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Complementary and Alternative Therapies in ALS

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Synopsis

Given the severity of their illness and lack of effective disease modifying agents, it is not surprising that most patients with ALS consider trying complementary and alternative therapies. Some of the most commonly considered alternative therapies include special diets, nutritional supplements, cannabis, acupuncture, chelation and energy healing. This chapter reviews these in detail. We also describe 3 models by which physicians may frame discussions about alternative therapies: paternalism, autonomy and shared decision making. Finally, we review a program called ALSUntangled which using shared shared decision making to review alternative therapies for ALS.

Keywords: Complementary and Alternative Medicine, Paternalism, Autonomy

I. Introduction

Complementary and alternative medicine (CAM) is defined as non-mainstream treatment used in addition to (complementary) or instead of (alternative) standard evidence-based care (1). At some point in their illness, the majority of people with ALS (PALS) will try at least one type of CAM (2,3). It is easy to see why. ALS rapidly disables and shortens the lifespan of its victims. While symptom management has improved in recent years (4–6) there remains no evidence-based clinically meaningful disease-modifying therapy for this dreaded condition. Surveys shed light on patient motivations and expectations for ALS CAMs: 10% believe they will find a cure, 30% believe they will improve, 50% believe they will slow progression (2,3). Other drivers we have encountered include peer pressure from family members and friends who have these expectations, and the belief that nothing worse than the present disease could possibly be encountered.

The Internet has made it easier than ever for PALS to find CAMs. A Google search of "ALS Treatment" for example, yields more than 100 million hits (7). While this breadth is impressive, there is often little depth within websites offering CAMs. Claims such as "clinically proven", and "perfectly safe" are too-often supported by data that ranges from absent, to flawed, to completely inaccurate. Real harms have come to PALS pursuing CAMs, including physical, financial, and psychological harms (8,9). There is also the potential for scientific harms, as pursuit of CAM is sometimes undertaken in place of enrollment in a trial, meaning trials may take longer, cost more and have to be stopped prematurely due to poor enrollment (10).

In this chapter we will describe the types of ALS CAMs that we have been asked about most often over the years. We will then discuss options for reviewing CAMs with PALS, including one called ALSUntangled.

II. Types of CAM that PALS Commonly Ask About

A. Diets and Nutritional Supplements

The importance of energy balance is well established in ALS, with both pre-clinical and human studies offering evidence to support a disease influencing effect of premorbid weight, weight maintenance and caloric intake (11–13). While studies in the healthy population suggest that reduced caloric intake provides survival benefits by reducing the risk for chronic disease, the opposite is true in ALS. ALS SOD1-mutant mice placed on a calorie-restricted diet showed reduced paw-grip strength and significantly reduced survival compared to animals receiving adequate nutrition (14). In contrast, several studies examining the effects of high calorie diets enriched in carbohydrates or fat have shown prolonged survival in SOD1 animals (15–18).

Evidence supporting a survival benefit related to energy balance in ALS patients has been collected primarily from population studies that include assessment of BMI and malnutrition. Malnutrition in ALS has been defined as the loss of greater than 10% baseline body weight or a body mass index (BMI) lower than 18.5 kg/m^2; both are considered negative predictors of survival in ALS. While the prevalence varies between studies, some report over half of all ALS patients meet criteria for malnutrition (19). The literature consistently shows that a higher BMI, between 30 to 35 kg/m^2, is associated with decreased risk of disease, later disease onset and prolonged survival (20). Low BMI or rapid weight loss negatively effects disease progression with reports suggesting a 7.7 fold relative risk of mortality in malnourished ALS patients (21). In addition, Lindauer et al. in their prospective study, assessing adiposity by MRI imaging, reported that increased subcutaneous fat mass was a statistically significant predictor of survival in men (22).

Weight loss is nearly ubiquitous in ALS and presents significant challenges for patients. In a cohort of 121 patients, queried by Korner et al., weight loss had a negative impact on quality of life with perception of reduced physical functioning and vitality. Patients who had lost weight and were subsequently placed on high calorie supplements or had undergone PEG (n = 23) reported weight stabilization or gain. Of those who chose PEG, 84.6% reported an improvement in QOL with no patients reporting worsened QOL (23). The etiology of weight loss and subsequent malnutrition in ALS is multifactorial and includes dysphagia from bulbar dysfunction, upper extremity weakness, and hypermetabolism. Dysphagia is present in 45% of patients with bulbar onset disease at diagnosis, and approximately 81% of all ALS patients will experience dysphagia as a symptom of ALS (23). Due to the involvement of cranial nerves IX, X and XII, patients with bulbar disease develop disruption in tongue, pharyngeal and esophageal function resulting in difficulty chewing and swallowing. The

weakened oral activities ultimately result in reduced calorie and fluid intake as patients often become fearful of choking and avoid eating and drinking, or are unable to spend the increased time it takes to consume a meal safely. Upper extremity weakness also interferes with weight maintenance as it impairs self-feeding and prolongs mealtime, which often results in early satiety and reduced caloric intake. Dietary modification, with changes in food texture and liquid viscosity, as well as behavioral modification, including safe swallowing techniques and caregiver assisted feeding, may help mitigate these problems, at least temporarily.

Hypermetabolism, defined as an increased resting metabolic rate, has been observed in ALS patients and SOD1 mice. The etiology of the hypermetabolism in ALS is poorly described, but has been attributed to increased energy utilization by weakened skeletal muscles; nonfunctional muscular activity such as spasticity, cramps, fasciculations, and/or pseudobulbar motor activities (uncontrolled laughing or crying); and the metabolic cost of increased protein catabolism (24,25). Calculating the total daily energy expenditure for ALS patients using standard methods such as the Harris-Benedict Equation does not provide adequate estimation of total daily energy expenditure. It has been suggested that ALS patients require anywhere from 10–20% more calories than what these predication strategies indicate. Kasarskis et.al. followed 80 individuals with ALS and their data provided evidence supporting the presence of hypermetabolism early in disease and the potential for broad fluctuation of energy imbalance within a single ALS patient (−2989 to +1395 kcal/d), illustrating the complexity of metabolic changes in ALS. This presents a challenge to the practitioner for providing accurate estimates and recommendations to meet each patient's nutritional needs over the course of disease. From their data, the authors (26) developed a more accurate caloric estimation tool using the ALSFRSr and the Harris-Benedict Equation; both patients and practitioners can access this tool online and use it to guide nutrition related interventions including the need for gastrostomy (27).

