Original Article

KPAX002 as a treatment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a prospective, randomized trial

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Abstract: Mitochondrial dysfunction and a hypometabolic state are present in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). KPAX002 consists of low-dose methylphenidate hydrochloride to treat a hypometabolic state combined with key micronutrients intended to broadly support mitochondrial function. The objective of this study was to evaluate KPAX002 as a treatment for fatigue and concentration disturbance symptoms in ME/CFS subjects. This phase 2 randomized, double-blinded, placebo-controlled trial was conducted at 4 sites in the United States. A total of 135 subjects with ME/CFS were randomly assigned to either KPAX002 (n=67) or placebo (n=68) for 12 weeks of treatment. The primary endpoint was change in the Checklist Individual Strength (CIS) total score from baseline to Week 12. Secondary measurements included visual analog scales for fatigue and concentration disturbance symptoms. In the intent-to-treat population, the mean reduction in the CIS total score from baseline to week 12 for the KPAX002 and placebo groups was -16.9 (± 23.52) and -13.8 (± 22.15), respectively (95% confidence interval, -11.1, 4.0; \( P = 0.359 \)). On the visual analog scale for fatigue, the mean reduction from baseline to week 12 was -18.2 mm (± 25.05) and -11.1 mm (± 22.08) for the KPAX002 and placebo groups, respectively (95% confidence interval, -11.5, 2.3; \( P = 0.189 \)). The two groups demonstrating the most robust response to KPAX002 were subjects with more severe ME/CFS symptoms at baseline (\( P = 0.086 \)) and subjects suffering from both fatigue and pain (\( P = 0.057 \)). The incidence of adverse events was not statistically different between the two groups. Treatment with KPAX002 resulted in a reduction in fatigue and concentration disturbance symptoms in multiple analyses. Two key subgroups of patients whose response approached statistical significance were identified.

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

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, chronic, and highly variable neurodegenerative disease producing numerous symptoms that span multiple domains. The disease is characterized by new-onset fatigue persisting for at least 6 months that is severe enough to produce a substantial decrease in activity or function [1]. In 2015, based on a comprehensive literature review, and with input from patients, advocates, and researchers, the Institute of Medicine recommended that, in addition to at least 6 months of disabling fatigue, a patient must also suffer from symptoms of post-exertional malaise, unrefreshing sleep, and either cognitive impairment or orthostatic intolerance [2]. Despite a total economic burden estimated at between $17 billion and $24 billion in the United States annually, ME/CFS has defied all efforts to identify a single cause or successful treatment [3].

Systemic mitochondrial dysfunction is an etiologic mechanism that can potentially...
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explain the multisystem range of symptoms experienced by patients with ME/CFS [4]. A growing body of evidence suggests that the presence of a highly oxidative environment, with decreased utilization of mitochondrial oxidative phosphorylation and an overreliance on anaplerotic amino acids to fuel the Krebs cycle, may play a significant role in this condition [5-7]. Recent reports by several independent researchers have provided additional metabolomic evidence, which suggests that mitochondrial dysfunction, associated with a hypometabolic state, is a key physiologic component of the ME/CFS phenotype. It is further postulated that ME/CFS symptoms may be adaptive in nature in order to prevent further oxidative damage to the individual, however this comes at the cost of a substantial decrease in functional capacity [8].

The combination of mitochondrial dysfunction coupled with the presence of a hypometabolic state suggests that potential benefit may be achieved by a treatment combining a targetted mitochondrial support intervention with a low-dose central nervous system (CNS) stimulant. The use of a CNS stimulant also has the potential to improve the decreased alertness and concentration disturbance symptoms frequently reported by ME/CFS patients [9].

KPAX002 is comprised of a low dosage of methylphenidate hydrochloride, a CNS stimulant previously shown to have a positive effect in ME/CFS patients [10], co-administered with a unique combination of mitochondrial-modulating nutrients. This mitochondrial modulator was initially developed as a means to reverse the mitochondrial toxicity associated with early HIV/AIDS antiviral drugs (i.e., nucleoside reverse transcriptase inhibitors) [11]. It contains key nutrients and cofactors integral to the normal process of mitochondrial metabolism [12].

After unexpectedly positive results using this combination therapy were observed in a clinical setting, a phase 1 trial was performed, which demonstrated that KPAX002 had a rapid and well-tolerated effect on reducing fatigue and concentration disturbance symptoms in ME/CFS patients [13]. The goal of this expanded, phase 2 investigation was to further explore the safety, tolerability, and efficacy of KPAX002 to reduce fatigue and concentration disturbance symptoms experienced by ME/CFS patients.

