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Original Article

A prospective, proof-of-concept investigation of KPAX002 in chronic fatigue syndrome

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Abstract: Stimulant drugs and various micronutrient interventions have previously been studied in chronic fatigue syndrome (CFS) but they have never been studied in combination. This proof of concept investigation seeks to examine the clinical effects and safety profile of KPAX002 (a combination of methylphenidate hydrochloride and mitochondrial support nutrients) in patients with CFS. Fifteen patients diagnosed with CFS by 1994 Fukuda criteria were recruited and treated with KPAX002 to explore a potential synergistic effect of this combination. Fatigue and concentration disturbance symptoms were measured at baseline, 4 weeks, and 12 weeks using two clinically validated tools: Checklist Individual Strength (CIS) and Visual Analog Scale (VAS). The primary outcome objective was a decrease in the total CIS score of ≥25% in at least 50% of the subjects. The mean total CIS score decreased by 36.4 points (34%) at 12 weeks ($P<0.0001$), corresponding to a ≥25% decrease in 87% of the participants. Treatment with KPAX002 was well tolerated and significantly improved fatigue and concentration disturbance symptoms in greater than 50% of patients with CFS. These results were statistically significant. This combination treatment is worthy of additional investigation.

Keywords: Chronic fatigue syndrome, methylphenidate, mitochondria, micronutrients, antioxidants

Introduction

Chronic fatigue syndrome (CFS) is a medically unexplained ailment characterized by new onset fatigue severe enough to produce a substantial decrease in activity, plus a number of infectious, rheumatologic, and neuropsychiatric symptoms [1]. It is estimated that up to 2.5 million Americans currently have CFS, many of whom have not yet been formally diagnosed [2]. CFS can be physically, mentally, and emotionally debilitating, and persons with this diagnosis are twice as likely to be unemployed as persons with fatigue who do not meet formal CFS diagnostic criteria [3].

No CFS treatments have to date received regulatory approval by either the US Food and Drug Administration or the European Medicines Agency. Current therapy consists of using over-the-counter and prescription medications to address specific symptoms, coupled with varying levels of physical and psychological support. Although the single or combined use of graded exercise therapy, cognitive behavioral therapy, prescription medications, and micronutrient supplements may achieve symptomatic relief in some patients, the majority of CFS patients achieve marginal improvement at best, while continuing to experience frequent fluctuations of their illness [4-7].

In addition to suffering from profound fatigue, many patients with CFS have neuropsychiatric symptoms including memory complaints, cognitive slowing, and concentration disturbances [8]. In an attempt to address these symptoms, medications such as antidepressants and stimulant drugs are sometimes prescribed [9]. However, no psychoactive medications have demonstrated a consistently significant reduction in either fatigue or the many neuropsychiatric symptoms found in CFS.

Mitochondrial dysfunction is an etiologic mechanism that may explain the multisystem range of symptoms experienced by CFS patients [10]. In a case-controlled study, electron micro-

Table 1. Demographics and baseline clinical data (n=15)

Participant	Gender	Age (years)	CFS Duration (yrs)	Baseline CIS Score (20-140)
1	F	56	19	109
2	M	28	6	115
3	F	38	1	107
4	F	57	27	112
5	M	62	21	121
6	M	49	22	121
7	F	34	7	110
8	F	58	26	93
9	F	65	20	84
10	M	37	2	97
11	M	36	11	109
12	M	31	4	104
13	F	65	14	115
14	F	30	3	110
15	M	35	3	117
Mean	-	45.4	12.4	108.3

graphs of muscle biopsies have revealed abnormal mitochondrial degeneration [11]. Evidence of oxidative damage and increased activity of antioxidant enzymes have also been chemically detected in muscle specimens [12].

Myhill and colleagues have utilized an ATP-profile assay to identify significant mitochondrial dysfunction in the neutrophils of CFS patients. The degree of mitochondrial dysfunction appeared to be strongly correlated with the severity of the patient's illness [13]. In an effort to correct this dysfunction, they prescribed a regimen of mitochondrial support nutrients to be taken for several months. Their results indicate that nearly all patients who complied with the regimen showed biochemical evidence of improved mitochondrial functioning [14].

Golomb et al. describes the classic presentation for an illness manifesting mitochondrial dysfunction as one that involves multiple symptoms spanning many domains. These typically include fatigue, cognitive impairment and other brain-related challenges, muscle weakness, exercise intolerance, and gastrointestinal problems [15]. The broad symptoms profile found in CFS is consistent with their description of a mitochondrial dysfunction disease.

