavins, flavoproteins, pyridine, porphyrins, and melanin that contain alternating single and double bonds) or b) metal complexes (e.g., cytochrome c oxidase which contains copper and iron, or iron-containing hemoglobin and myoglobin). Chromophore-containing enzymes allow for an efficient coupling of electromagnetic energy to chemical energy and conversion of substrates. Chromophore containing molecules include hemoglobin, myoglobin, superoxide dismutase, catalase, cytochrome b, cytochrome c, guanylate cyclase, NADH, and nitric oxide synthase.[77] Cytochrome c oxidase (COX or CCO), a large mitochondrial membrane protein, has been proposed as the primary photoreceptor for the red-near infrared range in mammalian cells;[78,79] LLLT photodissociates nitric oxide (NO) from COX, enabling more efficient mitochondrial respiration and energy production, increased production of ATP, increased RNA and protein synthesis, increased oxygen consumption, increasing the ratio of NAD to NADH, greater membrane permeability, calcium release, increased cAMP, generation of free radicals (including signaling molecules such as reactive oxygen species), and vasodilation.[67,80] Light-mediated vasodilation was first described by Nobel prize winner RF Furchgott in 1968.[81] COX is the most abundant metalloprotein in neural tissue, and its peak absorption spectra (670 nm and 830 nm) are highly correlated with its peaks in catalytic activity and ATP content in tissue culture.[77] Secondary effects of LLLT and COX activation include activation of second messengers to the mitochondria and nucleus, altering levels of gene expression, and thereby affecting inflammation, apoptosis, and energy metabolism hours to days after light exposure [77] (Table 3).

Studies conducted in tissue cultures and animals suggest that LLLT in the infrared range has numerous biological effects. For example, LLLT of fibroblasts increases metabolism, DNA synthesis, and growth rate.[82] LLLT also shows beneficial effects on epithelial cells; keratinocytes; lymphocytes; endothelial cells; mesenchymal, dental pulp, adipose, bone marrow, and cardiac stem cells; and neurons in tissue culture.[83–85] In neural tissue, LLLT can help restore function after exposure to toxins and trauma, prevent damage due to toxins, increase neurite outgrowth, regulate genes coding for repair and antioxidants, reduce inflammation, increase proliferation of several types of neurons including olfactory stem cells, Schwann cells, astrocytes, and oligodendrites.[77,81] In animals, LLLT has been shown to enhance neovascularization, increase collagen synthesis, and accelerate healing of skin and deeper tissues including cartilage, tendons, and nerves, decreasing inflammation and swelling caused by injuries, degenerative diseases, or autoimmune diseases.[81]

Transcranial photobiomodulation of the scalp has been shown to have effects on the brainstem, far beyond the direct reach of the light, suggesting indirect effects.[48] One hypothesized mechanism is the local release of cytokines, which can circulate to the brainstem. Another potential indirect mechanism is the activation of immune cells and stem cells near the scalp which then travel by intracranial circulation to affect the brainstem. Finally, a third potential mechanism involves influencing the activity of the motor cortex, which transmits neural chemical or electrical signals down to the brainstem.[48] Substantial additional research is necessary to determine what mechanisms actually account for the impact of transcranial PBM on deep brain structures and how best to promote healing there - -whether through transcranial approaches via the scalp, nose, pharynx, or via blood vessel catheterization or direct application of photostimulator probes intracranially.

