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1 Overview

Summary and Quick Facts for Amyotrophic Lateral Sclerosis (ALS)

- Amyotrophic lateral sclerosis (ALS) is a degenerative neuromuscular disease, also called Lou Gehrig's disease after the famous baseball player who died from this condition. The average survival time after being diagnosed with ALS is three to five years.
- This protocol describes possible causes of ALS, diagnosis and conventional treatment, emerging medical therapies and nutritional interventions.
- Conventional medicine, which has fared poorly in the treatment of ALS, attempts to lessen symptoms by slowing disease progression. By adding scientifically studied natural interventions to conventional therapies, one may be able to target pathogenic mechanisms of ALS from multiple angles in hopes of slowing disease progression and improving quality of life.

What is Amyotrophic Lateral Sclerosis?

Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) is a degenerative neuromuscular disease. ALS destroys motor neurons, the nerves that control movement, resulting in loss of motor function and eventual paralysis. Respiratory failure due to nerve damage that affects the muscles that control breathing is the most common cause of death in ALS patients.

There are two main forms of ALS: sporadic and familial. While familial ALS is typically caused by hereditary genetic mutations, the cause of sporadic ALS (comprising 90% of all cases) is not completely understood. It is generally believed that sporadic ALS is caused by multiple factors that converge to damage motor neurons, including oxidative stress and glutamate toxicity, among others.

Natural interventions such as **vitamin B12** and **ginseng**, in addition to conventional therapies, may help slow

disease progression and improve quality of life by targeting multiple pathogenic mechanisms of ALS.

What are the Causes and Risk Factors for Amyotrophic Lateral Sclerosis?

- Genetic mutations
- Oxidative stress
- Glutamate (an important neurotransmitter) accumulation and toxicity
- While causal relationships have not been established, exposure to heavy metals, pesticides, and other environmental toxins has been linked with ALS development.

What are the Signs and Symptoms of Amyotrophic Lateral Sclerosis?

Note: Early symptoms vary depending on which muscles are affected first. Common symptoms can include:

- Tingling in fingers or toes
- Cramping in arms or legs
- Difficulty with tongue and facial movements, including chewing and swallowing

What are the Conventional Medical Treatments for Amyotrophic Lateral Sclerosis?

- Riluzole—blunts the effects of glutamate accumulation and can extend survival by a few months
- Edaravone—a free radical scavenger that can reduce oxidative stress
- Other treatments may help relieve symptoms and improve quality of life:
  - Non-invasive positive pressure ventilation
  - Medications to relieve painful muscle cramps
  - Medications to reduce excessive salivation
  - Physical, occupational, and speech therapy
  - Mobility aids

What are Emerging Therapies for Amyotrophic Lateral Sclerosis?

- Stem cell therapy
- Multiple proteins and mutations have been linked to ALS pathogenesis. Gene replacement therapy and pharmaceutical interventions are being explored as potential treatments.
- Insulin-like growth factor-1 (IGF-1) modulates neuronal growth and function, and injections may help slow disease progression, but results have been mixed.
- Many other treatments are being explored. More updated information can be found online at the **ALS Association** website.

What Nutritional Interventions May Be Beneficial for Amyotrophic Lateral Sclerosis?

- **Vitamin B12**. Vitamin B12 deficiency has been associated with nerve damage in animal models. High intramuscular doses in ALS patients have been shown to slow muscle wasting.
- **Zinc**. Mutations in the superoxide dismutase enzyme (which stabilizes superoxide radicals and is implicated in the pathology of certain kinds of ALS) can decrease its affinity for zinc and cause it to become toxic to motor neurons. Altering brain zinc levels is being explored in many nervous system diseases.
- **Ginseng**. Ginseng significantly delayed the onset of symptoms in an animal model of ALS. Ginseng may also protect motor neurons from apoptosis and membrane damage.
- **Ginkgo biloba**. Ginkgo biloba has antioxidant properties that have shown in experimental models to protect

against glutamate-induced excitotoxicity and neuronal death due to oxidative stress.

