Letters & Reviews in Neurological Sciences

Vitamins in the Treatment of Amyotrophic Lateral Sclerosis / Motor Neuron Disease: A Narrative Review of Mechanisms, Clinical Evidence and Prospects

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ABSTRACT

Amyotrophic lateral sclerosis (ALS), also called motor neuron disease (MND), is a fatal neurodegenerative disease with few effective treatments. Because oxidative stress, mitochondrial dysfunction, neuro-inflammation and altered metabolism are implicated in motor neuron death, several vitamins have been studied as prevention or therapy. This review summarises the evidence for vitamins E, C, A (carotenoids), D, B_{12} and B_3, and notes the lack of dedicated ALS data for other vitamins. Vitamin E showed benefit in SOD1 mice [1], but randomised trials in patients were negative [2–4]; prospective cohorts suggest that long-term supplement use is associated with lower ALS risk [5,6]. Dietary carotenoids, but not vitamin C, were inversely associated with risk [7]. Vitamin D deficiency is common and associated with worse disease, yet supplementation trials are small and inconclusive [8–11]. Ultra-high-dose methylcobalamin did not benefit the whole cohort in a phase II/III study but showed a signal in early-stage disease [12], which a confirmatory trial supported over 16 weeks [13]. A nicotinamide riboside combination improved outcomes in a small pilot trial [14]. Mechanisms, tables and schemes are provided, and priorities for future research are outlined.

Key words: Amyotrophic lateral sclerosis; motor neuron disease; vitamin E; vitamin D; methylcobalamin; vitamin B_{12}; nicotinamide riboside; carotenoids; antioxidants; oxidative stress.

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1. Introduction

ALS is characterised by progressive degeneration of upper and lower motor neurons, with paralysis and death usually from respiratory failure within a few years of onset [15,16]. Most cases are sporadic, and disease-modifying treatment remains limited [16]. Proposed contributors include oxidative damage, mitochondrial dysfunction, excitotoxicity and inflammation [15,17].

Vitamins are attractive candidates because they are inexpensive and generally well tolerated, act on several of these pathways (Figure 1), and are widely used by patients. A Cochrane review noted that vitamins C and E continue to be used because of their safety and low cost, despite insufficient evidence of efficacy [4]. This review brings together animal, epidemiological and clinical evidence for the individual vitamins.

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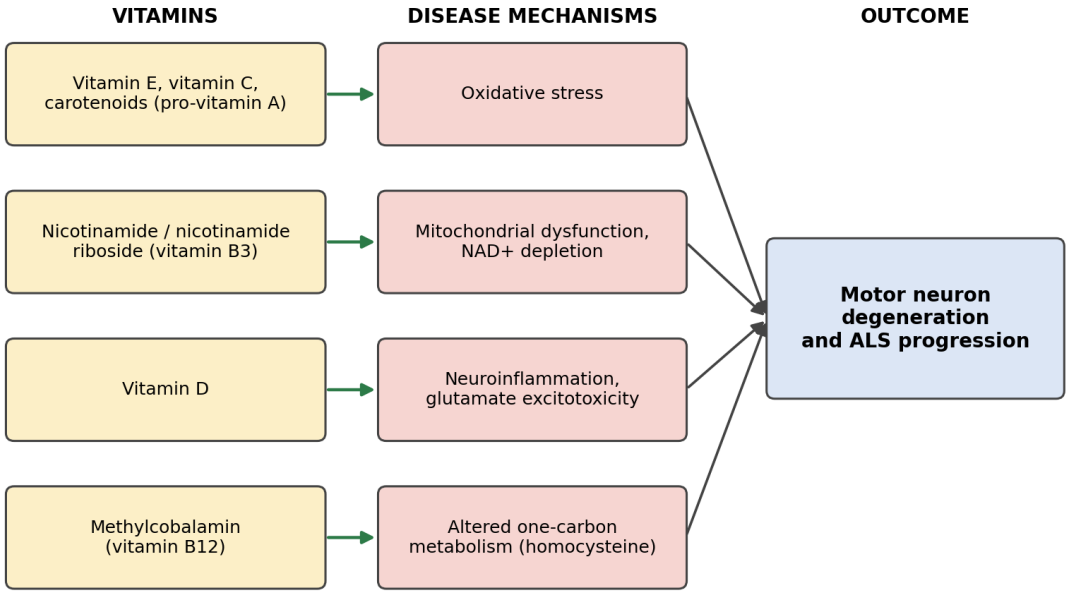


Figure 1. Disease mechanisms in ALS/MND and the vitamins proposed to act on them.

