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## Nutrition and Dietary Supplements in Motor Neuron Disease

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### Overview: The role of nutrition in motor neuron disease

Compromised nutrition leading to weight loss is a common and significant problem in the ALS patient population. Malnutrition and consequent weight loss are significant negative prognostic indices to survival<sup>1–3</sup>. The benefit of aggressive and early nutritional therapy can profoundly influence the disease course, quality of life and survival.

This chapter will review the role of nutrition, both as sustenance and treatment for patients with amyotrophic lateral sclerosis (ALS). In addition, self-medication with dietary supplements has become increasingly popular within this patient population. Despite their popularity, efficacy of these compounds has been largely unsupported by formal clinical trials. Available data will be highlighted to provide a basis upon which to advise patients requesting guidance.

The etiology of impaired nutrition leading to weight loss is multifactorial including dysphagia, weakness in the extremities, difficulty with mastication and the possibility of a hypermetabolic state resulting from enhanced energy expenditure<sup>4, 5, 6, 7</sup>. Interventions to maintain adequate nutritional intake may include altering food consistency, feeding assistance (hand braces, altered utensils, mobile arm supports, modified plates, bowls, cups) and high calorie nutritional supplements.

### Percutaneous Endoscopic Gastrostomy

Placement of a percutaneous endoscopic gastrostomy (PEG) tube is one of the most effective means of proactive intervention to maintain body weight and hydration<sup>8</sup>. Optimally, the PEG tube should be introduced early to supplement oral intake and reduce the stress of maintaining all nutritional needs by mouth. Patient acceptance of the PEG tube can be greatly improved by educating the patient that they may still enjoy favorite foods by mouth. Moreover, use of the PEG to meet the increased caloric requirements of the disease can conserve time and energy for both patient and caregiver. Patient's autonomy, confidence and quality of life are enhanced from knowing that they can aggressively affect their disease course by the use of a PEG tube, while minimizing their fear of choking and the caregiver burden.

The timing of PEG tube placement varies widely among practitioners. However, the American Academy of Neurology recommends PEG placement *before* the patient's forced vital capacity falls below 50% predicted in order to avoid risk of respiratory compromise during the procedure

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<sup>9</sup>. This is based on available outcomes data from studies meeting the qualifications for the guidelines. General consensus among practitioners suggest that adopting the tube early in the course of progressive dysphagia, even prior to significant weight loss, is well accepted and allows the patient the choice of incrementally using the PEG for their nutritional needs.<sup>5</sup> Alternative protocols for feeding tube placement, including insertion of the tube with radiographic guidance (RIG) have been endorsed as means of lessening the risk of aspiration.<sup>10</sup> Recently an alternative BiPAP mask was introduced allowing for continuous noninvasive ventilatory support during PEG placement reducing risk of respiratory compromise and improving patient comfort even when FVC falls much below 50%<sup>11</sup>

## Nutrition and Survival

The consequences of malnutrition in patients with ALS are well known. Inadequate dietary intake can exacerbate catabolism and atrophy of respiratory muscles, weaken the immune system and contribute to infection<sup>12, 13</sup>. Weight loss and below-normal body mass index (BMI) resulting from deficient energy intake among ALS patients are correlated with shortened survival<sup>14</sup>. Several more recent studies confirm the observation that weight loss (and / or malnutrition), defined as  $BMI \leq 18.5 \text{ kg/m}^2$ , is an independent, negative, prognostic indicator for survival<sup>3, 15, 16</sup>. In at least nine studies, evaluating a total of 469 ALS patients receiving enteral nutrition via PEG, a consistent benefit of either weight stabilization or weight gain was determined.<sup>16–21 22</sup>

The magnitude of the survival advantage from improved nutrition can even be greater than the magnitude of the treatment effects being targeted in current clinical drug trials. A population-based study from Italy, found a greater than 3 fold improved survival with patients using PEG compared to patients with oral intake,<sup>23 24</sup>

Despite these published reports, some controversy remains as to the magnitude of the survival benefit following PEG placement. These dissenting opinions have, however, followed retrospective and population based studies<sup>5, 8</sup>.