There have been conflicting opinions regarding the best diet to recommend for nutritional support in ALS. Some propose a diet high in carbohydrates while others recommend a diet high in fat. Still others hypothesize that a ketogenic diet may have therapeutic potential in ALS based on preclinical data in SOD1 mice showing strength gains mid-disease when compared to mice fed a traditional diet (28). While high calorie diets have shown survival benefit in SOD1 mice, the ketogenic diet did not. In a recent clinical trial, comparing the potential of high calorie diets enriched with either fat or carbohydrates to restore weight in 24 individuals with ALS, both strategies were reported as safe and effective after 12 weeks of treatment (29). However, there was a trend toward greater weight gain that did not reach statistical significance for those who consumed the high fat diet. This study was limited by small sample size and no conclusion could be drawn about survival, as this was not an end point. In contrast, a second small but randomized, double blind, placebo controlled phase II clinical study (n=24) compared the safety and tolerability of three diets; a regular diet (jevity 1.00; 29% fat calories), a hypercarbohydrate hypercaloric diet (Jevity 1.5; 29% fat calories), and a hyperfat hypercaloric diet (Oxepa; 55% fat calories with eicosapentaenoic acid and gamma-linolenic acid) with differing results (30). While this study was also limited by sample size, the data favored those who were treated with the hypercarbohydrate hypercaloric diet, who had fewer serious adverse events including death during the 5 month follow-up period (control deaths 3 of 7; HF/HC deaths 1 of 8; HC/HC deaths 0 of 9). Interestingly, the hyperfat hypercaloric cohort lost weight during the trial calling into question the accuracy of their methods for assessing calorie requirements. In addition, preclinical data assessing the benefits of omega 3 fatty acids, and more specifically eicosapentaenoic acid, in ALS SOD1 mice showed reduced survival in the animals receiving the omega 3 fatty acid (31). The authors cautioned

against its use in ALS. Further testing with a larger sample, and perhaps using a different hyperfat hypercaloric supplement is needed. However, there appears to be sufficient data to conclude that a diet high in calories provides benefit in ALS.

When ALS patients are unable to overcome negative energy balance and lose more than 10 percent of baseline body weight a gastrostomy tube is often indicated. Argued advantages of gastrostomy include alleviation of patient and family stress, improvement in quality of life and increased survival. While this has remained somewhat controversial, there is a growing body of evidence to support these benefits. Numerous studies have measured mortality rate post procedure with respiratory insufficiency being the most common cause of peri-procedural death. The AAN recommends that gastrostomy be placed when the force vital capacity is equal to or greater than 50% predicted to reduce associated risks (32). A study of 35 ALS patients with FVC greater than 50%, observed in three month intervals post PEG tube placement for up to 2 years, did not differ significantly in mortality from patients without PEG at 6 months, but did after 6 months, having lower mortality and significant improvement in BMI (33). Intra-procedural mortality of percutaneous gastrostomy has been shown to be 1.8%, 24-hour in-hospital mortality rate 3.6%, and 30-day mortality rate 11.5% (34). More recently, Dorst et al. followed 89 patients in a multi-center prospective study observing the safety of percutaneous endoscopic gastrostomy (PEG). They reported general safety of PEG placement with only 1.1% mortality in the peri-procedure period. In addition they had improved outcomes in patients receiving, single prophylactic injection of antibiotics during tube placement, slow initiation of nutritional supplementation (<200 kcal/day), and high calorie nutritional supplementation once at goal (35). There were no reports of refeeding syndrome and the patients who received high calorie supplementation showed a survival benefit at 18 months post gastrostomy placement. In addition, the authors concluded that the use of non-invasive ventilation in the peri-procedure period decreased the risk associated with PEG, allowing safe placement later in disease. However, some suggest that radiologically placed gastrostomy (RIG) is safer than PEG (36).

If nutrition has such a strong influence on disease onset and progression, are there disease-modifying effects of vitamin and mineral enriched diets? Supplements or “nutraceuticals” are ” products intended to supplement the diet that contain one or more of the following dietary ingredients: a vitamin; a mineral; an herb or other botanical; or an amino acid used as a dietary substance for man to supplement the diet by increasing the total dietary intake to promote wellness (37).” Since the passing of the Dietary Supplement Health and Education Act of 1994 supplements have not been regulated by the FDA and are widely available and easily obtained without physician oversight. In fact, there are few requirements, other than registering the manufacturing plant and following rules for labeling, that manufacturers have to meet to produce supplements or ensure product quality and safety. It is estimated that over 50% of United States citizens take supplements regularly for health. The prevalence of supplement users is even greater in the ALS community, with more than 75% of patients taking supplements as part of their health regimen (32,38). In the setting of a terminal disease without ample choices for disease-modifying therapies, these patients assert their autonomy and report that they self-medicate with dietary supplements to improve general wellbeing and slow disease progression (3). Importantly, as described in a study of 121 ALS patients, those who took supplements (52%) reported greater vitality, physical and social functioning, and an overall improved quality of life (QoL) in the early and mid-stages of disease (23). Whether this benefit was afforded or not by the physiologic effects of the supplements can be debated; however the health benefit, as measured by QoL, of a self-determined choice should not be considered trivial and may be tightly bound to a patient’s hope for improved health and prolonged life. While the vast majority of supplements have little or no supporting scientific evidence to back their use, patients will take them. Rosenthal and Ellis in their review of

nutrition and dietary supplements for motor neuron disease, suggest that it is the responsibility of the practitioner to remain aware of known adverse effects and "offer advice or caution as our patients explore their own therapeutic combinations (39)."

