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Nutritional, Micronutrient, Metal-Ion, Antioxidant, Gut-Directed and Pharmacological Approaches in Bulbar-Onset Motor Neuron Disease: A Narrative Review of Favourable Findings

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ABSTRACT

Bulbar-onset motor neuron disease (MND), the form of amyotrophic lateral sclerosis (ALS) that begins with speech and swallowing difficulty, carries a shorter survival than spinal-onset disease and creates an acute nutritional problem: dysphagia limits intake, saliva and aspiration threaten safety, and the form in which any supplement or drug can be taken changes as bulbar function declines. This narrative review brings together the favourable findings for nutritional substrates (D-glucose, lipids, proteins), vitamins, micronutrients and metal ions, antioxidants and food supplements, and gut-directed approaches, and lists the drugs with supportive evidence for disease modification or for bulbar symptoms. The strongest bulbar-linked signal is for riluzole, whose original trial reported markedly better one-year survival in bulbar-onset patients; the strongest signal for a vitamin is for ultrahigh-dose intramuscular methylcobalamin, now approved in Japan. Hypercaloric and high-fat feeds, long-term vitamin E and carotenoid intake, nanocurcumin, a nicotinamide riboside–pterostilbene combination, copper delivery and gut-microbiome-derived nicotinamide and butyrate have given encouraging results in clinical or experimental studies. Dextromethorphan–quinidine and botulinum toxin treat pseudobulbar affect and sialorrhoea. Almost all supplement evidence comes from mixed ALS populations or animal models rather than bulbar-specific cohorts, and a short section records agents that have not shown benefit so that the selection can be read in context. A staged, dietitian-led matching of supplement form to swallowing function is the most practical use of this evidence.

Key words: bulbar-onset motor neuron disease; amyotrophic lateral sclerosis; dysphagia; micronutrients; D-glucose; lipids; gut microbiome; methylcobalamin; riluzole; enteral nutrition.

1. Introduction

Motor neuron disease (MND), most commonly amyotrophic lateral sclerosis (ALS), is a progressive loss of upper and lower motor neurons with muscle weakness, dysphagia and respiratory failure [1]. In a substantial minority of patients, commonly cited as roughly a quarter to a third, the first symptoms are bulbar: slurred speech, difficulty chewing and swallowing, and drooling [2,3]. Median survival from symptom onset has been reported as 27.5 months for bulbar onset and 35.9 months for spinal onset [4] (Section 10), so any intervention that supports nutrition, comfort and function in this group matters disproportionately.

Few trials have analysed bulbar-onset patients separately, and most evidence for supplements comes from mixed ALS populations or from animal models. This review is therefore a synthesis of the favourable and promising findings for nutrients, micronutrients, metal ions, antioxidants, gut-directed approaches and drugs, read through the lens of bulbar disease. The focus on favourable findings is deliberate; to keep the selection transparent, each section states whether the evidence is bulbar-specific, general-ALS or preclinical, and Section 10 briefly lists the agents that have not shown benefit.

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2. Why bulbar-onset disease needs a distinct nutritional strategy

Loss of motor neurons in the brainstem nuclei and corticobulbar tracts underlies dysphagia, dysarthria and sialorrhoea, and many patients also develop pseudobulbar affect [3]. The cellular mechanisms are those of ALS in general: oxidative damage to proteins, lipids and DNA [5], reduced glutamate clearance and excitotoxic calcium load [6], mitochondrial dysfunction [7] and neuroinflammation [8]. What is distinctive about bulbar-onset disease is the speed with which these cellular problems become a nutritional one (Fig. 1).

Weight loss and malnutrition are associated with shorter survival in ALS [9], and patients with neurological disease are at increased risk of micronutrient deficiency and dehydration; ESPEN recommends dysphagia and nutritional screening in ALS from diagnosis [10]. The American Academy of Neurology practice parameter likewise addresses nutritional therapy, including gastrostomy, as part of ALS care [11]. The interventions reviewed here act at different points of this chain, as summarised in Fig. 2.