Methods

Design overview

This was a phase 2 randomized, double-blind, placebo-controlled, parallel-arm investigation. The study was conducted at four sites across the United States: Palo Alto, CA; Salt Lake City, UT; New York, NY; and Fort Lauderdale, FL. All participants provided written informed consent in accordance with the protocol approved by the Institutional Review Board at each site.

Study participants

Participants were eligible for inclusion if they were between ages 18 and 59, met the 1994 Centers for Disease Control and Prevention (CDC) Fukuda criteria for ME/CFS [14], complained of alertness and/or concentration deficits, and were otherwise in good health based on medical history and screening evaluation. Participants also had to be willing not to use any nutritional, herbal, or caffeine-containing supplements or any pseudoephedrine-containing products during the trial. Participants were excluded from the study for pregnancy, active substance abuse, major depression as defined by a Zung Depression Scale Score greater than 60, active medical conditions for which treatment with methylphenidate hydrochloride may be contraindicated, daily use of anxiety medications, daily concurrent use of more than one antidepressant, and use of medications such as monoamine oxidase inhibitors, other CNS stimulants, and narcotic opioids. Those who had clinically significant laboratory test values or electrocardiogram abnormalities were also excluded.

Randomization and blinding

Randomization allocation was 1:1 to active treatment and placebo, respectively. Random block sizes of 2 and 4 were used and blocking occurred by site. Appropriate randomization codes were automatically provided to the site by the electronic research management system used in this trial immediately after randomization was requested. During the entire study, the patients and study site personnel
were blinded to all study treatment assignments.

**Intervention**

The KPAX002 treatment consisted of the simultaneous administration of methylphenidate hydrochloride with a mitochondrial modulator. The mitochondrial modulator included vitamins, antioxidants, and amino acids designed to broadly support mitochondrial function (Table 1). The dosage of the mitochondrial modulator was four tablets twice daily. The dosage of the methylphenidate was 5 mg twice daily for week 1 and 10 mg twice daily for weeks 2 through 12. Subjects were allowed to decrease methylphenidate to the original lower dosage for tolerability issues. Both the treatment and matched placebos were taken twice daily with breakfast and lunch for 12 weeks.

**Clinical efficacy assessments**

The primary clinical efficacy assessment was the Checklist Individual Strength (CIS) total score. The CIS is a validated 20-question patient-reported outcome assessment tool that has previously been used in ME/CFS studies,[15] including two trials of methylphenidate hydrochloride for ME/CFS treatment[10, 13]. The CIS is made up of four subscales: fatigue, concentration, motivation, and physical activity. The total CIS score ranges from 20 to 140. A higher score indicates increased fatigue and reduced concentration, motivation, and activity.

The primary outcome was the change from baseline to week 12 in CIS total score. Secondary outcomes included changes in a visual analog scale (VAS) for fatigue and a VAS for concentration disturbance symptoms from baseline to week 12, and safety.

**Statistical analysis**

Efficacy of the treatment was assessed by comparing the mean change from baseline in treatment and placebo groups for the primary endpoint: the CIS total score. The primary efficacy analysis was the test of the treatment effect at week 12, tested with a 2-sided test at significance level α=0.05, and was performed on the intent-to-treat (ITT) population, using last observation carried forward imputation. CIS total scores were analyzed with a repeated-measures mixed effects model, visit (week 4 or week 12), treatment-by-visit interaction, baseline CIS total score as fixed effects, and site and patient, nested within site, as random effects. A treatment-by-site interaction effect was explored in the analysis and retained in the model if the significance was at a level of α=0.10. The placebo group was used as the reference group, where applicable.

Each secondary efficacy outcome was analyzed in a similar manner as described for the primary efficacy analysis. Safety was assessed with summaries of adverse events for each treatment group and visit.

**Results**

**Baseline characteristics**

Between December 2013 and September 2014, a total of 180 subjects were screened for eligibility at four ME/CFS research sites in the United States. Of the 135 subjects randomized, 128 took at least one treatment dose (ITT population) with 105 subjects completing the trial per protocol (Figure 1).