2. Antioxidant vitamins: E, C and carotenoids

2.1 Vitamin E

Vitamin E (α-tocopherol) is the main lipid-soluble antioxidant of cell membranes. In a transgenic mouse model of familial ALS, vitamin E delayed disease onset and progression [1], which prompted human studies.

Epidemiological data are suggestive. In a prospective cohort, regular vitamin E supplement users had a lower risk of dying from ALS, with relative risks of 0.59 for under 10 years of use and 0.38 for 10 years or more, whereas vitamin C and multivitamins showed no association [5]. A pooled analysis of five cohorts (1,055,546 participants, 805 ALS cases) found no overall association with supplement use, but ALS rates declined with longer duration of use, and dietary intake showed a borderline inverse association (RR 0.79, 95% CI 0.61–1.03 for top versus bottom quartile) [6] (Figure 2).

Clinical trials have not confirmed benefit. A 12-month trial of 500 mg/day of α-tocopherol found no effect on survival or motor function [2], and an 18-month trial of 5000 mg/day added to riluzole did not influence survival [3]. The Cochrane review of 10 studies (1015 patients) concluded that the evidence for individual antioxidants, or antioxidants in general, was insufficient [4].

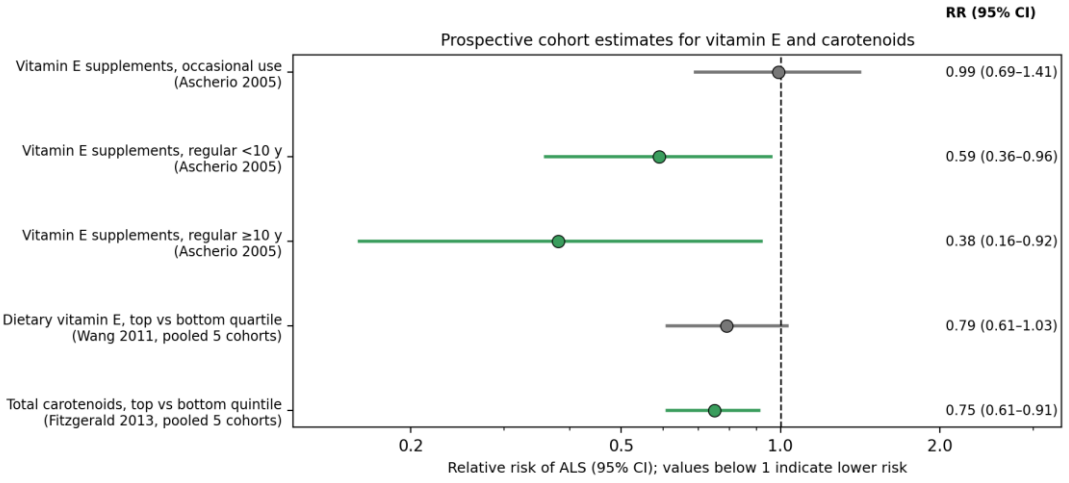


Figure 2. Relative risks as reported in the cited studies (not re-analysed).

2.2 Vitamin C and carotenoids (provitamin A)

In the pooled cohort analysis, higher total carotenoid intake was associated with lower ALS risk (RR 0.75, 95% CI 0.61–0.91 for the highest versus lowest quintile), driven by β-carotene and lutein; vitamin C, lycopene and β-cryptoxanthin were not associated with reduced risk [7]. These findings relate to dietary intake and do not by themselves support supplementation. Vitamin C supplement use was likewise not associated with lower risk in earlier work [5].

3. Vitamin D

Vitamin D acts through its nuclear receptor and has been linked to pathways relevant to ALS, including inflammation, glutamate signalling and calcium handling [18]. In the G93A mouse model, high-dose vitamin D_3 improved, and vitamin D_3 restriction worsened, functional capacity [18].

In patients, deficiency has been associated with faster functional decline [9]. An observational study of 37 patients found that 2000 IU/day raised median 25-hydroxyvitamin D from 18.5 to 31.0 ng/mL at six months, was safe over nine months, and may have had a beneficial effect on ALSFRS-R scores [8] (Figure 3b). A later study of 57 patients, however, found that oral supplementation was not associated with a better prognosis than no treatment [10]. A systematic review and meta-analysis concluded that supplementation should be offered to avoid deficiency-related problems, but that evidence is insufficient to support vitamin D as a therapy for ALS [11]. High-dose regimens need monitoring for hypercalcaemia.

