Deanna Protocol Program for ALS:

Substantiation and Putative Mechanisms

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Executive Summary

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects upper and lower motor neurons. Upper motor neuron disease causes slowness, hyperreflexia, and spasticity while lower motor neuron disease causes weakness, muscle atrophy, and fasciculations. Four out of five people with ALS will present with asymmetric limb weakness, while the remaining 20% will first exhibit dysarthria/dysphagia. ALS may negatively affect cognition in up to 50% of patients, though this is usually mild. Autonomic symptoms of ALS include constipation, excessive sweating, and urinary urgency without incontinence. The disease usually becomes life-threatening when respiratory muscles/motor units are involved. In most cases, death occurs within two to five years of diagnosis.

The exact etiology of ALS is unknown; however, a number of abnormalities have been discovered. Alterations in RNA and protein processing likely play a major role in the pathogenesis of ALS. Genetic studies of families with ALS have revealed a number of mutations in genes coding for RNA binding proteins. Moreover, abnormalities in the superoxide dismutase-1 enzyme likely contribute to ALS neuropathology. There are also inflammatory and excitotoxic components of the disease. Primary dorsal motor neuron cultures and transgenic mouse models of ALS have been extensively used to uncover these pathophysiological mechanisms and test prospective treatments.

While many medications have been clinically tested, few have been successful in treating ALS. In fact, the only prescription medication that improves survival in patients with ALS is riluzole—and this effect is modest. The median increased survival time in patients taking riluzole is about two to three months. Riluzole is believed to reduce glutamate-induced excitotoxicity by inhibiting glutamate release from excitatory neurons, noncompetitively blocking NMDA receptors, and directly acting on voltage-dependent sodium channels. However, the precise mechanism by which riluzole extends survival in ALS is unknown.

The Deanna Protocol is a combination of nutritional supplements that are available over-the-counter that have been organized into a daily treatment regimen. The original Deanna Protocol was developed by an

orthopedic surgeon, Dr. Vincent Tedone, who formulated the regimen for his daughter, Deanna, and is now administered by the non-profit organization Winning the Fight. The current document describes the components of the Deanna Protocol and additional supplements that complement the Deanna Protocol, collectively called the Deanna Protocol Program for ALS. Many of the ingredients in the Deanna Protocol and the dosing scheme have been streamlined for ease of use. This document describes the theoretical foundations of the Deanna Protocol Program for ALS and provides possible mechanisms by which each of the ingredients could beneficially affect patients with ALS. Importantly, the statements contained in this document have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.

Deanna Protocol Program for ALS: Substantiation and Putative Mechanisms

Amyotrophic Lateral Sclerosis

Clinical Features

Amyotrophic Lateral Sclerosis (ALS) is the most common motor neuron disease in adults. The most notable feature of the disease is that it afflicts motor neurons specifically. When upper motor neurons (i.e., neurons traveling from the cortex in the brain to the spinal cord) are affected, it results in spasticity, exaggerated reflexes, and reduced coordination. Conversely, the death and dysfunction of lower motor neurons (i.e., neurons traveling from the spinal cord to muscles) causes muscle cramps, atrophy, fasciculations, and generalized weakness (Fig. 1).

ALS is a progressive, neurodegenerative disease. The disease progresses rapidly—most people will die within two to five years of symptom onset—though there are notable exceptions to this, such as Stephen Hawking. The risk of developing ALS increases with each decade of life, peaking at age 74.[1] Approximately 5 to 10 percent of people who develop ALS will have a familial form of the disease, while the rest have sporadic ALS.[2] Several mutations are present in familial ALS and, in some cases, sporadic ALS.

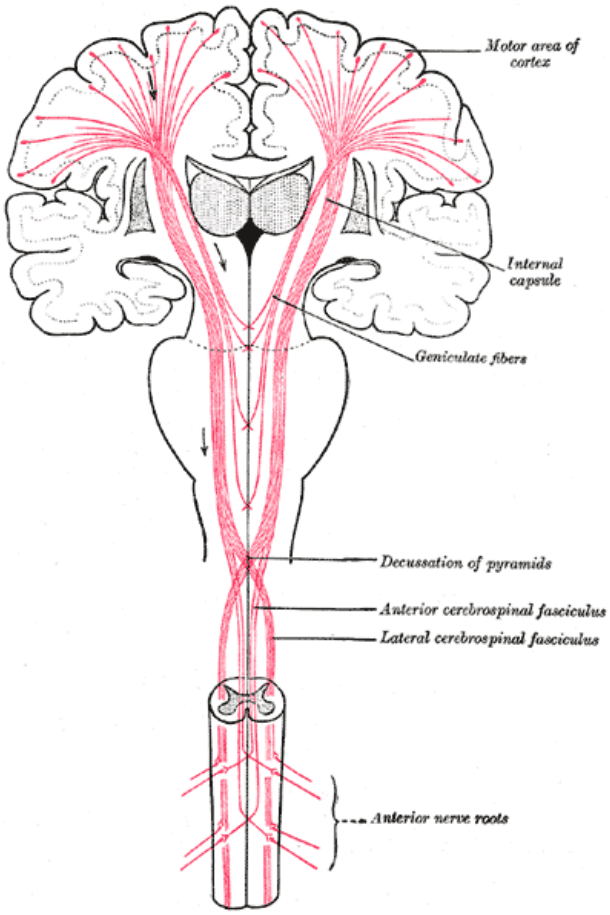

Figure 1. Upper motor neurons extend from the motor cortex in the brain. Lower motor neurons originate in the spinal cord. Adapted from Gray's Anatomy of the Human Body.

Putative genetic associations to ALS include mutations of SOD1, TARDBP, ANG, FUS, C9ORF72, OPTN, and SETX genes.[3] ATXN2 mutations are present in a small portion of patients with sporadic ALS.[3] Duplication of the survival motor neuron 1 (SMN1) gene may be a risk factor for sporadic ALS in adults.[4]

Age and family history are the only confirmed risk factors for ALS, though dozens of others have been explored. Other (unconfirmed) potential risk factors for ALS are environmental exposures (e.g., heavy metal, vaporized plastics) or occupational interactions (e.g., military service, agricultural work, welders).

Pathophysiology

The main pathological feature of ALS is motor neuron degeneration and death. As the nerve cells die, glia increase in number and replace lost neurons. Affected areas of the cortex and spinal cord undergo atrophy, especially the frontal cortex and ventral roots of the spinal cord. Why or how these cells specifically die is unknown; however, several pathological features of the disease suggest possible causative mechanisms.

Inclusions

Most neurons that eventually die in the cortex are large (pyramidal) neurons. These dysfunctional and dying neurons commonly develop intracellular inclusions. These inclusions include Bunina bodies[5], neurofilamentous inclusions, and aggregates of an RNA-binding protein called TDP-43 (Fig. 2). While it is unclear whether these inclusions are simply a byproduct of the disease or a primary toxic substance, their presence is common in various neurodegenerative diseases, including ALS. There are potential mechanisms by which these aggregates are neurotoxic. For example, the presence of abnormal levels of TDP-43 suggests that abnormal RNA processing plays a role in the pathophysiology of ALS.

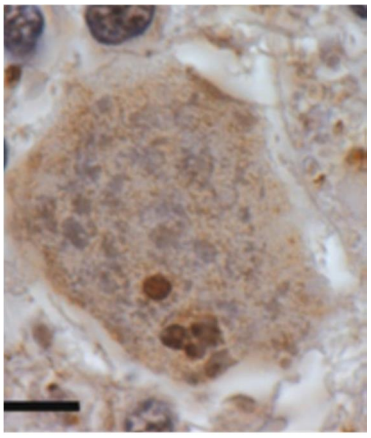

Figure 2. Bunina bodies appear as dark circles within the affected cell. Adapted from Momeni P et al.[5]

Superoxide Dismutase Type 1 Abnormalities

Superoxide Dismutase Type 1 or SOD1 mutations are common in people with familial ALS and occur infrequently among those with sporadic ALS.[6] Abnormal SOD1 proteins could be toxic to nerve cells for a variety of reasons. Since SOD1 knockout mice do not exhibit motor neuron disease, it is more likely that ALS patients acquire a pro-oxidant, gain-of-function SOD1 mutation, which leads to a harmful production of reactive oxygen species.[7] Mutant SOD1 may also lead to abnormal protein folding and subsequent protein

aggregation within neuronal cell bodies. While this is more frequently a feature of late-stage disease, even small accumulations of SOD1 aggregates can be neurotoxic.[8]

Inflammation

Inflammation may also play a role in ALS disease progression.[9,10,11] Non-neuronal cells such as astrocytes and microglia are activated in the disease. Through cytokine release and other cellular attractants, these cells recruit immune cells such as natural killer cells and monocytes to cross the blood-brain barrier. Moreover, activated microglia release a number of substances that are toxic to neurons including nitric oxide, oxygen radicals and glutamate.[7,12,13]

Excitotoxicity and Mitochondrial Dysfunction

Excitotoxicity is the well-characterized process of neuron death that follows excessive stimulation by excitatory neurotransmitter ligands. Excessive stimulation of neurons causes abnormally high levels of calcium to enter the cell body. Excessive intracellular calcium initiates a cascade of events that kills the cell. Specifically, high levels of intracellular calcium lead to peroxidation of membrane lipids, damage to RNA and DNA, and disruption of mitochondria. One effect on mitochondria is that pores in the mitochondrial membrane (mitochondrial transition pore) open and release reactive oxygen species into the cytoplasm. This is one trigger apoptosis (programmed cell death).