The demographic characteristics of the ITT population at baseline were well balanced between the two groups (Table 2). The mean age
of subjects was 42.8 years in the KPAX002 group and 42.3 years in the placebo group. Seventy-two percent of the subjects were female and 28% were male. A significant majority was white (91%) and non-Hispanic (92%), reflecting the demographics of the study sites. The average duration of ME/CFS symptoms in both groups was similar (11.3 years, treatment group vs. 11.8 years, placebo group). The mean score for the primary outcome measure (CIS total score) at baseline was also similar in both groups (112.2, treatment group and 112.4, placebo group). There were no statistically significant differences in this value between the four sites (P=0.165).

A review of concomitant medication use in the ITT population revealed the following usage at baseline: anti-viral medications (16%), anti-depressant therapy (27%), prescription medication for sleep (34%), and non-opioid medications for pain management (48%).

**Efficacy outcomes**

In the ITT population, the mean change in the CIS total score from baseline to week 12 for the KPAX002 and placebo groups was -16.9 (± 23.52) and -13.8 (± 22.15), respectively (95% confidence interval [CI], -11.1, 4.0; p=0.359) (Figure 2).

On the VAS for fatigue, the mean change from baseline to week 12 was -18.2 mm (± 25.05) and -11.1 mm (± 22.08) for the KPAX002 and placebo groups, respectively (95% CI, -11.5, 2.3; p=0.189). With respect to the VAS for concentration disturbance symptoms, the
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Figure 2. Mean change in CIS total score from baseline to week 12 in treatment and placebo groups. Higher scores represent more severe ME/CFS symptoms.

The mean change from baseline to week 12 was -16.8 mm (± 27.68) and -12.8 mm (± 29.82) for the KPAX002 and placebo groups, respectively (95% CI, -12.1, 4.6; p=0.379).

Planned efficacy sub-analyses identified two key subgroups of ME/CFS subjects who demonstrated the best response to KPAX002. In the subjects with more severe ME/CFS symptoms at baseline (baseline CIS total score ≥110), the mean change in CIS total score from baseline to week 12 for the KPAX002 and placebo groups was -22.4 (± 20.70) and -11.0 (± 21.40), respectively (95% CI, -17.6, 1.2; p=0.086) (Figure 3A). In the subjects with both fatigue and pain (subjects taking analgesics for >5 days during the study), the mean reduction in CIS total score from baseline to week 12 for the KPAX002 and placebo groups was -17.4 and -8.2, respectively. The difference between the two arms in this sub-analysis approached statistical significance (95% CI, -18.7, 0.3; p=0.057) (Figure 3B).

Adverse events

The incidence of adverse events was not statistically different between the treatment and placebo groups (Table 3).

In the treatment group, the most commonly reported adverse events (Grade 2 or greater) were headache (14%), anxiety (8%), fatigue (8%), and dizziness (6%). In the placebo group, the most commonly reported adverse events (Grade 2 or greater) were headache (7%), anxiety (7%), fatigue (6%), and dizziness (1%).

A total of 11 subjects reported adverse events leading to early discontinuation from the study, including 8 subjects in the KPAX002 group and 3 subjects in the placebo group. There was one serious adverse event reported during the study in a subject randomized to the KPAX002 group. This subject was diagnosed with pyelonephritis a day after completing the trial. This event was assessed as being unrelated to the study medication and resolved 3 days after onset with appropriate treatment.

Discussion

This phase 2 double-blind, placebo-controlled trial adds to the findings of a previously published phase 1 trial exploring the safety and efficacy of KPAX002 as a potential treatment for ME/CFS [13]. The results of all planned efficacy analyses showed a trend in favor of the KPAX002 treatment group when compared to placebo. The treatment and placebo groups showed no significant difference with regard to rates of treatment-emergent adverse events (Grade 2 or greater), which is notable since side effects such as anxiety, palpitations, dizziness, and insomnia are frequently reported with methylphenidate administration [16, 17].

During 12 weeks of treatment, KPAX002-treated subjects demonstrated improvement in multiple outcome measures, including the CIS total score and the VAS for fatigue and concentration disturbances. Two key subgroups with the greatest treatment response were identified: 1) subjects with more severe ME/CFS symptoms at baseline and 2) subjects with both fatigue and pain. Subjects in
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Figure 3. Pre-planned sub-analyses identified two key subgroups. A. Subgroup 1: Subjects with worse ME/CFS symptoms at baseline ($p=0.086$). B. Subgroup 2: Subjects with concomitant analgesic use for >5 days during the study ($p=0.057$).

both these groups experienced a greater treatment effect and a diminished placebo response when compared to the total sample. It is reasonable to assume that sicker (more symptomatic) ME/CFS subjects are more likely to have significant mitochondrial pathology and would therefore demonstrate an enhanced response to a mitochondrial support treatment [18].

