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Treatment for Gulf War Illness (GWI) with KPAX002 (methylphenidate hydrochloride + GWI nutrient formula) in subjects meeting the Kansas case definition: A prospective, open-label trial (revision 2)

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ABSTRACT

This study tested the safety, tolerability, and efficacy of KPAX002—a combination of methylphenidate hydrochloride plus a micronutrient formula designed to support mitochondrial function—as a treatment for Gulf War Illness (GWI). This open-label trial enrolled 17 subjects meeting the Kansas case definition for GWI. Of the 17 subjects enrolled, 15 qualified for the Intent-to-Treat (ITT) population with 10 subjects completing the trial per protocol. All analyses were on the ITT population. At 12 weeks, subjects taking KPAX002 experienced a mean 25% reduction in their overall GWI symptoms severity as measured by the GWI Symptoms Assessment Tool (SAT) ($p < 0.001$). Visual analog scale scores were also significantly reduced for fatigue ($p = 0.019$), cognitive symptoms ($p = 0.006$), sleep problems ($p = 0.026$), and pain ($p = 0.05$). Twelve weeks of KPAX002 administration resulted in a significant improvement in GWI symptoms with an acceptable side effect profile. A larger randomized, double-blinded, placebo-controlled trial is necessary to determine if the observed benefit can be replicated.

1. Introduction

Gulf War Illness (GWI) is a complex, chronic, and highly variable disease producing numerous symptoms spanning multiple domains. In 1996, the Centers for Disease Control (CDC) conducted a study of nearly 4000 military personnel which showed that US veterans of the 1990–1991 Gulf War were reporting more medical and psychiatric conditions than their military peers. Approximately one-third of these veterans presented with multiple symptoms. This constellation of symptoms is now called Gulf War Illness (GWI). GWI symptoms include chronic fatigue, cognitive dysfunction, depression, immune-mediated respiratory disorders including asthma and bronchitis, and gastrointestinal (GI) complaints (Kang et al., 2000). Despite over 20 years of research, a definitive pathophysiologic mechanism for GWI has not been conclusively identified although many objective abnormalities have been defined.

Although no unanimously accepted GWI definition exists, several definitions have been proposed that incorporate GWI symptoms into multiple domains, including mood/cognition, musculoskeletal, gastrointestinal, respiratory, and neurological. These include the CDC definition and the Kansas case definition (Steele, 2000), which is the most discriminating definition. A 2013 Institute of Medicine report on GWI recommended that the Veterans Administration systematically assess existing data to identify additional features of GWI, such as onset, duration, severity, frequency of symptoms, and exclusionary criteria to produce a more robust case definition (Institute of Medicine. 2013. *Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Re-examined*. Washington, DC: The National Academies Press. https://doi.org/10.17226/18623.)

There are currently no treatments for GWI that have been approved by the Food and Drug Administration. Treatment often consists of the use of over-the-counter and prescription medications to address specific symptoms, coupled with an appropriate level of emotional and psychological support. Symptom relief is currently the primary goal of a GWI treatment plan.

Emerging evidence supports the possibility that GWI may represent a secondary mitochondrial disease resulting from long-term exposure to multiple toxicants leading to a cellular buildup of oxidative stress

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(Golomb, 2012). Primary mitochondrial diseases occur due to genetic mutations in mitochondrial DNA and/or nuclear DNA genes responsible for encoding key mitochondrial proteins. Though not directly due to germline mutations, secondary (acquired) mitochondrial diseases exhibit mitochondrial dysfunction and have been increasingly implicated in adult-onset multifactorial disorders (Niyazov et al., 2016). Mitochondrial dysfunction can simultaneously affect the cells of many organ systems and is frequently associated with a waxing and waning pattern of symptoms. 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 (Byun and Baccarelli, 2014; Niyazov et al., 2016).

