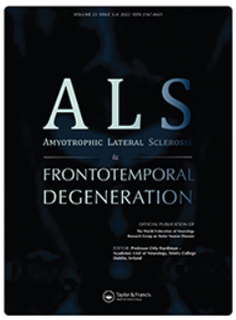

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: informahealthcare.com/journals/iafd20

ALSUntangled #60: light therapy

Richard Bedlack, Paul Barkhaus, Ben Barnes, Michael Bereman, Tulio Bertorini, Gregory Carter, Jesse Crayle, Sky Kihuwa-Mani, Robert Bowser, Pamela Kittrell, Christopher McDermott, Gary Pattee, Kristiana Salmon & Paul Wicks

To cite this article: Richard Bedlack, Paul Barkhaus, Ben Barnes, Michael Bereman, Tulio Bertorini, Gregory Carter, Jesse Crayle, Sky Kihuwa-Mani, Robert Bowser, Pamela Kittrell, Christopher McDermott, Gary Pattee, Kristiana Salmon & Paul Wicks (2022) ALSUntangled #60: light therapy, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 23:3-4, 315-319, DOI: 10.1080/21678421.2021.1883668

To link to this article: https://doi.org/10.1080/21678421.2021.1883668

Published online: 08 Mar 2021.

Submit your article to this journal

Article views: 4816

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://informahealthcare.com/action/journalInformation?journalCode=iafd20

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2022; 23: 315–319

Taylor & Francis
Taylor & Francis Group

Check for updates

REVIEW ARTICLE

ALSUntangled #60: light therapy

RICHARD BEDLACK[1], PAUL BARKHAUS[2], BEN BARNES[3], MICHAEL BEREMAN[4], TULIO BERTORINI[5], GREGORY CARTER[6], JESSE CRAYLE[7], SKY KIHUWA-MANI[8], ROBERT BOWSER[9], PAMELA KITTRELL[10], CHRISTOPHER MCDERMOTT[11], GARY PATTEE[12], KRISTIANA SALMON[13] & PAUL WICKS[14]

[1]Department of Neurology, Duke University, Durham, NC, USA, [2]Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA, [3]Department of Neurology, Augusta University Medical Center, Augusta, GA, USA, [4]Department of Chemistry, North Carolina State University, Raleigh, NC, USA, [5]Department of Neurology, Methodist University Hospital, Memphis, TN, USA, [6]Department of Neurology, St Lukes Rehabilitation Hospital, Chesterfield, MO, USA, [7]Department of Neurology, Washington University in St Louis School of Medicine, St Louis, MO, USA, [8]University of North Carolina at Greensboro, Lloyd International Honors College, Greensboro, NC, USA [9]Department of Neurology, Barrow Neurological Institute, Phoenix, AZ, USA, [10]Department of Neurology, University of Texas Health Science Center, Houston, TX, USA, [11]Department of Neuroscience, University of Sheffield, Sheffield, UK, [12]Department of Neurology, Nebraska Medicine, Omaha, NE, USA, [13]Department of Neurology, McGill Centre for Research in Neuroscience, Montreal, QC, Canada, [14]Independent Consultant, United Kingdom

Abstract

ALSUntangled reviews alternative and off-label treatments for people with ALS. Here we review light therapy. We show that it has theoretically plausible mechanisms, three flawed pre-clinical data, studies, and one incompletely documented case report supporting its use. We explain why further studies are needed to determine whether any specific light therapy protocol can help people with ALS.

Keywords: *Light, energy, alternative therapy, epidemiology, ethics, therapy*

The ALSUntangled group

ALSUntangled reviews alternative and off-label treatments for people with ALS (PALS). Here we review the use of light therapy (LT), sometimes called "photobiomodulation". This will include the two specific types of LT we have been asked about (1), low level laser light treatments and infrared sauna, the latter of which is currently advertised as an ALS treatment on multiple websites (2–4).