Methylphenidate alone at a dosage of 20 mg/day has previously been shown to significantly improve fatigue and concentration disturbance symptoms in ME/CFS patients when compared to placebo [10]. Blockmans et al. used methylphenidate alone at the same dosage as our investigation and utilized the same primary outcome variable (change in CIS total score). One goal of the current trial was to investigate a possible potentiating effect by combining a mitochondrial modulator with methylphenidate as a treatment for ME/CFS.

Adding the mitochondrial modulator to the same dosage of methylphenidate used in the Blockmans trial provided an additional reduction of 4.2 points in the CIS total score at 4 weeks (16 vs. 11.8 points). However, the change in the CIS total score in the placebo arms varied greatly between the two trials. The placebo arm in the Blockmans trial declined by only 3 points compared to a placebo arm reduction of 13.1 points in the current trial [10].

Since both trials encompassed a similar target population (1994 CDC Fukuda case definition), primary outcome measure (change in CIS total score), and stimulant drug and dosage (methylphenidate 20 mg/day), the wide disparity in the placebo effect between these two trials warrants additional examination.

The placebo effects reported in previous ME/CFS intervention trials differ widely. A 2005 meta-analysis showed a pooled placebo response of 19.6% for ME/CFS intervention trials [19]. In recent ME/CFS randomized controlled trials, placebo responses have ranged from 18% to 40% [20-22]. In comparison, the average placebo response reported in trials in major depressive disorder is 29.7%
Table 3. Treatment-Emergent Adverse Events (Grade II or greater) in ≥ 5% of Patients, n (%)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>KPAX002 (n=64)</th>
<th>Placebo (n=67)</th>
<th>p valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>9 (14)</td>
<td>4 (6)</td>
<td>0.1500</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (8)</td>
<td>5 (7)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4 (6)</td>
<td>5 (7)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (6)</td>
<td>1 (2)</td>
<td>0.2011</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

a, KPAX002 vs. Placebo comparison used the Fisher’s exact test.

[23], while the pooled placebo response in fibromyalgia trials has been reported as 18.6% [24]. Intervention trials that rely on patient-reported outcomes or observer-reported outcomes (with patient involvement) are associated with larger placebo effects [25]. ME/CFS trials may also be subject to publication bias, in which trials that find no significant differences between treatment and placebo (possibly due to large placebo effects) are less likely to be published.

The design of future ME/CFS intervention trials should take into consideration the placebo responses reported above. In addition, incorporating more objective outcome measures, such as activity tracking with wearable devices, may more accurately distinguish between a clinically relevant treatment response and a pure placebo effect.

Study limitations

Interpretation of this study’s results is limited by a relatively small sample size as well as the use of subjective outcome measurement tools. Additionally, the use of the 1994 CDC Fukuda diagnostic criteria, which do not require the presence of post-exertional malaise, may have allowed the inclusion of subjects whose fatigue was due to conditions other than ME/CFS as it is currently defined by the 2015 Institute of Medicine recommendations [2].

Treatment rationale

Mitochondrial dysfunction can simultaneously affect the cells of many organ systems and is frequently associated with a waxing and waning pattern of symptoms [26]. Emerging evidence supports the possibility that ME/CFS represents a secondary mitochondrial disease resulting from long-term exposure to excessive oxidative stress [26-28]. Primary mitochondrial diseases occur due to genetic mutations in mitochondrial DNA and/or nuclear DNA genes responsible for encoding key mitochondrial proteins. Secondary (acquired) mitochondrial diseases exhibit mitochondrial dysfunction not directly due to germline mutations but have been increasingly implicated in adult-onset multifactorial disorders including diabetes, fibromyalgia, and several neurodegenerative disorders [29-32]. Primary and secondary mitochondrial diseases are difficult to distinguish and often include symptoms of fatigue, muscle weakness, neuropathic pain, migraines, neurocognitive abnormalities and exercise intolerance [26].

There are several reasons why a mitochondrial modulator comprises one component of KPAX002. The initial reason was based on the findings of several studies identifying mitochondrial dysfunction as a significant component of ME/CFS pathophysiology. Myhill et al. demonstrated measurable evidence of abnormal mitochondrial functioning in a cohort of 138 ME/CFS patients using an adenosine triphosphate (ATP) profile assay. The observed decrease in ATP production correlated with patients’ illness severity and may be due to a lack of essential nutrient substrates [33, 34]. Additionally, Shunghu et al. reported increased levels of ventricular lactate in the brains of ME/CFS patients, an acknowledged marker of mitochondrial dysfunction [35].