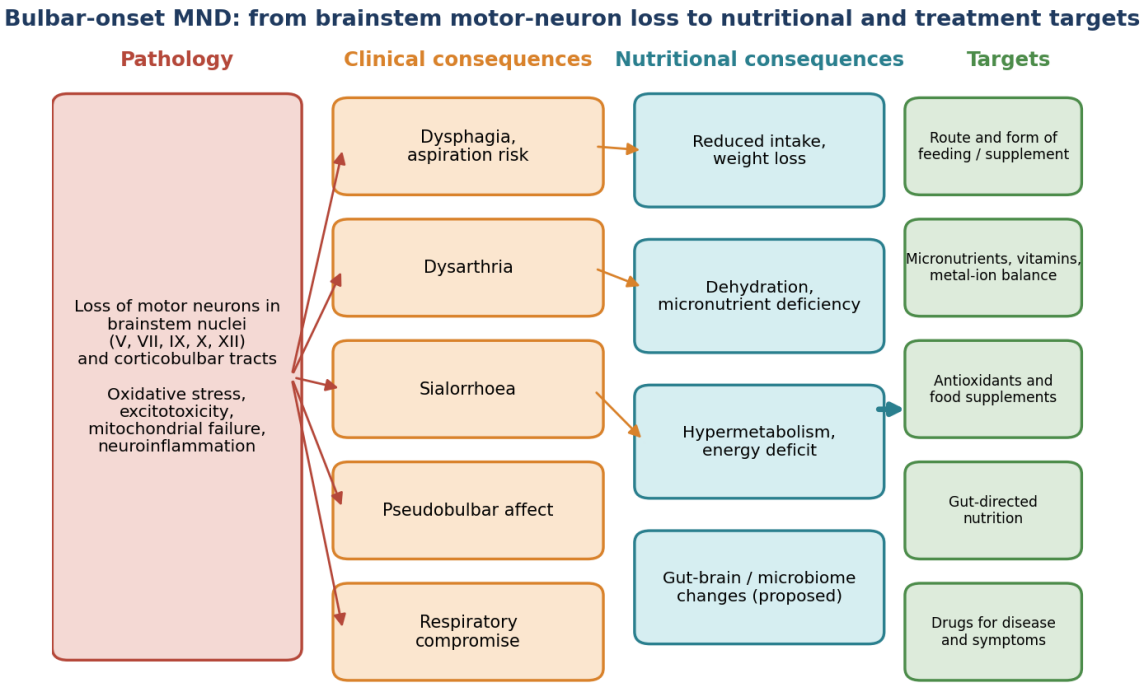


Fig. 1. Scheme linking brainstem motor-neuron loss in bulbar-onset MND to its clinical and nutritional consequences and to the main classes of intervention discussed in this review. Based on [3,9,10].