## Neutraceuticals, Functional Foods, and Dietary Supplements

“Neutraceuticals”, “functional foods” and “dietary supplements” are terms used to describe chemical components of foods that may display unique, disease-fighting pharmacokinetics and pharmacodynamics when ingested in amounts above that of one’s typical diet<sup>25</sup>. The emergence of neutraceutical use within the patient population has defined a growing and substantial treatment modality. Often such dietary supplements are self-prescribed based on theoretical benefit(s) or anecdotal reports, addressing proposed mechanisms leading to motor neuron death. A sense of autonomy and self-determination along with the reality of advancing disability and the ease of availability for many supplements combine to make the practice attractive to patients. Most dietary supplements are easily obtained in retail outlets or by internet. Despite the absence of documented benefits in controlled trials, these supplements are conservatively estimated to be used by at least 75% of the patient population<sup>26</sup> based solely on the *potential* of efficacy.

The etiology of motor neuron cell death is multifactorial. Oxidative injury, calcium dysregulation, inflammation, excitotoxicity, mitochondrial dysfunction and cytoskeletal abnormalities are all hypotheses implicated with substantial evidence from both animal models and/or patient samples.<sup>27 28</sup> Most dietary supplements directed to ALS patients are touted as having relevance to mechanisms with substantial preclinical data in motor neuron cell death. Study and evaluation of dietary supplement use in the ALS patient population is also complicated as most patients take several supplements simultaneously hoping to address synergistic or complementary pathways.<sup>29</sup> The use of such combination or “cocktail” therapy

is appealing to patients and intuitive to physicians but currently not supported with data from blinded clinical trials. Regardless, it is a common practice with potential adverse health implications as well as benefits.

Our current approach toward the use of nutraceuticals as nutritional supplements has been to remain aware of known adverse effects and unfounded or unrealistic claims. The role of the practitioner has been largely to offer advice or caution as our patients explore their own therapeutic combinations. Since passage of the Dietary Supplement Health and Education Act in 1994, entry to the market of dietary supplements has been faster, often without any regulation or oversight common in prescription medications.

## Rationale for the use of dietary supplements in ALS

### Oxidative injury

Oxidative damage is thought to be a major contributing factor in the death of motor neurons<sup>30</sup>. Oxidative injury can have both a primary role as well as a secondary role triggered by other mechanisms mentioned below. Reactive oxygen species (ROS) include superoxide, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), hydroxyl free radicals (OH) and nitric oxide (NO). ROS readily react with lipids, proteins, and DNA to induce cellular damage<sup>31–33</sup>. The high metabolic activity of neurons leads to considerable ROS formation in these cells<sup>34</sup>. The high content of lipids and iron in nervous tissue may make the nervous system particularly sensitive to ROS damage<sup>31</sup>. Glutathione peroxidase, catalase, and superoxide dismutase (SOD) are all endogenous antioxidants that counteract ROS damage. Toxicity resulting from mutated SOD has been directly implicated in the pathophysiology in familial ALS. Further support for the ROS hypothesis comes from elevated levels of protein carbonyls and 8-hydroxy-2-deoxyguanosine (8-OHdG), both markers of oxidative damage, in the motor cortex of sporadic ALS patients<sup>35</sup>. In addition, elevated plasma levels of 8-OHdG<sup>36</sup> and thiobarbituric acid reactive substances (TBARS)<sup>37</sup> have been identified in sporadic ALS patients compared to healthy controls. Possible benefit from exogenous nutraceuticals may result from their direct antioxidant activity and/or effects on endogenous enzyme pathways<sup>38</sup>.

### Excitotoxicity

Glutamate is primary excitatory neurotransmitter in CNS. Dysfunction in synaptic uptake of glutamate may lead to prolonged opening of glutamate-dependent Ca<sup>++</sup> channels in neuron, which may in turn, generate free radicals and directly damage intracellular organelles (i.e. mitochondria). Glutamate release and reuptake is usually tightly regulated, however increased glutamate in cerebrospinal fluid was found in sporadic ALS patients. Riluzole, the only FDA-approved drug with indication for ALS, acts by blocking the presynaptic release of glutamate<sup>39, 40</sup>. Supplements that likewise act to block glutamate release, enhance reuptake, or protect cells against the damaging effects of excessive glutamate may aid in the medicinal management of ALS.

