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ALSUntangled #60: light therapy

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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/cm²) and/or “energy density” or “fluence” (measured in joules per square centimeter; J/cm², 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).
In isolated cultures, LT delivered via laser at 904 nm, low power (45 mW), and low energy density (5 J/cm²) for brief periods (35 s) can reach motor neurons and surrounding glial cells in humans. In rat tissue, laser LT can also directly activate the antioxidant protein superoxide dismutase (14). In rat cortical neurons exposed to different excitotoxins were then treated with laser LT (810 nm wavelength, 3 J/cm², 2 min duration). LT increased mitochondrial membrane potential, increased ATP synthesis, reduced intracellular calcium concentrations, reduced markers of oxidative stress, and prevented cell death. 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 600–900 nm, low power (15 mW), and low energy density (<10 J/cm²) 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/cm²) 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/cm² (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/m² (treatment area “entire head”, 30-min single exposure) penetrates injured 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/cm², 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/cm², 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 rototrod 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/cm², 20 individual stimulation points, 20 s per point, once or twice per week; protocol B-980 nm, 6–12 W, 14–21 J/cm², 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

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Grade</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical</td>
<td>C</td>
<td>Flawed studies in 1 relevant cell and 2 animal models suggest some benefits associated with LT</td>
</tr>
<tr>
<td>Cases</td>
<td>D</td>
<td>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</td>
</tr>
<tr>
<td>Trials</td>
<td>U</td>
<td>We found no completed trials of LT in people with ALS</td>
</tr>
<tr>
<td>Risks</td>
<td>A</td>
<td>Across many human trials using LT with power density 1–700 mW/cm² we found no evidence of related adverse events</td>
</tr>
</tbody>
</table>

Table 1. Table of Evidence for Light Therapy (LT).
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/cm², spot sizes 5 cm; B-890 nm, 4 J/cm², 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 only 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/cm²) 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/cm², 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.

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Declaration of interest

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References

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