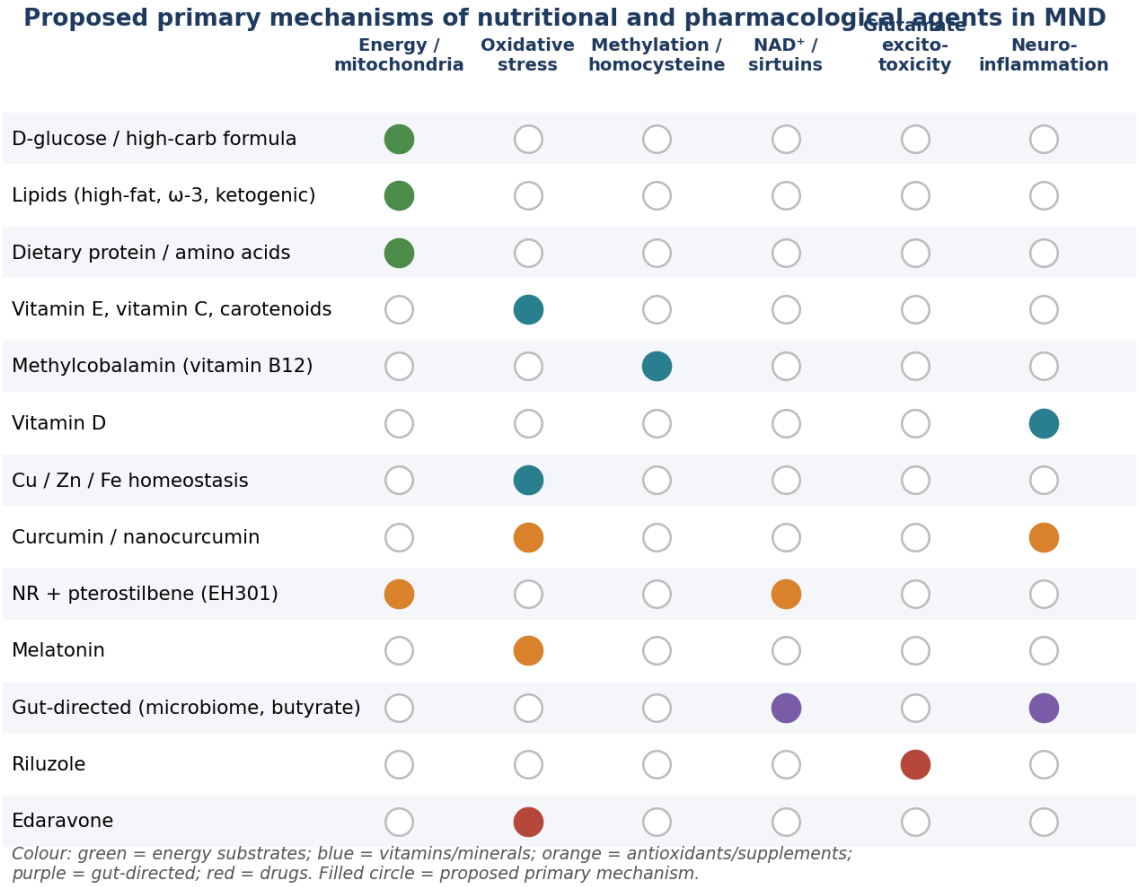


Fig. 2. Proposed primary mechanisms of the nutritional and pharmacological agents discussed. Filled circles indicate the mechanism most often proposed in the cited literature; most agents have additional effects, and the mapping describes proposed rather than proven action in patients. Compiled by the author from [5–8].

3. Energy substrates: D-glucose, lipids and proteins

Energy metabolism is disturbed in ALS, with hypermetabolism, altered glucose handling and changes in lipid metabolism described in patients and models [12]. Table 1 summarises the substrates that have given favourable findings.

3.1 D-glucose and carbohydrate-based feeds

Glucose is the main fuel of neurons and the primary substrate of carbohydrate-based oral and enteral formulas, and supplying it restores the energy balance that dysphagia has disrupted. In a randomised phase 2 trial, hypercaloric enteral nutrition was safe and well tolerated in patients with ALS [13]. Because these feeds are delivered by tube or as thickened oral supplements, they are directly compatible with bulbar dysfunction. The dose and glucose load should be individualised by a dietitian.

3.2 Lipids

Lipids are energy-dense, which is useful when intake volume is limited by dysphagia. In a prospective interventional study, high-caloric food supplements were associated with weight stabilisation in patients with ALS [14], and in the phase 3 LIPCAL-ALS trial of a high-caloric fatty supplement a survival benefit was reported in the subgroup of faster-progressing patients, although the primary analysis was not significant [15]. In a patient cohort, an elevated LDL/HDL cholesterol ratio was associated with longer survival [16]. A ketogenic diet slowed motor decline in a transgenic mouse model [17], and in pooled prospective cohorts a higher intake of ω-3 polyunsaturated fatty acids was associated with a lower risk of developing ALS [18]. These findings support energy-dense, fat-containing formulas, but the ketogenic and ω-3 data are preclinical or observational.

3.3 Proteins

An adequate protein intake is needed to limit muscle loss in a hypermetabolic patient. ALS-specific randomised data on protein or amino-acid supplementation are lacking, and ESPEN guidance addresses overall nutritional adequacy rather than a particular protein supplement [10]; protein is therefore best provided within complete nutritional formulas.

Table 1. Energy substrates: forms, rationale and favourable findings in ALS/MND.

Substrate	Form	Rationale	Favourable finding
D-glucose / carbohydrate	Oral or enteral formula	Neuronal fuel; spares muscle protein	Hypercaloric enteral nutrition safe and well tolerated [13]; hypermetabolism documented [12]
High-fat, high-calorie supplements	Oral or tube feeds	Energy density when intake volume is limited	Weight stabilisation [14]; survival benefit in faster progressors [15]
Blood lipids	(Observation)	Lipid reserve in hypermetabolism	Higher LDL/HDL ratio associated with longer survival [16]
Ketogenic diet	Experimental	Ketone bodies as alternative fuel	Slowed motor decline in SOD1 mice [17]
ω-3 fatty acids	Dietary	Membrane and anti-inflammatory effects	Higher intake associated with lower risk [18]
Protein	Within complete formulas	Substrate for muscle maintenance	No ALS-specific positive trial; adequacy recommended [10]

4. Vitamins and micronutrients

Table 2 summarises the vitamins and trace elements with favourable findings. As in the wider ALS literature, observational data on intake before disease onset are more favourable than interventional data after diagnosis.

4.1 Vitamin E and carotenoids

Vitamin E is the principal lipid-soluble, chain-breaking antioxidant of membranes. In large cohorts, long-term vitamin E supplement use was associated with a lower risk of ALS [19], and in a pooled analysis of five cohorts the rate declined progressively with longer duration of use (relative risk about 0.64 for the longest users) [20]. In a separate pooled analysis, a higher dietary intake of total carotenoids was associated with a lower risk of ALS (relative risk 0.75 for the highest versus lowest quintile) [21]. These are observational findings about risk rather than treatment, and high-dose supplements are not harmless: β-carotene increased lung-cancer incidence in smokers [22], and high-dosage vitamin E has been associated with increased all-cause mortality in a meta-analysis [23]. For patients with bulbar disease, carotenoid-rich foods can be taken in puréed or fortified form.