### Mitochondrial dysfunction

There is strong evidence for mitochondrial dysfunction in motor neuron disease. Morphological changes in mitochondria have been identified in SOD-1 mice<sup>41</sup> and in sporadic ALS patients without SOD-1 mutations<sup>42</sup>. Structural abnormalities within the electron transport chain and mutations within mitochondrial DNA have been implicated in the pathogenesis of ALS<sup>41</sup>. The primary role of mitochondria in cells is energy production by oxidative phosphorylation. Given the high metabolic demand of neurons, energy supply and utilization is critical and is reflected by the large number of neuronal mitochondria. Mitochondrial damage may be due to, or result in, increased free radical activity, increased intracellular free Ca<sup>++</sup><sup>43, 44</sup>, defective electron transport enzymes (complexes I–IV), or

coenzymes<sup>45, 46</sup>. Dysfunctional mitochondria leads to overproduction of ROS, and abnormalities in the mitochondrial transition pore may activate a caspase cascade resulting in further oxidative damage<sup>41</sup>.

Mitochondrial activity and the underlying physiology may also differ in neurons from the brain and spinal cord<sup>47,48</sup>. These differences may ultimately provide essential insights into disease heterogeneity in upper versus lower motor neuron clinical presentations.

Nutritional supplements that prevent free radical damage, stabilize mitochondrial membranes, or stimulate electron transport chain complexes may be of value.

## Dietary Supplements Commonly Used in the ALS Patient Population: Fact vs. Fiction

### Vitamin E

Reports of alpha-tocopherol, an isomer of vitamin E, as a trial therapy for ALS date back to the 1940's when Lou Gehrig received weekly intramuscular injections as putative therapy<sup>49</sup>. Despite the absence of documented clinical benefit in controlled trials vitamin E continues to be among the most popular of the dietary supplements. This is likely the result of preclinical data, the association of vitamin E and motor neuron disease from other species and the ease of availability with few or no documented side effects.

**Preclinical data**—In the G93A/SOD1 mouse model of ALS vitamin E supplementation had no effect on survival, however, did significantly delay symptom onset and slow disease progression as assessed by wheel activity<sup>34</sup>. The mutant SOD-1 mouse model is associated with an increase of hydrogen peroxide production, yielding an increase in hydroxyl free radicals<sup>50</sup>. Because alpha-tocopherol can directly neutralize hydroxyl radicals and some effect on disease progression has been demonstrated, it is commonly implicated as an ideal candidate for neuroprotection in ALS<sup>51</sup>.

In the equine population, vitamin E deficiency has also been closely linked to motor neuron disease with implications to human disease<sup>52</sup>. In an inherited canine motor neuron disease, vitamin E levels were found to be lower than in controls further suggesting a potential role for supplementation<sup>53</sup>. Furthermore, experimentally induced vitamin E deficiency has been reported to affect nerve regeneration and perhaps affect the axonal integrity of healthy motor neurons<sup>54</sup>.

**Clinical data**—The hypothesis that patients with motor neuron disease(s) suffer from a deficiency of vitamin E is unfounded in data from at least three studies comparing both serum and or CSF levels in ALS patients and healthy matched controls<sup>37, 55, 56</sup>.

Presymptomatic use of vitamin E has also been implicated in the patient population as a source of neuroprotection in vulnerable motor neurons in patients showing early signs. No direct studies have been reported testing this hypothesis, however, a large epidemiological evaluation of 957,740 adults participating in the American Cancer Society's Cancer Prevention Study II was collected in 1982. Information about the use of vitamins A, C, E, (all antioxidants) and multivitamins revealed that respondents categorized as "regular users of vitamin E for 10 or more years" demonstrated a significantly improved mortality related to ALS. The risk of death in this group was 62% lower than non-users of vitamin E. The study was limited (observational design, use of other supplements, patient assessed at only time, no detail on dose), however, these data have helped propagate speculation leading to ongoing use<sup>57</sup>. In a separate case-control study, food-frequency questionnaires were administered to 132 ALS patients and 220 age and sex-matched controls. Comparing highest to lowest tertiles, individuals with highest

polyunsaturated fat intake and highest vitamin E intake demonstrated 60% and 50% lower risk of developing ALS, respectively<sup>58</sup>. These data revealed significant reductions in the odds ratio for vitamin E and polyunsaturated acids together, suggesting a synergistic benefit.