The CFS nutrient formula used in this trial contains micronutrients and cofactors that have consistently been shown to enhance the biochemical efficiency of mitochondrial metabolism [16]. By broadly supporting mitochondrial health and energy production in this fashion, it may be possible to significantly improve the functioning of the nervous, endocrine, and immune systems; three key bodily systems compromised by this illness.

Though many CFS patients have tried both central nervous system (CNS) stimulants and micronutrient supplements either alone or in combination, there has never been a formal research investigation studying the metabolic and clinical effects of using both concurrently. The author's hypothesis is that, when pharmacologically stimulating the cells of the central nervous system to be more active, the mitochondria of these cells may require increased micronutrient support to function more effectively.

After observing unexpectedly positive results using this innovative combination in CFS patients in the clinic, the author designed a prospective, proof-of-concept trial to systematically measure the treatment's effect on fatigue and concentration disturbance symptoms in prospectively recruited CFS patients from the general community.

Methods

Participants

Fifteen patients with CFS (8 females, 7 males; mean age 45.4 years) were prospectively recruited from the general community between November 2011 and June 2012. The subjects were consented, screened, and enrolled if they met the 1994 Fukuda criteria for a diagnosis of CFS. The majority of enrolled subjects also described moderate to severe post-exertional malaise as part of their symptoms profile. Subjects were excluded from enrollment if they possessed any medical condition that may have contributed to their chronic fatigue symptoms including systemic treatment for cancer (within the past two years), major depressive disorder, diabetes mellitus, and fibromyalgia. A trigger point examination was used to exclude patients with fibromyalgia and a normal score on the Zung Self-Rating Depression Scale was used to eliminate subjects with major depres-

Table 2. Composition of the CFS Nutrient Formula

Micronutrient	Total Daily Dosage	Micronutrient	Total Daily Dosage
N-acetyl-cysteine	1,200 mg	Magnesium	200 mg
Acetyl L-carnitine	1,000 mg	Selenium	200 mcg
Alpha lipoic acid	400 mg	Iodine	150 mcg
Beta carotene	20,000 IU	Zinc	30 mg
Vitamin C	2,000 mg	Copper	2 mg
Vitamin B_1	60 mg	Boron	2 mg
Vitamin B_2	60 mg	Potassium	100 mg
Pantothenic acid	60 mg	Iron	18 mg
Niacinamide	60 mg	Manganese	10 mg
Inositol	60 mg	Biotin	200 mcg
Vitamin B_6	60 mg	Chromium	100 mcg
Vitamin B_{12}	1,000 mcg	Molybdenum	300 mcg
Vitamin D	1,000 IU	Choline	60 mg
Vitamin E	400 IU	Bioflavonoid	300 mg
Folic acid	800 mcg	L-Glutamine	200 mg
Calcium	400 mg	Betaine HCL	150 mg

sive disorder. Additionally, any medical conditions with a contraindication to the use of methylphenidate hydrochloride (including cardiovascular disease and epilepsy) were exclusion criteria. Inclusion in this study also required a normal safety laboratory profile including complete blood count, liver function profile, kidney function tests, thyroid function tests, and fasting blood sugar. Patients were also excluded for pregnancy, current prescription stimulant use, and active substance abuse. The mean duration of a CFS diagnosis in this population was 12.4 years. Additional baseline characteristics are summarized in **Table 1**.

Experimental protocol

The study subjects were treated in open-labeled fashion with KPAX002, a combination of low-dose methylphenidate hydrochloride and mitochondrial support nutrients currently under development by K-PAX Pharmaceuticals, Mill Valley, California. **Table 2** provides the composition of the mitochondrial support nutrient formula. This treatment is nearly identical to a nutrient formula that was shown to demonstrate a statistically significant positive effect on the CD4 counts of HIV-infected patients experiencing drug-induced mitochondrial toxicity when tested in double-blinded, placebo-controlled fashion [17].

Both the mitochondrial support nutrients and the methylphenidate hydrochloride were taken b.i.d with breakfast and lunch. The dosage of the nutrient formula was 4 tablets b.i.d. The dosage of methylphenidate was initiated at 5 mg b.i.d. for the first 5 days and then dose-escalated to 10 mg b.i.d.