KPAX002 consists of two co-administered components: a low dosage of methylphenidate in combination with a micronutrient formula specifically designed to support mitochondrial metabolism. This micronutrient formula (i.e., mitochondrial modulator) is comprised of key antioxidants and other micronutrients selected based on research findings demonstrating their ability to produce clinical benefits in patients with mitochondrial dysfunction (Hart et al., 2004; Herzenberg et al., 1997; Kaiser et al., 2006). Improved mitochondrial metabolism would be supportive of the functioning of all bodily systems, including the nervous, endocrine, and immune systems.

Methylphenidate hydrochloride (Ritalin®) is well known to stimulate CNS neuronal activity by increasing dopamine and norepinephrine levels via a reuptake inhibitor mechanism. It is our hypothesis that augmenting methylphenidate treatment with broad-spectrum mitochondrial support will significantly enhance the drug's ability to generate a sustained improvement in fatigue and cognitive dysfunction symptoms in GWI subjects. Without concurrent mitochondrial support, the benefit of CNS stimulation by methylphenidate is potentially blunted by a shortage of adenosine triphosphate (ATP) generation due to compromised mitochondrial function. The dosage of methylphenidate used in this investigation was based on extensive clinical experience using this combination treatment in patients with GWI and Chronic Fatigue Syndrome (Kaiser J.D., 2015).

Herein, we describe the clinical effects of KPAX002 administration in veterans with GWI.

2. Methods

2.1. Design overview

This was a Phase 2 open-label investigation. The clinical site for this study was the Veterans Affairs Palo Alto Health Care System (VAPAHCS) located in Palo Alto, California. All participants provided written informed consent in accordance with the protocol approved by the Stanford University Institutional Review Board and the Human Research Protection Office (HRPO) of the United States Army Medical Research and Material Command.

2.2. Study participants

Participants were eligible for inclusion if they were between ages 18 and 64 years and met the Kansas case definition for GWI. The Kansas GWI case definition has both exclusionary and inclusionary components. Veterans are excluded from consideration as a GWI case if they have been diagnosed by a physician with (1) chronic conditions (e.g., cancer, heart disease) that are not associated with Gulf War service but can produce diverse symptoms (e.g. fatigue, cognitive problems, pain) similar to those affecting Gulf war veterans, or (2) conditions that might interfere with respondents' ability to report their symptoms (e.g. serious psychiatric conditions). Inclusionary criteria require that veterans possess moderately severe and/or multiple symptoms in at least 3 of 6 symptom domains, and that those symptoms first became a problem during or after the 1990–91 Gulf War.

Screening for GWI was performed with an initial pre-visit telephone interview followed by an in-person screening evaluation. As conditions for participating in this trial, participants were asked to cease the use of any nutritional, herbal, or caffeine-containing supplements, any pseudoephedrine-containing products, and any prescribed stimulant medications (other than the study treatment). Participants were excluded from participation in the case of pregnancy, active substance abuse, prior hospitalization for alcohol or drug dependence within the previous five years, major depressive disorder, or post-traumatic stress disorder. Exclusion criteria also included active medical conditions for which treatment with methylphenidate may be contraindicated. This included the daily use of any medication to treat anxiety (since anxiety disorder is a contraindication to methylphenidate use). Subjects with clinically significant clinical laboratory test values or electrocardiogram abnormalities were also excluded.

2.3. Recruitment

Subjects were recruited for this study through the posting of study information flyers within the VAPAHCS campus, video announcements through closed-circuit TV in inpatient rooms and clinic waiting rooms, briefings given to Veterans service organizations and the posting of study information on Veteran service organization websites. While these efforts primarily reached GWI patients within the geographical region served by the VAPAHCS campus, several subjects became aware of the trial from outside the VAPAHCS region and traveled a significant distance to participate.

2.4. Intervention

The GWI Nutrient Formula (mitochondrial modulator) was manufactured by K-PAX Pharmaceuticals (Mill Valley, California) as per Good Manufacturing Practices guidelines and was dispensed by the Palo Alto Veteran's Administration pharmacy. The dosage of the GWI Nutrient Formula was four tablets taken twice daily with food. The exact nutrient dosages contained in the GWI Nutrient Formula can be found in Table 1.