- **Coenzyme Q10 (CoQ10)**. Patients with ALS have a higher percentage of oxidized CoQ10. Administering CoQ10 in an animal model of ALS extended lifespan.
- **Acetyl-L-carnitine**. Acetyl-L-carnitine has been found to reduce neuromuscular degeneration and increase lifespan in animal models of ALS. Acetyl-L-carnitine also appears to enhance the growth and repair of neurons.
- **Lipoic acid**. Lipoic acid is an antioxidant shown to protect cells against glutamate-induced excitotoxicity. In one study, administering lipoic acid improved survival in a mouse model of ALS.
- **Whey protein**. Protein supplementation may help improve the nutritional and functional status of ALS patients. Preliminary data suggest whey protein may protect motor neurons from oxidative damage.
- **Creatine**. In several animal studies, creatine has been shown to provide protection against neurodegenerative diseases. Additionally, a small study found that creatine supplementation improved muscle strength in ALS patients.
- Other natural interventions that may be helpful for ALS patients are **glutathione** and **N-acetyl-cysteine (NAC)**, **green tea**, **pycnogenol**, and **resveratrol**.

2 Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease)

Amyotrophic lateral sclerosis (ALS) is a degenerative neuromuscular disease, also called Lou Gehrig's disease after the famous baseball player who died from this condition. ALS affects the nervous system and destroys motor neurons (nerve cells that help control movement) while sparing the abilities to see, hear, feel, touch and taste. ALS is characterized by progressive dysfunction resulting in symptoms such as tripping, clumsiness, difficulty talking, slurred speech, muscle cramps, twitching and ultimately, paralysis. The most common cause of death among ALS patients is respiratory failure, which occurs when nerve damage eventually affects the muscles that control breathing. The average survival time after being diagnosed with ALS is three to five years (ALSA 2012).

There are two main forms of ALS: sporadic and familial. The sporadic form comprises 90 percent of all ALS cases. However, many scientists study the familial forms in order to try to understand the mechanisms of the disease. While familial ALS is typically caused by mutations in different genes (including a gene known as SOD1), researchers still do not completely understand the pathogenesis of sporadic ALS. Scientists are pursuing a number of theories including oxidative stress, glutamate toxicity, and mitochondrial dysfunction (Rowland 1994; Cleveland 1999; Rothstein 2009). Other possible risk factors include viral infections (Woodall 2004) and environmental toxins (Mitchell 2000). The current consensus is that many factors may converge to cause the motor neuron damage typified by ALS (Rothstein 2009).

Conventional medicine, which has fared poorly in the treatment of ALS, attempts to lessen symptoms by slowing disease progression. There are only two disease-modifying drugs currently approved in the United States for ALS patients: riluzole and edaravone (Miller 2007; FDA 2017). By adding scientifically studied natural interventions to conventional therapies, one may be able to target pathogenic mechanisms of ALS from multiple angles in hopes of slowing disease progression and improving quality of life.

3 Possible Causes of ALS

Superoxide Dismutase

Because SOD1 gene mutations can cause familial ALS, many researchers have studied this protein to determine how it plays a role in the death of motor neurons. SOD1 is a gene that codes for superoxide dismutase (SOD), an enzyme which helps convert superoxide radicals into less harmful molecules. Superoxide molecules are a form of free radical or reactive oxygen species, a class of molecules that can damage the DNA, proteins, and membranes of cells causing them to die (Rothstein 2009). If SOD is either functioning poorly or is present in inadequate quantities, rampant oxidative stress driven by unabated superoxide molecules can damage tissue and contribute

to disease.

Approximately 20% of familial cases and 2% of all ALS cases are linked to SOD1 gene mutations (Sung 2002; Andersen 2006; Chiò 2008). This suggests that the accumulation of superoxide molecules and other free radicals could contribute to ALS. In addition to increasing superoxide levels, SOD1 mutations can damage neurons in other ways. For example, mutant SOD1 produces abnormal SOD molecules which are theorized to serve as the seed for large clusters of misfolded proteins that are toxic to neurons (Karch 2009; Lindberg 2002).