Several lines of evidence suggest that excitotoxicity plays a role in the pathophysiology of ALS. Glutamate levels are abnormally high in patients with sporadic ALS[14] perhaps due to deficiencies in glutamate reuptake transporters.[15] Abnormal glutamate receptors on nerve cell membranes may also contribute to excessive excitatory stimulation. In addition, trials with riluzole lend clinical support for an excitotoxic mechanism in ALS. Riluzole is the only prescription medication shown to improve survival in patients with ALS.[16,17,18] While the precise therapeutic mechanism of action in ALS is not known, riluzole inhibits glutamate release, inactivates voltage-dependent sodium channels, slows potassium channel inactivation, and inhibits protein kinase C[19,20,21,22]—all of which contribute to excitotoxic cell death.

Mitochondria may be affected by the disease before and apart from excitotoxicity, however. Cells collected from patients with ALS exhibit impaired mitochondrial function, specifically in mitochondrial complex I.[23,24] This deficit can be counteracted by the addition of ketone bodies, which are used by complex II.[25] In other words, ALS impairs complex I function, but ketone bodies seem to act as a "fuel" source in the mitochondrial membrane at complex II and later.

The only prescription drug approved for the treatment of ALS is riluzole (Fig. 3). Riluzole is generally administered twice a day at a dose of 50 mg. The most common side effects are gastrointestinal problems and elevated liver enzymes. Rarely, neutropenia may occur. While riluzole is the only medication that can prolong survival in people with ALS, the median additional time of survival is only between two to three months (Fig. 4).[16]

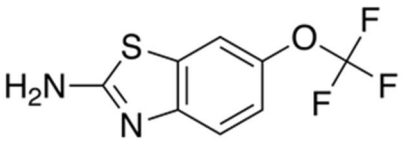

Figure 3. The chemical structure of riluzole.

While various other treatments have shown promise in laboratory and animal studies, clinical trials have been disappointing. Celecoxib (Cox-2 inhibitor), gabapentin (GABA analog), lamotrigine (antieplileptic, mood stabilizer), lithium (mood stabilizer), topiramate and valproic acid (antieplileptics), verapamil (calcium channel blocker), and minocycline (antibiotic with neurological effects) have failed to meet clinical endpoints in ALS trials.

Future research is focused on several avenues, but definitive results are several years off, if they are fruitful at all. One promising approach is the use of antisense oligonucleotide therapy for familial ALS with SOD-1 mutations. If this approach is successful, it will only be useful for a fraction of patients with ALS. Trials are underway with memantine, a drug that presumptively blocks glutamatergic neurotransmission through NMDA-type glutamate receptors. Phase II trials of creatine are currently underway. The use of stem cells and gene therapy remains promising, but these technologies will require considerable laboratory research before any agents can be trialed.

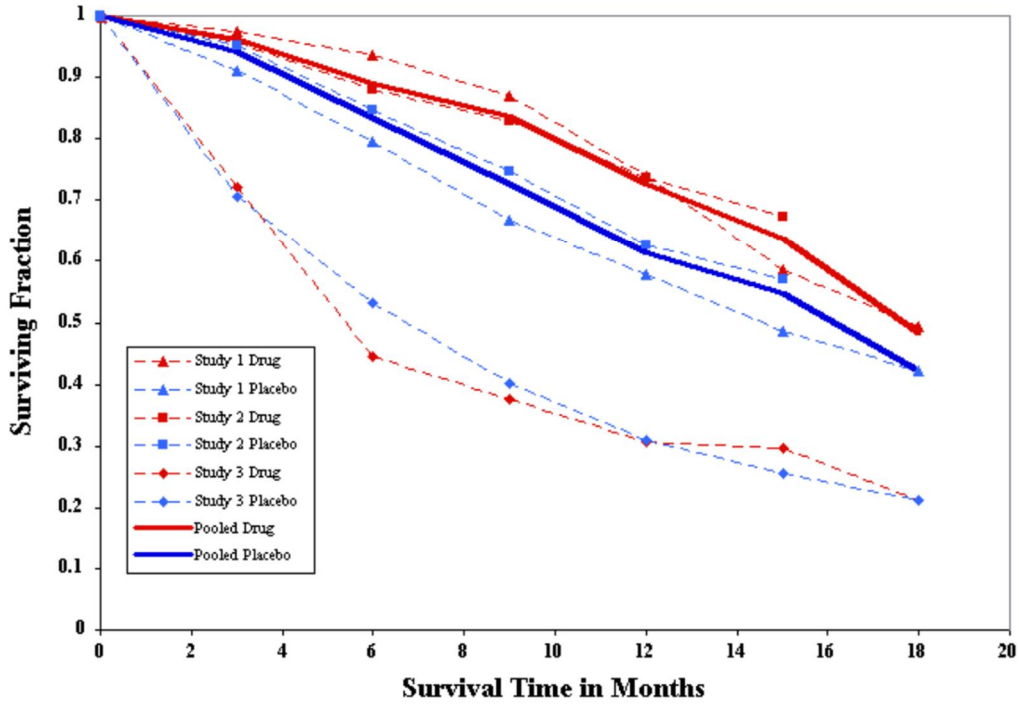

Figure 4. Effect of riluzole on survival in ALS. Adapted from Miller et al.[16]

The Deanna Protocol Program for ALS

The original Deanna Protocol was developed by an orthopedic surgeon, Dr. Vincent Tedone, who wanted to formulate a treatment regimen for his daughter, Deanna, when she was diagnosed with ALS. Dr. Tedone had anecdotally reported that his daughter had good experience with various versions of the protocol. The current Deanna Protocol Program for ALS includes supplements that have been proven in the laboratory to be effective in ALS and slow the progression of the disease. These substances, known as the DP™ Plan Essentials, include AAKG, AKG, GABA, Ubiquinol (CoQ10), Niacin (non-flush) and 5-HTP (5-hydroxtrytophane). The Deanna Protocol Program for ALS also includes ancillary substances which go beyond the Deanna Protocol® DP™ Plan Essentials in offering potential benefits to ALS patients. They are not included in the DP™ Plan Essentials because they have not been proven in a lab to be effective in ALS patients.

The Deanna Protocol DP™ Plan Essentials

The Deanna Protocol® DP™ Plan Essentials consists of the necessary supplements to follow the Deanna Protocol. These include AAKG, AKG, GABA, Ubiquinol (CoQ10), Niacin (non-flush) and 5-HTP (5-hydroxtrytophane). Simplesa AAKG+ Core Powder contains the full recommended daily dosages of GABA, Ubiquinol and Niacin and the minimum recommended daily dose of AAKG. Higher dosages of AAKG can be obtained with AAKG Powder, used to increase the AAKG level above the minimum daily recommended dosage of 9 grams to a maximum daily dosage of 18 grams. 5-HTP is taken every evening, and AKG is taken every hour between three daily doses of the Core Powder.

The Winning the Fight Program for ALS

The Winning the Fight Program for ALS, also known as the Deanna Protocol Comprehensive Approach, consists of ancillary supplements that have been found to be effective in Deanna, but have not been proven in a lab to be effective in ALS patients, and additional ingredients which the National Institutes of Health (NIH) claims maintain the health of the nervous system and muscles. Many of these ancillary substances can be supplied by a healthy diet. However, individuals with ALS may need more of them than healthy individuals, which is why taking the ancillary substances makes sense for those who can afford to cover the cost. The NIH has published a manuscript "Nutrition and Supplements in Motor Neuron Diseases" which emphasizes the importance of nutrition to support quality of life for ALS patients.

While adherence with the Deanna Protocol Comprehensive Approach may still be challenging for some patients, the current protocol and product offerings streamline treatment as much as possible while taking into account the pharmacokinetics of the supplements.