Dose-optimization occurred during the first 10 days. Subjects were allowed to take the maximum tolerated dosage of methylphenidate (either 10 mg, 15 mg or 20 mg per day), divided into one dose taken with breakfast and one dose taken with lunch (but not later than 3 p.m.). Patients were instructed to maintain their fluid intake at 6-8 glasses per day and to not substantially increase their level of activity during the 12-week duration of the trial.

Primary outcome measurement tool

The Checklist Individual Strength is a self-administered questionnaire consisting of 20 statements for which the person indicates on a seven-point Likert scale to what extent each particular statement applies to him or her. The CIS was developed specifically for clinical studies of patients with CFS. This multidimensional questionnaire was originally developed in 1994 by Vercoulen et al. after assessing the symptomatology of 298 CFS patients who had experienced severe disabling fatigue for greater than one year [18]. It assesses both fatigue-related symptoms and fatigue-associated behaviors (i.e., activity level, social functioning, etc.). The CIS has shown sensitivity to treatment intervention in a randomized clinical trial of cognitive behavioral therapy for patients with CFS [5], other chronic diseases [19], as well as in a study of methylphenidate hydrochloride alone (without mitochondrial support nutrients) in CFS patients [20].

The CIS is comprised of four subscales. The subscores are calculated for fatigue, concentration disturbances, motivation and physical activity. The total composite CIS score (ranging from 20-140) is obtained by adding the four individual subscales. A score of >76 is defined as the cutoff that identifies individuals at significantly increased risk of being unable to continue working [21]. The mean baseline CIS total score of the participants in this study was 108.3.

Primary endpoint: fatigue symptoms

Fatigue symptoms were measured using two clinically validated tools: (1) The CIS total score

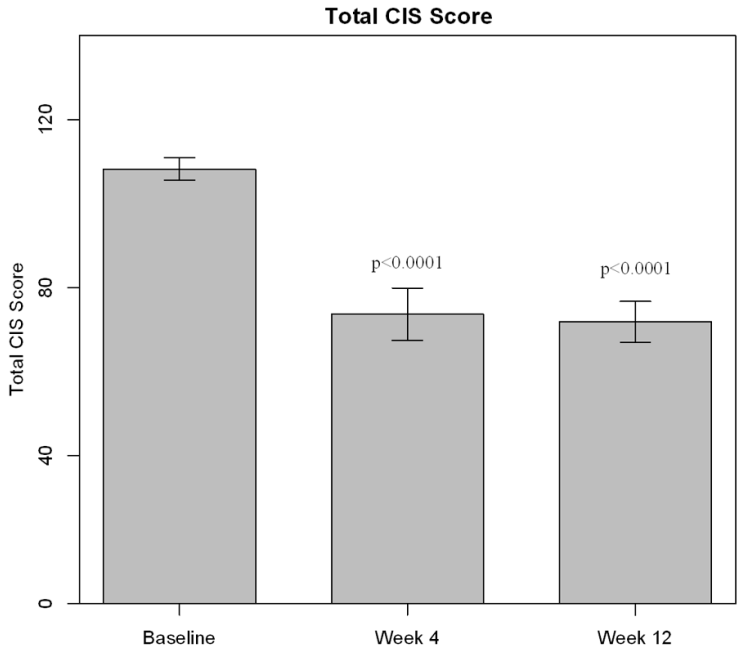

Figure 1. Mean total score on the Checklist Individual Strength at baseline, week 4, and week 12. Higher scores indicate more CFS symptoms. Statistically significant differences are compared to baseline. Error bars represent plus or minus one standard deviation.

Table 3. CIS total scores and percent changes from baseline

Participant	Baseline	4 weeks	12 weeks
1	109	104 (-5)	104 (-5)
2	115	88 (-23)	84 (-27)
3	107	64 (-40)	58 (-46)
4	112	77 (-31)	62 (-45)
5	121	40 (-67)	82 (-32)
6	121	110 (-9)	65 (-46)
7	110	33 (-70)	43 (-61)
8	93	76 (-18)	69 (-26)
9	84	56 (-33)	61 (-27)
10	97	61 (-37)	69 (-29)
11	109	105 (-4)	72 (-34)
12	104	43 (-59)	46 (-56)
13	115	74 (-36)	73 (-37)
14	110	81 (-26)	113 (-3)
15	117	93 (-21)	77 (-34)
Mean	108	73.7 (-32)	71.8 (-34)

(2) A visual analog scale (VAS) measuring subjective fatigue with a range of 0 to 10. Data was collected at baseline, 4 weeks, and 12 weeks.