Overview

Light is a type of electromagnetic radiation, which comes in discrete quantized packages known as photons (5). It can be characterized according to its wavelength (measured in nanometers, nm). Visible light has wavelengths between 400 and 700 nm. Light with wavelengths below this range is referred to as "ultraviolet", and light with wavelengths above this range is referred to as "infrared" (5). Light can be generated by different sources (ex. lamps, LEDs, lasers). In addition to having different wavelengths, these different sources can deliver different amounts of energy (measured in joules, J) and power (measured in watts, W). When describing power or energy, it is important to state the area the energy is delivered over. This is called "power density" or "irradiance" (measured in milliwatts per square centimeter; mW/cm^2) and/or "energy density" or "fluence" (measured in joules per square centimeter; J/cm^2, 5,6).

As light comes in contact with our bodies, the above-described source parameters help determine whether it gets scattered or absorbed (6,7).

Correspondence: Richard Bedlack, MD PhD, Department of Neurology, Neurology, Duke University, 932 Morreene Rd, Durham, 27702 United States, Email: bedla001@mc.duke.edu

(Received 6 January 2021; Accepted 24 January 2021)

ISSN print/ISSN online © 2021 World Federation of Neurology on behalf of the Research Group on Motor Neuron Diseases
DOI: 10.1080/21678421.2021.1883668

Table 1. Table of Evidence for Light Therapy (LT).

	Grade	Explanation
Mechanism	D	Transcutaneous LT can reach the surface of the brain and spinal cord in animals, and can affect potentially relevant mechanisms there. However, we have yet not found evidence that it can reach motor neurons and surrounding glial cells in humans
Pre-clinical	C	Flawed studies in 1 relevant cell and 2 animal models suggest some benefits associated with LT
Cases	D	We found 1 reported case of LT improving function in a person with ALS; we felt there was insufficient detail to be confident in the diagnosis or the improvements
Trials	U	We found no completed trials of LT in people with ALS
Risks	A	Across many human trials using LT with power density 1–700 mW/cm^2 we found no evidence of related adverse events

Analysis of light scattering is the basis of some medical diagnostic imaging (7). Light that is absorbed can cause a wide variety of biological effects (again depending largely on source parameters), including "photothermal" effects (heating) and "photochemical/photobiological" effects (changes in gene expression and protein function). Through these biological effects, LT has been utilized to treat a variety of medical illnesses for decades (6,7).

Mechanistic plausibility

In isolated cultures, LT delivered via laser at 600–900nm, low power (15 mW), and low energy density (<10 J/cm^2) for a few seconds can activate a protein called cytochrome C oxidase, resulting in improved mitochondrial ATP synthesis (8–13). It can also directly activate the antioxidant protein superoxide dismutase (14). In rat tissue, laser LT at 904 nm, low power (45 mW), and low energy density (5 J/cm^2) for brief periods (35 s) can reduce trauma-induced markers of oxidative stress (15) and inflammation (including (NF)-kappa B, 16). Since mitochondrial dysfunction, (NF)-kappa B-mediated neuroinflammation and oxidative stress are all believed to play roles in ALS progression (reviewed in 17), these findings introduce theoretically plausible mechanisms by which LT could slow the progression of ALS.

Of course, in order for LT to be used as an ALS treatment, it would need to be able to pass through the skin, skull and spine, and find its way to motor neurons and glial cells with therapeutic amounts of energy. With certain specific LT parameters, there is evidence that it can at least reach the surface of the spinal cord and brain in animals. Transcutaneous LT via laser at 810 nm, 150 mW, 1589 J/cm^2 (focused over the injury site, 2997 s of treatment per day for 14 consecutive days) penetrates into the injured rat spinal cord (7,18) and is associated with reduced markers of neuroinflammation, preservation of axons, and improved locomotor recovery (7,18,19). Transcutaneous LT applied via LED array at 670 nm, 252 W/m^2 (treatment area "entire head", 30-min single exposure) penetrates injured rate optic nerve and brain and is associated with reduced markers of oxidative stress and improved recovery of vision (20).