One of the chief features of the Deanna Protocol Comprehensive Approach is that it is all-inclusive. In other words, the Deanna Protocol Comprehensive Approach has been formulated to include a multitude of agents that could potentially work to improve ALS symptoms, improve functioning, or slow progression of the disease. It is unlikely that any one agent included in this protocol will exert a clinically meaningful effect on the disease. Indeed, the only approved drug for ALS that lengthens survival is riluzole, which only provides a median of 2-3 months of additional life. Thus, the approach of the Deanna Protocol® DP™ Plan Essentials and the Deanna Protocol Comprehensive Approach is to include several agents, all of which are generally considered safe at the doses provided. In this way, the risk of omitting a potentially useful ingredient or under-dosing one of the ingredients in minimized.

Just as no single, known agent is likely to significantly alter the course of ALS, it is possible that some of the ingredients of the Deanna Protocol Comprehensive Approach may not add additional benefit. However, when attempts have been made to alter the Deanna Protocol and eliminate some components, anecdotal evidence suggests that the efficacy has been reduced. In other words, when ingredients are removed, patients report less beneficial effect. Consequently, the Deanna Protocol Comprehensive Approach has been developed to be more inclusive but to increase the ease of consumption and to augment the dosages of certain ingredients.

AM Liquid Blend - Once every morning	PM Liquid Blend - Once every evening	Base Powder - Three times a day
•Creatine •Phosphatidylcholine •Glycine •l-Taurine •l-Carnitine •Thiamine (Vitamin B1) •l-Glutathione •Phosphatidylserine •N-Acetylcysteine •alpha-Lipoic Acid •Methylcobalamin (Vitamin B12) •Methyl Folic Acid •Cholecalciferol (Vitamin D3) •Riboflavin (Vitamin B2) •Pyridoxine (Vitamin B6) •Biotin (Vitamin B7)	•Phosphatidylcholine •N-Acetylcysteine •Glycine •l-Taurine •Propolis Extract •Magnesium Lactate •l-Theanine •Methyl Folic Acid •Ginko Biloba	•Arginine alpha keto-glutarate •Ubiquinol (CoQ10) •GABA •Niacin (Non Flush)

Liposomal Glutathione - Once daily	5-Hydroxytryptophan - Once daily with PM Blend	Caprylic Acid – Take to tolerance

Alpha-ketoglutarate – Once per each waking hour

Synergistic Effects: The Sum is Greater Than any Component

Virtually all clinical trials and laboratory studies in ALS have tested single ingredients. Some of the more ambitious trials have tested two or three ingredients simultaneously. This is unfortunate because the greatest potential therapeutic benefit of the Deanna Protocol® DP™ Plan Essentials and the Deanna Protocol Comprehensive Approach is the additive or synergistic effect of the ingredients taken together.

One potential synergism is that of N-acetylcysteine and glutathione. Glutathione is critically important for detoxification. Molecules that must be removed from the body are conjugated with glutathione to facilitate excretion. Since each molecule destined for elimination requires at least one molecule of glutathione, the detoxification process is limited by the amount of glutathione in cells. One obvious and effective solution is to supplement with glutathione. While glutathione supplementation can provide increased metabolic capacity, there are inherent limitations (e.g. there is a maximal amount of glutathione that can enter cells). N-Acetylcysteine, however, can rapidly and profoundly replenish glutathione reserves in cells. Thus, N-acetylcysteine supplementation can work in conjunction with glutathione to maintain a constant pool of glutathione.

Another potential synergism comes from CoQ10 and alpha-ketoglutarate. CoQ10 performs a key role in the electron transport chain in mitochondria, serving as an electron carrier. Alpha-ketoglutarate, on the other hand, is a key substrate in the Kreb's/citric acid cycle. It generates the energy required to maintain the proton gradient across the inner mitochondrial membrane, through NAD^+/NADH). Thus, alpha-ketoglutarate supports the action of CoQ10 and energy creation in the electron transport chain requires CoQ10 (Fig. 5). Inadequate amounts of either substance or an overabundance of either substance renders cellular energy production less efficient. Therefore, the Deanna Protocol® DP™ Plan Essentials and the Deanna Protocol Comprehensive Approach includes both ingredients.

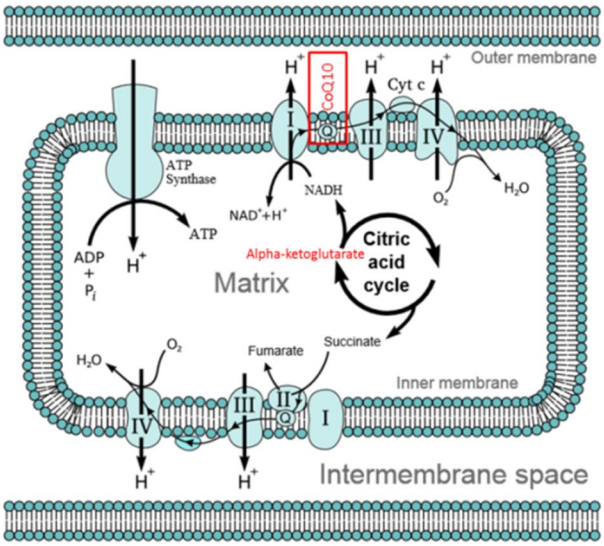

Figure 5. Complimentary actions of alpha-ketoglutarate and CoQ10 in mitochondria.

Another combination is folic acid and Vitamin B12. These vitamins both participate in the conversion of homocysteine to methionine. They are commonly replenished at the same time, mainly because replacing one can mask deficiencies in the other. For example, folic acid supplementation can partially reverse some of the

hematologic abnormalities of Vitamin B12 deficiency, but neurologic abnormalities will continue to progress. Thus, both molecules are required in adequate amounts for proper neurologic function.

GABA, glutamate, and alpha-ketoglutarate are quite similar structurally, yet they have profoundly different functions in the central nervous system. New research is demonstrating that the main driver of neuronal dysfunction and destruction in ALS is related to a disinhibition rather than excitotoxicity. While excitotoxicity may play a role in later stages, new evidence suggests that removal of key controls on excitatory neurotransmission (namely GABA and glycine) cause many of the symptoms seen in ALS (e.g., fasciculations). The Deanna Deanna Protocol Comprehensive Approach supplements both GABA and glycine to improve inhibitory synaptic function. On the other hand, glutamate (and aspartate) levels are abnormally high in brain and spinal cord tissue in ALS.[26] Likewise, there is an increase in the glutamate/glutamine ratio. These increases in glutamate occur at the expense of GABA and alpha-ketoglutarate (Fig. 6).

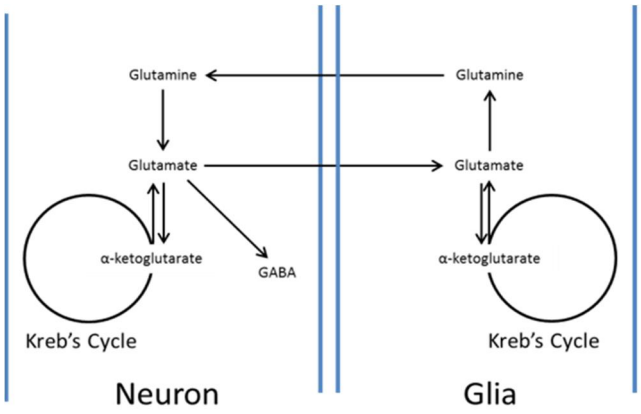

Figure 6. The relationship of glutamate, glutamine, GABA, and alpha-ketoglutarate in neurons and glia

The Deanna Protocol in a Mouse Model of ALS

While most ingredients have been tested individually or in small groups, parts of the current Deanna Protocol Program for ALS have been tested in a mouse model of ALS. SOD1G93A mice exhibit all of the pathological characteristics of ALS and die prematurely. Researchers from University of South Florida's Morsani College of Medicine tested these mice under various conditions. They compared four groups in total; two of the four groups were fed a standard diet and the other two groups received a ketogenic diet. A ketogenic diet is a low-carbohydrate diet that increases ketone bodies in the blood. Those ketone bodies are used as cellular fuel in place of glucose. Two groups (one fed a standard diet and one fed a ketogenic diet) were also given supplemented with Deanna Protocol ingredients. Mice fed the standard

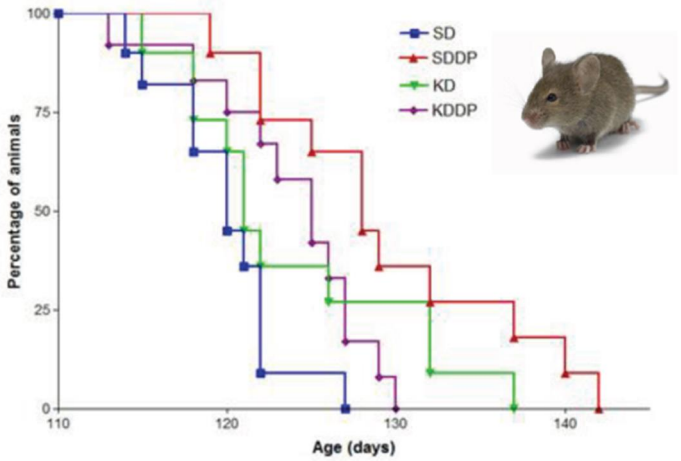

Figure 7. Effect of diet and supplementation on transgenic SOD1G93A mice. SD – Standard Diet; KD – Ketogenic Diet; DP – Deanna Protocol

diet and the Deanna Protocol lived significantly longer than mice in the other groups (Fig. 7).