The primary endpoint of this study was an improvement of ≥25% in the CIS total score in at least 50% of the study subjects.

Secondary endpoint: concentration disturbance symptoms

Concentration disturbance symptoms were measured with the concentration disturbances subscale of the CIS (5 items, range 5-35) and with a VAS (range 0-10) at time points 0, 4 weeks, and 12 weeks.

Statistical analysis

All analyses were performed on the intent-to-treat population, using the last observation carried forward method to impute missing data. The percentage of subjects achieving the primary endpoint of at least 25% improvement in total CIS score was estimated. An exact binomial 95% confidence interval for the percentage was calculated. The total CIS score, the CIS concentration disturbances subscore, and the VAS for fatigue and concentration disturbances at 12 weeks were compared to baseline values with a paired t-test. Ninety-five percent (95%) confidence intervals (CI) were also calculated for the change from baseline to 12 weeks for each of these measures.

Results

At 12 weeks, a decrease in the total CIS score of ≥25% was observed in 87% of the participants (95% confidence interval [CI], 60%-98%). The mean change in this measure at 12 weeks was -36.4 points (95% CI, -47.0 to -25.8 points), a decrease that was statistically significant (P<0.0001). This mean change corresponds to a 34% reduction from the baseline mean (**Figure 1**). The individual responses of the 15 study subjects are presented in **Table 3**.

On the VAS for fatigue, there was a statistically significant (P<0.0001) mean change of -3.5 points (95% CI, -4.9 to -2.2 points). This reduction on the VAS corresponds to a 46% reduction in fatigue symptoms from the mean baseline value.

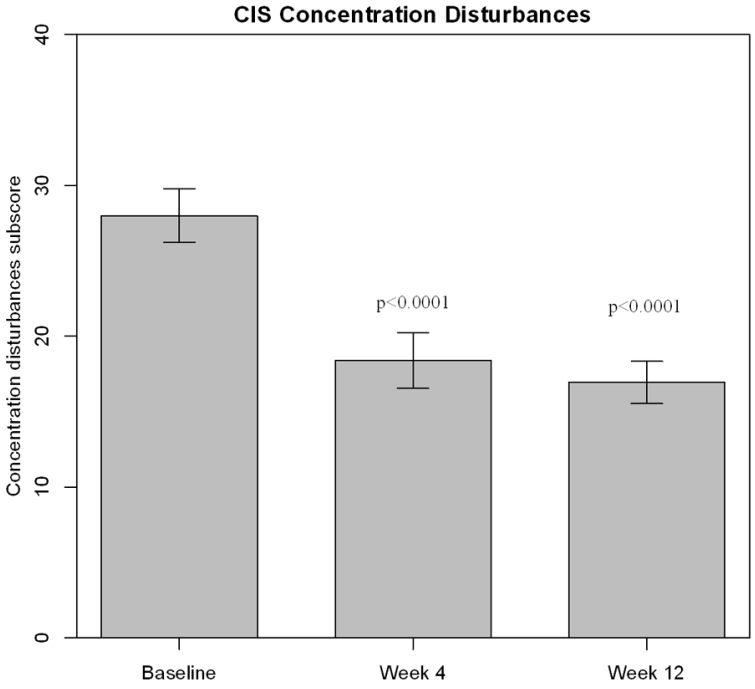

Figure 2. Mean concentration disturbances subscore on the Checklist Individual Strength at baseline, week 4, and week 12. Higher scores indicate more concentration disturbances. Statistically significant differences are compared to baseline. Error bars represent plus or minus one standard deviation.