Considering all of the population data collectively, available studies suggest that higher intakes of vitamin E may have a positive, protective effect on developing ALS. Nevertheless, data from formal clinical trials in the patient population is less convincing. The first such trial randomized 289 ALS patients in France to receive either alpha-tocopherol 1000 mg daily or placebo for 12 months. The primary outcome was function as assessed by the Norris Limb score, a validated four-point rating scale of physical function. Secondary outcomes included survival and biological markers of oxidative stress. Although supplementation did significantly decrease plasma concentration of TBARS and increase plasma concentrations of plasma glutathione peroxidase compared to placebo, there were no significant effects on the functional rating scale or survival<sup>59</sup>. In a separate open, randomized clinical trial assessing the same outcomes of survival and functional status, 35 Polish patients were randomized to receive vitamin E (600 IU/day) and selegiline (10mg/day) for 18 months, while 32 patients received only symptomatic treatment. Again there were no significant differences between groups<sup>60</sup>. Another study examined vitamin E in conjunction with riluzole. Participants were 160 ALS patients from Germany who were all receiving riluzole at the standard dosage. They were randomized to receive either 5000 mg of vitamin E or placebo daily for 18 months. The primary outcome was survival, and secondary outcomes were Norris function scale score, spasticity scale score, manual muscle testing, and the score of a validated quality-of-life scale. Again, no treatment effect for vitamin E was seen for any of the outcomes measured<sup>61</sup>. A separate observational study also confirmed no differences in quality-of-life scores between patients either taking or not taking vitamin E supplements at a dosage of 600 mg/day<sup>62</sup>. A current randomized, double-blind, placebo-controlled, crossover study to evaluate vitamin E for the treatment of muscular cramps is currently underway.

In summary, although vitamin E appeared promising in population studies and in the transgenic mouse model, clinical trials have thus far failed to show benefits for outcomes of survival, functional status, or quality of life.

## **B Vitamins (folic acid, B6, B12)**

Use of the B vitamins, particularly folic acid and methylcobalamin, have been largely driven by the observation that patients with ALS may have elevated plasma homocysteine levels<sup>63</sup>. In the transgenic SOD-1 mouse model similar elevation of plasma homocysteine was found<sup>64</sup>. Vitamin B12 and folate are involved in reactions that convert homocysteine to methionine, thereby potentially reducing homocysteine levels. Furthermore, vitamin B6 functions in an alternative pathway to convert homocysteine to sulfur amino acids<sup>65</sup>.

In 1998, a double-blind, randomized clinical trial examined the effects of megadose methylcobalamin, an analog of vitamin B-12, on averaged compound muscle action potential amplitudes (CMAPs) in ALS patients. Twenty four ALS patients with similar CMAPs at baseline were randomly assigned to two groups. Group 1 received 25 mg of methylcobalamin daily by intramuscular injection for 28 days. Group 2 received a lower dose (0.5 mg/day) for 28 days. CMAPs of selected muscle groups were measured at baseline, day 14, and day 28. The low-dose methylcobalamin group showed no significant changes in CMAPs from baseline, while the 8 patients in the higher-dose group showed significantly higher CMAPs at 28 days compared to baseline. The investigators classified these eight subjects as “responders” and the remaining four subjects as “non-responders.” Based on these data, it was concluded that among certain ALS patients, high-dose methylcobalamin enhances neuronal functioning. Despite the small sample size, the absence of a placebo group, and the absence of any documented improvement in clinical function, this study has contributed to speculation that such therapy

may be of benefit.<sup>66</sup> The study does implicate the important possibility that the ALS patient population may be quite heterogeneous, consisting of responders and nonresponders to a certain supplement or medication. If the disease pathophysiology is accepted as multifactorial then the possibility emerges that there may be a subgroup of responders to selected treatments. Such possibilities have propagated the use of B complex vitamins, again due to their availability and low side effect profile<sup>66</sup>.