While formal clinical trials using the Deanna Protocol have not been performed, there are numerous anecdotal reports that the Deanna Protocol decreased fasciculations, spasms, tremors, salivary secretions, speech impediments and weakness along with improved respiratory symptoms, swallowing capacity, and balance.

Creatine

Creatine is a molecule that is formed endogenously by several organs including the kidneys and liver. It is synthesized from the amino acids arginine and glycine with the addition of a methyl group from methionine (Fig. 8). The molecule is actively taken up into brain, muscle, and heart tissue through transporter proteins. Creatine is critical for normal neurological functioning. Most notably, people who lack the enzymes to create creatine have several neurological problems including developmental delay, extrapyramidal movement disorders, and seizures, which can be partially or fully ameliorated with creatine supplementation.

Creatine supplementation may be helpful in the treatment of ALS for several reasons.[27] Increasing creatine levels during periods of muscle relaxation increases the reserve of phosphocreatine and helps protect muscles against fatigue.[28] Creatine also enhances anaerobic metabolism and may increase lean muscle mass.[27] Thus, creatine may be of functional/symptomatic benefit in ALS.

However, the cellular energy benefits of creatine may be outweighed by the molecule's potential role in neuroprotection. The energy buffering ability of creatine and its ability to stabilize mitochondrial membranes may partially counteract the mitochondrial dysfunction seen in ALS.[27] For example, creatine/phosphocreatine blocks the opening of the mitochondrial permeability transition pore, interrupting apoptosis-signaling pathways.[29] Likewise, creatine has direct and indirect antioxidant activity, which could dampen damage caused by reactive oxygen species. Creatine may help protect against excitotoxic cell death in two separate ways. The supplement can enhance glutamate uptake into synaptic vesicles without ATP[30], which may help remove glutamate from the synaptic cleft without requiring additional cellular energy. In addition, creatine helps normalize aberrant intracellular calcium systems by increasing the uptake of calcium into the sarcoplasmic reticulum.

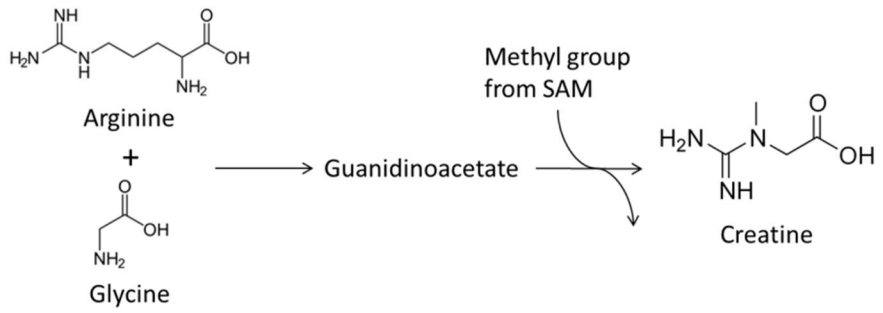

Figure 8. The synthesis of creatinine from arginine, glycine, and methionine.

Animal studies with creatine have been promising. For example, creatine supplementation in the G93A mouse model of ALS delayed the onset of motor deficits and weight loss.[31] Likewise, creatine attenuated pharmacologically induced increases in cortical glutamate. Early Phase I studies of creatine showed that the supplement is safe at large doses, crosses the blood-brain barrier, and decreases glutamate concentrations in the brain in patients with ALS.[32] Later studies have shown minimal to modest benefit in ALS patients.[33,34,35]

Phosphatidylcholine and Phosphatidylserine

Phosphatidylcholine and phosphatidylserine are phospholipids, which are critical components of cell and mitochondrial membranes. Nerve cell membranes are particularly "active" since neurotransmission involves the nearly constant fusion and recapture of synaptic vesicles. In ALS and other neurodegenerative diseases (e.g., Alzheimer's disease), excitotoxic mechanisms are believed to play a role in pathogenesis. Excessive stimulation of the NMDA glutamate receptor, for example, is the standard model for excitotoxicity and for studying neurodegenerative disease. When NMDA receptors are excessively stimulated, *de novo* phospholipid synthesis is inhibited.[36] More importantly, this decreased synthesis is independent from membrane breakdown. This is true of AMPA and NMDA stimulation, but not kainite receptor–mediated excitotoxicity.[37] Thus, the membrane degradation that occurs during excitotoxic neuron damage is an active process that involves decreased phospholipid synthesis in cell membranes.[36] Thus, supplementation of phosphatidylcholine and phosphatidylserine may stabilize neuronal cell membranes by providing these phosphoplipids in the absence of *de novo* synthesis.

Reactive oxygen species are particularly damaging to cell membranes and the enzymes within cell membranes.[38] Through aging and diseases such as ALS, these structures undergo oxidative modification—reactive oxygen species interact with and structurally change cell membrane constituents. This oxidative modification can interfere with the structural integrity of the membrane, negatively affect its performance, and ultimately destroy cells. Phosphatidylcholine supplementation exerts protective effects in an animal model of neuroinflammation.[39] Phosphatidylserine, on the other hand, is particularly abundant in neuronal cell membranes and may have an anti-apoptotic effect under stressful conditions.[40] Supplementation with these substances may help preserve neuronal cell membrane structure and function.

Glycine

Glycine is an essential amino acid. Its primary action in the central nervous system is as an inhibitory neurotransmitter, especially in the spinal cord. Glycine neurotransmission opens chloride channels in the

postsynaptic cell causing an inhibitory postsynaptic potential (IPSP) and further polarizing the cell membrane. Glycine is also a "co-agonist" at NMDA glutamate receptors in the brain.

Glycine levels are reduced in the lumbar ventral and dorsal horns of the spinal cord in patients with ALS.[41] It has been suggested that decreases in the level of the major inhibitory neurotransmitter in the spinal cord, glycine, leads to increased excitatory activity and even excitotoxicity.[41] Indeed, transgenic mice that express mutant SOD1 have poor glycine receptor currents, smaller clusters of receptors on their cell membranes, and lower expression of glycine receptor mRNA in their motor neurons.[42] Since selectively targeting NMDA receptors with pharmacological agents can be challenging, researchers have postulated that enhancing glycine inhibitory activity may be a promising therapeutic approach.[43]

L-Taurine

Taurine is an organic acid that has several important biological functions (Fig. 9).[44] By the strictest of definitions, taurine is not an amino acid and is not incorporated into proteins. Nonetheless, taurine is a major constituent of bile salts and is found abundantly in brain, retina, muscle, and other organs. It is still a matter of speculation whether taurine is a true neurotransmitter; however, when it is applied to neurons it exerts an inhibitory effect.[45] Taurine appears to be a potent, endogenous cytoprotectant. This cell-protecting effect is presumably due to its antioxidant actions,[46] its ability to stabilize mitochondrial enzymes involved in the electron transport chain, and its capacity to reduce reactive oxygen species generation.[47] Taurine protects neurons from several different destructive mechanisms including dibromoacetonitrile-induced neurotoxicity[48] and acrylonitrile-induced oxidative stress.[49] When combined with vitamins C and E, taurine blocked the pro-oxidant effects of 3-nitropropionic acid.[50]

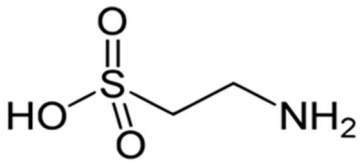

Figure 9. The chemical structure of taurine.