4. B vitamins

4.1 Vitamin B12 (methylcobalamin)

Methylcobalamin is an active form of vitamin B_{12} and a cofactor in the re-methylation of homocysteine to methionine. In a phase II/III study of 373 patients given placebo, 25 mg or 50 mg of intramuscular methylcobalamin, the whole cohort showed no significant benefit; post hoc analysis of patients treated within 12 months of onset showed longer time to the primary event and slower ALSFRS-R decline [12]. A confirmatory randomised trial enrolled 130 patients with early-stage disease and moderate progression and gave 50 mg twice weekly for 16 weeks; mean ALSFRS-R change was −2.66 with methylcobalamin versus −4.63 with placebo, with similar adverse event rates [13] (Figure 3a). Because the trial was short, restricted to Japanese patients at an early stage, and treatment-related unblinding is possible, longer multinational studies are needed.

4.2 Vitamin B3 (nicotinamide and nicotinamide riboside)

Nicotinamide and nicotinamide riboside are precursors of NAD+, which supports mitochondrial and sirtuin function [14]. In SOD1 mice, nicotinamide produced by the gut commensal *Akkermansia muciniphila* accumulated in the CNS, and systemic nicotinamide improved motor symptoms; lower nicotinamide levels were reported in patients' serum and cerebrospinal fluid in a small comparison [19]. A pilot trial randomised 32 patients to EH301, a combination of nicotinamide riboside and pterostilbene (1,200 mg daily), or placebo for four months and reported improved ALSFRS-R, pulmonary function and muscle strength [14]. The trial was small, 12 of 32 participants dropped out, and some authors had a commercial interest, so a larger confirmatory trial is required.

4.3 Other B vitamins

Thiamine (B_1), riboflavin (B_2), pyridoxine (B_6), folate (B_9) and biotin have essential roles in energy and one-carbon metabolism, but I did not identify dedicated ALS trials for them in the sources used for this review. Their use should be limited to correcting documented deficiency, and they should be regarded as research questions rather than treatments.

5. Vitamin K and other vitamins

Vitamin K and the remaining vitamins have physiological roles in coagulation, bone and cellular metabolism, but no ALS-specific clinical studies were identified in the sources used here. Nutritional status is nevertheless important in ALS, so deficiency should be sought and corrected as part of standard care. The observational and clinical studies discussed above are tabulated in Tables 1 and 2.

Table 1. Observational studies of vitamin intake and ALS risk.

Study	Design	Main finding (as reported)
Ascherio et al. [5]	Prospective cohort; supplement use	Regular vitamin E use associated with lower ALS mortality (RR 0.59 for <10 y; 0.38 for ≥10 y); no association for vitamin C or multivitamins.
Wang et al. [6]	Pooled analysis of 5 cohorts; 1,055,546 participants, 805 cases	Supplement use not associated overall; rates declined with years of use; dietary RR 0.79 (0.61–1.03).
Fitzgerald et al. [7]	Pooled analysis of 5 cohorts	Total carotenoids RR 0.75 (0.61–0.91); β-carotene and lutein inverse; vitamin C not associated.
Camu et al. [9]	Patient cohort; vitamin D status	Vitamin D deficiency was a prognostic factor for faster decline.

Table 2. Clinical studies of vitamins in ALS/MND.

Study	Intervention	Design	Outcome (as reported)
Desnuelle et al. [2]	α-Tocopherol 500 mg/day	Randomised, placebo-controlled; 12 months	No effect on survival or motor function.
Graf et al. [3]	α-Tocopherol 5000 mg/day with riluzole	Randomised, placebo-controlled; 18 months	No influence on survival.
Karam et al. [8]	Vitamin D 2000 IU/day	Observational; 37 patients, 9 months	25(OH)D rose 18.5 to 31.0 ng/mL; safe; possible ALSFRS-R benefit.
Libonati et al. [10]	Oral vitamin D	Pilot study; 57 patients	Supplementation not associated with better prognosis.
Kaji et al. [12]	Methylcobalamin 25 or 50 mg IM	Phase II/III; 373 patients	No overall benefit; early-onset subgroup improved (post hoc).
Oki et al. [13]	Methylcobalamin 50 mg IM twice weekly	Randomised; 130 patients; 16 weeks	ALSFRS-R change −2.66 *vs* −4.63; similar adverse events.
de la Rubia et al. [14]	EH301 (nicotinamide riboside + pterostilbene)	Randomised pilot; 32 patients; 4 months	Improved ALSFRS-R and strength; small, high dropout.