## Zinc

Zinc is implicated as a supplement with potential benefit due to its integral role in the function of SOD-1. Mutant forms of SOD-1, as found in the transgenic model of ALS, have impaired ability to bind zinc and are toxic<sup>67</sup>. Zinc supplementation has been shown to up-regulate metallothioneins, and facilitate antioxidant function<sup>68</sup>. Zinc has, therefore been implicated especially in patients possessing a mutated SOD-1 protein (familial ALS patients).

Two experiments examining this hypothesis in the transgenic mouse model have yielded contrasting results. In the first experiment, three groups (11 transgenic mice per group) were given 75mg/kg zinc, 375 mg/kg zinc, or no zinc in their drinking water. Contrary to their hypothesis that zinc would be protective, supplementation actually decreased survival in a dose-dependent manner. Zinc had no effect on symptom onset, or motor neuron numbers. These results suggested that zinc supplementation may actually accelerate motor neuron loss<sup>68</sup>.

In a second study, more moderate dosages of zinc (12 mg/kg) delayed death in G93A-mutant SOD mice by 11 days compared to mice on a zinc-deficient diet<sup>69</sup>. Slightly higher doses (approximately 18 mg/kg) significantly shortened survival and this effect was blocked by concurrent supplementation with copper, which may have been displaced by the higher zinc dose. These data highlight the importance of dosage in supplementing zinc and the synergistic interaction of copper and zinc in predicting the toxic or neuroprotective effects<sup>69</sup>.

Careful attention to the daily dosage of zinc, often found in compounded nutraceutical supplements, in the patient population is advised. It may be most prudent to simply assure adequate intake of zinc to meet the recommended dietary allowance.

## Genistein

Genistein is a phytoestrogen that has been implicated in oxidative insult resulting from cerebral ischemia. Estrogen compounds have also been implicated as neuroprotective agents promoting survival of motor neurons. Survival differences between males and female SOD-1 transgenic mice have been attributed to the role of estrogen. This hypothesis was tested using genistein (16 mg/kg, twice daily) in that model. Genistein significantly delayed symptom onset and prolonged survival in male animals, but not females. The study concludes that phytoestrogens in genistein pose gender-specific neuroprotection, likely by the same mechanism of endogenous estrogen. This provides support that the estrogenic effects of genistein may be neuroprotective but not at levels above normal, endogenous estrogen<sup>65</sup>. Clinical trials using genistein have not been reported.

## Melatonin

Melatonin displays a wide array of antioxidant activities, including activation of glutathione peroxidase and inhibition of nitric oxide synthase<sup>70</sup>. Treatment with melatonin resulted in a significant, dose-dependent attenuation of glutamate-induced cell death *in vitro* using a motor neuron cell line. In transgenic mice, melatonin has been tested by administration prior to symptom onset or on the day of symptom onset. Symptom onset was delayed and survival prolonged when administered prior to symptom onset, however not when administered after symptom onset.

In the ALS population, 31 ALS patients were given high-dose melatonin (300 mg/day) by rectal suppository for 24 months and compared with healthy, matched controls. The extent of oxidative injury was accessed by measurement of protein carbonyl levels in serum. At baseline ALS patients displayed significant elevations of serum protein carbonyl groups. After 4 months of treatment with melatonin, serum protein carbonyl levels were the same in ALS patients as in healthy controls, indicating that melatonin attenuated oxidative damage. No report on symptom modification or alteration in disease course have been reported <sup>71</sup>.

## Creatine

Creatine has received much attention within the patient population based largely on preclinical data and anecdotal patient reports. The use of creatine in combination with other agents has also been encouraging, albeit unproven in clinical trials. Creatine monohydrate displays many pharmacokinetic properties relevant to mechanisms of motor neuron loss in ALS. Enhancing energy production within mitochondria and possibly limiting the uptake of glutamate into cells have been proposed as putative neuroprotective effects <sup>72</sup>. The compound also displays antioxidant properties by acting as a mitochondrial membrane stabilizer <sup>73</sup>.