The ability of a mitochondrial modulator to ameliorate medication side effects was previously demonstrated by Kaiser et al., who used an intervention similar to that used in KPAX002 to reduce mitochondrial-toxic side effects linked to two early HIV antiviral medications: stavudine and didanosine. In a double-blinded, placebo-controlled trial in 40 HIV-infected patients with mitochondrial-related toxic neuropathy, neuropathic pain symptoms were reduced by 42% in the subjects treated with the mitochondrial support intervention for 12 weeks [36].

The addition of a mitochondrial modulator may also enable methylphenidate to exert a positive clinical effect at less than its usual and customary dosage. This is based on the
assumption that, at baseline, CNS neurons of ME/CFS patients are incapable of generating the energy necessary to meet the demands of the stimulant drug. By supporting mitochondrial bioenergetics with key antioxidants and other nutrient cofactors, cellular metabolism can be improved, rendering the stimulant drug more effective at a given dosage.

**The mitochondrial modulator**

The mitochondrial modulator is comprised of key antioxidants and other micronutrients not found in most multivitamins. These nutrients were selected based on prior research findings demonstrating their ability to produce clinical benefits in patients with mitochondrial dysfunction [36-38]. The following nutrients were dosed at therapeutic levels designed to address the metabolic needs of dysfunctional mitochondria and comprise the therapeutic core of the intervention.

**Acetyl-L-carnitine** (ALCAR) is an ester of the amino acid L-carnitine. It is integral to healthy mitochondrial functioning and is highly bioavailable. ALCAR facilitates the transport of long-chain fatty acids across the inner mitochondrial membrane to provide substrates for energy production by the beta-oxidation pathway [39]. ALCAR has been more widely utilized than L-carnitine in animal research and human clinical trials. It is also better absorbed and more efficient at crossing the blood-brain barrier when compared to L-carnitine [40]. Significant experimental evidence has demonstrated that ALCAR can boost mitochondrial ATP production when supplemented in pharmacologic dosages [41, 42].

**Alpha lipoic acid** (ALA; thioctic acid) is a highly potent antioxidant that acts as a critical cofactor in mitochondrial oxidative decarboxylation reactions [43, 44]. As a potent electron donor, ALA is capable of regenerating reduced glutathione, thus ameliorating oxidative stress [45]. Ames and colleagues published seminal work on the benefits of combining ALA and ALCAR as an intervention for improving mitochondrial function [46]. In rats, supplementation with ALA plus ALCAR for several weeks significantly improved oxidative stress levels, restored mitochondrial functioning, lowered neuronal RNA oxidation, and increased ambulatory activity and cognition (as assayed with the Skinner box and Morris water maze) [47-49].

**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®). As an approved treatment for acetaminophen overdose, intravenously administered NAC acts to replenish depleted glutathione reserves in the liver, thereby reversing the buildup of oxidative stress and improving hepatic mitochondrial recovery [50]. NAC has also been shown in multiple clinical investigations to increase serum glutathione levels [51, 52]. Furthermore, a recent study demonstrated that NAC exposure produces significantly increased survival rates in human embryonic stem cell neurons exposed to rotenone, a potent mitochondrial toxin [53]. Supplementing NAC may help stabilize mitochondrial redox balance and improve cellular energy production in patients with ME/CFS.

**L-tyrosine.** Methylphenidate acts to potentiate dopamine and norepinephrine via a presynaptic, reuptake inhibitor mechanism. The amino acid L-tyrosine is a dopamine precursor whose oral supplementation has been shown to increase dopamine and norepinephrine levels [54]. Supporting dopamine and norepinephrine metabolism in this manner may allow methylphenidate to be more potent at a given dosage.

**Conclusion**

ME/CFS has been described as a hypometabolic state with significant underlying mitochondrial pathology. In this study, combining a mitochondrial modulator with low-dose methylphenidate hydrochloride exhibited potential to improve the drug’s safety and efficacy as a treatment for ME/CFS. Despite the primary outcome not achieving statistical significance in this relatively small trial, two key subgroups were identified on preplanned sub-analyses that demonstrated a more robust treatment effect. These included subjects with more severe ME/CFS symptoms and those experiencing both fatigue and pain. Based on these results, additional investigation of KPAX002 is warranted.
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Disclosure of conflict of interest

None.

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References


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