9. Conclusion and research challenges for complementary light therapies

Despite conventional care's focus on biochemical and surgical treatment strategies, light therapy using the full electromagnetic spectrum, originally a highly suspect alternative therapy, has found its way into multiple roles in modern medicine.[86] Xrays are standard tools in radiology; oncologists use gamma knives to treat intracranial tumors; dermatologists uses light from ultraviolet to infrared to treat a variety of skin conditions; dentists and oral surgeons also use a variety of light therapies. Light therapy has also been combined with traditional healing approaches such as acupuncture, e.g., laser acupuncture using cold lasers. Laser acupuncture has been successfully used to treat many conditions that are usually treated with acupuncture needles (such as musculoskeletal pain, headache, and TMJ pain),[87–89] leading to compelling research questions about the mechanisms by which it achieves these benefits. Many questions remain about the precise role of specific wavelengths of light to treat different conditions. What chromophores respond best to which wavelengths, and how does their activation affect DNA expression and cell signaling? Can light directed at a local body part have distant effects through generation of cytokines and other signaling molecules? How can light therapy most safely be applied to deeper structures in the brain and brainstem? What are the effects of combining light with other mainstream and complementary therapies such as music and sound, diet and exercise, herbs and meditation?[90] We hope that in the coming years we receive many research papers addressing the fascinating field of healing with light, a clear example of an alternative therapy that has moved into the mainstream and can be used in combination with therapies still considered complementary to benefit a wide range of human health conditions.

References

1. Borella E, Nesher G, Israeli E, Shoenfeld Y. Vitamin D: a new anti-infective agent? *Ann N Y Acad Sci.* 2014;1317:76–83.
2. Campbell D, Reed H. *Edgar Cayce on the power of color, stones, and crystals.* Grand Central Publishing; Warner Books; 1989.
3. Steiner R. *Colour.* Rudolf Steiner Press; 1992.
4. Anders JJ, Lanzafame RJ, Arany PR. Low-level light/laser therapy versus photobiomodulation therapy. *Photomed Laser Surg.* 2015;33(4):183–184.
5. Finsen NR. Remarks on the red-light treatment of small-pox: is the treatment of small-pox patients in Broad daylight warrantable? *Br Med J.* 1903;1(2214):1297–1298.
6. Cremer RJ, Perryman PW, Richards DH. Influence of light on the hyperbilirubinaemia of infants. *Lancet.* 1958;1(7030):1094–1097.
7. Porto SO, Hsia DY. The mechanism of blue light on neonatal jaundice. *J Pediatr.* 1969;74(5):812–813.
8. McDonagh AF. Phototherapy: from ancient Egypt to the new millennium. *J Perinatol.*

2001;21(Suppl. 1):S7–S12.
9. Ablon G. Phototherapy with light emitting diodes: treating a broad range of medical and aesthetic conditions in dermatology. *J Clin Aesthetic Dermatol.* 2018;11(2):21–27.
10. Zhang P, Wu MX. A clinical review of phototherapy for psoriasis. *Lasers Med Sci.* 2018;33(1):173–180.
11. Perera S, Eisen R, Bhatt M, et al. Light therapy for non-seasonal depression: systematic review and meta-analysis. *B J Psych Open.* 2016;2(2):116–126.
12. Pail G, Huf W, Pjrek E, et al. Bright-light therapy in the treatment of mood disorders. *Neuropsychobiology.* 2011;64(3):152–162.
13. Meesters Y, Duijzer WB, Hommes V. The effects of low-intensity narrow-band blue-light treatment compared to bright white-light treatment in seasonal affective disorder. *J Affect Disord.* 2018;232:48–51.
14. Carcioppolo N, Chen Y, John KK, et al. The development and validation of the mood-based indoor tanning scale. *Am J Health Behav.* 2017;41(1):42–51.
15. Barrett DW, Gonzalez-Lima F. Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. *Neuroscience.* 2013;230:13–23.
16. Shechter A, Kim EW, St-Onge MP, Westwood AJ. Blocking nocturnal blue light for insomnia: a randomized controlled trial. *J Psychiatr Res.* 2018;96:196–202.
17. Costa DF, Mendes LP, Torchilin VP. The effect of low- and high-penetration light on localized cancer therapy. *Adv Drug Delivery Rev.* 2018(Sep) https://doi.org/10.1016/j.addr.2018.09.004 pii: S0169-409X(18)30224-2 [Epub ahead of print].
18. Zhu H, Cheng P, Chen P, Pu K. Recent progress in the development of near-infrared organic photothermal and photodynamic nanotherapeutics. *Biomater Sci.* 2018;6(4):746–765.