While all this is promising, we have not yet found evidence that transcutaneous LT via any source parameters can affect the physiology of motor neurons or surrounding glial cells within the human brain or spinal cord. As a result, we assign LT a TOE "Mechanisms" grade of D (Table 1).

Pre-clinical

We found 3 relevant pre-clinical studies. In the first (21), cultured mouse cortical neurons exposed to different excitotoxins were then treated with laser LT (810 nm wavelength, 3 J/cm^2, 2 min duration). LT increased mitochondrial membrane potential, increased ATP synthesis, reduced intracellular calcium concentrations, reduced markers of oxidative stress, and prevented cell death.

A second study (22) compared clinical and histological outcomes in G93A mSOD1 mice who received either no treatment ($n=12$), riboflavin ($n=11$), transcutaneous LT (via laser at 810 nm, 140 mW, 12 J/cm^2, 2 min duration) at 3 different sites daily ($n=11$), or the combination of riboflavin and LT ($n=11$). Treatments started at 51 days of age (pre-symptomatically). Treatment with LT was associated with reduced glial fibrillary astrocytic protein staining, improved body weight, and transiently preserved rotorod ability (out to day 130). There was no appreciable difference in motor neuron counts or survival between the groups. Problems with this study include its small sample size, lack of clear randomization or blinding, and pre-symptomatic initiation of treatment (23).

The third study (24) compared clinical outcomes in 20 dogs with canine degenerative myelopathy (a naturally occurring disease caused by mutations in the canine form of SOD1) who received 2 different transcutaneous laser LT protocols (protocol A-904 nm 0.5 W, 8 J/cm^2, 20 individual stimulation points, 20 s per point, once or twice per week; protocol B-980 nm, 6–12 W, 14–21 J/cm^2, continuously moving grid pattern, 25 min per treatments, once or twice per week). All 20 participants also had the same exercise therapy regimen. Treatments were started between 3 and 26 months after symptom onset. Dogs

assigned to protocol B had longer preserved ambulation and longer survival compared to dogs in the less intensive LT protocol or historical controls from other studies. Problems with this study include its small sample size and lack of clear randomization or blinding (23).

Based upon these flawed pre-clinical studies showing some benefit associated with LT, we assign a TOE "Pre-Clinical" grade of C (Table 1).

Cases

On the website PatientsLikeMe, we found one person with ALS reporting the use of laser LT, and one person reporting the use of an infrared sauna. Neither shared treatment evaluations.

We found one relevant case report published in a conference proceeding (25). This described a 69 year old with 4 years of progressive limb onset ALS, whose diagnosis was said to be confirmed by neurological exams, electromyography, and neuroimaging to exclude mimics. At the time the LT therapy started, he was using a wheelchair and using BiPAP at night. The LT protocol consisted of 2 different lasers (A-810 nm, 12–15 J/cm^2, spot sizes 5 cm; B-890 nm, 4 J/cm^2, spot sizes 1 cm) administered transcutaneously over the forehead, vertebral column, brachial plexus, sternum, umbilicus, and pelvis, brachial plexus. LT was administered in 3 cycles, each consisting of 2 sessions per day for 10 days, with 40 days between cycles. The duration of each session was not specified. LT reportedly resulted in improved breathing and limb strength (including recovery of the ability to hold a knife and fork, button a shirt, and ambulate more than 100 meters). These benefits were said to be transient, with regression noted 20–30 days after each cycle. Problems with this report include lack of sufficient details to independently confirm the ALS diagnosis, lack of blinding, vague description of the treatment protocol, and lack of standardized ALS outcome measures (ex. ALSFRS-R, FVC).

Although the one available case is published, there is insufficient detail for us to be confident in the ALS diagnosis or the reported improvements. Therefore we assign LT a "Cases" grade of D.

Trials

We found evidence of a planned trial of LT for people with ALS (NCT00673140) in 2008. It is not clear if this trial was ever started or completed. We have not been able to reach the study sponsor or find any results from this. Therefore we assign a TOE "Trials" grade of U (Table 1).