4.2 Vitamin B12 (methylcobalamin)

Methylcobalamin is the cofactor of methionine synthase, which remethylates homocysteine, and it activates Erk1/2 and Akt signalling in experimental nerve injury [24]. A long-term phase 2/3 study of ultrahigh-dose methylcobalamin did not show a significant overall effect, but a subgroup with early disease and moderate progression appeared to benefit [25]. This was tested in the phase 3 JETALS trial: in 130 patients within one year of symptom onset, 50 mg intramuscularly twice weekly for 16 weeks slowed functional decline (change in ALSFRS-R −2.66 versus −4.63 with placebo) [26]. On the strength of this trial an ultrahigh-dose formulation (Rozebalamin) was approved in Japan in September 2024 [27]. The route is intramuscular, which bypasses the swallowing difficulty entirely and is therefore attractive in bulbar disease. The trial population was early-stage ALS overall, so bulbar-specific benefit has not been established.

4.3 Vitamin D

Vitamin D influences calcium handling and immune function and has been proposed as an adjunct in ALS [28]. A clinic-based study examined vitamin D deficiency and its supplementation in patients with ALS [29]. Correcting a documented deficiency is sensible, particularly in patients who are housebound, but no randomised trial has shown a disease-modifying effect.

Table 2. Vitamins and micronutrients: forms, rationale and favourable findings.

Agent	Form	Rationale	Favourable finding
Vitamin E	Dietary; long-term supplement	Membrane chain-breaking antioxidant	Lower risk with long-term use in pooled cohorts [19,20]
Carotenoids	Dietary (vegetables, fruit)	Quench singlet oxygen	Lower risk with higher intake (RR 0.75) [21]
Methylcobalamin	Intramuscular, 50 mg twice weekly	Methionine synthase cofactor; Erk/Akt signalling	Slowed decline in early-stage ALS [26]; approved in Japan [27]
Vitamin D	Oral	Calcium and immune modulation	Deficiency correctable; supplementation examined [28,29]
Copper (CuATSM)	Experimental complex	Delivers copper to SOD1 in the CNS	Effective in SOD1 mice [30]
Iron	Avoid excess; chelation	Redox-active metal	Conservative chelation proposed as neuroprotective [31]

5. Metal ions

Copper and zinc are cofactors of SOD1, and disturbed copper handling is considered a therapeutic target in SOD1-related ALS [32]. The copper complex CuATSM delivered copper to the central nervous system and effectively treated motor neuron disease in SOD1 mice [30], which is among the most favourable results for any metal-based approach, although it is preclinical. Iron is redox-active, and conservative iron chelation has been proposed as a neuroprotective strategy [31]; blood trace-metal concentrations have also been related to ALS risk [33]. For the clinician, the message is to correct documented deficiencies and to avoid empirical high-dose mineral supplements, as the human evidence is limited and homeostasis, not supplementation, is the target.

6. Antioxidants and food supplements

Table 3 summarises the antioxidant and food supplements for which favourable results have been reported. The most promising are curcumin, in oral and nano-formulated form, and the nicotinamide riboside-pterostilbene combination.

6.1 Curcumin and nanocurcumin

In a double-blind trial, patients who received a curcumin preparation (600 mg/day) for six months showed a stable ALSFRS-R score and reduced oxidative-stress marker levels compared with those who received placebo first [34]. In a 12-month pilot trial of 54 patients, nanocurcumin (80 mg/day) added to riluzole was associated with fewer events of death or ventilator dependence (3.7% versus 22.2%, $p = 0.036$ for the survival curves), although no other outcome differed significantly [35] (Fig. 5d). Because nano-formulations improve bioavailability, they can be given at lower doses, which suits patients who cannot swallow large capsules.

6.2 Nicotinamide riboside and pterostilbene

In a pilot randomised trial of the combination (EH301) in 32 patients over four months, the treated group showed significant improvements in ALSFRS-R, pulmonary function and muscle strength relative to placebo; only 20 patients completed the study, and some authors were affiliated with the manufacturer [36]. A larger randomised trial (NO-ALS) is registered [37].

6.3 Melatonin

High-dose enteral melatonin was safe and was associated with reduced oxidative damage in a prospective study [38]. The enteral route shows how a supplement can be delivered through a feeding tube once swallowing fails.

Table 3. Antioxidants and food supplements with favourable findings in ALS/MND.

