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REVIEW ARTICLE

ALS Untangled No. 20: The Deanna Protocol

The ALSUntangled Group

The Christian Broadcasting Network (CBN) aired a story in November 2012 giving anecdotal information about the 'Deanna Protocol', a regimen of nutritional supplementation that has been proposed as a treatment for amyotrophic lateral sclerosis (ALS) (1). Vincent Tedone, a retired orthopedic surgeon, created the protocol for his daughter, Deanna, when she was diagnosed with ALS. Tedone states that the protocol was designed after surveying the literature to prevent nerve cells from dying, and he has observed slowing of disease progression in his daughter. Although he is not the treating physician for any patients with ALS, he has disseminated his protocol and reports that other ALS patients have noted slowing of disease progression or improvement in symptoms after initiating this regimen. Here, on behalf of patients with ALS who require more information, ALSUntangled reviews the evidence for the Deanna Protocol.

What is the Deanna Protocol?

The Deanna Protocol is a collection of commercially available nutritional supplements listed below in Table I. The protocol also recommends daily massage of extra virgin coconut oil into the muscles along with oral coconut oil supplementation if tolerated. In addition, Tedone recommends resistance, aerobic, stretching, and range of motion exercises.

According to Tedone and advocates of the protocol, the crucial supplement in this regimen is arginine alpha ketogluturate (AAKG). Alpha ketoglutarate (AKG) is produced in the citric acid cycle, a series of chemical reactions that takes place in mitochondria to generate energy by oxidizing fuel molecules such as amino acids, fatty acids, and carbohydrates (2). L-arginine is an amino acid that plays a role in protein synthesis and serves as a precursor for nitric oxide (3). AKG has been used as a nutritional supplement based on the belief that it can boost protein metabolism and prevent muscle breakdown during exercise (4) or after surgical procedures (5), and L-arginine supplementation is thought to potentially increase blood flow to muscle during exercise through nitric oxide production and enhance protein synthesis (6).

Additional supplements in the Deanna Protocol include nicotinamide adenine dinucleotide (NADH), coenzyme Q10 (CoQ10), and ubiquinol (a CoQ10 formulation), which are substances that also play a role in the citric acid cycle. Ibedenone is a synthetic compound that is structurally related to CoQ10 and is marketed as an antioxidant (7).

Gamma-aminobutyric acid (GABA) is a naturally occurring inhibitory neurotransmitter that possibly is reduced in the motor cortex of patients with ALS compared to normal controls (8). Glutathione is a tripeptide that can be synthesized in the body from amino acids and plays a role as an antioxidant and free radical scavenger (9).

Why might the Deanna Protocol work in ALS?

Some of the supplements in the Deanna Protocol are given in hope that they will provide a more efficient energy source for mitochondria. Previous research shows that mitochondrial dysfunction plays an important role in ALS pathophysiology (10). Cells extracted from patients with ALS show decreased complex 1 activity (11), which contributes to impaired energy production. In cultured neurons treated with drugs that impair complex 1 function, the addition of ketone bodies restored complex 1 function (12). It is possible that supplementation of ketone bodies or increasing mitochondrial efficiency by other means could be beneficial to counteract the impaired cellular energy production in patients with ALS.

Other supplements in the Deanna Protocol aim to prevent glutamate excitotoxicity. Excess glutamate causes damage to nerve cells due to calcium dysregulation and repetitive cell firing (13). The transporter that clears glutamate from motor nerve terminals is depleted in patients with ALS (14).

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Table I. The original Deanna Protocol, as provided by Tedone. The purpose of each supplement described in the table is according to Tedone and is not based on the evidence provided in this paper. The protocol below has recently been revised to now include additional AKG supplementation hourly while awake.