Of potential interest, there have been clinical trials of LT in people with cognitive impairment, traumatic brain injury, stroke and spinal cord injury; some but not all of these trials showed benefits (26, reviewed in 27,28). These trials are difficult to compare to each other due to incomplete methodological descriptions and variability in the type of LT utilized.

Dosing, risks and costs

Optimal dosing parameters for LT in ALS have not yet been elucidated and will require further study. In terms of light sources, most of the relevant preclinical studies and the one relevant case report we described above used lasers. Lasers have theoretical advantages over other light sources including the ability to produce a single wavelength, higher power and more narrow focus area (29). Other possible light source options that are less well-studied include LED arrays (20), helmets (30), endonasal devices (28,31), garments (reviewed in 32) and infrared saunas (reviewed in 32). In terms of wavelengths, as we have described, 700–900 nm appear most promising due to their ability to penetrate to the surface of the brain and spinal cord and activate cytochrome C oxidase; wavelengths much outside this range will not penetrate (29). In terms of energy density a surprisingly low amount (< 15 J/cm^2) may be sufficient to produce biological effects in the brain and spinal cord. We do not know the optimal LT stimulation sites, cycle duration or cycle frequency for ALS. Future ALS trials could start with a protocol similar to that used in the one positive case report (25): laser LT at 810–890 nm, 4–15 J/cm2 administered transcutaneously, widely over the head and spine, twice daily in 20 day cycles. Since the positive effects in this case were reported to last 20–30 days, cycles could be 20 days apart.

In terms of safety, in the human trials of LT for cognitive impairment, traumatic brain injury and stroke, where the power density range was 1–700 mW/cm^2, there were no related side effects (reviewed in 28). One rat study showed that LT could produce thermal brain damage, but that used a power density 100 times greater than needed for biological effect (33). Based upon this excellent safety record at appropriate wavelengths, power and energy densities, we assign a TOE "Risks" grade of A.

Costs of LT will vary widely depending on the selected protocol and whether one purchases a light source or pays for time in one. Medical lasers can cost more than $50,000 (34). Saunas claiming to release LT with optimal wavelength and power to treat medical conditions can cost more than $6,000 (35). Individual sessions in one of these saunas cost $35 each (36). The development of LEDs have made light therapy more affordable, but attention needs to be paid to the specific light

parameters these deliver in order to optimize the plausibility of a biological effect.

Conclusion

Light therapy has not yet been convincingly shown to help people with ALS. However, at specific wavelengths and energy densities, LT appears safe and has theoretically plausible mechanisms. There is a single case report suggesting benefits for light therapy in ALS, but it contains insufficient detail to independently confirm diagnosis or treatment benefit. Further studies are needed to determine whether LT is useful for people with ALS, and via what specific protocols.

Acknowledgements

The authors thank Dr. Aleksander Videnovic for reviewing the manuscript and providing helpful comments.

Declaration of interest

ALSUntangled is sponsored by the ALS Association. Richard Bedlack has research support from ALSA, Orion, MediciNova, and the Healey Center, and consulting support from Alexion, ALSA, Amylyx, Biogen, Brainstorm Cell, Guidepoint, ITF Pharma, Mallinkrodt, New Biotic, Orphazyme, and Woolsey Pharma.

Funding

This work was supported by Amyotrophic Lateral Sclerosis Association.

ORCID

Robert Bowser http://orcid.org/0000-0001-5404-7259
Christopher McDermott http://orcid.org/0000-0002-1269-9053
Paul Wicks http://orcid.org/0000-0002-2293-9284

