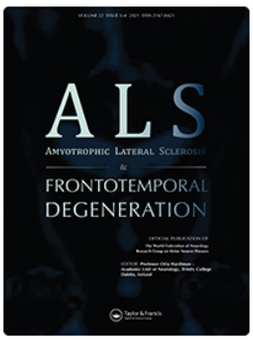

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ALSUntangled #61: melatonin

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RESEARCH ARTICLE

ALSUntangled #61: melatonin

THE ALSUNTANGLED GROUP

Abstract
ALSUntangled reviews alternative and off-label treatments for people with amyotrophic lateral sclerosis (ALS). Here we review melatonin. We show that it has plausible mechanisms, some positive (and some negative) pre-clinical studies, two cases in which cocktails of supplements including melatonin were associated with recovery of lost motor function, and a very small, flawed retrospective study suggesting that patients in the PRO-ACT database who reported taking melatonin progressed more slowly and lived longer compared to those who were not taking it. Melatonin appears safe, but an optimal dose and route of administration for ALS have not been determined. Based on all this, we support a pilot trial of melatonin in people with ALS but we cannot yet recommend it as a treatment.

Keywords: *Melatonin, antioxidant, neuroinflammation, alternative therapy, clinical trials, nutrition, survival*

ALSUntangled reviews alternative and off-label treatments on behalf of people with amyotrophic lateral sclerosis (PALS) who asked us about them. Here we review the use of melatonin for which we have had more than 500 requests (1).

Overview

Melatonin is a hormone that has long been known to play a role in regulating sleep (2). Melatonin supplements are commonly used to treat insomnia (2), though symptomatic treatments such as this are outside the scope of ALSUntangled reviews. In recent years, melatonin has been found to play a wider role in human physiology, including regulation of oxidative stress and inflammation (2). Given these effects, and the observation that melatonin levels decline with aging, the possibility of using melatonin supplements to treat age-related neurodegenerative diseases has arisen (2–5). Indeed, melatonin is currently being advertised on the Internet as a way to prevent the onset of or slow the progression of ALS (6).

Mechanistic plausibility

Free radicals and oxidative stress are prominent pathophysiological features of ALS and are expressed both systemically (7) and within the CNS (8,9). Melatonin is a potent antioxidant with both lipophilic and hydrophilic properties enabling it to readily enter the CNS (2,10). Melatonin reacts directly with reactive oxygen as well as reactive nitrogen species (RNS), leading to the formation of antioxidant metabolites; it also acts indirectly by binding to melatonin receptors which stimulate protective antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase. Thus melatonin can affect multiple pathways that are potentially relevant in the progression of ALS including autophagy (5), oxidative stress (2–5,11), and neuroinflammation (2,4,5,12,13). While most of this data is from cell or animal models, human trials have demonstrated that melatonin supplementation can reduce biomarkers of inflammation and/or oxidative stress in patients with several different diseases (2). Of particular interest, melatonin treatment reduced interleukin 1 beta, tumor necrosis factor-alpha, lipoperoxides, and nitric oxide catabolites in patients with multiple sclerosis (14,15) and serum protein carbonyls in patients with ALS (16). Based on this human data, we assign a Table of Evidence (TOE) "Mechanisms" grade of A (Table 1).

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Table 1. Table of evidence for melatonin.

	Grade	Explanation
Mechanism	A	Melatonin treatment can reduce biomarkers of oxidative stress and inflammation in humans with MS and ALS
Pre-clinical	C	Some (but not all) flawed studies in an ALS mouse model suggest benefits
Cases	B	2 patients with validated ALS diagnoses experienced validated improvements (ALS reversals) on cocktails of treatments including melatonin
Trials	U	We found no trials comparing clinical outcomes in PALS on melatonin versus controls
Risks	B	Across many human trials melatonin appears reasonably safe, even at fairly high doses

Pre-clinical

In a study of isolated motor neurons (from hypoglossal nucleus which controls tongue) from a G93A mutant SOD1 mouse model of ALS, melatonin treatment (as opposed to riluzole) failed to demonstrate any neuroprotection (17). In one live mouse model of ALS (mutant SOD1 G93A), melatonin treatment appeared to exacerbate disease and shorten survival (18); however, there are two other similar live ALS mouse model studies that showed benefits, including delayed onset of weakness, preserved motor neuron counts, and prolonged survival (16,19). The reason for these differing results is not clear to us. The two positive studies were well-designed including use of randomization and rater blinding, but they were both flawed by starting melatonin prior to symptom onset (which limits generalizability to PALS). Based on these positive, flawed studies, we assign a TOE "Pre-Clinical" grade of C (Table 1).