Supplement	Dosage	Hypothesized purpose
Arginine alpha ketoglutarate (AAKG)*	Up to 18 g daily	Delivers energy to nerves
Nicotinamide adenine dinucleotide (NADH)*	20 mg 2 times daily	Stops nerve cell death
GABA*	250 mg 2 times daily	Inhibitory neurotransmitter
Glutathione*	350 mg 3 times daily	Free radical scavenger in the nervous system
Ibedenone*	180 mg daily	Facilitates energy to nerves
Ubiquinol (CoQ100)*	200 mg daily	Helps energy cycle in mitochondria
B complex	Standard dosage from bottle	General nerve health
Bee Propolis	200 mg daily	Antioxidant for nervous system
CoQ10	Standard dosage from bottle	Helps energy cycle in mitochondria
5-hydroxy tryptophan	50 mg nightly	Serotonin and melatonin precursors
Creatine	1758 mg daily	General muscle health and recovery
Cysteplus	500 mg daily	Counteracts glutamate hyperactivity
Ginkgo Biloba	120 mg daily	Protects against glutamate excitotoxicity
Glutathione	3000 mg IV weekly	Free radical scavenger
Glycine	500 mg twice daily	Balance neurotransmitters
Magnesium	400 mg daily	Calms nerves
Methyl folic acid (5-MTHF)	1 mg twice daily	Needed with B12 for metabolism
Neurochondria	1 pill daily, one dose contains: 1500 mcg of Vitamin B12; 300 mcg of Folate; 250 mg of Benfotiamine; 150 mg of CoQ10; 120 mg of R-Lipoic acid; 150 mg of Glutathione; 300 mg of Acetyl-L-Carnitine; 150 mg of Phosphatidylserine Nerve metabolism	
Opti Zinc	30 mg daily	Increases bioavailability of zinc, stabilized calcium channels
Phosphatidylcholine	840 mg twice daily	Needed for cellular maintenance
Taurine	500 mg twice daily	Protects against glutamine overstimulation
Theanine	200 mg daily	Enhances and increases GABA
Vitamin D3	5000 IU daily	Most active form of D3
Vitamin D	10,000 IU daily	Helps with balance

*These supplements are indicated by Tedone as the most important supplements in the protocol.

Riluzole, currently the only FDA approved medication to slow the progression of ALS, inhibits glutamate neurotransmission as part of its mechanism of action (15).

Additionally, some supplements are recommended in the Deanna Protocol to exert antioxidant effects. Markers of oxidative damage are elevated in the brain and spinal cord in patients and animal models of ALS (16). In some familial cases of ALS, impaired copper/zinc superoxide dismutase (SOD1) leads to toxic accumulation of reactive oxygen species and free radicals with subsequent death of motor neurons (17).

What relevant animal data exist for the Deanna Protocol?

Currently, no published studies could be found regarding AKG supplementation and ALS. As mentioned in the CBN story, Dominic D'Agostino and his group at the University of South Florida are currently studying the Deanna Protocol in a SOD1-G93A ALS mouse model. The mice are being given AAKG, idebenone, GABA, and R-alpha lipoic acid as supplementation to the standard rodent feed, and survival data will be collected. His group is also studying a ketogenic diet high in caprylic acid, capric acid, and omega-3 in the ALS mouse model and is monitoring motor performance. According to D'Agostino, the preliminary data are encouraging, but experiments are still ongoing and cannot yet be interpreted (18).

Additional preclinical data are available regarding ketogenesis and ALS, which may be relevant given the proposed mechanisms of AKG and coconut oil in ALS. A small study in the SOD1 mouse model found that mice that were fed a ketogenic diet had improved motor performance and decreased motor neuron death compared to mice that were fed a standard diet (19). However, there was no difference in survival between the two groups. The authors proposed that increasing the availability of ketone bodies could allow for more ATP production, which would counteract the mitochondrial

dysfunction seen in SOD1 mice and perhaps in humans with ALS.

CoQ10 and creatine showed promise in preclinical studies due to their neuroprotective properties (20,21); however, clinical trials in patients with ALS showed no benefit of either supplement compared to placebo (22,23). No significant safety concerns were identified in patients taking CoQ10 or creatine.

While many preclinical studies implicate glutamate excitotoxicity as a contributing mechanism to ALS and have found benefits when anti-glutamaterigic therapies are used in an animal model (24–27), these findings have not translated into successful therapies when studied in human clinical trials. Lithium (28), ceftriaxone (29), memantine (30), lamotrigine (31), and gabapentin (32) all block glutamate excitotoxicity and showed promise in animal studies yet showed no benefit in ALS human trials. Based on this precedent, it is necessary to interpret results of ALS animal studies cautiously rather than assume successful translation into ALS patients.