Oxidative stress

Studies have found elevated levels of oxidative stress within the central nervous system as well as peripherally in ALS (Miana-Mena 2011; Hensley 2006; Ilieva 2007; Kanekura 2009). This suggests that motor neuron death in ALS is related to increased levels of reactive oxygen species. These conditions contribute to the neuronal death and muscle wasting common in ALS. Oxidative stress can be relieved by increasing the concentration of antioxidants such as beta-carotene (Dawson 2000), vitamins C (Mandl 2009) and E (Colombo 2010), as well as the mineral selenium (Sanmartin 2011). Many other supplements, such as coenzyme Q10, also have antioxidant properties.

Glutamate Toxicity

Glutamate is an important neurotransmitter. Under normal conditions, its concentrations are tightly regulated. However, it appears the system regulating glutamate concentration in patients with ALS may be disturbed (Rothstein 1995b), resulting in an accumulation of glutamate in the space (synapse) between cells (Cameron 2002). This excess glutamate may excite nerve cells beyond their capacity resulting in nerve cell death. Patients with ALS have elevated levels of glutamate in their cerebrospinal fluid, support this hypothesis (Rothstein 1990, Shaw 1995). Mutant glutamate transport proteins are also associated with sporadic forms of ALS, further supporting the idea that elevated levels of glutamate-mediated excitation can kill motor neurons in ALS patients (Lin 1998; Rothstein 1995; Dunlop 2003). Some of the most powerful evidence supporting the critical role that glutamate plays in the pathology of ALS is the effectiveness of the medication riluzole, which inhibits glutamate's effects on the nervous system. It modulates the release of glutamate, thereby improving survival for ALS patients. Its effect however is modest, suggesting that excess glutamate is not the sole cause of the disease.

Mitochondrial Dysfunction

The mitochondria provide energy for all cells, including neurons. Unfortunately, mitochondria also produce reactive oxygen species as a byproduct of energy generation. Mitochondrial dysfunction can result in the production of excessive amounts of superoxide, causing extensive cell damage and death. Accumulation of superoxide is prevented by SOD and other enzymes (Brand 2011).

There are a number of ways in which the mitochondria in motor neurons may become impaired in ALS (Shi 2010). In animal models of ALS, dysfunction of mitochondria in motor neurons occurs before any other observable pathologic changes, suggesting this is an early event in the progression of the disease (Kong 1998). Mutant forms of SOD appear to lead to mitochondrial dysfunction (Liu 2004). Studies of both human and animal neurons have found extensive mitochondrial dysfunction associated with ALS (Cassarino 1999; Beal 2005; Martin 2011; Cozzolino 2011; Kawamata 2011; Faes 2011). In addition, some patients with ALS appear to have impaired mitochondrial function in their muscle fibers (Crugnola 2010).

Animal models of ALS show abnormal transport of mitochondria in their motor neurons which could further contribute to the progression of the disease (De Vos 2007). Additionally, because proper mitochondrial function is so essential, other yet unidentified processes could be altered when mitochondrial health is impaired (Fosslien 2001). Along these lines, an emerging theory linking excitotoxicity and mitochondrial dysfunction suggests that an accumulation of lactate, a metabolic byproduct which is toxic (especially to nerve cells) at high concentrations may play a role in ALS progression (Vadakkadath Meethal 2012). This theory (a.k.a. the *lactate dyscrasia* theory) proposes that mitochondrial dysfunction partly contributes to an accumulation of lactate in the junction of motor neurons and muscle cells (the neuromuscular junction (NMJ)) leading to death of both the nerve and muscle cells, thereby requiring the remaining muscle cells to work harder-than-normal to generate the force necessary for motor control. However, since lactate is a metabolic byproduct and greater metabolic demand increases lactate production, the remaining muscle cells produce even more lactate than usual due to their increased workload,

hastening the accumulation of lactate and exacerbating neuronal destruction and muscular atrophy. This theory also proposes that malfunction of an as yet undiscovered lactate shuttle within the NMJ may be a pathological feature of ALS, suggesting that supporting mitochondrial function may optimize lactate metabolism and combat the toxicity caused by accumulation of excess lactate. If this theory is correct, then combining drugs that inhibit lactate accumulation such as nizofenone (Matsumoto 1994) with nutrients that support mitochondrial function (like coenzyme Q10 and pyrroloquinoline quinone (PQQ) might be an effective therapy for ALS.