Table 4. CIS concentration subscores and percent changes from baseline

Participant	Baseline score	4 weeks	12 weeks
1	35	21 (-40)	21 (-40)
2	32	18 (-44)	20 (-38)
3	22	11 (-50)	11 (-50)
4	33	25 (-24)	20 (-39)
5	27	11 (-59)	20 (-26)
6	33	29 (-12)	15 (-55)
7	29	6 (-79)	11 (-62)
8	17	11 (-35)	10 (-41)
9	10	11 (10)	10 (0)
10	25	17 (-32)	18 (-28)
11	31	29 (-6)	21 (-32)
12	30	19 (-37)	14 (-53)
13	31	20 (-35)	17 (-45)
14	32	23 (-28)	30 (-6)
15	33	25 (-24)	16 (-52)
Mean	28	18.4 (-34)	16.9 (-40)

At 12 weeks, a decrease in the concentration disturbances subscore of the CIS of ≥25% was observed in 87% of the participants (95% CI, 60%-98%). The mean change in this measure at 12 weeks was -11.1 points (95% CI, -14.1 to -8.0 points), a decrease that was statistically significant (P<0.0001). This mean change corresponds to a 40% reduction from the baseline mean (**Figure 2**). The individual responses of the 15 study subjects are provided in **Table 4**.

The VAS for concentration disturbance symptoms also showed a statistically significant decrease (P<0.0001). The mean decrease was -3.4 points (95% CI, -4.6 to -2.1 points) corresponding to a 50% reduction in concentration disturbance symptoms from the mean baseline value.

Fourteen of the 15 patients reported improvement in their overall condition in response to a global impression of change questionnaire, ranging from somewhat to markedly improved. The one patient who reported no improvement was taking a long-acting morphine medication to treat back pain secondary to a motor vehicle accident that occurred several years after his CFS began. It is possible that the long-acting narcotic may have blunted the treatment effect of the CNS stimulant. One subject withdrew consent after the 4-week study visit. This was the only instance in which a last observed value was carried forward.

The investigational treatment was well tolerated. The study subjects reported no nausea, diarrhea, dyspepsia, or other gastrointestinal symptoms despite consuming eight pills per day of the mitochondrial support nutrients. There were no reported exacerbations of fatigue or sleep disturbance symptoms during the trial. Occasional reports of headache resolved with increased fluid consumption. Infrequent complaints of anxiety or jitteriness resolved completely with dose reduction of the methylphenidate hydrochloride.

Discussion

This open-label, proof-of-concept trial demonstrates that co-administering low-dose methylphenidate hydrochloride with mitochondrial

support nutrients significantly improved fatigue and concentration disturbances in a majority of 15 subjects meeting the 1994 Fukuda criteria for CFS. At 12 weeks, 87% of the participants had a statistically significant ≥25% reduction in the CIS total score, meeting the primary endpoint of the study which was an improvement of ≥25% in at least 50% of the study subjects. The mean decrease in the CIS total score from baseline was -34% ($P<0.0001$). The VAS for fatigue symptoms confirmed this trend, with a reduction of 46% from baseline ($P<0.0001$). The treatment's effect on concentration disturbance symptoms was similarly positive. All patients tolerated the treatment well.

The rationale for co-administering low-dose methylphenidate hydrochloride in combination with mitochondrial support nutrients to CFS patients is that the nutrients may support mitochondrial metabolism to the extent that the benefits of the CNS stimulant (improved energy and alertness) may be experienced without long-term side effects and toxicity. The mitochondrial nutrients may also support and enhance the functioning of the nervous, immune, and endocrine systems to a level at which the stimulant drug is able to produce a positive clinical effect on CFS symptoms at less than the usual and customary dosage.

To date, the use of prescription stimulants alone as a treatment for CFS has produced inconsistent and erratic results. While modest reductions in fatigue may occur in a minority of CFS patients, many patients are either completely intolerant or experience only short-term improvement from this class of drugs. Furthermore, CFS treatment providers often counsel patients against the use of CNS stimulants due to a concern that stimulants may increase the risk of symptom exacerbations.

Stimulant trials in CFS

The only double-blinded, placebo-controlled investigation of prescription stimulants for the treatment of CFS to date demonstrated only modest benefit in a minority of patients. Blockmans et al. studied methylphenidate alone at the same dosage used in our investigation with the same primary outcome endpoint. This trial demonstrated clinically significant improvement in only 17% of subjects after four weeks of treatment [20]. Dry mouth was the only adverse event found to be significantly more common in the methylphenidate group. Their data support the view that prescribing methylphenidate to CFS patients, while not especially effective, is relatively safe for a period of 4 weeks.