Taurine levels are higher in the brains and spinal cords of people with ALS.[41,51] Indeed, G93A mice (ALS mouse model) have higher levels of brain taurine and higher levels of the taurine transporter.[52] Expression of this transporter increases under periods of oxidative stress and is controlled by heat shock factor 1, a heat shock protein. This work strongly suggests that increased expression of taurine transporters and uptake of taurine in motor neurons in ALS is a compensatory mechanism.[52] In other words, neurons affected by the ALS disease process attempt to recruit the neuroprotectant taurine to partially attenuate the oxidative stress of the disease. It is conceivable that augmented levels of taurine (e.g., through supplementation) would enhance this protective effect.

L-Carnitine

L-Carnitine is a naturally occurring compound found in virtually every type of human cell. It is derived from the amino acids methionine and lysine. Its main role in the cell is in the cellular energy process—carnitine shuttles long-chain fatty acids from the cytosol to the mitochondrial matrix for beta-oxidation.[53] The molecule is instrumental in converting fats into cellular energy. L-Carnitine also inhibits apoptosis and can minimize the effects of oxidative stress-induced damage to mitochondria.[54]

Enhancing any or all of these actions could be advantageous in ALS. For example, lipid peroxidation increases during the course of ALS with a concomitant increase in free radical production.[55] As a result, free fatty acids levels increase in cells. Additional carnitine could enhance normal intracellular shuttling, but also stem the increase in cytosolic free fatty acids and prevent the release of cytochrome c or activation of caspases (i.e., apoptotic signals).[56]

In laboratory studies of male G93A animals (ALS disease model), L-carnitine supplementation significantly delayed the onset of disease phenotypes such as hind limb muscle and spinal cord abnormalities. Supplementation also reduced markers of oxidative stress and prevented muscle cell apoptosis.[57] Interestingly, L-carnitine supplementation prolonged the lifespan of ALS model animals.[57]

Acetyl-L-carnitine performed favorably when compared to placebo in patients with definite/probable ALS.[58] In this trial, all patients were taking riluzole and receiving standard medical care during the yearlong trial. Patients in the carnitine group were more likely to remain self-sufficient during the study period. Also, forced vital capacity (i.e., a test of pulmonary function) remained higher in the carnitine group. Median survival time was also significantly longer in the carnitine group (45 months) versus placebo (22 months).[58] Moreover, patients tolerated carnitine supplementation well—adverse event rates were similar in both groups.

B Vitamins: Thiamine, Riboflavin, Niacin, Pyridoxine, and Biotin

The B vitamins, namely thiamine (Vitamin B1), riboflavin (Vitamin B2), niacin (Vitamin B3), pyridoxine (Vitamin B6), and biotin (Vitamin B7) are water-soluble vitamins that are critical cofactors in various cellular processes. Deficiencies in any of these vitamins can have deleterious effects on the body as a whole. For example, Vitamin B1 deficiency causes Beriberi, a disease that causes profound changes in carbohydrate and lipid metabolism, and deficits in glutamate and GABA neurotransmitter synthesis.

Thiamine Deficiency	Riboflavin Deficiency	Niacin Deficiency	Pyridoxine Deficiency	Biotin Deficiency
•Causes Beriberi •Causes Wernicke-Korsakoff syndrome •High output cardiomyopathy •Polyneuritis	•Angular stomatitis •Glossitis •Seborrheic dermatitis	•Causes Pellagra •Dermatitis •Diarrhea •Dementia •Weakness •Neuropathy •Irritability •Headache •Insomnia •Memory loss •Emotional instability	•Seizures •Irritability •Nonspecific stomatitis •Glossitis •Cheilosis •Confusion •Weight loss •Depression	•Rashes •Changes in hair quality •Hair loss •Anemia •Seborrheic dermatitis •Lethargy •Anorexia •Myalgias •Paresthesias

There is some evidence to suggest that patients with ALS have deficits in enzymes that require B vitamins as cofactors. Expression of riboflavin kinase, which catalyzes the formation of flavin mononucleotide from riboflavin, is reduced in ALS.[59] Human motor neurons are particularly susceptible to decreases in oxidative metabolism, which results from reduced expression of enzymes in the pathway.[59] People with ALS also have diminished thiamine levels in their cerebrospinal fluid.[60] In fact, decreases of thiamine with respect to its related intracellular compound, thiamine monophosphate, are very specific to sporadic ALS; so much so that some have proposed using the thiamine/thiamine monophosphate ratio as a biochemical marker of the disease.[61]

Methylcobalamin and Methyl-Folic Acid

Methylcobalamin (Vitamin B12) and folic acid (Vitamin B9) are often discussed together because they participate together in various cellular functions. Moreover, deficits in one of these vitamins can mimic or mask deficits in the other. They are also usually administered together for purposes of repletion.

These two vitamins are also described together because they both play a role in homocysteine metabolism. Homocysteine is an amino acid related to cysteine, but is not incorporated into proteins. High levels of homocysteine have been detected in various diseases, including heart disease and ALS.[62,63] Since the conversion of homocysteine to methionine requires the presence of Vitamin B12 and folic acid, deficiencies in these vitamins lead to accumulation of the toxic substance. Conversely, methylcobalamin was able to rescue neurons from the homocysteine toxicity in vitro.[64] Curiously, methylfolate did not rescue these neurons; however, folic acid did protect motor neurons from homocysteine, inflammation, and apoptosis in a SOD1 G93A transgenic mouse model of ALS.[65] Moreover, Zhang and colleagues suggest that decreased 5-methyltetrahydrofolate is sufficiently specific to people with pre-symptomatic ALS that it should be considered a biomarker for early stage disease.[66]

Cholecalciferol (Vitamin D3)

Cholecalciferol or Vitamin D3 is one of the main compounds within the Vitamin D family. Vitamin D3 can be synthesized from cholesterol in sun-exposed skin (photoreaction). Nonetheless, Vitamin D deficiencies are surprisingly common in developed nations. Vitamin D is critical for calcium and phosphorus homeostasis in the body—it controls absorption from the gut, deposition in bones, and excretion in the kidney.

Supplementation with Vitamin D also increases the expression of calcium-binding proteins parvalbumin and calbindin-D28K.[67] This is potentially important in ALS for several reasons. Calcium influx at synaptic buttons is a critical part of excitotoxic processes presumed to contribute to ALS neuropathology. Increased

expression of calcium binding proteins (in this case, by Vitamin D supplementation) could act as a buffer to chelate/bind excess calcium. This could conceivably halt the excitotoxic process.[68] Indeed, decreased expression of calbindin-D28K and/or parvalbumin occurs in motor neurons that are particularly vulnerable in ALS.[69] Thus, in addition to combating demineralization of bone that can occur in ALS[70], Vitamin D supplementation may increase expression of calcium-binding proteins in motor neurons and subsequently interfere with excitotoxic processes. Dietary Vitamin D3 supplementation improves functional performance in G93A transgenic mice; mice treated with high levels of Vitamin D3 had greater paw grip endurance and motor performance.[71] Conversely, Vitamin D3 deficiency impairs motor performance in these animals after disease onset.[72]

L-Glutathione and N-Acetylcysteine

L-Glutathione is a chain of three amino acids (tripeptide) that can be synthesized from cysteine, glutamate, and glycine. It is present in various tissues, especially the liver, where it participates in various metabolic processes. The molecule is a reductant (i.e., antioxidant) at the thiol group, where it quenches hydrogen peroxide and other reactive oxygen species. Glutathione can also be conjugated with various exogenous compounds so that they can be more readily eliminated from the body.

N-Acetylcysteine is very similar to cysteine, structurally, with an acetyl group covalently bound at the nitrogen atom. It has a number of clinical uses, such as acting as an antidote in acetaminophen/paracetamol overdose and for kidney protection prior to intravenous contrast administration. N-acetylcysteine is a precursor of glutathione—supplementation with N-acetylcysteine increases the concentration of glutathione in cells.