19. Norouzi H, Khoshgard K, Akbarzadeh F. In vitro outlook of gold nanoparticles in photo-thermal therapy: a literature review. *Lasers Med Sci.* 2018;33(4):917–926.
20. Deng K, Li C, Huang S, et al. Recent progress in near infrared light triggered photodynamic therapy. *Small.* 2017;13(44).
21. Saneja A, Kumar R, Arora D, Kumar S, Panda AK, Jaglan S. Recent advances in near-infrared light-responsive nanocarriers for cancer therapy. *Drug Discovery Today.* 2018;23(5):1115–1125.
22. Grober U, Spitz J, Reichrath J, Kisters K, Holick MF. Vitamin D: update 2013: from rickets prophylaxis to general preventive healthcare. *Dermato-Endocrinol.* 2013;5(3):331–347.
23. Maclean M, McKenzie K, Anderson JG, Gettinby G, MacGregor SJ. 405 nm light technology for the inactivation of pathogens and its potential role for environmental disinfection and infection control. *J Hosp Infect.* 2014;88(1):1–11.
24. Gerba CP. Use of an ultraviolet light at point-of-dispense faucet to eliminate pseudomonas aeruginosa. *Am J Infect Control.* 2015;43(5):528–529.
25. Delcourt C, Cougnard-Gregoire A, Boniol M, et al. Lifetime exposure to ambient ultraviolet radiation and the risk for cataract extraction and age-related macular degeneration: the Alienor study. *Investig Ophthalmol Visual Sci.* 2014;55(11):7619–7627.
26. Linetsky M, Raghavan CT, Johar K, et al. UVA light-excited kynurenines oxidize ascorbate and modify lens proteins through the formation of advanced glycation end products: implications for human lens aging and cataract formation. *J Biol Chem.* 2014;289(24):17111–17123.
27. Fernandez-Garcia E. Skin protection against UV light by dietary antioxidants. *Food Funct.* 2014;5(9):1994–2003.
28. Calzavara-Pinton P, Zanca A, Arisi M, et al. Prevalence of phototherapy in the age of biologics. *Dermatology.* 2018:1–7.
29. Hum M, Kalia S, Gniadecki R. Prescribing home narrowband UVB phototherapy: a review of current approaches. *J Cutan Med Surg.* 2018:1203475418800947.
30. Mitrofanis J, Jeffery G. Does photobiomodulation influence ageing? *Aging.* 2018(Sep) https://doi.org/10.18632/aging.101556 [Epub ahead of print].
31. Poloni MM, Marques NP, Ribeiro Junior NV, Sperandio FF, Hanemann JAC, de Carli ML. Bell's palsy treated with photobiomodulation in an adolescent: rare case report and review of the published literature. *Int J Paediatr Dent.* 2018.
32. Andreo L, Soldera CB, Ribeiro BG, et al. Effects of photobiomodulation on experimental models of peripheral nerve injury. *Lasers Med Sci.* 2017;32(9):2155–2165.
33. da Silva MM, Albertini R, et al. Randomized, blinded, controlled trial on effectiveness of photobiomodulation therapy and exercise training in the fibromyalgia treatment. *Lasers Med Sci.* 2018;33(2):343–351.
34. Vladimirovich Moskvin S, Ivanovich Apolikhin O. Effectiveness of low level laser therapy for treating male infertility. *BioMedicine.* 2018;8(2):7.
35. Holanda VM, Chavantes MC, Silva DF, et al. Photobiomodulation of the dorsal root ganglion for the treatment of low back pain: a pilot study. *Lasers Surg Med.* 2016;48(7):653–659.
36. Kohale BR, Agrawal AA, Raut CP. Effect of low-level laser therapy on wound healing and patients' response after scalpel gingivectomy: a randomized clinical split-mouth study. *J Indian Soc Periodontol.* 2018;22(5):419–426.
37. Huang Z, Ma J, Chen J, Shen B, Pei F, Kraus VB. The effectiveness of low-level laser therapy for nonspecific chronic low back pain: a systematic review and meta-analysis. *Arthritis Res Ther.* 2015;17:360.