Heavy metals and environmental agents. The role of heavy metals in ALS is highly controversial. Since clusters of ALS patients have been found in certain geographical areas, researchers have searched for an underlying environmental theme such as heavy metal poisoning. For example, researchers have found that elevated levels of lead are associated with a higher risk of ALS (Fang 2010). Another toxin which has been identified as a potential mediator for ALS is mercury, though the link between mercury and ALS risk is not as clear (Callaghan 2011, Mano 1990). These toxins can lead to subtle cellular changes such as interfering with the methylation of DNA (Rooney 2011). Other studies however have failed to show a link between ALS and any of the common heavy metals (Gresham 1986).

Beta-N-methylamino-L-alanine (BMAA), a neurotoxin made by certain bacteria may play an important role in the development of ALS. BMAA may be implicated in the high incidence of ALS in Guam, where these bacteria are commonly found in the seeds of the *Cycas circinalis* plant (Banack 2010).

Exposure to pesticides may also increase the risk of developing ALS (Johnson 2009). Exposure to pesticides in the grass on the playing field is one theory put forth to explain the unusually high incidence of ALS in Italian soccer players (Chio 2009).

While there is good reason to think that neurotoxic agents like these may be somehow linked to degenerative brain and nerve conditions like ALS, researchers have been unable to meet the demanding scientific standard needed to establish a causal relationship (Caban-Holt 2005, Johnson 2009).

4 Diagnosis and Conventional Treatment of ALS

Like many neuromuscular diseases, it can be difficult to make an early diagnosis of ALS. Depending on which muscle group is affected first, its symptoms vary from person to person and can include:

- tingling in the fingers or toes
- cramping in the arms or legs
- trouble with tongue and facial movements, including chewing and swallowing.

As the disease progresses, it spreads through the affected limb until eventually all muscle groups become involved. This spread into all muscle groups is the defining characteristic of ALS. In fact, the term amyotrophy refers to the atrophy (wasting) of muscle tissue, while lateral sclerosis refers to the hardening of the spinal column from the buildup of scar tissue (Rowland 2001). The diagnosis of ALS is primarily a clinical one and requires the appearance of both upper (increased tone and reflexes) and lower (fasciculations and muscle atrophy) motor neuron involvement in many segments of the body. Electromyography, nerve conduction studies, and transcranial magnetic stimulation can all be used to support the diagnosis of amyotrophic lateral sclerosis.

Riluzole, an FDA approved drug for the treatment of ALS, blunts the effects of glutamate by decreasing its release and blocking the ability of glutamate to bind to its receptors, thereby decreasing the excitotoxicity that leads to cell death. Albeit small, its two to three month increase in survival time (Miller 2007) indicates that controlling glutamate levels in the brain could be an essential component in fighting ALS and provides valuable information toward ultimately finding a more effective treatment for the disease (Carlesi 2011).

Edaravone (Radicava) was approved by the FDA in 2017 to treat ALS patients (FDA 2017). Edaravone has free radical-scavenging abilities and may reduce oxidative stress, an important aspect of ALS pathogenesis. Edaravone was shown in two controlled clinical trials to slow functional deterioration in a certain subset of ALS patients. The first was a randomized trial of 206 subjects treated with intravenous infusions of either edaravone or placebo for 24 weeks (Abe 2014). While there was no significant difference in overall ALS functional rating scores

(ALSFRS-R) between the groups after treatment, post-hoc analysis revealed that subjects in earlier stages of the disease showed a greater treatment effect (Edaravone [MCI-186] ALS 16 Study Group 2017). In order to demonstrate the efficacy in this subgroup, a second trial including 137 subjects in early stages of ALS was conducted. The edaravone group experienced a 33% slower decline in function than the placebo group (Writing Group 2017). Edaravone is generally recommended in addition to riluzole as an adjuvant therapy.

Concerns have been raised regarding the safety and efficacy of edaravone treatment (Turnbull 2018). The majority of patients in the second study experienced treatment-related adverse events, likely due to the nature of drug delivery (ie, intravenous infusion). Edaravone has also only been shown to be effective in a small subset of patients with ALS.