The Deanna Protocol is a supplement regimen that many PALS currently ask about. It was developed by an orthopedic physician who became frustrated by the lack of effective disease-modifying treatments when his daughter was first diagnosed with ALS (40). The regimen combines multiple supplements targeted to improve mitochondrial function and cellular energy production, and to provide neuroprotection. The exact regimen itself changes; the most recent version can be found on the "Winning the Fight" website (41). This website reports "Scientific studies have proven that the Deanna Protocol significantly slows the progression of ALS and extends life span (41)." We are aware of only 1 published study on the Deanna Protocol, and this was done in animals. Poff and colleagues compared standard and ketogenic diets, both with and without added key supplements from the Deanna Protocol in SOD1 mutant mice (42). Their data demonstrated significant improvements in function mid-disease, and prolonged longevity in animals fed both the supplemented diets compared to the non-supplemented diets. Furthermore, the supplement enriched standard diet provided the longest and most statistically significant survival benefit (7.5% increase; p=0.001), while the mice fed the supplement enriched ketogenic diet showed the earliest functional benefit with a shorter but still significant increase in survival (4.2% increase; p=0.006). This animal study has multiple methodological flaws identified by published guidelines (43) and has not been independently replicated. There are anecdotal reports of patients having improved energy and slowed progression on the Deanna Protocol, but neither the ALS diagnosis nor the reported improvements could be independently validated (40). The cost to obtain the entire supplement list from one version of the protocol has been estimated to be greater than $400.00 per month and is not reimbursable by insurance (40). Further investigations are warranted to evaluate its efficacy.

Although limited, both pre-clinical and clinical studies have been completed for various nutritional supplements in ALS. Below is a select list of supplements, most with antioxidant properties, that have been proposed as potentially beneficial for the ALS Patient.

Catechins Catechins are polyphenolic flavonoids which possess strong antioxident properties and include, epigallocatechin, epicatechin, and epicatichin-3-gallate. Catechins are considered free radical scavengers found in high concentrations in some plants, fruits and vegetables. They are considered the health promoting constituent of green tea, blue berries, cocoa, prune juice, red wine, and Ginko Baloba to name a few. Studies have shown that catechins cross the blood brain barrier and are incorporated into brain tissue where they exert potent neuroprotective actions by modulating mitochondrial responses to oxidative insults. Clinical studies in Parkinson's disease have had promising results, however, no clinical studies have been completed in ALS. Supporting biologic plausibility for catechins in the treatment of ALS, *in vitro* studies revealed that epicatichin-3-gallate reduced hyperexcitability in SOD1 motor neurons by interfering with glutamate hyperexcitability, and had a rescue effect in motor neurons exposed to H2O2 (44). Preclinical investigation in the G93A SOD1 mouse showed that pre-symptomatic oral administration of epicatichin-3-gallate significantly delayed the onset of disease, and extended life span. In addition, the treated mice had increased number of motor neurons, diminished microglial activation, reduced immunohistochemical reaction of NF-kappaB and cleaved caspase-3 as well as reduced protein levels of iNOS and NF-kappaB in the spinal cords.

Co-Q10 Co-enzyme Q10 (CoQ10) is a fat soluble vitamin-like substance found in mitochondria, that is part of the electron transport chain, participating in aerobic cellular respiration and the generation of ATP. Both pre-clinical and clinic studies have been completed assessing CoQ10 in ALS. SOD1 transgenic mice, fed daily CoQ10, demonstrated an increase in survival by 6 days compared to controls, which met modest statistical significance (45). Although high doses of up to 3000mg/day were well tolerated in patients (46), a phase II clinical trial did not confirm superiority of CoQ10 when compared to patients taking placebo (47). Advancement to a phase III clinical trial was not recommended.

Creatine Creatine is a nitrogenous organic acid that participates in cellular energy production. In addition, creatine appears to have neuroprotective properties related to its role in stabilizing the mitochondrial membrane by suppressing the opening of the mitochondrial permeability transition pore and release of cellular pro apoptotic factors (48). In ALS, supplementation with creatine was found to improve motor performance, improve weight maintenance and extend survival in G93A transgenic mice (49). However, a second group showed no effect of creatine on muscle bulk and strength in SOD1 mice (50). A randomized double-blind, placebo controlled trial in humans, did not show significant benefits (51,52). A recent Cochrane review, including 3 trials and 386 ALS participants taking creatine, by Bedlack et al, concluded that "in patients already diagnosed with clinically probable or definite ALS, creatine at doses ranging from 5 to 10 g per day did not have a statistically significant effect on survival, ALSFRS-R progression or percent predicted FVC progression (53)." However, it is unknown if, at higher doses, creatine may be beneficial to PALS (54). Interestingly, a recent phase II study showed that high dose creatine supplementation is safe, tolerable, and may have some positive effects in Huntington Disease. We await further studies with high dose creatine in ALS patients to determine whether it is beneficial.

Idebenone Idebenone is quinone anologue of CoQ10 that was developed in Japan in the 1980's for the treatment of neurodegenerative disorders. Idebenone is an antioxidant that has been shown to inhibit lipid peroxidation in brain mitochondria. In one series, Idebenone was the most potent antioxidant of 70 related quinones evaluated (55). Idebenone has been most extensively evaluated in patients with Friedreich's ataxia, a trinucleotide repeat disorder with impaired iron metabolism and redox homeostasis (56). The result of multiple clinical trials in this patient population have been mixed ranging from documented improvement in function to lack of efficacy (56,57). While there are concerns that Idebenone has the potential to form superoxide radicals causing increased cellular damage, it was well tolerated in all clinical studies and was subsequently marketed in Canada. However, in 2013, Santhera Pharmaceuticals voluntarily pulled it from market, citing lack of efficacy (57). Idebenone continues to be available online through neutraceutical providers, and is included as one of the key supplements in the Deanna Protocol. While clinical trials are ongoing in multiple sclerosis and other neuromuscular diseases, no preclinical or clinical studies have been published in ALS.