In the transgenic SOD-1 model of ALS, creatine supplementation resulted in a dose-dependent increase in survival and motor performance as well as dose-dependent decreases in motor neuron loss and biomarkers of oxidative damage <sup>74</sup>. Another study reported that supplementation significantly attenuated chemically-induced increases in glutamate, delay in symptom onset and prolonged survival <sup>75</sup>. By contrast, a third study examining the effects of creatine on muscle function and muscle metabolism showed no improvements in rotorod performance, grip strength, ATP concentrations, or glycogen concentrations <sup>76</sup>.

Combination therapies using creatine have been tested in several forms. The effects of riluzole, creatine, or the combination of both yielded delay in symptom onset and prolonged survival compared to control mice, however no significant differences between treatment groups were observed <sup>77</sup>. The combination of minocycline, creatine and the combination showed significant delay of symptom onset and prolonged survival compared to unsupplemented mice. The combination appeared to have additive, synergistic effects on these outcome measures compared to the control group or either agent alone <sup>78</sup>. Celecoxib and rofecoxib (both COX-2 inhibitors), were also tested alone and in combination with creatine and this resulted in significantly improved motor performance, reduced motor neuron loss, and extended survival. In combination with creatine, the effects on survival were significantly additive <sup>79</sup>.

Despite such promising results from these animal studies, clinical trials have failed to show any significant effects of creatine for any outcomes examined. To date three large clinical trials of creatine have been completed in the ALS population. All three studies concluded no efficacy in the primary endpoint(s). <sup>80, 81 82</sup> While the studies differed somewhat in either dose and/or design, the conclusion followed that creatine, by itself using available clinical outcomes, did not help. An interesting trend in improved survival in the creatine treatment groups from two of the studies have prompted a meta analysis. A significant trend of improved survival was noted when the two trials recently completed in North America were combined. This benefit was more modest (not significant) when the third European trial was also included. The implication followed that larger study of survival in the patient population may be warranted (submitted).

## Coenzyme Q10

Coenzyme Q10 (CoQ10) is a critical component of the electron transport chain of mitochondria. It also exhibits antioxidant properties <sup>83</sup>. Although serum levels of CoQ10 do not differ between sporadic ALS patients and healthy controls <sup>84</sup>, sporadic ALS patients do

display significantly higher levels of oxidized CoQ10<sup>42, 85</sup>. Oxidized CoQ10 can generate superoxide and hydrogen peroxide. Hydrogen peroxide can then react with iron-rich cytochromes to form hydroxyl free radicals<sup>33</sup>.

In an open-label dose escalation study, 31 ALS patients received Coenzyme Q10, formulated with 300 IU of vitamin E on a monthly dosage escalation scale (1200–3000 mg/day). CoQ10 was found to be safe and well-tolerated at the maximum dosage.

When compared to a placebo group from a previous clinical trial, no differences between CoQ10 and historical placebo groups were observed in strength, grip, forced vital capacity, or ALS functional rating scale scores<sup>86</sup>. These pilot data have yielded a follow-up randomized, double-blind, placebo-controlled multicenter trial now in progress<sup>87</sup>.

### **Alpha-lipoic Acid**

Alpha-lipoic acid is an antioxidant and also a cofactor for mitochondrial enzymes. In a study with G93A/SOD-1 mice, alpha-lipoic acid (0.05% in food) beginning at 4 weeks of age showed a significant delay in onset of impaired motor performance, increased survival, and attenuated weight loss in treated mice compared to controls<sup>88</sup>.

### **L-Carnitine**

L-carnitine is an essential cofactor for the beta-oxidation of long-chain fatty acids in mitochondria. It has also been shown to inhibit mitochondrial damage and apoptosis in vitro and in vivo. Early oral administration of L-carnitine significantly delayed symptom onset, prolonged motor function as assessed by rotarod, and extended survival in SOD-1 transgenic mice. In a second experiment 20 transgenic mice were injected with L-carnitine every two days after symptom onset. Survival of these mice was compared to that of 20 transgenic mice not receiving injections. Treatment with subcutaneous L-carnitine increased survival<sup>89</sup>.