Mitochondrial dysfunction in CFS

In addition to the work by Myhill et al. identifying markers of mitochondrial dysfunction in neutrophils, evidence of mitochondrial dysfunction in the central nervous system of CFS patients has been reported by Shungu and colleagues [22]. Their findings demonstrated significantly decreased glutathione levels as well as increased levels of ventricular lactate in the brains of CFS patients. This investigation utilized sophisticated imaging techniques (^{1}H magnetic resonance spectroscopic imaging and structural magnetic resonance imaging) whose validity has been replicated across several CFS cohorts [23-26]. The authors have postulated that sustained oxidative stress levels, with resultant oxidative damage, leads to cerebral hypoperfusion that can potentially explain the elevated levels of ventricular lactate. The occurrence of cerebral hypoperfusion may further increase the oxidative strain on CNS neurons, thereby leading to a vicious cycle of mitochondrial damage in the brains of patients with CFS [22, 26].

Targeted mitochondrial therapy

In order to compensate for the increased levels of oxidative stress postulated to be present in CFS sufferers, the author utilized a micronutrient supplement designed to provide highly potent antioxidants and other metabolic cofactors necessary for optimal mitochondrial functioning (K-PAX Immune®). This broad-spectrum antioxidant compound closely resembles a nutrient formula that was originally developed in 2001 as a potential antidote to the mitochondrial toxicity linked to two early HIV antiviral medications: stavudine and didanosine [27]. These medications were associated with free radical-induced distal peripheral neuropathy (DSP) in a significant percentage of patients [28].

When the prior version of this mitochondrial support nutrient formula was provided in double-blinded, placebo-controlled fashion to HIV-

infected patients with antiviral drug-induced DSP, the neuropathy scores in the micronutrient group declined by 42% compared to a 33% decline in the placebo arm. Of note, patients in the micronutrient arm also experienced a mean increase in their CD4 count of 24% compared to 0% change in the placebo arm (P=0.01) [16]. The CD4 count is an accepted measure of immunocompetence in HIV-infected patients. It is reasonable to assume that the improvement in these parameters was due to enhanced mitochondrial functioning in both peripheral neurons and CD4 lymphocytes. Bristol-Myers Squibb, maker of the aforementioned drugs exhibiting mitochondrial toxicity, provided the funding for this trial.

Given this nutrient formula's prior peer-reviewed research, commercial availability, and favorable safety record, it was a rational choice to use in combination with methylphenidate hydrochloride for this investigation.

Key mitochondrial support nutrients

There are three key micronutrients contained in the mitochondrial support nutrient formula that bear special mention due to their reported effects on improving mitochondrial metabolism. They can be viewed as comprising the "therapeutic core" of the formula.

Acetyl-L-carnitine

Acetyl-L-carnitine (ALCAR) is an ester of the amino acid, L-carnitine. It is synthesized in the human brain, liver, and kidneys by the enzyme ALCAR-transferase. It should be noted that the dosage of ALCAR contained in this nutrient formula (1,000 mg/day) is pharmacologic and not intended to correct a deficiency of this nutrient.

ALCAR is highly bioavailable and integral to mitochondrial function. ALCAR and L-carnitine facilitate the transport of long chain fatty acids across the inner mitochondrial membrane to become substrates for energy production by the beta-oxidation pathway [29]. ALCAR has been more widely utilized than L-carnitine in animal research and clinical trials exploring its potential to generate clinical benefits in conditions of disease. ALCAR is also better absorbed and more efficiently crosses the blood-brain barrier when compared to L-carnitine [30].

ALCAR has been shown to enhance acetylcholine production in neurons and to stimulate protein and membrane phospholipid synthesis [31]. Significant experimental evidence has demonstrated that ALCAR can boost mitochondrial ATP production when supplemented in pharmacologic dosages [32, 33]. Previous placebo-controlled studies of L-carnitine supplementation in elderly patients have shown significant reductions of both physical and mental fatigue [34, 35].

Alpha lipoic acid

Alpha-Lipoic acid (ALA; thioctic acid) is a highly potent antioxidant with both hydrophilic and hydrophobic properties allowing it to exert its antioxidant effects on both the interior and exterior surfaces of lipid membranes. ALA acts as a critical cofactor in mitochondrial alpha-keto-acid dehydrogenases, and thus is important in mitochondrial oxidative-decarboxylation reactions [36, 37]. It should be noted that the dosage of ALA contained in this nutrient formula (400 mg/day) is also pharmacologic and not intended to correct a deficiency.