L-Carnitine An essential cofactor for the beta-oxidation of long-chain fatty acids, L-carnitine is a quaternary ammonium compound required for the transport of fatty acids into the mitochondrial matrix for use in energy metabolism. Its antioxidant properties include superoxide anion radical and hydrogen scavenging that reduces mitochondrial injury and apoptosis both in vitro and in vivo (58). In transgenic mice carrying a human SOD1 gene, oral L-carnitine significantly delayed the onset of signs of disease, delayed deterioration of motor activity, and extended life span (59). Furthermore, subcutaneous injection prolonged survival even when treatment was initiated after the onset of symptoms (59). A small (n=42 treated, 40 placebo) randomized double-blind placebo-controlled pilot study of acetyl-L-

carnitine, showed an increase in median survival and slower ALSFRS-R and FVC decline in the patients taking L-carnitine 3g/day. No significant side effects were reported and the authors concluded that a phase III trial is needed to confirm these preliminary findings (60).

Omega-3 Omega-3 polyunsaturated fatty acids have been associated with significant health benefits (61). Omega 3 is thought to reduce neuroexcitotoxicity and neuroinflammation, and activate anti-apoptotic pathways (62). In a study combing the data from 5 large prospective cohorts, there was an associated reduced risk for developing ALS in those consuming a diet high in omega 3 polyunsaturated fatty acids (63). A single preclinical study has been completed in transgenic SOD1 mice to evaluate disease-modifying effects of omega 3 (64). They fed the mice a diet high in eicosapentaenoic acid, a murine derived omega 3 fatty acid. Omega 3 did not affect the course of motor deficit or the length of survival, whether administered at disease onset or if given during the symptomatic stage of the disease, and accelerated disease progression in those fed omega-3 during the pre-symptomatic stage of ALS. Those animals fed omega 3 fatty acids showed an increase in vacuolization of anterior horn cells and associated glial cells abnormalities. In their conclusion, the authors advised against the use of omega-3 supplementation in patients with ALS (64). While there have been no clinical trials directly assessing the efficacy of a diet high in omega 3 fatty acids, a small clinical trial discussed earlier in this chapter, did compare a standard diet, high carbohydrate diet and a high fat diet with 55% of its calories provided by omega 3 fatty acids. The high fat diet had increased adverse events including deaths, as compared to the high carbohydrate diet (29,30).

Resveratrol Resveratrol is a polyphenol found in the skin of grapes, blueberries, raspberries and mulberries. It is reported to have neuroprotective effects through cellular pathways affecting mitochondrial biogenesis and autophagy, with implicated pathways activating Surtuins, AMPK and PGC-1alpha. A few pre-clinical studies have been completed studying the effects of Resveratrol (65–67). All studies reported a delay in disease onset and statistically significant increases in survival. In addition, Resveratrol improved survival with post disease onset treatment in the SOD1 ALS mouse model (65–67). Over 30 clinical trials have been conducted examining the effects of Resveratrol in cancer, diabetes and heart disease, to name a few (68). The supplement has had varying affects but has been well tolerated in all the studies. There have been no clinical trials in patients with ALS.

Vitamin A Vitamin A is a fat soluble vitamin with multiple functions including growth and development, vision, and maintenance of the immune system. While some authors have suggested that retinoid signaling is altered in ALS, serum vitamin A levels have been evaluated and have not differed from controls (69). A pre-clinical investigation using transgenic ALS mice, demonstrated shortened lifespan in mice receiving daily retinoic acid supplementation. The authors cautioned against its use in ALS (70). There have been no human clinical trials assessing the efficacy of retinoic acid.

Homocysteine Homocysteine is involved in the formation of free radicals and cytosolic calcium accumulation, mitochondrial dysfunction, apoptotic pathway activation, and excitotoxic amino acid–mediated damage (71). These pathological pathways have been implicated in ALS. A small clinical study found that plasma homocysteine levels are increased in PALS compared with healthy controls. PALS with shorter time to diagnosis were found to have higher homocysteine levels. The authors concluded that a higher plasma homocysteine may be linked to faster progression of the disease (72). Another small study showed that homocysteine level in the cerebrospinal fluid is also increased in patients with ALS compared to healthy controls. The authors hypothesized that homocysteine may be a biomarker of ALS and may be involved in the pathophysiology (73). Folate and vitamin B12 are thought to reduce the level of homocysteine via remethylation. Studies using SOD1 mouse models have shown a beneficial effect of folate on reducing the levels of homocysteine, delaying onset of

disease and prolonging lifespan (74). However, in one study, B12 alone did not show any effect on homocysteine levels, onset of disease or survival. However, a more recent in vitro study had opposite results, showing better survival against homocysteine toxicity in vitro, in cells pretreated with B12 but not in those treated with folate (75). Furthermore, in one small pre-clinical study, ALS mice were supplemented with Galactooligosaccharides (GOS), a prebiotic that is thought to improve the absorption and synthesis of B Vitamins. GOS and prebiotics yogurt administration were shown to significantly delay the disease onset and prolong the lifespan in SOD1G93A mice. Also, these products increased the concentration of folate and VitB12, and reduced the level of homocysteine (76). However, there have been no clinical trials examining the role of B12, folate or GOS supplementation in ALS.

Thiamine Thiamin-thiamin monophosphate (T/T TMP) ratio has been shown to be reduced in the CSF of PALS in 2 small studies. There have been no studies evaluating supplementation with thiamin (vitamin B1) in PALS (77,78).

Riboflavin Riboflavin or vitamin B2 supplementation was evaluated in one pre-clinical study using the SOD1 transgenic mouse model. There was no significant effect of riboflavin on either survival or motor performance (79).

Vitamin C Vitamin C is considered an antioxidant but several studies have failed to show an association between vitamin C intake and ALS progression (80). There have been no ALS clinical trials addressing vitamin C supplementation.