Agent	Form and dose	Design	Favourable finding	Ref.
Curcumin	Oral, 600 mg/day	Double-blind then open-label, 6 months	Stable ALSFRS-R; lower oxidative marker	[34]
Nanocurcumin	Oral nano-formulation, 80 mg/day	Pilot RCT, n = 54, 12 months	Events 3.7% vs 22.2%	[35]
EH301 (NR + pterostilbene)	Oral	Pilot RCT, n = 32, 4 months	Improved ALSFRS-R, FVC, strength	[36]
Melatonin	High-dose enteral	Prospective study	Reduced oxidative damage markers	[38]
Vitamin E, carotenoids	Dietary / long-term	Pooled cohorts	Lower risk of ALS	[20,21]

7. Gut health

The gut–brain axis offers an additional, food-based route. In SOD1 transgenic mice, supplementation with *Akkermansia muciniphila* ameliorated symptoms, whereas *Ruminococcus torques* and *Parabacteroides distasonis* worsened them; the benefit was accompanied by accumulation of nicotinamide in the central nervous system, and systemic nicotinamide improved motor symptoms and spinal-cord gene expression. A small human comparison found reduced nicotinamide in blood and cerebrospinal fluid of patients with ALS [39]. In another mouse study, sodium butyrate and butyrate-producing bacteria were reported to delay disease onset and prolong survival [40] (Fig. 3).

These results support dietary approaches that favour beneficial bacteria and short-chain fatty acid production, such as fibre-containing or fermented foods adapted to the swallowing ability of the patient. They remain experimental, and no controlled human trial of a microbiome-directed intervention has been reported specifically in bulbar-onset disease; enteral feeds with fibre may be a practical way to test such approaches in patients who are tube-fed.

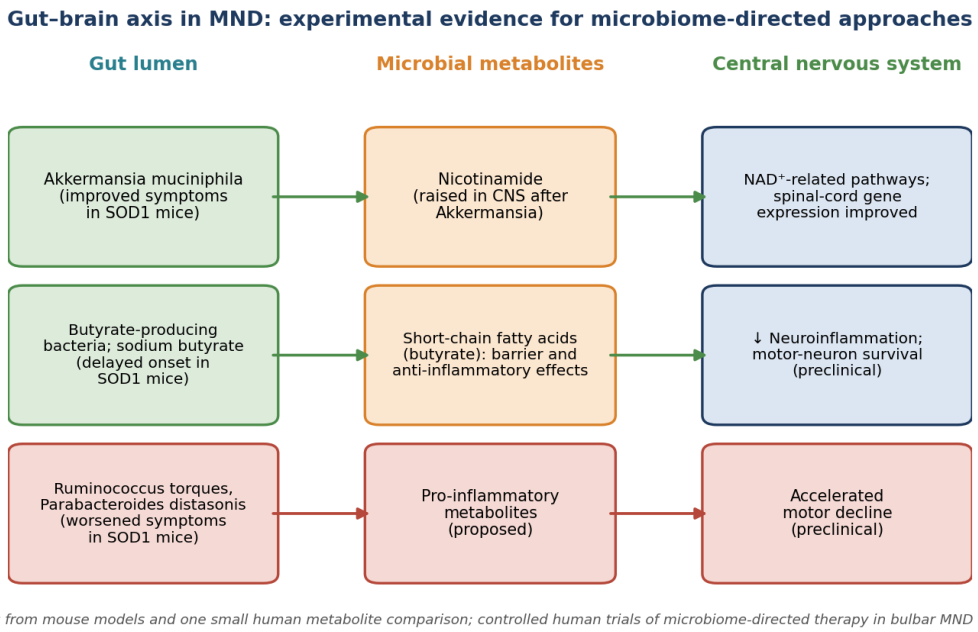


Fig. 3. Gut–brain mechanisms reported in SOD1 mouse models: beneficial bacteria and their metabolites (nicotinamide, butyrate) were associated with improved motor outcomes, whereas other commensals worsened symptoms. Based on [39,40].

8. Drugs with favourable evidence

Table 4 lists the drugs and procedures with favourable findings in ALS/MND and indicates their relevance to bulbar disease. None of them reverses bulbar dysfunction; they slow progression or relieve specific bulbar symptoms.

8.1 Disease-modifying drugs

Riluzole is the best-established agent and probably prolongs median survival by two to three months [41]. In the original trial, one-year survival in bulbar-onset patients was 73% with riluzole versus 35% with placebo (P = 0.014), a benefit larger than in limb-onset disease, although the subgroup was small [42] (Fig. 5b). Riluzole is available as tablets and in forms for patients who cannot swallow tablets [43]. Edaravone slowed functional decline in a defined subgroup of patients with early disease [44]. Ultrahigh-dose methylcobalamin is described in Section 4.2. Tofersen, an antisense oligonucleotide, lowered CSF SOD1 protein and plasma neurofilament levels in SOD1-ALS, a rare genetic form [45].