The remainder of conventional medical treatment for ALS patients focuses on relieving symptoms and improving quality of life. For example, non-invasive positive pressure ventilation is often used to help patients with ALS breathe, especially at night (Mustfa 2006; Lo Coco 2006). Physicians frequently recommend prescription medications to relieve painful muscle cramps (e.g. carbamazepine and phenytoin) (Andersen 2005), excessive salivation (e.g. atropine, amitriptyline, hyoscamine, and injections of botulinum toxin into the salivary glands) (Giess 2000; Lipp 2003; Stone 2009), and other symptoms. ALS patients are often advised to engage in moderate exercise and seek physical therapy to maintain muscle strength and function. As the disease progresses, splints, braces, and wheelchairs are used to help with mobility. Also, higher toilet seats, headrests and specialized utensils may help improve the quality of life for ALS patients (Borasio 2001). Occupational and speech therapy help patients as their motor control gradually deteriorates.

5 Emerging Medical Therapies

Stem Cells

Stem cells, immature cells that can differentiate into specialized adult cells, may represent the next generation of ALS therapy.

However, due to federal restrictions on stem cell therapy as well as the difficulty of designing studies, very few trials have been conducted to date on the treatment of ALS with stem cells. Those that have been conducted, however, are encouraging and early trials show great promise. Researchers have found the following:

- Bone marrow derived “stem-cell transplantation in the motor cortex delays ALS progression and improves quality of life” (Martinez 2009).
- Direct injection of bone marrow derived stem cells into the frontal motor cortex (a brain region) of human ALS patients is generally safe and well tolerated (Martinez 2012).

Researchers have also experimented with the use of stem cells that express beneficial growth factors as a way of comprehensively treating ALS (Suzuki 2008; Lunn 2009). This therapy offers the potential to alter the course of ALS in afflicted patients.

TAR DNA-binding protein 43 (TDP-43) and FUS (fused in sarcoma)

Research has identified the cellular protein TDP-43 as an important factor in the cause of ALS, especially the sporadic forms (Mackenzie 2007). TDP-43 binds DNA and RNA in cells, including motor neurons. Aggregates of TDP-43 are found in the motor neurons of patients with ALS, suggesting that they may contribute to ALS pathogenesis. Identification of TDP-43’s involvement in ALS rapidly fueled a breakthrough discovery of an additional causative mutation in the gene encoding another RNA/DNA binding protein called FUS (fused in sarcoma) (Kwiatkowski 2009; Vance 2009). Because both of these proteins have been implicated in ALS, they may represent a novel pathway by which the motor neurons are damaged. This has also opened up the potential for gene therapy, allowing researchers to try to replace defective genes with functional ones, thus slowing or reversing the loss of motor neurons associated with ALS (Lagier-Tourenne 2009; Hester 2009). Researchers are also searching for ways to inhibit TDP-43 aggregation using chemicals such as methylene blue and latrepirdine (Yamashita 2009).

IGF-1 and Growth Hormone

Insulin-like Growth Factor-1 (IGF-1) is a potent modulator of neuronal growth and function. This neurotrophic factor has the ability to protect neurons both in the central and peripheral nervous system. Researchers have examined the possibility in cell and animal models that IGF-1 could be an effective therapeutic treatment for ALS (Sakowski 2009). Human studies, however, have produced mixed results. Whereas one study found some slowing of the progression of ALS in patients treated with IGF-1 injections (Nagano 2005), others found that subcutaneous (under the skin) injections are not effective in ALS patients (Sorenson 2008). However, the lack of effect with subcutaneous injections could be due to an inability to access the central nervous system. Intraspinal cord delivery has shown promise in animal models (Franz 2009). The use of retroviruses as a potential delivery method for administering IGF-1 to ALS patients has also shown promise (Lepore 2007).

Similarly, growth hormone (GH) may be related to ALS as one trial found that ALS patients had impaired GH secretion compared to healthy controls (Morselli 2006). However, the potential therapeutic value of GH replacement therapy needs further investigation as a recent clinical trial found no improvement in ALS patients receiving GH compared to placebo (Sacca 2012).