Vitamin D Vitamin D is a fat-soluble secosteroid. Sources of vitamin D include direct skin exposure to sunlight, few foods, and dietary supplements. Skin exposure to ultraviolet B radiation from the sun provides the predominant source of vitamin D. After hydroxylation in the liver and kidney to 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D respectively, the active metabolite binds to the vitamin D-receptor in a cell, and induces transcription of a responsive gene. The vitamin D receptor has been found in many tissues including motor neurons, bone and muscle cells suggesting wide physiologic influence. Vitamin D participates in several distinct pathways that are potentially important in ALS physiopathology including calcium regulation and potentiation of protective neurotrophic factors (81). In a retrospective study of 74 ALS patients, risk of death was significantly increased in those with severe vitamin D deficiency (<25 nmol/L) compared to patients with normal vitamin D (82). The authors concluded that serum vitamin D may be a reliable prognostic indicator (82). Supplementation with vitamin D in ALS mouse models has yielded mixed results (83–85). A small clinical study showed that patients with ALS tended to have low vitamin D levels and that oral vitamin D supplementation with 2000 I.U./day was safe and may be of benefit (86). Screening for 25-OH vitamin D deficiency and providing vitamin D3 supplementation for those who are deficient is reasonable (87).

Vitamin E Vitamin E is a fat soluble antioxidant comprised of tocopherols and tocotrienols. Studies in transgenic mice have shown that vitamin E can delay the onset of ALS but does not affect survival (88). Randomized trials of vitamin E supplementation did not prove efficacy (89,90). Interestingly, vitamin E intake may reduce the risk of developing ALS (91). Patients who chose to augment their vitamin E by supplementation should be cautioned that hypervitaminosis E can increase the risk of bleeding.

B. Cannabis

There is a growing body of evidence that that cannabinoids (the active ingredient in cannabis) may hold a significant therapeutic benefit for patients with amyotrophic lateral sclerosis (ALS). Moreover, through manipulation of the endocannabinoid system, cannabis may hold disease-modifying potential in ALS (92–105). There are a number of animal studies suggest that the endocannabinoid system is implicated in the pathophysiology of ALS (93–99). This may be through a direct action or disease mechanism. Conversely this may be as part of a failure of homeostatic functioning of the neuromuscular system that may be governed by this system. There is now good animal based evidence that that cannabinoids are capable of slowing disease progression of ALS in mice (93–96). The mechanisms are not entirely clear but it is likely this occurs partially by cannabinoids acting as anti-oxidants and neuromodulators, although other mechanisms are likely as well.

Cannabis has also been reported to be useful in managing the symptomatology in ALS (104). There are many symptoms of the disease, including pain, spasticity, loss of appetite, depression, and management of saliva that could be helped by cannabis use. In a survey of 131 patients with ALS, those who were able to obtain cannabis found it preferable to prescription medication in managing their symptoms (104). However, this study also noted that the biggest reason ALS patients were not using cannabis was their inability to obtain it, either due to legal or financial reasons or lack of safe access (104).

Thus there could be a potential dual role of cannabis for both clinical symptom management and a positive disease-modifying effect. There are both physiological and pharmacological mechanisms identified to support these roles. The basic mechanism of action for cannabis is the endocannabinoid system. Our understanding of the receptors and ligands composing the endogenous cannabinoid system has increased tremendously over the past few decades (106–111). There are now identified 2 major cannabinoid receptor subtypes (111,112). The type 1 (CB1) cannabinoid receptor is predominantly expressed in the central nervous system (CNS), while the type 2 (CB2) receptor is primarily found in the peripheral nervous system (PNS), immune system, cardiovascular and gastrointestinal systems, among others.

Biochemistry of the Cannabis Plant The cannabis plant is complex, with several types of subtypes of cannabis, each containing over 400 chemical moieties (113,114). Approximately 60 are chemically classified as cannabinoids (114). The cannabinoids are 21 carbon terpenes, biosynthesized predominantly via a recently discovered deoxyxylulose phosphate pathway (115). The molecular mechanism of action of the cannabinoids became much more clear with the characterization and cloning of the CB1 and CB2 receptors. Interestingly while these receptors appear to mediate most of the pharmacological actions of cannabis, there may be other orphan receptors for plant based cannabinoids (phytocannabinoids)(115,17). There are other natural plant based compounds, including flavonoids, which are structurally similar to phytocannabinoids. Over the last decade, a number of potential alternative receptors for phytocannabinoids have been suggested, based on ligand binding studies. This may also extend to the endocannabinoids, and possibly even synthetic cannabinergic drugs (116). The most recent data on these emerging “non-CB1, non-CB2 receptors cannabinoid receptors” suggests that there are still many uncharacterized or “orphan” endocannabinoid mediated G-protein-coupled receptors that have yet to be fully delineated. Moreover there are likely a whole host of cannabis plant based terpenoids that may hold therapeutic promise, including compounds such as limonene and myrcene. (118). Terpenoids share a precursor with phytocannabinoids, but display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts. There continues to be growing evidence that these non-cannabinoid components from the cannabis plant may have tremendous therapeutic potential for disease such as ALS, without any intoxicating effects (118).

The cannabinoids themselves are all lipophilic and not soluble in water. Among the most psychoactive of the cannabinoids is delta-9-tetrahydrocannabinol (THC), the active ingredient in dronabinol (119). This is the primary intoxicant in cannabis. Other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN), both of which may modify the pharmacology of THC or have distinct effects of their own (120). CBD is not psychoactive but has significant anticonvulsant, sedative, and other pharmacological activity likely to interact with THC (121–125).