Glutathione is abnormally low in patients with ALS as are the activities of the enzymes that produce glutathione.[73] Moreover, certain ALS animal models display naturally and greatly reduced levels of glutathione (70 to 80%).[74] This deficiency in glutathione may contribute to motor neuron vulnerability in ALS[75] and may

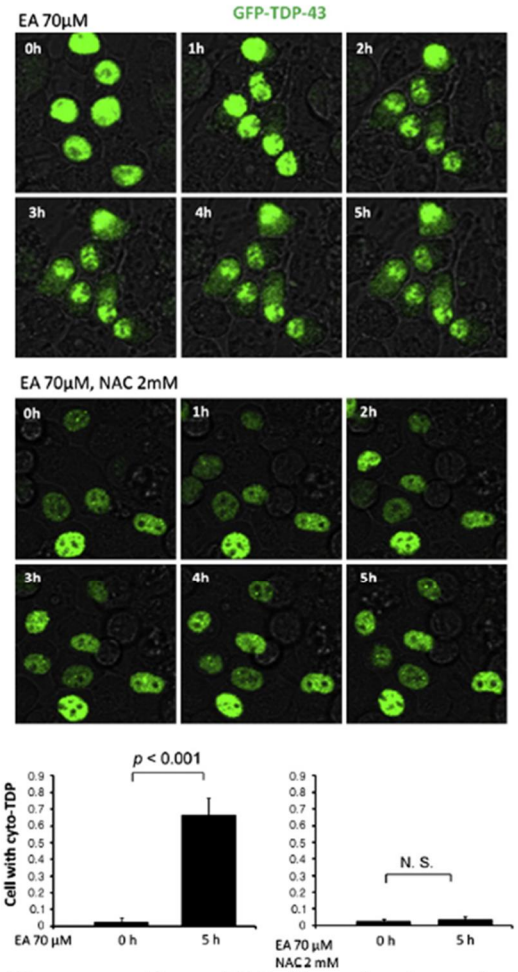

Figure 10. TDP-43 levels by immunohistochemistry after an inducing agent (EA; ethacrynic acid) and N-acetyl-cysteine. N-acetyl-cysteine blocks the increase in TDP-43 caused by EA. Adapted from Iguchi et al. [75]

also increase aggregation of TDP-43 proteins (Fig. 10).[76]

This suggests that glutathione supplementation is potentially beneficial in reversing or halting these pathological consequences.[77] Indeed, N-acetylcysteine treatment prolonged survival and delayed symptom onset in G93A transgenic mice.[78] In a small clinical trial, there was a trend for N-acetylcysteine to improve survival and delay limb onset of symptoms; however, the results did not reach statistical significance.[79] Similarly, glutathione administration resulted in a slight, but not statistically significant slowing of ALS progression.[80] In both trials, small numbers of patients may have limited the power of the statistical analyses, so additional studies are warranted.

Alpha-Lipoic Acid

While not a vitamin per se, alpha-lipoic acid is a key cofactor for multi-enzyme complexes, e.g., alpha-ketoglutarate dehydrogenase, pyruvate dehydrogenase, and glycine decarboxylase.[81] It also has the rather unique property of acting as an antioxidant in both aqueous and lipid phases.[81] Lipoic acid is inert in its native form, but it is readily converted in the body to its active form, dihydrolipoic acid. In addition to being a potent antioxidant, alpha-lipoic acid supplementation also restores glutathione levels (Fig. 11).[82] When aged rats were given lipoic acid supplementation, they exhibited decreased oxidative damage and improved mitochondrial function, which was associated with enhanced ambulation.[83] The molecule also enhances blood flow to small vessels around nerves and reduces lipid peroxidation.[83]

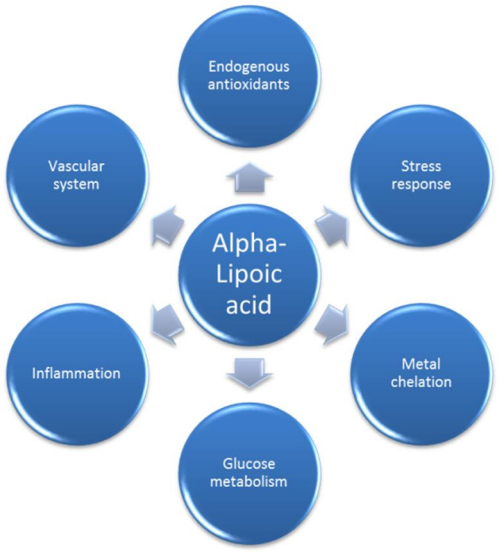

Figure 11. The putative biological actions of alpha-lipoic acid. Adapted from Shay et al.[81]

Magnesium

The element magnesium exerts several actions on cells. It is well known that magnesium blocks NMDA excitatory glutamate receptors. Excessive stimulation at these receptors leads to excitotoxic cell death. Likewise, magnesium also inhibits calcium influx at calcium channels.[84] Magnesium protects neurons from glutamate-mediated cell death.[85] Magnesium is particularly high in brain tissue of people with ALS.[86] Results from animal[87] and human[88] studies suggest that magnesium supplementation does not decrease the risk of developing ALS symptoms or ALS. On the other hand, magnesium depletion may accelerate the uptake of aluminum into brain and contribute to degenerative processes.[89]

GABA

GABA, or gamma-aminobutyric acid, is the major inhibitory neurotransmitter in the brain, just as glutamate is the major excitatory neurotransmitter and glycine is the major inhibitory neurotransmitter in the spinal cord. GABA stimulates GABA receptors to produce inhibitory post-synaptic potentials. These potentials further hyperpolarize neurons and make them less likely to fire an action potential.

Recent research suggests that GABA may play a fundamental role in the pathophysiology of ALS, specifically because the anatomical location and known function of GABAergic neurons elegantly explains a paradox of ALS. The paradox: Why do neurons die in ALS but also increase in activity (become hyperexcitable)? One reason could be that inhibitory GABA input is decreased.[90] Decreased inhibition results in increased excitation. Thus, inefficient GABA neurotransmission could cause symptoms of ALS, particularly muscle fasciculations.

Notably, GABA does not cross the blood-brain barrier under normal circumstances; however, the blood-brain barrier and the blood-cerebrospinal fluid barrier become impaired during the progression of ALS[91], which could allow the passage of GABA into the central nervous system. GABA levels in brain tissue of people with ALS are either reduced, normal, or increased, depending on the study.[92,93] This may vary depending on the stage of the disease.

L-Theanine

L-Theanine is an amino acid that has few natural sources; *Camellia* and *Xerocomus badius* are notable examples. L-Theanine readily crosses the blood-brain barrier and works as an anxiolytic, especially in people who report high levels of anxiety.[94] L-Theanine increases serotonin, dopamine, and GABA levels in the brain.[95] L-theanine exerts neuroprotective effects via activity at GABA(A) receptors.[96] However, it appears that the compound exerts an anxiolytic effect separate from GABA receptors, since it works synergistically with the benzodiazepine, midazolam.[97] There are no human studies of L-theanine in ALS patients, though its role as a neuroprotectant against excitotoxicity in this disease has been proposed.[95]

Ubiquinol (CoQ10)

Coenzyme Q10 (CoQ10) is a lipid soluble molecule, sometimes incorrectly referred to as a vitamin, that exists in three major forms: ubiquinone, ubisemiquinone, and ubiquinol. Ubiquinol is the fully reduced (least oxidized) form of CoQ10 and is therefore the most preferred form. It is found in high concentrations in the heart, liver, and kidney. The chief action of CoQ10 is that of an electron carrier in electron transport chain complexes I, II, and III. However, the molecule also protects against lipid peroxidation, LDL peroxidation,

mitochondrial toxins, and DNA damage.[104,105] The reduced form ubiquinol is a potent, lipid-soluble antioxidant. Interestingly, CoQ10 functions as an extracellular superoxide dismutase[106], one of the enzymes that are abnormal in ALS.[7,107]

CoQ10 administration in an ALS mouse model (mutant SOD1 overexpression) starting at 70 days significantly increased their lifespan compared to control animals.[108] While high-dose CoQ10 is well tolerated by patients with ALS[109], phase II results with the compound were disappointing.[110] CoQ10 supplementation did not significantly change forced vital capacity, daily functioning scores, or biochemical markers of oxidative stress.[110] The authors of the Phase II trial suggest that Phase III evaluation is unwarranted.[110] Moreover, it is unlikely that CoQ10 alone is useful in treating humans with ALS; the supplement should probably be combined with other agents for clinical effect.