38. Panhoca VH, Lizarelli Rde F, Nunez SC, et al. Comparative clinical study of light analgesic effect on temporomandibular disorder (TMD) using red and infrared led therapy. *Lasers Med Sci.* 2015;30(2):815–822.
39. Peoples C, Shaw VE, Stone J, Jeffery G, Baker GE, Mitrofanis J. Survival of dopaminergic amacrine cells after near-infrared light treatment in MPTP-treated mice. *ISRN Neurol.* 2012;2012:850150.
40. Peoples C, Spana S, Ashkan K, et al. Photobiomodulation enhances nigral dopaminergic cell survival in a chronic MPTP mouse model of Parkinson's disease. *Parkinsonism Related Disord.* 2012;18(5):469–476.
41. Reinhart F, Massri NE, Chabrol C, et al. Intracranial application of near-infrared light in a hemi-parkinsonian rat model: the impact on behavior and cell survival. *J Neurosurg.* 2016;124(6):1829–1841.
42. Reinhart F, Massri NE, Darlot F, et al. 810nm near-infrared light offers neuroprotection and improves locomotor activity in MPTP-treated mice. *Neurosci Res.* 2015;92:86–90.
43. Oueslati A, Lovisa B, Perrin J, et al. Photobiomodulation suppresses alpha-synuclein-induced toxicity in an AAV-based rat genetic model of Parkinson's disease. *PLoS One.* 2015;10(10):e0140880.
44. Darlot F, Moro C, El Massri N, et al. Near-infrared light is neuroprotective in a monkey model of Parkinson disease. *Ann Neurol.* 2016;79(1):59–75.
45. El Massri N, Johnstone DM, Peoples CL, et al. The effect of different doses of near infrared light on dopaminergic cell survival and gliosis in MPTP-treated mice. *Int J Neurosci.* 2016;126(1):76–87.
46. El Massri N, Moro C, Torres N, et al. Near-infrared light treatment reduces astrogliosis in MPTP-treated monkeys. *Exp Brain Res.* 2016;234(11):3225–3232.
47. Moro C, El Massri N, Darlot F, et al. Effects of a higher dose of near-infrared light on clinical signs and neuroprotection in a monkey model of Parkinson's disease. *Brain Res.* 2016;1648(Pt A):19–26.
48. Hamilton C, Hamilton D, Nicklason F, El Massri N, Mitrofanis J. Exploring the use of transcranial photobiomodulation in Parkinson's disease patients. *Neural Regener Res.* 2018;13(10):1738–1740.
49. Zhao G, Guo K, Dan J. 36 case analyses of Parkinson's disease treated by endonasal low energy He-Ne laser. *Qingdao Daxue Xue-bao Yixue Ban.* 2003;39:398.
50. Hamilton C, Hamilton D, Nicklason F, Mitrofanis J. Transcranial photobiomodulation therapy: observations from four movement disorder patients. In: Hamblin MR, ed. *Photobiomodulation in the brain.* San Diego, CA: Elsevier Academic Press; 2018.
51. Henderson TA, Morries LD. Multi-watt near-infrared phototherapy for the treatment of comorbid depression: an open-label single-arm study. *Front Psychiatry.* 2017;8:187.
52. Schiffer F, Johnston AL, Ravichandran C, et al. Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: a pilot study of 10 patients with major depression and anxiety. *Behav Brain Funct.* 2009;5:46.
53. Cassano P, Petrie SR, Hamblin MR, Henderson TA, Iosifescu DV. Review of transcranial photobiomodulation for major depressive disorder: targeting brain metabolism, inflammation, oxidative stress, and neurogenesis. *Neurophotonics.* 2016;3(3):031404.
54. Baxter GD, Liu L, Petrich S, et al. Low level laser therapy (photobiomodulation therapy) for breast cancer-related lymphedema: a systematic review. *BMC Cancer.* 2017;17(1):833.
55. Chambrone L, Ramos UD, Reynolds MA. Infrared lasers for the treatment of moderate to severe periodontitis: an American Academy of Periodontology best evidence review. *J Periodontol.* 2018;89(7):743–765.