Clinical Uses Cannabis in Patients with ALS The cannabinoids found in cannabis have many pharmacological mechanisms of action that can be immediately useful to help manage clinical symptoms in ALS. For example, cannabinoids been shown to produce an anti- inflammatory effect by inhibiting the production and action of tumor necrosis factor (TNF) and other acute phase cytokines (102). Additionally, cannabis may reduce pain sensation, through action at peripheral, spinal, and supra-spinal levels. It likely also operates through a brainstem circuit that also contributes to the pain suppressing effects of morphine (126–128) Cannabinoids produce analgesia by modulating rostral ventromedial medulla neuronal activity in a manner similar to, but pharmacologically distinct from, that of morphine (127,128). Cannabinoids are centrally and peripherally acting analgesics with a different mechanism of action than opioids, although the analgesia produced by cannabinoids and opioids may involve similar pathways at the brainstem level. There are now multiple, well-controlled clinical studies using cannabis to treat pain, showing ample evidence of analgesic efficacy (129,130). A recent systematic review and meta-analysis of double-blind randomized controlled trials that compared any cannabis preparation to placebo among subjects with chronic pain showed a total of eighteen completed trials. The studies indicate that that cannabis is moderately efficacious for treatment of chronic pain (129,130). In the setting of ALS, cannabis use should be dose-titrated to the point of comfort. If additional opiate medications are needed to get effective pain control then the anti-emetic effect of cannabis may help with the nausea sometimes associated with use of opioids. Use of cannabis may lower the need for opiate medications and may be safely used concomitantly as the opioid receptor system is distinct from the cannabinoid system. Additionally, the use of cannabis does not cause respiratory suppression or decreased gut motility, which are particularly helpful in this setting.

In addition to pain, spasticity is also a major problem for patients with ALS. Cannabis has an inhibitory effect via augmentation of gamma-amino-butyric acid (GABA) pathways in the central nervous system (131–133). This produces motor neuron inhibition at spinal levels in mice. Several past studies have suggested that cannabinoid therapy provide at least a subjective reduction of spasticity, although virtually all of the studies have been done in patients with multiple sclerosis (MS) (134–137). In addition to pain and spasticity, there are other pharmacological effects of cannabis that may be useful for ALS patients. Patients with ALS and bulbar symptoms also usually have difficulty controlling and swallowing the saliva that is normally present in the oral cavity. Cannabis is a potent anti-salivary compound that swiftly dries the oral cavity and upper airway, potentially reducing the risk for aspiration pneumonia and increasing patient comfort. Cannabis also increases appetite and may help prevent “ALS cachexia”, a phenomenon experienced by some patients where weight loss occurs in excess of that caused by muscle atrophy and reduced caloric intake. In addition to improving appetite, cannabis may also help with mood state and sleep. Patients with ALS previously have reported that cannabis is at least moderately effective at reducing symptoms of pain, spasticity, drooling, appetite loss, and depression (104).

The American Academy of Neurology recently published some excellent systematic literature reviews regarding the use of cannabis in neurological disorders as well as specifically in another neurodegenerative disorder, multiple sclerosis (MS) (136–137). The authors concluded that in patients

with MS, oral cannabis extracts are effective to treat spasticity "painful spasms" as well as central pain. This included including spasticity-related pain. Risk of serious adverse psychopathologic effects was estimated to be approximately 1%.

Route of administration is an important determinant of the pharmacokinetics of the various cannabinoids in cannabis, particularly absorption and metabolism (138). Cannabis does not need to be smoked to get a medical beneficial effect. Inhalation does have the advantage of rapid onset of effect and easy dose titration. However, due to their volatility, cannabinoids will vaporize at a much lower temperature than combustion, allowing them to be inhaled as a warm air mist, which is a much healthier option than smoking. Cannabinoids in the form of an aerosol in inhaled smoke or vapors are absorbed and delivered to the brain and circulation rapidly, as expected of a highly lipid-soluble drug. Cannabis may also be ingested orally, but this delivery route has markedly different pharmacokinetics compared with inhalation. The onset of action is delayed and titration of dosing is more difficult. Maximum cannabinoid blood levels are only reached up to 6 hours post ingestion, with a much longer half-life, as long as 20–30 hours (138). This would also apply to any orally ingested cannabinoid, including dronabinol (Marinol). Dronabinol is available as a Schedule III (CIII) controlled substance per the Drug Enforcement Agency (DEA) guidelines (138). The DEA still considers botanical cannabis as a Schedule I (CI) controlled substance, dangerous and without medical use (139). However, consider that natural cannabis contain, at best, 20% THC. As noted previously, there are beneficial physiological effects when the other cannabinoid forms are present, as is the case with natural cannabis plant material. Most patients with ALS would find likely find dronabinol too sedating and associated with too many psychoactive effects and it is not an appropriate substitute for natural cannabis. Finally the cannabinoids may also be made in to a liniment and absorbed through the skin, although this is the least efficient mode of delivery.

Although the medicinal use of cannabis is now allowed in a growing number of states in America, obtaining the medicine must be done through "cooperatives" as it will not be available in a typical pharmacy. This may create varying degrees of psychological stress for patients with ALS and their caregivers (140). Moreover, third party payers and insurance companies will not likely pay for cannabis use even for medical use as it is not Food and Drug Administration (FDA) approved for any indication. As long as cannabis remaining as schedule one compound, there will not likely be much interest from the pharmaceutical industry to finance the massive costs of clinical trials needed to get FDA approval for a given indication.

C. Acupuncture

Acupuncture is a technique that involves the insertion of thin needles through the skin at specific points with the goal of achieving a therapeutic effect, most often pain reduction (141). Acupuncture originated in ancient China and is a key component of traditional Chinese medicine. In the West, several different acupuncture schools and modalities are available. There are traditional Chinese and Japanese techniques and "fusion" Contemporary Western approaches, and needle insertion is sometimes accompanied by the application of small electric currents (electroacupuncture) or injection of chemicals (acupuncture injection therapy) (141,142). Such diversity is a challenge when discussing the intended effects and results of acupuncture. It is also one of the reasons why few systematic studies exist on the topic as acupuncture treatments are highly individualized, dynamic, difficult to blind, and heavily dependent on practitioner training and experience. Acupuncture has been proposed as both a symptomatic ALS treatment (pain control) and a way to slow, stop or reverse progression (143–145).