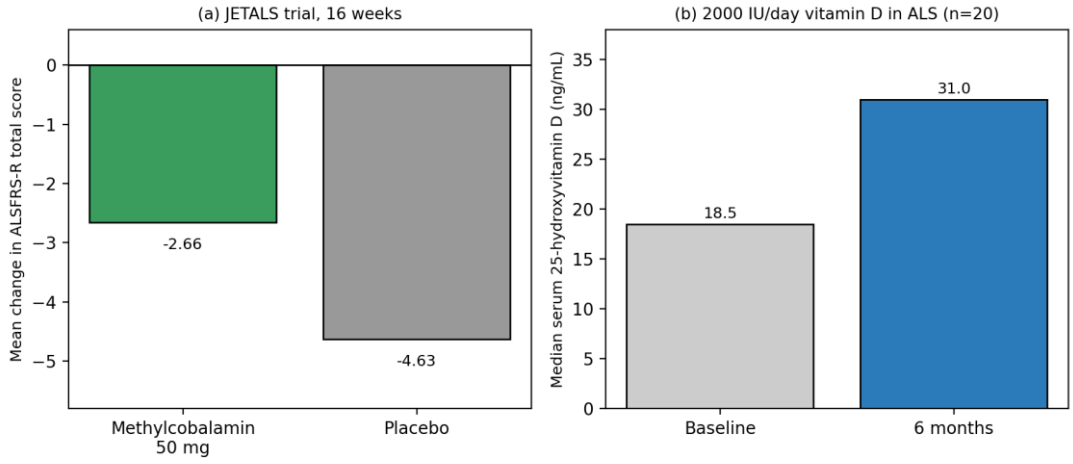


Figure 3. Reported values from Oki et al. 2022 (a) and Karam et al. 2013 (b); plotted from values given in the text of each paper.

6. Mechanisms of action

The proposed actions are summarised in Table 3 and Figure 4. Oxidative stress is supported by biomarkers of oxidative damage in patients and by SOD1 mutations [17], which provides the rationale for vitamins E and C and carotenoids. Vitamin D acts on inflammatory, glutamatergic and calcium pathways [18]. Methylcobalamin supports homocysteine re-methylation and has been proposed to be neuroprotective [12]. Nicotinamide and nicotinamide riboside raise NAD^+ and support mitochondrial and sirtuin function [14], and nicotinamide of microbial origin is linked to disease modification in mice [19]. Most of this mechanistic evidence is preclinical.

Table 3. Vitamins considered for ALS/MND: proposed role and level of evidence.

Vitamin	Proposed role in ALS	Key evidence	Assessment
Vitamin E	Membrane antioxidant; limits oxidative damage [1,17]	Mouse benefit; negative randomised trials [2–4]	Not effective as treatment; prevention unproven
Vitamin C	Water-soluble antioxidant	No association with risk [5,7]	No support
Carotenoids / vitamin A	Radical-quenching pigments	Dietary intake inversely associated with risk [7]	Dietary pattern only
Vitamin D	Inflammation, glutamate, calcium pathways [18]	Mouse benefit; small and mixed human data [8,10,11]	Correct deficiency; not proven therapy
Vitamin B_{12}	Homocysteine remethylation; neuroprotection [12]	Early-stage signal in two trials [12,13]	Promising; needs confirmation
Vitamin B_3	NAD^+ precursor; mitochondrial support [14,19]	Mouse benefit; small positive pilot [14,19]	Promising; early
B_1, B_2, B_6, folate, biotin, K	Essential metabolic cofactors	No dedicated ALS trials identified in this review	Treat deficiency only