Propolis

Propolis is a natural product that is collected from various plants by honeybees. It contains over 300 compounds including polyphenols, amino acids, steroids and inorganic compounds.[111] One of the constituents of propolis that has been extensively studied as a potential neuroprotectant is caffeic acid phenethyl ester (CAPE). CAPE is a potent antioxidant that can prevent several types of neuronal injury including neurotoxicity from MPTP[112], 6-hydroxydopamine[113,114], kainate[115], glutamate[116], and permanent focal ischemia (Fig. 13).[117] CAPE is also a potent anti-inflammatory agent and has inhibitory effects on myeloperoxidase and NADPH oxidase.[118] In a screening test of over 2000 small molecules for the ability to rescue dorsal motor neurons from imminent cell death (in vitro ALS model), CAPE was one of the top three most successful and potent substances.[119] Interestingly, mice expressing mutant SOD (ALS mouse model) lived significantly longer when they were given CAPE than those fed simply a standard diet.[120]

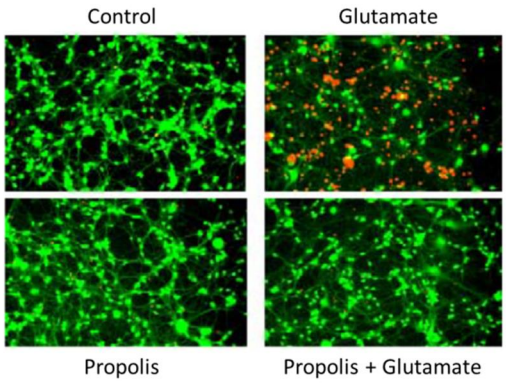

Figure 13. The protective effect of propolis (CAPE) on glutamate-induced neurotoxicity. Neurons can be visualized in green. Markers of cell death are in orange.

Caprylic Acid

Ketogenic diets consist of high fat and low carbohydrate meals and are intended to increase circulating levels of ketone bodies. The ketogenic diet has demonstrated beneficial effects in several neurological diseases—perhaps none more profound than in epilepsy. When SOD1-G93A transgenic mice are fed a

ketogenic diet, they have increased survival and improved motor function compared to mice fed a standard diet.[121]

Caprylic acid is a saturated fatty acid with eight carbon atoms in its hydrocarbon backbone. It is found in the milk of various animals, most notably goat milk, and is a minor constituent of coconut oil. Caprylic acid readily crosses the blood-brain barrier[122] and is commonly used to induce ketogenesis in patients with epilepsy.[123] When SOD1-G93A transgenic mice are fed caprylic triglyceride (three caprylic acid chains in a triglyceride molecule; Fig. 14), they experienced a significant increase in serum ketone bodies.[124] Just as occurred with the ketogenic diet, caprylic triglyceride delayed the motor deficits seen in the transgenic mouse ALS model.[124] Moreover, spinal cord motor neurons were relatively protected from treatment with caprylic triglyceride. Unlike the previous ketogenic diet study, longevity was not increased with caprylic triglyceride treatment. Given that this study was published in 2012, human clinical trials with caprylic acid are not available. Nevertheless, the molecule has a good safety record as evidenced by its widespread use in other neurological diseases.

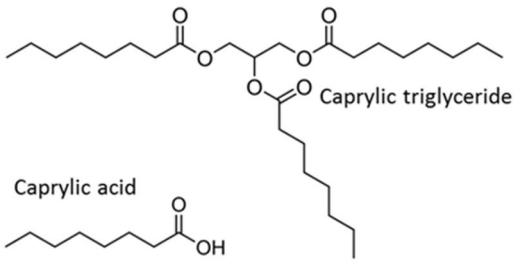

Figure 14. The chemical structures of Caprylic acid and caprylic triglyceride.

5-Hydroxytryptophan

5-Hydroxytryptophan (5-HTP) is a precursor for two pathways; it can be converted to serotonin (5-hydroxytryptamine) or tryptophan. Tryptophan is further converted to kynurenine and kynurenic acid, the latter being a noncompetitive antagonist at the glycine site of the NMDA receptor. Melatonin is also derived from tryptophan.

There is remarkable overlap between the serotonin-containing neurons and the cells that degenerate in ALS.[125] Conversely, neurons that are relatively spared in ALS are only modestly innervated by serotoninergic cells.[125] Likewise, serotonin levels are decreased in the spinal cords of ALS patients.[126] Serotoninergic cells have a complex interaction with glutamate neurotransmission. Selective destruction of serotonin containing cells would increase glutamate excitation of postsynaptic cells.[125] Thus, one strategy for ALS treatment is to augment serotonin neurotransmission.[125]

One way to do this is to supplement with the precursor molecule, 5-hydroxytryptophan. 5-Hydroxytryptophan crosses the blood-brain barrier and is converted to serotonin by aromatic L-amino acid decarboxylase. Interestingly, when transgenic SOD1 G93A mice were given 5-hydroxytryptophan prior to the onset of disease symptoms, hind limb weakness and mortality were significantly delayed compared to untreated animals.[127]

Alpha-Ketoglutarate and Arginine Alpha-Ketoglutarate

Alpha-ketoglutarate is one of the main constituents of the Kreb's cycle/citric acid cycle. As such, it participates in the cell's energy making process. Alpha-ketoglutarate is integral to the conversion of ingested sugar into adenosine triphosphate. Within the citric acid cycle, alpha-ketoglutarate is converted to succinyl-Coenzyme A (succinyl-CoA) through the enzyme alpha-ketoglutarate dehydrogenase. With this enzymatic conversion, a molecule of NAD^+ (nicotinamide adenine dinucleotide) is protonated to become NADH. NADH is a high-energy molecule and can convert ADP to ATP, the main energy carrier of cells.

α-ketoglutarate + NAD+ + CoA→ succinyl CoA + CO2 + NADH + H+

Alpha-ketoglutarate dehydrogenase also appears to be a major participant in mitochondrial function and neurodegenerative disease. For example, there are reduced levels of alpha-ketoglutarate dehydrogenase in the brains of people with Parkinson's disease.[128] Likewise, alpha-ketoglutarate dehydrogenase activity is reduced in Alzheimer's disease.[129] Reductions in the enzyme complex can make neurons vulnerable and reduced activity causes apoptosis without mitochondrial involvement.[130] Thus, as enzyme levels decrease, one corrective intervention may be to supplement with additional amounts of the substrate, alpha-ketoglutarate, to compensate for this loss of enzyme. Activity of alpha-ketoglutarate dehydrogenase relates to the production of reactive oxygen species and fatty acid metabolism.[130]

Arginine alpha-ketoglutarate is the water-soluble salt of the amino acid arginine and alpha-ketoglutarate. In addition to the effects of alpha-ketoglutarate listed above, arginine may exert separate beneficial effects. Arginine is an amino acid that is a key substrate for various enzymes. The amino acid is also abnormally low in patients with ALS patients, a state that is exacerbated by malnutrition in more advanced states of the disease. However, the supplementation of arginine may not simply be useful in reversing deficiencies. When SOD1G93A mice are given arginine, they exhibit significantly less motor neuron destruction and glial activation. Furthermore, the amino acid slows the progression lumbar spinal cord degeneration and delays the onset of motor dysfunction in SOD1G93A mice. Importantly, arginine also significantly prolonged life in these mice.

Safety

All of the ingredients contained in the Deanna Protocol® DP™ Plan Essentials and the Deanna Protocol Comprehensive Approach are available over-the-counter, without a prescription. The ingredients in the

Deanna Protocol® DP™ Plan Essentials and the Deanna Protocol Comprehensive Approach that have been evaluated by the US Food and Drug Administration were deemed Generally Recognized as Safe (GRAS). The dosages of ingredients included in the formulations have been derived from analogous dosages used in laboratory work, published clinical studies, and commercially available dosages.

Disclaimer

The statements contained within have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease. You should contact a qualified medical provider before starting any dietary regimen. While information in this document has been compiled from peer-reviewed journal articles, the clinical action of the combined ingredients of the Deanna Protocol® DP™ Plan Essentials and the Deanna Protocol Comprehensive Approach have not been tested in clinical trials.

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Appendix 1: Nutritional Supplements, Products and Dosages

A. Simplesa AAKG+ Core Powder

This formula provides the minimum recommended dosage* of Arginine Alpha Ketoglutarate (AAKG), as well as the recommended dosages of Ubiquinol (CoQ10), GABA (Gamma Aminobutyric Acid) and Niacin (Non-Flush) in every serving. Simplesa AAKG+ Core Protocol Blend has a 1:1 ratio of Arginine to Alpha Ketoglutarate. Taken three times a day, a daily serving includes:

- Arginine Alpha Ketoglutarate (AAKG) – 9 grams per day
- Ubiquinol (CoQ10) - 1,200 mg per day
- GABA (Gamma Aminobutyric Acid) – 500 mg per day
- Niacin (Non-Flush) – 250 mg per day

*Begin with 9 grams of Arginine Alpha Ketoglutarate daily and increase slowly to 18 grams per day. DO NOT exceed 18 grams per day. A daily serving of Simplesa AAKG+ Core Protocol Powder contains 9 grams of AAKG. For those people taking more than 9 grams of AAKG per day, combining Simplesa AAKG+ Core Protocol Powder with pure AAKG (1:1 ratio) increases the amount of AAKG while still providing for the proper amounts of Ubiquinol, GABA and Niacin.