### **Glutathione, N-Acetyl-cysteine, and Pro-cysteine**

Glutathione peroxidase activity has been shown to be lower in plasma and cerebrospinal fluid of ALS patients<sup>90</sup>. This observation has led to an open-crossover study, which failed to demonstrate any benefit in measures of manual muscle testing, Norris functional scale ratings, or forced vital capacity<sup>90</sup>.

Cysteine supplementation has been hypothesized to increase intracellular concentrations of glutathione, however, neither intravenous nor oral pro-cysteine had any effect on cerebrospinal concentrations of glutathione with 29 days of treatment<sup>91</sup>. Likewise, in a randomized, double-blind, placebo-controlled clinical trial of acetylcysteine in ALS patients, no significant differences were seen in survival and disease progression between the two groups<sup>92</sup>.

Studies of N-acetylcysteine (NAC) in transgenic mice models have produced conflicting results. In at least one study, transgenic mice given NAC (1%) in drinking water beginning 4–5 weeks of age, showed significantly improved survival and delayed symptom<sup>93</sup>. An earlier study with similar dose given after symptom onset showed no benefit<sup>94</sup>.

### **Herbs (and L-carnosine)**

In vitro experiments with ginseng suggest that it may act to decrease calcium flux into neurons. In the SOD-1 transgenic mice Panax quiquefolium ginseng (100mg, 200mg vs. control) was added to drinking water. Ginseng treated mice had significantly delayed symptom onset and prolonged survival<sup>95</sup>. Similar controlled trials have not been done in the patient population.

EGb761 is a standardized extract of *Ginkgo biloba* that has shown antioxidant properties in vitro. When tested in the same G93A/SOD-1 transgenic mice, EGb761 (0.022% or 0.045% via diet) significantly prolonged survival and decreased loss of motor neurons in the spinal cords of male transgenic mice but not females. This gender-specific protection, while provocative, is currently unexplained<sup>96</sup>.

### Functional Foods

Red wine is known to be rich in antioxidant compounds. Lyophilized red wine was dissolved in the drinking water of 8 transgenic mice. Supplemented mice were compared to a control group of 7 control transgenic mice not receiving treatment. The treatment group displayed significantly prolonged survival<sup>97</sup>.

Epigallocatechin gallate (EGCG) is a major catechin in green tea. It has been shown to display antioxidant, anti-inflammatory, and iron-chelating properties in vitro. 11 transgenic mice and 6 wild-type mice received EGCG by intraoral injection (10mg/kg). 11 transgenic mice serving as controls did not receive the injections. EGCG significantly delayed symptom onset and prolonged survival. The compound also significantly decreased markers of neuroinflammation and oxidative stress<sup>98</sup>.

In another study of transgenic mice receiving intraoral injections of one of three different dosages of EGCG or control vehicle, dosages of 2.9 and 5.8 mcg/g of EGCG also significantly delayed symptom onset and prolonged survival. Treatment was also associated with protective effects on markers of cell signaling associated with cell death and cell survival<sup>99</sup>.

### Summary

The benefit(s) of aggressive nutritional support in affecting disease course and survival are well documented. Enteral nutrition is best thought of as an early adjunctive therapy rather than a late palliative therapy. The patient population has embraced the use of dietary supplements in the form of vitamins, nutraceuticals and functional foods, often despite the absence of documented efficacy. The axiom that *the absence of proof does not equate to the proof of absence*<sup>100</sup> has fueled speculation among patients that these compounds should be tried even if the benefit is solely theoretical. Our role as practitioners is to provide oversight into potential adverse consequences from especially high doses or drug interactions. The concept of combining compounds or drugs is currently empiric although controlled trials are needed to address this logical treatment approach. The multifactorial pathophysiology of ALS has resulted in hypotheses that there may be subgroups of patients, eventually defined by a specific underlying etiology or clinical presentation, which selectively respond to a particular treatment. Future research endeavors exploring nutritional management and drug therapy will need to address this possibility.

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