Other Treatments

- Arimoclomol is an investigational drug that improves the expression of “heat shock proteins”, thereby helping prevent the accumulation of misfolded proteins. Comprehensive in vivo and in vitro studies demonstrated its effect in the prevention of neuronal loss and promotion of motor neuron survival, even after the onset of symptoms. Clinical trials have reported good safety and tolerability (Phukan 2010).
- Ceftriaxone, a commonly used antibiotic, may also be able to treat ALS by improving reuptake of glutamate. When used in an animal model of ALS, ceftriaxone delayed loss of neurons and muscle strength, thus increasing survival (Rothstein 2005).
- Dexpramipexole is under development by Knopp Neurosciences and Biogen Idec as a potential neuroprotective therapy for ALS (Cheah 2010). While it has been shown to be safe and well tolerated (Bozik 2011), more research needs to be done to determine its efficacy.
- Another new medication which is currently being studied in clinical trials is TRO19622 (clinicaltrials.gov 2010). TRO19622 is a cholesterol-like molecule and displays remarkable neuroprotective properties both in vitro and in vivo. TRO19622 is expected to preserve existing neuronal function by delaying or even stopping further progression of the disease. TRO19622 has been granted orphan drug designation status for the treatment of ALS in the USA. This status allows the opportunity to seek ‘fast track’ review by the FDA (Trophos.com 2012).

6 Nutrients

Adequate nutrition is crucial for ALS patients. As the disease progresses, patients gradually lose the ability to chew or swallow with ease. At the same time, the abdominal and pelvic muscles weaken, oftentimes resulting in depression. Patients often lose the ability and desire to eat, making malnutrition a common problem. The recognition that aggressive nutritional intervention is paramount among ALS patients has spurred ardent research efforts aimed at elucidating the potential therapeutic value of dietary supplementation (Cameron 2002).

Vitamins and Minerals

Vitamin B12 (methylcobalamin). Whereas ultra-high (25mg daily for 4 weeks) intramuscular doses of methylcobalamin (a form of vitamin B12) have been shown to slow muscle wasting (Izumi 2007), low levels of vitamin B12 have been associated with nerve damage in many different animal models. One of the main problems associated with low levels of vitamin B12 is elevated levels of methylmalonic acid (MMA) which is toxic to neurons (Ganji 2012). Low levels of vitamin B12 are also associated with poorly functioning peripheral nerves which can be exacerbated by ALS (Leishear 2011). Vitamin B12 can also prevent damage to the opthalmic nerves by reducing MMA and homocysteine levels, both being associated with oxidative damage (Pott 2012). Low levels of vitamin B12 have also been associated with neuronal degeneration in other models (Moore 2012).

Zinc. Mutations to the copper/zinc superoxide dismutase gene are responsible for 2-3% of ALS cases. These mutations result in the SOD enzyme having a reduced affinity for zinc (Ermilova 2005). In fact, the loss of zinc

from SOD1 results in the remaining copper in SOD1 becoming extremely toxic to motor neurons (Trumbull 2009). Altering zinc levels within the brain is being studied as a method for treating many different nervous system diseases, including ALS (Grabrucker 2011). However, a study conducted at the Linus Pauling Institute found that large doses of zinc inhibit copper absorption, which can lead to anemia. In the study, researchers added a small dose of copper to animal ALS models receiving zinc and found that the copper prevented early death associated with high doses of zinc (Ermilova 2005). In summary, adding a small amount of copper to the subject's diets prevented this lethal anemia, suggesting that moderate amounts of zinc supplementation combined with small amounts of copper might help prevent neuron death in ALS.

Herbal Supplements

Ginseng. In an animal model of ALS, ginseng was shown to significantly delay the onset of ALS symptoms (Jiang 2000). An extract from the ginseng plant called ginsenoside has also been found to increase the expression of SOD1 (Kim 1996). Ginseng and its extracts may also be able to protect motor neurons from apoptosis and membrane damage, further helping to slow the progression of ALS (Radad 2011).