8.2 Drugs for bulbar symptoms

Dextromethorphan combined with quinidine reduced pseudobulbar affect in ALS in randomised trials [46,47]. Botulinum toxin type B reduced sialorrhoea in a randomised double-blind study [48], and anticholinergic drugs and other measures for sialorrhoea and dysphagia are reviewed in [3]. Gastrostomy is part of the nutritional care recommended in the practice parameter [11].

Table 4. Drugs and procedures with favourable evidence in ALS/MND and their relevance to bulbar disease.

Agent	Class / mechanism	Favourable finding	Bulbar relevance	Ref.
Riluzole	Antiglutamate agent	Survival prolonged by 2–3 months; bulbar-onset one-year survival 73% vs 35%	Strongest bulbar-linked signal	[41,42]
Edaravone	Free-radical scavenger	Slower ALSFRS-R decline in selected early patients	No bulbar-specific data cited here	[44]
Methylcobalamin, ultrahigh dose	Methylation cofactor	Slowed decline in early ALS; approved in Japan	IM route bypasses swallowing	[26,27]
Tofersen	SOD1 antisense oligonucleotide	Lowered CSF SOD1 and plasma neurofilament	SOD1-ALS only	[45]
Dextromethorphan–quinidine	Sigma-1 / NMDA modulation	Reduced pseudobulbar affect	Direct bulbar symptom	[46,47]
Botulinum toxin B	Neuromuscular blockade of salivary glands	Reduced sialorrhoea	Direct bulbar symptom	[48]
Anticholinergics	Antimuscarinic	Used for sialorrhoea	Direct bulbar symptom	[3]
Gastrostomy and enteral feeding	Nutritional route	Part of recommended nutritional care	Direct, for dysphagia	[11,13]

9. Forms of delivery in bulbar disease

Because swallowing becomes unsafe, the form of every supplement and drug must change with the stage of disease (Fig. 4). Early on, food-based sources and capsules or tablets are usually sufficient. With mild dysphagia, thickened liquids, soft fortified foods, powders, oral suspensions and nano-formulations extend oral use, and ESPEN recommends that modified liquids or textures be prescribed only after a swallowing assessment [10]. When oral intake becomes unsafe, enteral nutrition through a gastrostomy delivers high-calorie feeds [13,15] and, in principle, tube-compatible supplements such as enteral melatonin [38]; injectable routes such as intramuscular methylcobalamin [26] and botulinum toxin for sialorrhoea [48] bypass the oral route entirely. Table 5 summarises the forms.