56. Page MJ, Green S, Mrocki MA, et al. Electrotherapy modalities for rotator cuff disease. *Cochrane Database Syst Rev.* 2016(6):CD012225.
57. Page MJ, Green S, Kramer S, Johnston RV, McBain B, Buchbinder R. Electrotherapy modalities for adhesive capsulitis (frozen shoulder). *Cochrane Database Syst Rev.* 2014(10):CD011324.
58. Oosterveld FG, Rasker JJ, Floors M, et al. Infrared sauna in patients with rheumatoid arthritis and ankylosing spondylitis. A pilot study showing good tolerance, short-term improvement of pain and stiffness, and a trend towards long-term beneficial effects. *Clin Rheumatol.* 2009;28(1):29–34.
59. Yao X, Liu C, Feng D, Yin J, Chen G. Transcranial near-infrared laser therapy in improving cognitive recovery of function following traumatic brain injury. *Curr Neuropharmacol.* 2018(Apr) https://doi.org/10.2174/1570159X16666180321100439 [Epub ahead of print].
60. Naeser MA, Saltmarche A, Krengel MH, Hamblin MR, Knight JA. Improved cognitive function after transcranial, light-emitting diode treatments in chronic, traumatic brain injury: two case reports. *Photomed Laser Surg.* 2011;29(5):351–358.
61. Rocha JG, dos Santos P, Paiva WS, Teixeira MJ. Transcranial light-emitting diode therapy for neuropsychological improvement after traumatic brain injury. *Med Devices: Evid Res.* 2018;11:139–146.
62. Hamblin MR. Shining light on the head: photobiomodulation for brain disorders. *BBA Clin.* 2016;6:113–124.
63. Hennessy M, Hamblin MR. Photobiomodulation and the brain: a new paradigm. *J Opt.* 2017;19(1):013003.
64. Purushothuman S, Johnstone DM, Nandasena C, Mitrofanis J, Stone J. Photobiomodulation with near infrared light mitigates Alzheimer's disease-related pathology in cerebral cortex - evidence from two transgenic mouse models. *Alzheimer's Res Ther.* 2014;6(1):2.
65. Berman MH, Halper JP, Nichols TW, Jarrett H, Lundy A, Huang JH. Photobiomodulation with near infrared light helmet in a pilot, placebo controlled clinical trial in dementia patients testing memory and cognition. *J Neurol Neurosci.* 2017;8(1).
66. Comerota MM, Krishnan B, Taglialatela G. Near infrared light decreases synaptic vulnerability to amyloid beta oligomers. *Sci Rep.* 2017;7(1):15012.
67. Huang YY, Sharma SK, Carroll J, Hamblin MR. Biphasic dose response in low level light therapy - an update. *Dose-Response: A Publ Int Hormesis Soc.* 2011;9(4):602–618.
68. Shui S, Wang X, Chiang JY, Zheng L. Far-infrared therapy for cardiovascular, autoimmune, and other chronic health problems: a systematic review. *Exp Biol Med (Maywood).* 2015;240(10):1257–1265.
69. Ikeda Y, Biro S, Kamogawa Y, et al. Repeated sauna therapy increases arterial endothelial nitric oxide synthase expression and nitric oxide production in cardiomyopathic hamsters. *Circulation J.* 2005;69(6):722–729.
70. Akasaki Y, Miyata M, Eto H, et al. Repeated thermal therapy up-regulates endothelial nitric oxide synthase and augments angiogenesis in a mouse model of hindlimb ischemia. *Circulation J.* 2006;70(4):463–470.
71. Shinsato T, Miyata M, Kubozono T, et al. Waon therapy mobilizes CD34+ cells and improves peripheral arterial disease. *J Cardiol.* 2010;56(3):361–366.

72. Masuda A, Miyata M, Kihara T, Minagoe S, Tei C. Repeated sauna therapy reduces urinary 8-epi-prostaglandin F(2alpha). *Jpn Heart J.* 2004;45(2):297–303.
73. Kawaura A, Tanida N, Kamitani M, et al. The effect of leg hyperthermia using far infrared rays in bedridden subjects with type 2 diabetes mellitus. *Acta Med Okayama.* 2010;64(2):143–147.