B. Alpha Ketoglutarate Acid (AKG)

300 mg of Alpha-Ketoglutarate should be taken once per hour during each waking hour between doses of the Core Powder formula.

C. DPS-AM Morning Protocol Blend

This 2-ounce liquid supplement should be taken in the morning. It contains the following nutrients:

Ingredient	Dosage
Creatine	880 mg
Phosphatidylcholine	840 mg
Glycine	500 mg
l-Taurine	500 mg
l-Carnitine	300 mg
Thiamine (Vitamin B1)	262 mg
l-Glutathione	150 mg
Phosphatidylserine	150 mg
N-Acetylcysteine	126 mg
a-Lipoic Acid	125 mg
Methylcobalamin (Vitamin B12)	2400 mcg
Methyl Folic Acid (5-MTHF)	1200 mcg
Cholecalciferol (Vitamin D3)	5000 IU
Riboflavin (Vitamin B2)	12 mg
Pyridoxine (Vitamin B6)	12 mg
Biotin (Vitamin B7)	12 mg

D. DPS-PM Evening Protocol Blend

This 2-ounce liquid supplement should be taken in the evening. It contains the following nutrients:

Ingredient	Dosage
Phosphatidylcholine	840 mg
N-Acetylcysteine	500 mg
Glycine	500 mg
l-Taurine	500 mg
Propolis Extract	500 mg
Magnesium Lactate	400 mg
l-Theanine	210 mg
Methyl Folic Acid (5-MTHF)	1200 mcg
Vitamin E	125 mg

E. Other Nutrients

Liposomal Glutathione: Take approximately 425 mg once per day.
5-Hydroxytryptophan: Take 50 mg once per day in the evening with the Evening Protocol Blend.
Caprylic Acid: Found in coconut oil or MCT oil. Take to tolerance.

Exhibit 1. Products from Simplesa LLC

A. Simplesa AAKG+ Core Powder

Supplement Facts

Serving Size: 1 leveled scoop (4 grams) Servings Per Container: 90

Ingredients	Amount Per Serving	% Daily Value*
L-Arginine Alpha Ketoglutarate (1:1 ratio)	3,000 mg	**
Ubiquinol (CoQ10 Reduced)	400 mg	**
GABA (Gamma Aminobutyric Acid)	167 mg	**
Niacin (Inositol Hexanicotinate)	83 mg	**

* Based on a 2,000 calorie diet ** Daily value not established

Other Ingredients: Stevia and Natural Flavor

DIRECTIONS: As a dietary supplement, add 1 leveled scoop to any beverage or food with a consistency that permits easy mixing. Stir until thoroughly mixed. Take three times daily or as directed by a physician.

Contains no sugar, salt, starch, yeast, milk, egg, shellfish, preservatives, artificial flavors or color.

These statements have not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

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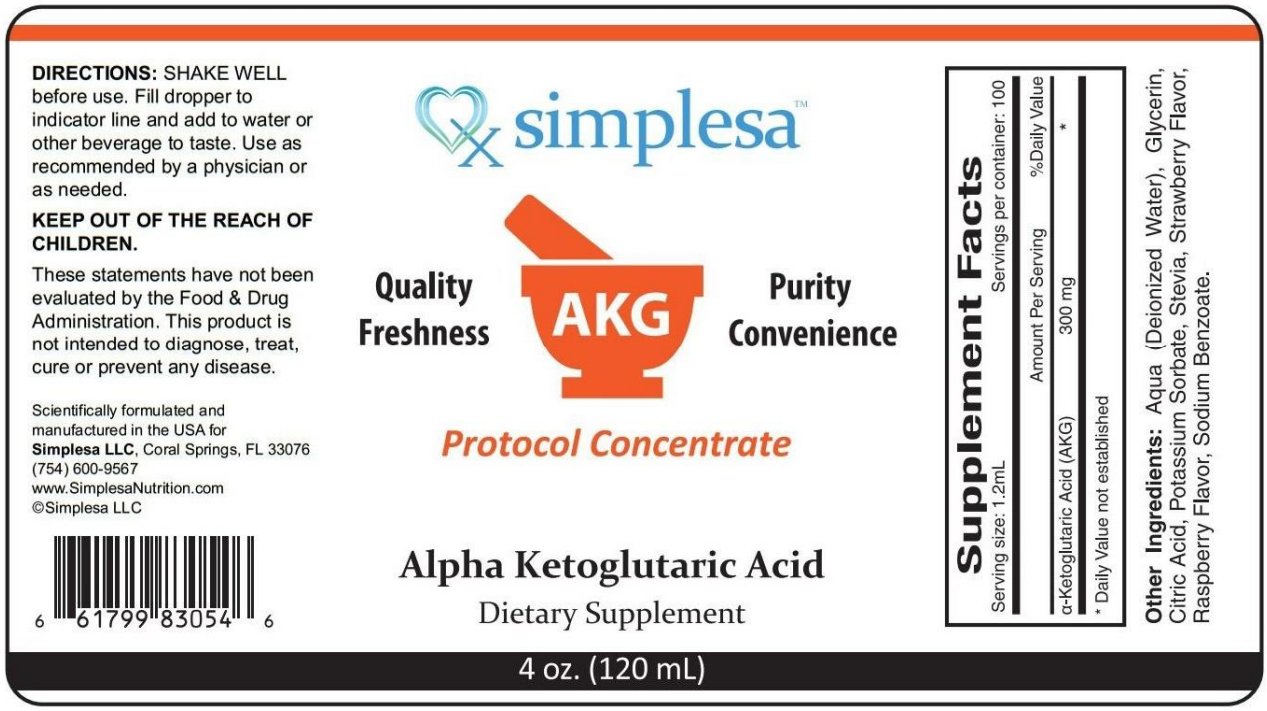
simplesa
Quality Freshness AAKG+ Purity Convenience
Core Protocol Blend
Dietary Supplement
Net Wt. 360 G (13 Oz)

B. Simplesa Alpha Ketoglutarate Acid (AKG) Liquid Concentrate



C. Simplesa DPS-AM Morning Protocol Blend

DIRECTIONS: SHAKE WELL before use. Add contents of bottle to approximately 8 ounces of water or other beverage to taste and drink in the MORNING. Can also drink or put down a feeding tube without diluting.

KEEP OUT OF THE REACH OF CHILDREN.

These statements have not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Supplement Facts

Serving size: 2 oz — Servings per container: 1

	Amount Per Serving	%DV**
Creatine	880 mg	*
Phosphatidylcholine	840 mg	*
Glycine	500 mg	*
l-Taurine	500 mg	*
l-Carnitine	300 mg	*
Thiamine (Vitamin B1)	262 mg	*
l-Glutathione	150 mg	*
Phosphatidylserine	150 mg	*
N-Acetylcysteine	126 mg	*
a-Lipoic Acid	125 mg	*
Methylcobalamin (Vitamin B12)	2400 mcg	*
Methyl Folic Acid (5-MTHF)	1200 mcg	*
Cholecalciferol (Vitamin D3)	5000 IU	*
Riboflavin (Vitamin B2)	12 mg	*
Pyridoxine (Vitamin B6)	12 mg	*
Biotin (Vitamin B7)	12 mg	*

* Daily Value not established ** Percent Daily Value

Other Ingredients: Aqua (Deionized Water), Glycerin, Sodium Hydroxide, Citric Acid, Potassium Sorbate, Sodium Benzoate.

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simplesa™

Quality Freshness AM Purity Convenience

Morning Protocol Blend

DPS-AM

Dietary Supplement

2.0 fl. oz. (60 mL)

D. Simplesa DPS-PM Evening Protocol Blend

DIRECTIONS: SHAKE WELL before use. Add contents of bottle to approximately 8 ounces of water or other beverage to taste and drink in the EVENING. Can also drink or put down a feeding tube without diluting.

KEEP OUT OF THE REACH OF CHILDREN.

These statements have not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Supplement Facts

Serving size: 2 oz — Servings per container: 1

	Amount Per Serving	%DV**
Phosphatidylcholine	840 mg	*
N-Acetylcysteine	500 mg	*
Glycine	500 mg	*
l-Taurine	500 mg	*
Propolis Extract	500 mg	*
Magnesium Lactate	400 mg	*
l-Theanine	210 mg	*
Methyl Folic Acid (5-MTHF)	1200 mcg	*
Ginko Biloba	125 mg	*

* Daily Value not established ** Percent Daily Value

Other Ingredients: Aqua (Deionized Water), Glycerin, Sodium Hydroxide, Potassium Sorbate, Sodium Benzoate.

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Evening Protocol Blend

DPS-PM

Dietary Supplement

2.0 fl. oz. (60 mL)