Cases

In the PatientsLikeMe Community, five PALS provided treatment evaluations on melatonin (20). Their doses ranged from 5 to 300 mg daily. All reported they "couldn't tell" if it had any effectiveness. Within the cohort of "ALS Reversals" being studied at Duke University (21,22), two were taking melatonin (along with many other treatments) during their recovery; one reported taking 9mg daily and the other reported taking between 5 and 15 mg daily. Based upon these two cases with validated diagnoses and recovery associated with melatonin treatment, we assign a TOE "Cases" grade of B (Table 1). As we have mentioned previously, an association between a treatment and an ALS Reversal does not mean one caused the other; there are many possible explanations for ALS Reversals (22).

Trials

We found no prospective trials in which clinical outcome measures in PALS taking melatonin were compared to an appropriate control group. Therefore we assign a TOE "Trials" grade of U (Table 1).

We did find a retrospective study utilizing the PRO-ACT database (23). The 18 PALS in this database that reported taking melatonin had significantly slower ALSFRS-R and FVC progression, and significantly longer survival, compared to 1604 PALS who were not on melatonin. The authors point out several significant flaws in their study, including the small number of melatonin users, the lack of information on melatonin dosing and adherence, and the fact that the two groups were somewhat imbalanced at baseline, with melatonin users being younger and having better breathing measurements.

We also found two cohort studies in which safety and tolerability were measured in PALS taking melatonin (3,16). These are discussed in the next section.

Dosing, risks, and costs

Optimal melatonin dosing for PALS has not been established and will be challenging due to its short half-life of around 30 min (2). There is a slow-release form which has a half-life of 6 h (3). In one small case series using this slow-release form, three PALS tolerated daily doses of 30–60 mg orally for over 1 year (3). No adverse events were reported, and a panel of safety labs including CBC, electrolytes, lipid panels, and liver functions was unchanged. Melatonin can also be administered by suppository. This route of administration reduces the burden of swallowing pills or capsules and mitigates the "first-pass" metabolism of melatonin by the liver (16). In a series using this route of administration, 31 PALS were given daily doses of 300 mg for 1 year (16). Thirteen of these patients died (all due to ALS progression), eight patients dropped out (five reportedly due to disease progression and the desire to stop all medications). The authors note that "mean routine laboratory data remained essentially unchanged." Initially elevated levels of an oxidative stress marker called "serum protein carbonyls" declined coincident with melatonin treatment to the levels of healthy controls (16).

Reviews of melatonin trials in adults with a variety of different conditions conclude that it is safe, even at fairly high doses (2,24,25). Adverse events included sedation, dizziness, headache, and nausea; these were generally mild and occurred in less than 10% of patients (2,24,25). We thus assign a TOE "Risks" grade of B (Table 1).

Oral melatonin at 30 mg daily costs around $60 per month (26).

Conclusion

Melatonin has plausible mechanisms, some positive (and some negative) pre-clinical data, and two case reports in which it was part of a cocktail of treatments associated with recovery of lost motor function. As we have stated previously, there are multiple possible explanations for cases like these. There was also a very small, flawed retrospective study suggesting that PALS taking it progressed more slowly and lived longer than PALS were not taking it. Melatonin appears safe at high doses, but evidence is lacking for a proven benefit in slowing disease progression in ALS. Furthermore, an optimal dose and route of administration have not been established. Based on this data, a pilot trial of melatonin in PALS would be reasonable, but we cannot yet recommend it as an ALS treatment.

Disclosure statement

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