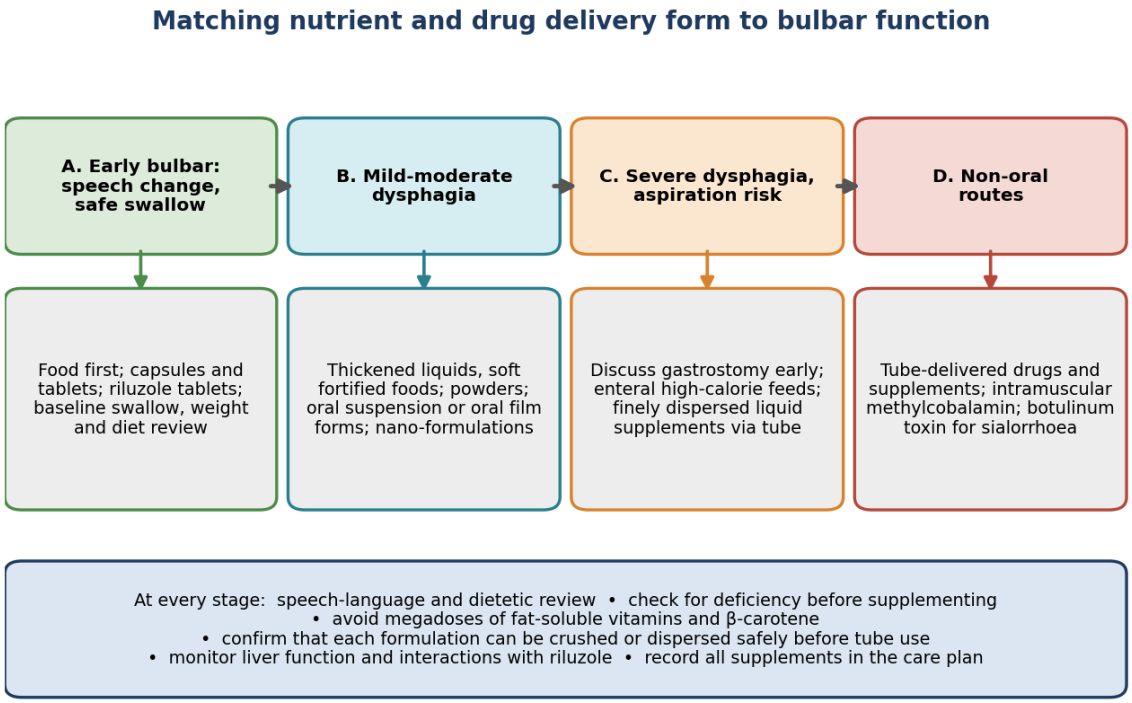


Fig. 4. Suggested matching of supplement and drug form to bulbar function. The stages are illustrative, not diagnostic criteria. Based on [10,11] and the routes used in the trials discussed.

Table 5. Forms of delivery for bulbar-onset MND.

Form	Examples	Advantages	Limitations
Food-based	Carotenoid-rich purées, fortified foods [21]	Safe; no pill burden	Texture; uncertain active dose
Oral solid	Capsules and tablets in trials [34,36]	Simple while swallowing is safe	Large capsules hard to swallow
Thickened liquid, powder, suspension	Modified liquids and textures [10]; alternative riluzole forms [43]	Adapts to mild dysphagia	Needs swallowing assessment
Nano-formulation	Nanocurcumin [35]	Better bioavailability at lower dose	Few long-term data
Enteral tube	High-calorie feeds [13,15]; enteral melatonin [38]	Bypasses swallowing; reliable dosing	Procedure; formulation must pass the tube
Injection	Intramuscular methylcobalamin [26]; botulinum toxin [48]	Bypasses the oral route	Frequent visits

10. Summary of the evidence and agents without demonstrated benefit

Fig. 5 plots the principal quantitative findings. The bulbar-specific results are the survival difference by onset site (Fig. 5a) and the riluzole subgroup (Fig. 5b); the methylcobalamin and nanocurcumin results come from mixed ALS populations. To avoid giving a one-sided picture, Table 6 lists the agents that have not shown benefit in randomised trials.