In addition to its potent electron-donating power, ALA is capable of regenerating reduced glutathione (GSH) by regulating glutathione synthesis thus ameliorating oxidative stress [38]. The use of ALA as a treatment for chronic fatigue syndrome has not been studied in controlled clinical trials, but its widespread application as a safe supplement (usually prescribed at dosages of 200-600 mg/d) to support mitochondrial functioning and reduce oxidative stress has justified its incorporation into various supplement mixtures [37, 38].

Ames and colleagues have published seminal work on the benefits of combined ALA and ALCAR supplementation on mitochondrial functioning in rats [39]. Supplementation of ALCAR alone to older rats has produced substantial metabolic benefits including improved mitochondrial membrane potential, restored cardiolipin levels, improved cellular oxygen consumption, and increased ambulatory activity. While supplementing ALCAR alone to older rats markedly reverses the age-associated decline in many indices of mitochondrial function, it does not decrease cellular oxidative stress [40]. However, supplementing old rats with a combination of ALCAR plus ALA for several weeks sig-

nificantly improved oxidative stress levels, restored mitochondrial functioning, lowered neuron RNA oxidation, and increased rat ambulatory activity and cognition (as assayed with the Skinner box and Morris water maze) [41, 42]. These positive effects associated with combining ALCAR with ALA may be helpful in restoring the redox balance and mitochondrial health of patients with CFS.

N-acetyl-cysteine

N-acetyl-cysteine (NAC) is the n-acetyl derivative of the amino acid L-cysteine. NAC is available both as a nutritional supplement and as a pharmaceutical product (Mucomyst®, Acetadote®). In the treatment of acetaminophen overdose, intravenously administered NAC acts to replenish depleted glutathione reserves in the liver thereby reversing the buildup of free radicals and improving hepatic mitochondrial respiration [43]. NAC has also been shown in multiple other investigations to increase serum glutathione levels [44, 45].

The use of NAC supplementation, as a means to raise mitochondrial glutathione levels, may help stabilize mitochondrial redox balance and improve cellular energy production in patients with CFS. The pharmacologic dosage of NAC used in this trial may help mitigate the depletion of nutrient reserves which act as cofactors for healthy mitochondrial functioning [46]. By providing antioxidant support to the mitochondria during long-term methylphenidate treatment, CFS patients may experience improved energy and alertness without the long-term side effects normally seen when taking stimulant medications, such as methylphenidate.

Broad-spectrum supplementation

Mitochondrial enzymatic reactions require a wide range of vitamins and mineral cofactors to function. Therefore, when attempting to stimulate the mitochondria to generate more energy output, all micronutrients required for increased mitochondrial metabolism may need to be supplemented in broad-based fashion to achieve optimal results. Rather than utilizing a high dosage of a single antioxidant nutrient (e.g. vitamin C, vitamin E, acetyl-L-carnitine, or coenzyme Q-10), a broad-spectrum supplement approach was used in this investigation.

Long-term goals in CFS

While the precise etiological factors and pathophysiologic mechanisms of CFS have yet to be elucidated, it is possible that successful long-term CFS treatment will require reconstituting the nervous, endocrine, and immune systems into a functional and robust neuro-endocrine-immune axis. This effect may take a considerable amount of time to achieve and may be dependent on both the severity and duration of the patient's illness. Combining micronutrient support of mitochondrial functioning with a low dosage of methylphenidate may be able to produce a positive clinical effect on CFS symptoms over time without further depleting these systems. The need for the methylphenidate component may also diminish over time. The credibility of these assertions will require additional investigation.

There are several limitations and a source of potential bias associated with this open-label trial. First, as a current employee of K-PAX Pharmaceuticals, the author may be viewed as biased toward the success of this treatment. Second, any open-label treatment may benefit from the positive influence of a placebo effect. Third, due to the very small sample size, the treatment effect in this trial could inadvertently be skewed. Therefore, the results of this trial should be considered preliminary and need to be confirmed by a randomized, double-blinded, placebo-controlled investigation.

Conclusion

In this prospective, open-label, proof-of-concept trial, treatment of CFS patients utilizing low-dose methylphenidate co-administered with a mitochondrial support nutrient formula significantly lessened both overall CFS symptoms and concentration disturbances in a majority of CFS patients. Although lessening these two symptoms in patients with CFS is an important first step, this investigation did not formally measure the treatment's effect on the subject's functional status. The treatment was well tolerated by all the participants. A double-blinded, placebo-controlled trial is currently being conducted to further investigate the long-term potential of this intervention.

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Disclosure of conflict of interest

None.

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