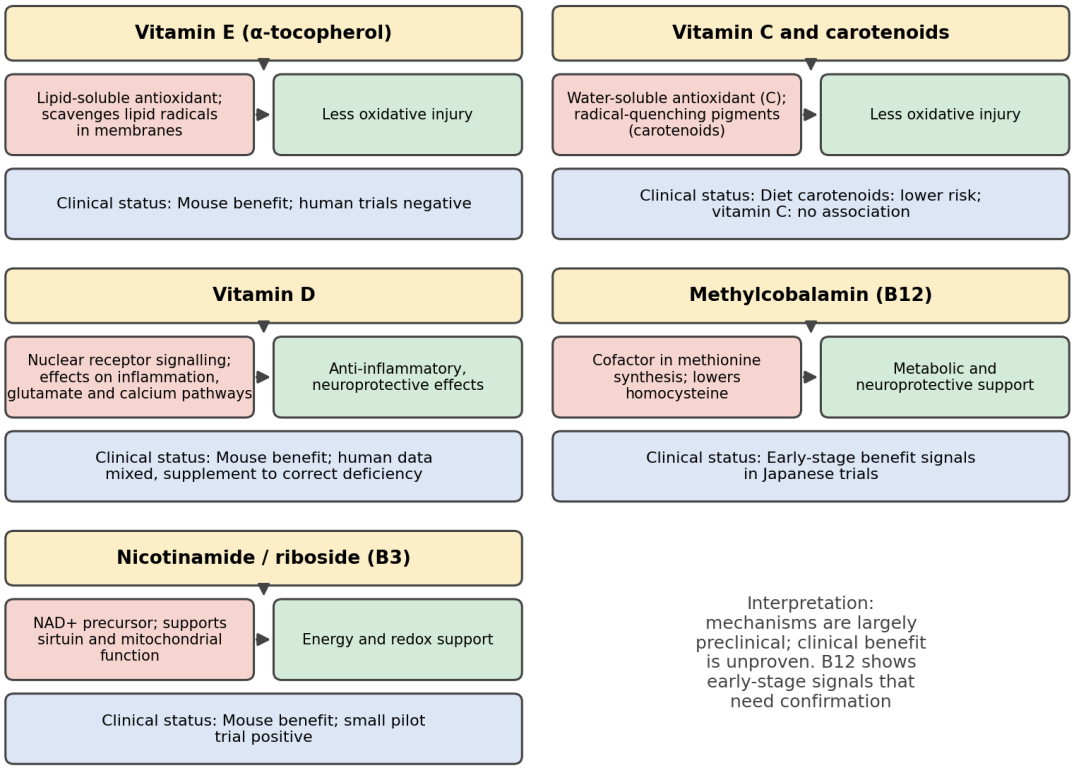


Figure 4. Proposed mechanisms of action of the vitamins most studied in ALS/MND.

7. Evidence summary, safety and limitations

Figure 5 maps the type of evidence available for each vitamin. Positive signals come mainly from animal studies and small or short human studies, whereas the largest randomised trials of vitamin E were negative [2–4]. Observational associations may be confounded by healthier lifestyles; for example, high carotenoid intake clusters with other healthy behaviours [7]. Many vitamin trials in ALS are small, short and open to bias, and unblinding is plausible for intramuscular or distinctive formulations. High-dose vitamin D can cause hypercalcaemia, and supplements should be taken under medical supervision.



Figure 5. Qualitative evidence map based on studies cited in this review; cells reflect reported direction, not effect size.

8. Future directions

Priorities include: (i). adequately powered, multinational placebo-controlled trials of methylcobalamin in early-stage ALS with long-term survival endpoints [12,13]; (ii). confirmatory trials of NAD^+ precursors [14]; (iii). vitamin D trials that stratify by baseline status and use defined dosing [11]; (iv). biomarker-guided designs that link vitamin status to disease progression [9]; and (v). combination and microbiome-informed approaches [19]. Studies should report effect sizes with confidence intervals, adverse events and adherence.

9. Conclusions

No vitamin has been shown to alter the course of ALS. Vitamin E and C do not have trial support, carotenoids are associated with lower risk only as dietary intake, vitamin D should be used to correct deficiency, and methylcobalamin and nicotinamide riboside are the most promising agents but need larger confirmatory trials. Vitamin supplements should be used as adjuncts under medical supervision, alongside approved therapy and supportive care.

Declaration, Conflict of interest and funding

The content provided herein is developed using AI tools, and is meant to help Researchers who are working in the fields of neurological sciences.

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Data availability: No new datasets were generated or analyzed.

Author Note

This manuscript is a literature review and is not a treatment recommendation for an individual patient. Mineral supplementation or chelation should be undertaken only for a clinically justified indication and with appropriate medical monitoring.

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