References

1. ALSUntangled [online]. [accessed 2020 Oct 22]. Available from: https://www.alsuntangled.com/future-reviews/
2. Functional Medicine University [online]. [accessed 2020 Oct 26]. Available from: https://www.functionalmedicineuniversity.com/public/833.cfm
3. Well Body Field [online]. [accessed 2020 Oct 26]. Available from: http://www.wellbodyfield.com/part-8---alternative-treatments.html
4. Even Better Health [online]. [accessed 2020 Oct 26]. Available from: https://evenbetterhealth.com/als.asp
5. Wikipedia [online]. [accessed 2020 Dec 13]. Available from: https://en.wikipedia.org/wiki/Light
6. Zein R, Selting W, Hamblin M. Review of light parameters and photobiomodulation efficacy: dive into complexity. J Biomed Opt. 2018;23:1–17.
7. Yun S, Kwok S. Light in diagnosis, therapy and surgery. Nat Biomed Eng. 2017;1:0008.
8. Anders J. The potential of light therapy for central nervous system injury and disease. Photomed Laser Surg. 2009;27:379–80.
9. Hamblin M, Demidova T. Mechanisms of low level light therapy. Proc SPIE. 2006;6140:1–12.
10. Passarella S, Casamassima E, Molinari S, Pastore D, Quagliariello E, Catalano IM, et al. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. FEBS Lett. 1984;175:95–9.
11. Karu T, Pyatibrat L, Kalendo G. Irradiation with He-Ne laser increases ATP level in cells cultivated in vitro. J Photochem Photobiol.1995;27:219–33.
12. Yu W, Naim J, McGowan M, Ippolito K, Lanzafame R. Photomodulation of oxidative metabolism and electron chain enzymes in rat liver mitochondria. Photochem Photobiol. 1997;66:866–71.
13. Hu W, Wang J, Yu C, Lan C, Chen G, Yu H. Helium-neon laser irradiation stimulates cell proliferation through photostimulatory effects in mitochondria. J Invest Dermatol. 2007;127:2048–57.
14. Vladimirov Y, Gorbatenkova E, Paramonov N, Azizova O. Photoreactivation of superoxide dismutase by intensive red (laser) light. Free Radic Biol Med. 1988;5:281–6.
15. Fillipin LI, Mauriz JL, Vedovelli K, Moreira AJ, Zettler CG, Lech O, et al. Low-level laser therapy (LLLT) prevents oxidative stress and reduces fibrosis in rat traumatized Achilles tendon. Lasers Surg Med. 2005;37:293–300.
16. Rizzi C, Mauriz J, Freitas Correa D, Moreira A, Zettler C, Filippin L, et. al. Effects of low-level laser therapy (LLLT) on the nuclear factor (NF)-kappaB signaling pathway in traumatized muscle. Lasers Surg Med. 2006;38:704–13.
17. Van Damme P, Robberecht W, Van Den Bosch L. Modelling amyotrophic lateral sclerosis: progress and possibilities. Dis Model Mech. 2017;10:537–49.
18. Byrnes KR, Waynant RW, Ilev IK, Wu X, Barna L, Smith K, et al. Light promotes regeneration and functional recovery and alters the immune response after spinal cord injury. Lasers Surg Med. 2005;36:171–85.
19. Wu X, Dmitriev AE, Cardoso MJ, Viers-Costello AG, Borke RC, Streeter J, et. al. 810nm wavelength light: an effective therapy for transected or contused rat spinal cord. Lasers Surg Med. 2009;41:36–41.
20. Fitzgerald M, Bartlett C, Payne S, Hart N, Rodger J, Harvey A, et al. Near infrared light reduces oxidative stress and preserves function in CNS tissue vulnerable to secondary degeneration following partial transection of the optic nerve. J Neurotrauma. 2010;27:2107–19.
21. Huang Y, Nagata K, Tedford C, Hamblin M. Low-level laser therapy (810 nm) protects primary cortical neurons against excitotoxicity in vitro. J Biophotonics. 2014;7:656–64.
22. Moges H, Vasconcelos O, Campbell W, Borke R, McCoy J, Kaczmarczyk L, et. al. Light therapy and supplementary riboflavin in the SOD1 transgenic mouse model of familial amyotrophic lateral sclerosis (FALS). Lasers Surg Med. 2009;41:52–9.
23. Ludolph A, Bendotti C, Blaugrund E, Chio A, Greensmith L, Loeffler J, et al. Guidelines for preclinical animal research in ALS/MND: a consensus meeting. Amyotroph Lateral Scler. 2010;11:38–45.
24. Miller LA, Torraca D(G), De Taboada L. Retrospective observational study and analysis of two different photomodulation therapy protocols with rehabilitation therapy as therapeutic intervention for canine degenerative