Mechanism(s) There are both traditional and modern theories on the mechanisms of acupuncture. Traditional Chinese Medicine (TCM) holds that an energy called "qi, " which flows along specific paths or meridians, regulates body functions (141,142). Disease occurs when there are disruptions or blockages in the flow of this energy, and insertion of needles into specific locations (acupoints) restores energy flow and ameliorates disease (141,142). Science has yet to find convincing evidence for qi, meridians or acupoints (142,146,147).

More theories start with needle insertions activating vaso-active substances and neuropeptides such as histamine, calcitonin gene-related peptide (CGRP), neuropeptide Y, enkephalin, beta-endorphin, and dynorphin (142, 148–151). In fact, the skin around the needles often becomes red and a small weal can be seen under the skin. Needle manipulation by hand or addition of heat or electrical stimulation (electro-acupuncture) may potentiate these effects. Some of these substances, in turn are purported to have downstream effects on brain areas involved in pain perception (150). These substances may also modulate the immune system (151–154); in doing so, they could theoretically alter the progression of diseases where the immune system plays a pathogenic role, including ALS (155–156). Indeed, elevated beta-endorphin levels (150), altered functional MRI patterns, (156–161), and even altered inflammatory markers (162–165) including in ALS animal models (164,165) can occur following acupuncture. Opioid antagonists such as naloxone or genetic down regulation of opioid receptors can block the beneficial effects of acupuncture (150).

However, even these modern theories have problems. They do not explain acupoints. "Sham" acupuncture utilizing telescoping needles that do not break the skin can sometimes work as well as "real" acupuncture, raising the possibility that acupuncture works via a placebo effect (142). The above described mechanistic studies do not yield consistent results across investigators (142).

Potential Uses in ALS While the underlying mechanisms of acupuncture have not been completely elucidated, and may involve a significant placebo component, there is some evidence that it could help relieve 2 common ALS symptoms: pain (167–170) and spasticity (171).

More controversial is the possibility that acupuncture could slow, stop or reverse ALS progression. A small, flawed study in a mouse model of ALS showed that acupuncture was associated with improved motor neuron survival and delayed loss of motor performance compared to mice that did not receive any acupuncture (172). This has yet to be independently replicated. There is only 1 published trial of acupuncture in patients with ALS (173). In this trial, 18 patients were treated twice daily for 5 days, with before and after measurements of oxygen saturation, end-tidal carbon dioxide, respiratory rate, pulse rate and ALSFRS-R. Acupuncture treatments was associated with statistically significant improvements in oxygen saturation and pulse rate. However, the size of these improvements (mean oxygen saturation increased from 95.42% to 95.58% and mean pulse rate increased from 82.49 to 80.08) are of dubious clinical significance.

More impressive than the animal study or the small trial are 2 published case series describing the effects of acupuncture on ALS (174–177). Both these series describe improvements in motor function occurring with acupuncture. Unfortunately these reports suffer from the use of other treatments (such as Chinese herbs or detoxification regimens) at the same time as the acupuncture, lack of detail regarding the ALS diagnoses, lack of a control group, lack of blinding and failure to use validated ALS outcome measures (178).

Costs and Risks Costs of acupuncture will vary greatly depending on the specific type and frequency. Within the online community PatientsLikeMe, members with ALS report a range of costs from less than $25 to more than $200 per month (179).

Large series suggest that acupuncture is generally safe but not entirely without risk. Serious adverse events have been described including cardiac tamponade (142,180), pneumothorax (142,181), and transmission of infections (142,182). Mild adverse events such as pain or bleeding occur in 7–11% of patients (142, 183–185).

D. Chelation

Chelation therapy is a medical procedure in which a chelating agent is administered to the patient with the objective of removing a specific heavy metal from the body. The chelating agent binds to the heavy metal inactivating its toxic effect. This soluble compound is then excreted from the body. The chelating agent can be administered intravenously, orally or intramuscularly.

Approved Use Chelation therapy is the main treatment for heavy metal poisoning. The chelating agent used depends on the type of metal to which the patient has been exposed. For example, Dimercaptosuccinic acid (DMSA) and Ethylenediamine tetraacetic acid (EDTA) are used in lead poisoning, and Dimercapto-propane sulfonate (DMPS) in arsenic and mercury poisoning.

Alternative Use Chelation therapy has been, and continues to be used as an alternative therapeutic approach in various conditions including autism, cardiovascular disease and cancer. This practice is not based on scientific studies and may lead to death (186,187).

Use in ALS Patients In spite of intense study over many years, there is no consistent evidence that any heavy metal toxicity can cause ALS (188,189). It should not be surprising, then, that there is no evidence that chelation therapy is useful for the treatment of ALS. In fact, there is evidence to the contrary. One case report (190) described an ALS patient with elevated blood level and massive urinary excretion of mercury which did not respond to chelation treatment with DMSA. Another case report described a patient who developed bulbar onset ALS in the setting of chronic lead intoxication from drinking water. Again, treatment with DSMA was administered for six months and had no effect on clinical course (191). Finally, a study where 53 patients with ALS or SMA and a control group were given DMSA did not show a difference in the urinary excretion of lead and mercury between the 2 groups (192). A search of the World Wide Web reveals many other individual reports of patients who did not benefit from chelation therapy.

Risks Chelation is generally felt to be a safe treatment when used properly. The use of sodium EDTA instead of calcium EDTA has resulted in severe hypocalcemia that lead to death in at least 3 reported patients (193). Another reported side effect is elevated creatinine reflecting potential kidney damage (187).

E. Energy Healing

Energy healing, which also includes spiritual and faith healing, is a branch of alternative medicine where the healer channels healing energy onto a patient in order to cure them from a certain disease. This is usually performed when the healer lays their hands on the patient, although some healers do an “off hands” method or even do remote healing with the patient being in a different location. There are many different types of energy healing. The most commonly used are spiritual healing and psychic healing, distant healing, intercessory prayer, therapeutic touch, healing touch, esoteric healing, Reiki, magnetic healing, Qigong healing, Pranic healing and Crystal healing. Some forms of energy healing use an “observable energy” such a magnet or light although in most cases, the energy is channeled via touch.