Ginkgo biloba. Ginkgo biloba has antioxidant properties (Ernst 2002). Additionally, it has been shown to promote healthy mitochondrial function (Fosslien 2001). During an in vitro study, it was found to protect against glutamate-induced excitotoxicity (Kobayashi 2000). Ginkgo biloba also reduced weight loss in a mouse model of ALS (Ferrante 2001). Ginkgo biloba extract has been shown to protect neurons from death due to oxidative stress (Shi 2009).

Additional Support

Coenzyme Q10 (CoQ10) acts as an antioxidant and is essential for proper mitochondrial function (Mancuso 2010). Human studies have found that ALS patients have a higher percentage of oxidized CoQ10 (ubiquinone), a condition the researchers blamed on oxidative stress caused by the disease (Sohmiya 2005). Supplementation with ubiquinol, the reduced (non-oxidized) form of CoQ10 may ameliorate this problem, though no studies have tested this hypothesis. Several animal studies, including the following have supported the benefit of CoQ10 treatment in ALS:

- In an animal model of familial ALS, administration of coenzyme Q10 significantly extended life span and oral administration significantly increased CoQ10 concentrations in the brains and mitochondria of the test animals (Matthews 1998).

As a result of these promising studies in mice, researchers have been testing the benefits of CoQ10 on humans with ALS. One phase II study did not find any substantial benefit of CoQ10 supplementation in patients with ALS (Kauffman 2009). However, more research still needs to be done as CoQ10 plays an important role in mitochondrial function and controlling oxidative stress - two key components of ALS. In addition, it has been noted that high doses of CoQ10 are generally safe (Ferrante 2005).

Acetyl-L-carnitine has been shown to improve mitochondrial function (Carta 1993; Virmani 2002; Jin 2008). Acetyl-L-carnitine appears to increase the growth and repair of neurons (Wilson 2010; Kokkalis 2009) while protecting neurons from high levels of glutamate when combined with lipoic acid (Babu 2009). Acetyl-L-carnitine also protects neuron cell cultures from excitotoxicity, one of the putative mechanisms of disease in ALS (Bigini 2002). Acetyl-L-carnitine has also been found to reduce neuromuscular degeneration and increase life span in animal models of ALS (Kira 2006). In one animal study, the effects of acetyl-L-carnitine were increased when administered in conjunction with lipoic acid (Hagen 2002).

Lipoic acid. Lipoic acid has been shown to have antioxidant properties as well as increase intracellular levels of glutathione (Suh 2004a; Yamada 2011). It also chelates metals both in the test tube and in animal models (Suh 2004b and 2005). As a result, lipoic acid supplementation might protect neurons from some of the changes that lead to ALS (Liu 2008). Furthermore, lipoic acid has been shown to protect cells against glutamate-induced excitotoxicity (Muller 1995). In one study, administration of lipoic acid improved survival in a mouse model of ALS (Andreassen 2001b).

Protein and Amino acids. Adequate protein intake is essential for patients with amyotrophic lateral sclerosis. Protein supplementation may help improve the nutritional status of ALS patients, thereby slowing the progression

of the disease. A 2010 study found that patients with ALS taking whey protein supplements had improved nutritional and functional parameters as compared to the control group (Carvalho-Silva 2010). Some preliminary data suggests that whey protein may also directly protect motor neurons from oxidative stress, thus delaying the progression of ALS (Ross 2011). A Portuguese study suggested that dietary supplementation with amino acids may have some beneficial effects on the course of the disease (Palma 2005).

Creatine. In cells, creatine aids in the formation of adenosine triphosphate (ATP), the primary source of cellular energy. In multiple animal studies, creatine has been shown to provide protection against neurodegenerative diseases. For example, it has been suggested that creatine helps to stabilize cellular membranes (Persky 2001). Creatine may also lessen the burden of the excitotoxin glutamate in the brain, thus improving survival time in animals with ALS (Andreassen 2001a). In human ALS patients, there is evidence to suggest that creatine may improve mitochondrial function (Vielhaber 2001). In addition, a small preliminary study found that creatine supplementation improves muscle strength in ALS patients (Mazzini 2001). More recent research has confirmed that creatine can protect neurons from toxic processes such as those that drive the progression of ALS. Creatine, due to its antioxidant and anti-excitotoxic properties, has been found to have a significant therapeutic effect in mouse models of ALS (Klopstock 2011; Beal 2011). However, human studies have yielded mixed results (Pastula 2010) which may be due to insufficient sample size (Klopstock 2011). Creatine can cross the blood-brain barrier and gain access to the brain, a treatment which lowered levels of glutamate in the cerebrospinal fluid which may help to protect the brain (Atassi 2010).