myelopathy. Photomodulation, Photomedicine, and Laser Surgery.2020;38:195–205.
25. Longo L, Postiglione M, Gabellini M, Longo D. Amyotrophic lateral sclerosis (ALS) treated with low level laser therapy (LLLT): a case report. AIP Conference Proceedings 2009;1142:96–98.
26. Longo D, Longo L, Lippi P, Cherubini G, Mangé V. Effects of laser therapy and Grimaldi's muscle shortening manoeuvre on motor control of subjects with incomplete spinal cord injuries. Laser Ther. 2017;26:203–9.
27. Fitzgerald M, Hodgetts S, Van Den Heuvel C, Natoli R, Hart N, Valter K, et. al. Red/near-infrared irradiation therapy for treatment of central nervous system injuries and disorders. Rev Neurosci. 2013;24:205–26.
28. Johnstone D, Moro C, Stone J, Benabid A, Mitrofanis J. Turning on lights to stop neurodegeneration: the potential of near infrared light therapy in Alzheimer's and Parkinson's Disease. Front Neurosci. 2015;9:500.
29. Kim M, Darafsheh A. Light sources and dosimetry techniques for photodynamic therapy. Photochem Photobiol. 2020;96:280–94.
30. Yoon J, Young W, Hyun J, Ahn H. Low-level light therapy using a helmet-type device for the treatment of androgenetic alopecia. Medicine.2020;99:e21181.
31. Zhao G, Guo K, Dan J. 36 cases of Parkinsons disease treated by endonasal low energy He-NE laser. Acta Acad Med Quingdao Univ 2003;39:398.
32. Vatansever F, Hamblin M. Far infra-red radiation (FIR): its biological effects and medical applications. Photonics Lasers Med 2012;4:255–66.
33. Ilic S, Leichliter S, Streeter J, Oron A, DeTaboada L, Oron U. Effects of power densities, continuous and pulse frequencies, and number of sessions of low-level laser therapy on intact rat brain. Photomed Laser Surg. 2006; 24:458–66.
34. Medical Price [online]. [accessed 2020 Dec 21]. Available from: https://www.medicalpriceonline.com/company/medical-device-alliance/candela-gentlemax-pro-14347/?gclid=CjwKCAiArIH_BRB2EiwALfbH1CblGUAmisqmUPI7Fy2lTDqgfizHrsnIvnPerr_Cb7ZRAh3RjB_sKBoC8rsQAvD_BwE
35. Medical Saunas [online]. [accessed 2020 Dec 21]. Available from: https://www.medicalsaunas.com/medical6-fullspectrum.php?affid=Q5LBZgAJ1uGR0oMns9Pm2bShjep4k7EU&utm_source=google&utm_campaign=google_ad_sauna_shopping&utm_term=sauna_medical6_fullspectrum&utm_content=shopping_ad_sauna_medical6_fullspectrum&utm_medium=cpc&utm_term=&utm_campaign=Google+Ad+-+Sauna+-+Shopping&utm_source=adwords&utm_medium=ppc&hsa_acc=9767180294&hsa_cam=8974961998&hsa_grp=94268609681&hsa_ad=412581551275&hsa_src=g&hsa_tgt=pla-867975897788&hsa_kw=&hsa_mt=&hsa_net=adwords&hsa_ver=3&gclid=CjwKCAiArIH_BRB2EiwALfbH1B3N8YYQkJ1egg9OeHOzio6DnkeMefYzZadQ6KrVcYuvwu5lmc830hoCiccQAvD_BwE
36. Wellville Spa [online]. [accessed 2020 Dec 21]. Available from: http://wellvillenc.com/nav_pricing/sauna-pricing/