What are the efficacy, safety and cost of the Deanna Protocol in human ALS?

No data are available regarding the clinical progression of Deanna Tedone to either support or refute the claims in the CBN story. According to her father she was diagnosed by a neurologist but has not been seen in follow-up. The CBN story also mentions an ALS patient who noted improvement in his swallowing and breathing abilities after initiating the Deanna Protocol. Review of his records by the primary author (CF) indicates that he did have an objective improvement in vital capacity measurements after initiating the protocol. However, variability due to technical issues is not unusual and is possible in this scenario. By other objective measures, this patient has demonstrated slow progression of disease both before and after treatment with the Deanna Protocol.

At the Duke University ALS Clinic, five patients with ALS have reported trying the Deanna Protocol. All of these have continued to progress by objective measurements. Only one has had enough measurements to calculate slopes of decline in ALSFRS-R and FVC before and during the Deanna Protocol. Before starting, ALSFRS-R decline was 2.0 points per month; during three months on the Deanna Protocol it was 2.3 points per month. Before starting, FVC decline was 0.2 liters per month; during three months on the Deanna Protocol it was 0.3 liters per month.

Several patients have emailed Tedone, describing a wide variety of subjective improvements on the Deanna Protocol. Records have been requested by ALSUntangled in hope of verifying some of these, but have not yet been received. On the PatientsLikeMe website, 14 patients with ALS and one patient with primary lateral sclerosis (PLS) reported taking the Deanna Protocol, and eight ALS and one PLS patients gave accounts of perceived treatment effects. One ALS and one PLS patient endorse major effectiveness, one ALS patient reported moderate effectiveness, two reported slight effectiveness, two reported no effect, and two were unsure. Side-effects of diarrhea or upset stomach were described by four patients. All 15 patients have been on the protocol for three months or less, with five patients on the protocol for less than one month. Cost is reported as greater than $200 per month by 71% of patients. Patients seen at the Emory ALS center who have elected to try the protocol report that taking only the 'most important' supplements costs approximately $150–200 per month, while the entire protocol costs approximately $400 per month.

Dosing issues

From review of patient reports and emails, there appears to be significant variability in the number and brand of supplements being used by those attempting to follow the Deanna Protocol. Supplement content is known to vary widely across brands (33). Even further variability is introduced by the lack of specific instructions related to the dosing of certain supplements; for example, B-complex and Co-Q10 are to be taken at 'standard dosage from bottle' and both exist in a variety of formulations and dosages.

Where specific supplement dosages are provided, it is not clear how these were determined. Dosages of creatine and CoQ10 in the Deanna Protocol are far lower than the dosages that have failed to produce benefit in human ALS trials (22,23). On the other hand, dosages of magnesium, zinc, and vitamin D are in excess of daily doses recommended by the Food and Nutrition Board, Institute of Medicine (34).

Finally it has not yet been shown that the supplements in the Deanna Protocol, used at the recommended dosages and routes, can produce biologically meaningful changes in motor neurons or surrounding cells in the central nervous system.

Conclusions

Mitochondrial dysfunction, glutamate excitotoxicity, and oxidative stress have all been implicated in ALS pathogenesis, and targeting these mechanisms individually or by a cocktail such as the Deanna Protocol could play a role in future ALS therapies. However, many of the preclinical and animal studies related to these pathways have not translated into successful treatments in patients with ALS. While there are anecdotal reports of improvements in patients with ALS on the Deanna Protocol, there is no convincing objective evidence of benefit yet. Thus, at this time, ALSUntangled does not recommend the Deanna Protocol to patients with ALS

Before it can be recommended, a reproducible version of the Deanna Protocol should be shown to influence plausible physiologic mechanisms such as central nervous system ketone bodies, as well as clinically meaningful outcome measures such as ALSFRS-R and FVC in patients with ALS.

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Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

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