Glutathione and N-acetyl-cysteine (NAC). Glutathione is an antioxidant which is naturally synthesized by the body. Increasing glutathione levels could help prevent free radical damage to cells (Exner 2000). The glutathione precursor N-acetyl-cysteine (NAC) boosts blood levels of glutathione (Carmeli 2012). Patients with ALS tend to have higher levels of oxidized glutathione (glutathione that has already been used to protect the body from free radicals) (Baillet 2010). Increased levels of glutathione can also protect neurons from degeneration in models of ALS (Vargas 2008). Interestingly, cell culture models have shown that ALS is associated with reduced glutathione levels due to mitochondrial dysfunction, and that reduced glutathione levels can result in elevated levels of glutamate (D'Alessandro 2011). Along with being a glutathione precursor, NAC has antioxidant activity of its own. In animal models of ALS, NAC administration has been shown to decrease motor neuron loss, improve muscle mass, and increase survival time and motor performance (Andreassen 2000; Henderson 1996). In addition, NAC supplementation can help thin mucous secretions in the oral cavity which may make swallowing easier (Kuhnlein 2008).

Green tea. Green tea contains high concentrations of catechins, flavonoids with strong antioxidant properties (Hu 2002). Green tea extract has been demonstrated to have anti-inflammatory properties as well (Hong 2000). One of these catechins known as epigallocatechin-3-gallate (EGCG) is of particular interest in the context of ALS. EGCG and other catechins may be able to protect neurons from a variety of diseases (Mandel 2008). EGCG has been found to protect cultures of motor neurons from death due to excessive levels of glutamate (Yu 2010). Motor neurons can also be protected from mitochondrial dysfunction with the addition of EGCG in culture (Schroeder 2009). EGCG can also bind to and inactivate iron, which may help protect motor neurons from the effects of ALS (Benkler 2010). Epidemiological data further supports the following role of tea in its potential protection of neurons: green tea consumption reduces the risk of neurodegenerative diseases (Mandel 2011) and people who drink tea may have a lower risk of developing ALS (Morozova 2008).

Pycnogenol® is an extract of marine pine bark that includes procyanidins and phenolic acids (Packer 1999). It has been shown to have antioxidant properties (Packer 1999) as well as protective effects against glutamate excitotoxicity (Kobayashi 2000). Pycnogenol® is a common complementary therapy option among ALS patients (Cameron 2002). In addition, pycnogenol® increased the levels of SOD produced in an animal study (Kolacek 2010).

Resveratrol is a powerful antioxidant found in red grape skins and Japanese knotweed (*Polygonum cuspidatum*). Resveratrol has been found to suppress the influx of excitatory ions into some cell types which is associated with reduced glutamate-induced cell toxicity (Wu 2003). Another way resveratrol may target neurodegenerative diseases is by reducing oxidative stress (Sun 2010). Resveratrol administration has been shown to help protect ALS model motor neurons in cell culture (Kim 2007; Wang 2011). In addition, resveratrol can increase the activity

of SOD in cells and protect them from apoptosis and oxidative stress (Yoon 2011). Adding the cerebrospinal fluid from ALS patients to rat motor neuron cell cultures causes the cultured cells to die. One of the intriguing aspects of resveratrol is that it can protect the motor neuron cell cultures from death, which is something that riluzole, the only FDA approved drug for ALS, cannot do (Yanez 2011).

Update History

Disclaimer and Safety Information

References

†Ratings based on results of the 2025 ConsumerLab.com Survey of Supplement Users. Multivitamin rating based on results of the 2024 ConsumerLab.com Survey of Supplement Users. For more information, visit **www.consumerlab.com/survey**.