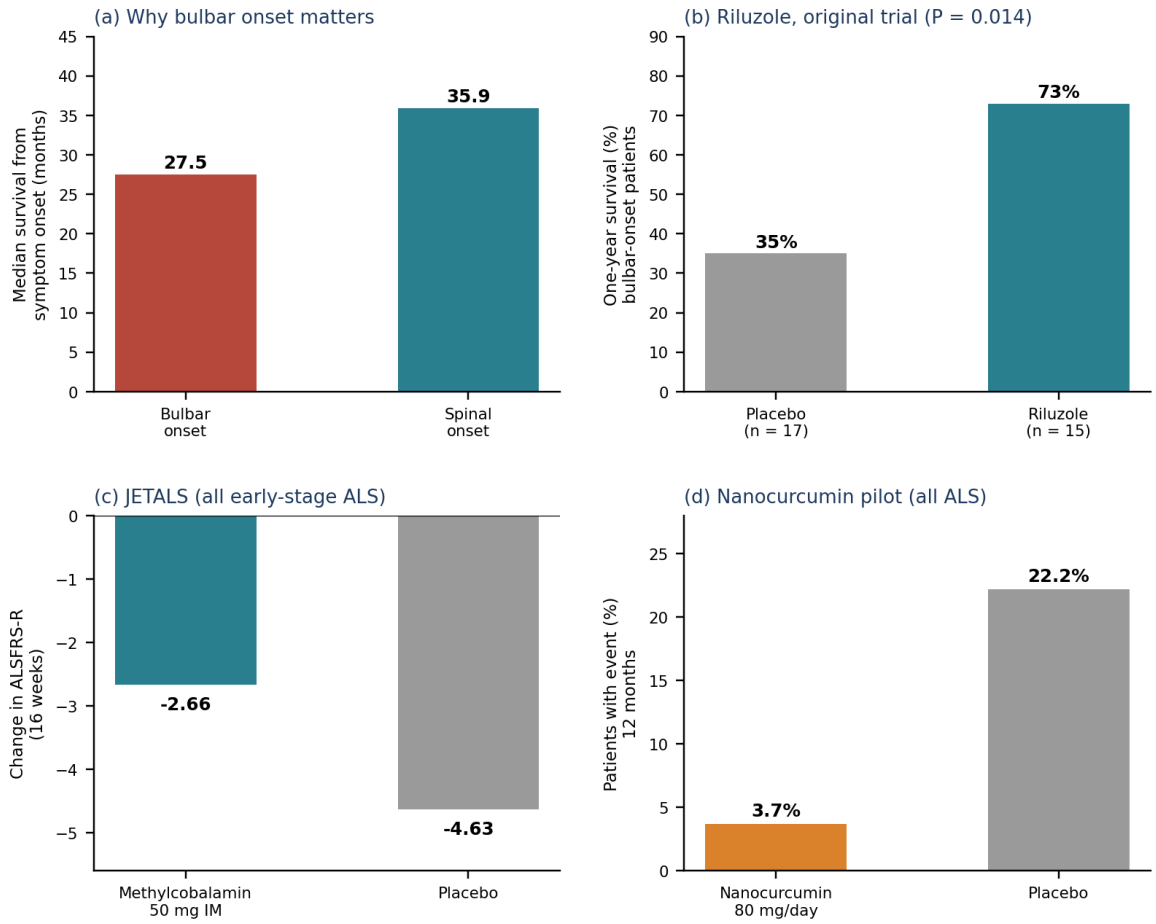


Fig. 5. Selected quantitative findings. (a) Median survival from symptom onset by onset site [4]. (b) One-year survival in bulbar-onset patients in the original riluzole trial (subgroup n = 17 placebo, 15 riluzole) [42]. (c) Change in ALSFRS-R at 16 weeks in JETALS (all early-stage ALS) [26]. (d) Event rate at 12 months in the nanocurcumin pilot trial (all ALS) [35]. Values are redrawn from the cited publications.

Table 6. Agents that have not shown benefit in randomised trials, for context.

Agent	Finding	Ref.
High-dose vitamin E (after diagnosis)	No significant survival benefit as add-on to riluzole	[49,50]
Coenzyme Q10	Insufficient evidence to justify phase III	[51]
Creatine	No benefit on survival or function	[52,53]
Sodium phenylbutyrate–taurursodiol	Positive phase 2 trial, but phase 3 PHOENIX failed its endpoints and the product was withdrawn from the US and Canadian markets	[54,55]
Methylcobalamin (phase 2/3)	No significant overall effect; benefit confined to a subgroup	[25]

11. Practical recommendations

The evidence supports a staged, team-based approach: (i) screen swallowing and nutrition from diagnosis and review them regularly [9,10]; (ii) maintain energy intake with high-calorie oral or enteral formulas, discussing gastrostomy before swallowing fails [11,13,15]; (iii) correct documented deficiencies of vitamins and minerals rather than giving megadoses [22,23]; (iv) offer riluzole, and consider edaravone or, where available, methylcobalamin within specialist care [26,41,44]; (v) treat sialorrhoea and pseudobulbar affect with the agents in Table 4; and (vi) reserve nanocurcumin, nicotinamide riboside–pterostilbene and microbiome-directed approaches for trials or specialist supervision [35–37]. Every supplement should be reviewed by a pharmacist for interactions and for suitability for crushing or tube delivery.

12. Limitations and future directions

The principal limitation is the scarcity of bulbar-specific data: most trials report ALS overall, and the supplement studies are small, short and heterogeneous. Observational associations are subject to confounding, preclinical findings (CuATSM, butyrate, *Akkermansia*, ketogenic diet) may not translate, and the nanocurcumin and EH301 results derive from single pilot trials [35,36]. Selection of favourable findings, as requested for this review, inherently overstates the benefit of the field as a whole. This narrative review did not follow a systematic search protocol. Future trials should report bulbar-onset subgroups, stratify by progression rate as JETALS did [26], test tube-compatible formulations and include swallowing and weight outcomes.

13. Conclusions

In bulbar-onset MND, the most reliable gains come from energy-dense nutrition delivered in a form that matches swallowing function, from riluzole (with its bulbar-linked survival signal), and from targeted drugs for sialorrhoea and pseudobulbar affect. Ultrahigh-dose methylcobalamin, nanocurcumin, nicotinamide riboside–pterostilbene, copper delivery and gut-derived nicotinamide and butyrate are promising but largely unconfirmed in bulbar disease. Evidence for the remaining supplements is limited, and megadoses carry risk. Future research should test these agents in bulbar-onset cohorts and in formulations designed for patients who cannot swallow.

Declaration, Conflict of interest and funding

The content presented herein is developed using AI tools, and is meant to help Researchers who are working in the fields of Neurological disorders.

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Data availability: No new datasets were generated or analyzed.

Author Note

This manuscript is a narrative review and is not a treatment recommendation for any individual patient. The treatment should be taken only for a clinically justified indication and with appropriate medical monitoring under the supervision of an expert neurologist.

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