Methylphenidate hydrochloride was also dispensed by the VAPAHCS pharmacy. The dosage of methylphenidate was 5 mg twice daily for Week 1 and 10 mg twice daily for Weeks 2 through 12. Subjects could decrease the methylphenidate component to a lower dosage, as needed based on tolerability. Phone calls were made to each subject on days 7 and 14 where study drug tolerance was assessed. Based on subject report, the decision was made to either increase methylphenidate dosing per protocol or maintain or decrease dosing. Study drug compliance was assessed during each study visit. Both components of the treatment were taken in separate tablet form twice

Table 1
Composition of GWI nutrient formula.

Micronutrient	Total Daily Dosage	Micronutrient	Total Daily Dosage
N-acetyl-cysteine	1000 mg	Folic acid	800 mcg
Acetyl L-carnitine	1000 mg	Calcium	200 mg
L-tyrosine	800 mg	Magnesium	100 mg
Alpha lipoic acid	400 mg	Zinc	30 mg
L-taurine	400 mg	Selenium	200 mcg
Beta carotene	10,000 IU	Iodine	150 mcg
Vitamin C	1000 mg	Copper	2 mg
Vitamin B1	60 mg	Boron	2 mg
Vitamin B2	60 mg	Potassium	100 mg
Pantothenic acid	60 mg	Iron	18 mg
Niacinamide	60 mg	Manganese	10 mg
Inositol	60 mg	Biotin	800 mcg
Vitamin B6	120 mg	Choline	60 mg
Vitamin B12	2000 mcg	Chromium	100 mcg
Vitamin D	2000 IU	Molybdenum	300 mcg
Vitamin E	400 IU		

daily with breakfast and lunch for 12 weeks.

2.5. Clinical efficacy assessments

The primary clinical efficacy assessment was the GWI Symptoms Assessment Tool (SAT). This is a modified version of the "GWI Screening Tool" created by Dr. Lea Steele to diagnose patients with GWI based on the Kansas case definition (Steele, 2000). The GWI Screening Tool asks several questions related to multiple domains, including fatigue, pain, cognitive, mood, skin, gastrointestinal, and respiratory. Each question is assessed on an ordinal scale, as either no or yes, with one of three severity levels (mild, moderate, or severe). We converted this screening tool into a quantitative evaluation of total GWI symptomatology by summing the scores in each domain into a quantitative overall score. The SAT total score represents the cumulative score of each GWI symptom present, including its severity rating, with a range from 0 to 87. Higher scores corresponded to more severe symptomatology. To qualify for a diagnosis of GWI based on the Kansas case definition, a subject needed to enter the study with a score of 2 or greater in at least three different domains, producing a minimum score of 6.

We also utilized a secondary efficacy assessment tool known as 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 myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) research studies (Vercoulen et al., 1994), including two previous trials of KPAX002 for the treatment of ME/CFS (Blockmans et al., 2006; Kaiser, 2015). The CIS is made up of four subscales: fatigue, concentration, motivation, and physical activity. This assessment tool was originally designed to measure the ability of individuals within a population to engage in work activities. The total CIS score ranges from 20 to 140 with a higher score indicating increased symptomatology and disability potential. Other secondary efficacy assessment tools included changes in a standard visual analog scale (VAS) with a continuous range from 0 to 100 mm, with 0 representing no symptoms and 100 representing the worst imaginable symptoms, assessed for fatigue, cognitive symptoms, pain, and sleep problems from baseline to Week 12.

Safety was assessed for adverse events (AEs) and serious adverse events (SAEs) throughout the course of the study, defined as unexpected or expected, and relationship to the study intervention as definitely, possibly, or unrelated as assessed by research investigators experienced in working with GWI patients. Laboratory safety assessments included routine hematology and chemistry panels, urinalysis, fourth-generation HIV-1/2 antibody test, serum pregnancy test (in women of child-bearing potential), thyroid-stimulating hormone level, and electrocardiogram, performed at screening and during follow-up visits.