74. Ryotokuji K, Ishimaru K, Kihara K, Namiki Y, Hozumi N. Preliminary results of pinpoint plantar long-wavelength infrared light irradiation on blood glucose, insulin and stress hormones in patients with type 2 diabetes mellitus. *Laser Ther.* 2013;22(3):209–214.
75. Lai CC, Fang HC, Mar GY, Liou JC, Tseng CJ, Liu CP. Post-angioplasty far infrared radiation therapy improves 1-year angioplasty-free hemodialysis access patency of recurrent obstructive lesions. *Eur J Vasc Endovasc Surg.* 2013;46(6):726–732.
76. Guo L, Kubat NJ, Nelson TR, Isenberg RA. Meta-analysis of clinical efficacy of pulsed radio frequency energy treatment. *Ann Surg.* 2012;255(3):457–467.
77. Rojas JC, Gonzalez-Lima F. Low-level light therapy of the eye and brain. *Eye Brain.* 2011;3:49–67.
78. Passarella S, Karu T. Absorption of monochromatic and narrow band radiation in the visible and near IR by both mitochondrial and non-mitochondrial photoacceptors results in photobiomodulation. *J Photochem Photobiol B, Biol.* 2014;140:344–358.
79. Hamblin MR. Mechanisms and mitochondrial redox signaling in photobiomodulation. *Photochem Photobiol.* 2018;94(2):199–212.
80. Salehpour F, Mahmoudi J, Kamari F, Sadigh-Eteghad S, Rasta SH, Hamblin MR. Brain photobiomodulation therapy: a narrative review. *Mol Neurobiol.* 2018;55(8):6601–6636.
81. Huang YY, Chen AC, Carroll JD, Hamblin MR. Biphasic dose response in low level light therapy. *Dose-Response: A Publ Int Hormesis Soc.* 2009;7(4):358–383.
82. Karu T. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. *J Photochem Photobiol B, Biol.* 1999;49(1):1–17.
83. AlGhamdi KM, Kumar A, Moussa NA. Low-level laser therapy: a useful technique for enhancing the proliferation of various cultured cells. *Lasers Med Sci.* 2012;27(1):237–249.
84. Tuby H, Maltz L, Oron U. Low-level laser irradiation (LLLI) promotes proliferation of mesenchymal and cardiac stem cells in culture. *Lasers Surg Med.* 2007;39(4):373–378.
85. Tuby H, Maltz L, Oron U. Induction of autologous mesenchymal stem cells in the bone marrow by low-level laser therapy has profound beneficial effects on the infarcted rat heart. *Lasers Surg Med.* 2011;43(5):401–409.
86. Moskvin SV. Low-level laser therapy in russia: history, science and practice. *J Lasers Med Sci.* 2017;8(2):56–65.
87. Law D, McDonough S, Bleakley C, Baxter GD, Tumilty S. Laser acupuncture for treating musculoskeletal pain: a systematic review with meta-analysis. *J Acupuncture Meridian Stud.* 2015;8(1):2–16.
88. Gottschling S, Meyer S, Gribova I, et al. Laser acupuncture in children with headache: a double-blind, randomized, bicenter, placebo-controlled trial. *Pain.* 2008;137(2):405–412.
89. Huang YF, Lin JC, Yang HW, Lee YH, Yu CH. Clinical effectiveness of laser acupuncture in the treatment of temporomandibular joint disorder. *J Formosan Med Assoc = Taiwan yi zhi.* 2014;113(8):535–539.
90. Calomeni MR, Furtado da Silva V, Velasques BB, Feijo OG, Bittencourt JM, Ribeiro de Souza ESAP. Modulatory effect of association of brain stimulation by light and binaural beats in specific brain waves. *Clin Practice Epidemiol Mental Health: CP & EMH.* 2017;13:134–144.

Kathi J. Kemper
College of Medicine, The Ohio State University, Columbus 43210, United States
E-mail address: Kathi.Kemper@osumc.edu