Energy Healing in Medicine Energy healing has been studied in randomized, placebo-controlled trials in multiple diseases such as asthma (194), cardiac bypass surgery (195), wound healing (196), postoperative oral pain (197), fatigue in breast cancer patients undergoing radiation therapy (198) and procedural pain in very preterm neonates (199). These robust studies have all shown no effect on the disease progression or symptoms.

Energy Healing in ALS There are no trials on the effect of energy healing in ALS patients. However, there are individual testimonials of improvement in patients with ALS with energy healing. One of these testimonials can be found on the webpage of Dean Kraft, one of the more famous energy healers in the United States. The following link: www.deankrafthealer.com/CaseHistory-NeldaBuss.html depicts the story of Nelda Buss, a patient diagnosed with ALS in 1985. Dean Kraft focused "a white stream of energy into her deteriorating respiratory system, her nerves…". She subsequently regained significant muscle strength including regaining the ability to walk. The diagnosis and improvement in this patient were independently validated (200). Many other healers have their own webpage with a story on curing ALS. In addition, there is a documentary film on healing ALS pending funding http://healingals.com/. The movie's mission is to educate people diagnosed with ALS and their families about holistic protocols for ALS that can slow, stop and even reverse the progression of ALS by showing multiple interviews with people who were diagnosed with ALS and had their disease cured through different holistic protocols. Unfortunately, along these claims of cure from ALS, there are many reports on ALS forums of lack of benefit, and high expenditure, with different type of energy healing. The fact that ALS can sometimes reverse spontaneously has to be considered as an alternate explanation for the above described improvements (201–203).

Costs and Risks The costs of energy healing vary depending on the practitioner, methods and frequency. Dean Kraft charged Nelda Buss $75 per session and $25,000 overall (200).

There appear to be no serious risks for energy healing on patient's health. However, some authors argue that promoting energy healing could be detrimental to patients and health care systems (204–206). According to the Ernst, for example, healing can be expensive and might divert patients from effective treatments. He argues that spiritual healing might promote the belief in a supernatural healing "energy," which undermines rationality in general and hence boost pseudoscience (204–206). It could also potentially divert patients from adequate, scientifically studied treatments.

III. Options for Reviewing CAM with PALS

There are at least 3 models by which decisions get made in the doctor-patient relationship. These are all options for reviewing CAM with PALS in clinic. Here we review these models and options.

A. Paternalism

The oldest model, which has existed since the beginning of medicine, is paternalism. In this, the doctor acts as a parent or guardian and defines the patient's goals and the methods for attaining these (207). Here, a patient's question about an alternative therapy might be met with a phrase from the doctor like "That is not likely to help you and may even be harmful. I do not want you to pursue that." There are several problems with this approach. While doctors do have many years of training and experience in evaluating care options, they may not always share the same goals, values and acceptable risk/benefit ratio with patients. This model ignores the fact that patients are different in terms of how they want their information presented (208). "Active seekers" want to know everything right away about their condition and all its treatment options. "Selective seekers" just want a trickle of information, just enough to make the decisions they need to make today. "Information avoiders" want to have

information and decisions filtered through someone else, often a family member or friend (208). Finally, and worst of all, paternalism has been abused, both at the bedside and in clinical research, resulting in modern malpractice and informed consent laws (209).

B. Autonomy

A newer model, fueled by the Internet, is autonomy. Here the patient's goals and methods for achieving them are assumed to be central, correct and absolute. The doctor becomes a "vending machine," helping the patient procure whatever it is they want. In this model, a question about an alternative therapy might be answered by the doctor as follows: "I understand what you want to do. How can I help?" Advantages of this model include respect for patient values and goals, and allowance for different information gathering preferences. Disadvantages include underutilization of physician education and experience, and the fact that the information being used by the patient to make their decision may be flawed or inaccurate (210).

C. Shared Decision Making

In between paternalism and autonomy is "shared decision making." Here the patient's values and goals are central, but recognized to be fluid and potentially modifiable based on new information. The physician helps define the pros and cons of different treatment options being considered, and may even make a suggestion based on their own synthesis of the data and their clinical experience. This model utilizes the talents and the skill set of the physician while sill allowing the patient to ultimately define their values, goals, acceptable risks and benefits. There is data suggesting that shared decision making is preferred by both patients (211) and doctors (212) and associated with improved compliance and better health outcomes (213). This biggest problem with shared decision making is that it takes significantly more physician time than paternalism or autonomy.

A group called ALSUntangled has developed a "shared shared decision making" model that helps with this time issue (210). There are 3 parts to this: inputs, reviews and outputs. Inputs on alternative ALS therapies come from patients and families, either via face to face visits with clinicians that are part of the group, or via email or Twitter (@alsuntangled). Reviews follow a specific standard operating procedure, with a group of 100 investigators from across 10 countries grading each alternative therapy's mechanism, preclinical data, case reports, trials and risk (214). Outputs follow a standard format as well, and are published via free open access in the journal Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration and on the website www.alsuntangled.org. Now when a patient asks about an alternative therapy, a busy clinician that wants to engage in shared decision making can refer them to an ALSUntangled review, rather than have to repeat the research themselves.

IV. Conclusions

Patients with ALS often consider CAM options, especially diets, nutritional supplements, cannabis, acupuncture, chelation and energy healing. This chapter reviews these CAM options for patients and clinicians who opt to engage in shared decision making. ALSUntangled is an international program that utilizes shared shared decision making to objectively review CAM options, reducing some of the physician time burden while helping patients make more informed treatment decisions.

Key Points

1. Patients with ALS often consider complementary and alternative therapies they read about on the Internet.
2. Common types of alternative therapies considered for ALS include special diets, nutritional supplements, cannabis, acupuncture, chelation and energy healing.
3. Physicians may handle discussions about alternative therapies via paternalism, autonomy or shared decision-making.
4. ALSUntangled reviews alternative therapies via a shared shared decision making model.

Footnotes

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