2.6. Mitochondrial function assessments

Direct respirometric profiling of mitochondrial function is not yet readily available in the clinical setting. Therefore, a search was undertaken to determine the best available mitochondrial function assay in order to identify a biomarker that might measure the effect of KPAX002 on mitochondrial functioning. After a thorough review, we chose the Oxidative Stress Analysis 2.0 panel (Genova Diagnostics, Asheville, NC) as an indirect means of assessing mitochondrial function for this clinical trial. This test panel included four assays and was obtained at each study visit: 1) serum glutathione (a key antioxidant nutrient) 2) serum glutathione peroxidase (a protective antioxidant enzyme complex) 3) serum SOD (a protective antioxidant enzyme complex) 4) serum lipid peroxides (a marker of oxidative damage to bodily lipids, including those in mitochondrial membranes). The lipid peroxide assay utilized thiobarbituric acid reactive substances (TBARS) methodology.

2.7. Statistical analysis

The primary efficacy endpoint was the change from baseline (CFB) in GWI symptoms, as measured by the GWI Symptoms Assessment Tool (SAT) total score, from Baseline to Day 28, Day 56, and Day 84; and from Day 84 to Day 112/ET (washout phase). Baseline values were computed as the average of Baseline 1 and Baseline 2 to minimize intrapatient variability. The last observation carried forward method was used to impute missing efficacy data unless otherwise specified. The Intent to Treat (ITT) population included all subjects who received at least one dose of KPAX002 and provided at least one efficacy assessment after starting treatment. All efficacy analyses were based on the ITT population. The ITT population was analyzed using an analysis of covariance (ANCOVA) model with response (CFB) and the terms Day and baseline SAT score as explanatory covariates to assess the change in mean SAT total score from baseline to Day 84. A sensitivity analysis for CFB in the GWI SAT total score was also done using a mixed model repeated measures (MMRM) analysis to account for all observed data without imputation. MMRM models handle missing data implicitly by assuming that unobserved data is missing at random, i.e., that data is missing according to a pattern determined by the clinical covariates included in the model. The change in results over time was assessed using both ANCOVA and MMRM methods.

The CFB to other study time-points (Day 28, Day 56, and Day 112); and from Day 84 to Day 112 [washout phase]) were assessed as supportive analyses. Continuous secondary endpoints were analyzed using the same approach as used for the primary endpoint analysis (i.e., ANCOVA).

3. Results

3.1. Baseline characteristics

Between December 2015 and April 2017, a total of 53 subjects were screened for eligibility at the VAPAHCS. Forty-five of 53 met the Kansas definition of GWI. Of these 45, 10 were excluded because of ongoing medical conditions and 13 because of travel distance; 5 declined to participate; and 17 subjects were enrolled. Of the 17 subjects qualifying for enrollment (safety population), 2 were withdrawn prior to receiving study drug, 1 because of exclusion criteria found at screening, and the other who voluntarily withdrew because of driving distance to the study site. Fifteen qualified for the ITT population with 10 subjects completing the trial per protocol (Fig. 1). The reasons for study discontinuation were adverse events (2), lost to follow-up (2), and other (family emergency unrelated to study participation) (1).

All subjects were characterized with respect to gender and race at the screening visit. Most subjects were male (88.2%) and white (70.6%). Table 2 provides the enrolled subjects' demographic characteristics and baseline weight. Our study cohort of deployed Veterans was representative of GW and GWI Veterans (Zundel et al., 2019, Smith et al., 2013, Maule et al., 2018). The mean baseline GWI SAT total score for the ITT population in this study was 35.9 (± 15.98).

3.2. Efficacy outcomes

In the ITT population, the mean change in the SAT total score from baseline to Week 12 was −8.8 (± 12.54) (95% confidence interval [CI], −13.2 to −4.5; $p < 0.001$). This represents a mean overall decrease in GWI symptomatology of 25%. The treatment effect was highly statistically significant when compared to baseline using both the ANCOVA ($p < 0.001$) and MMRM ($p = 0.007$) methods. The results of the ANCOVA and MMRM models were quite similar, demonstrating that the observed treatment effect is robust to alternative analysis models. The effect of KPAX002 on the primary outcome variable is shown in Fig. 2.

In the ITT population, the mean change in the CIS total score from

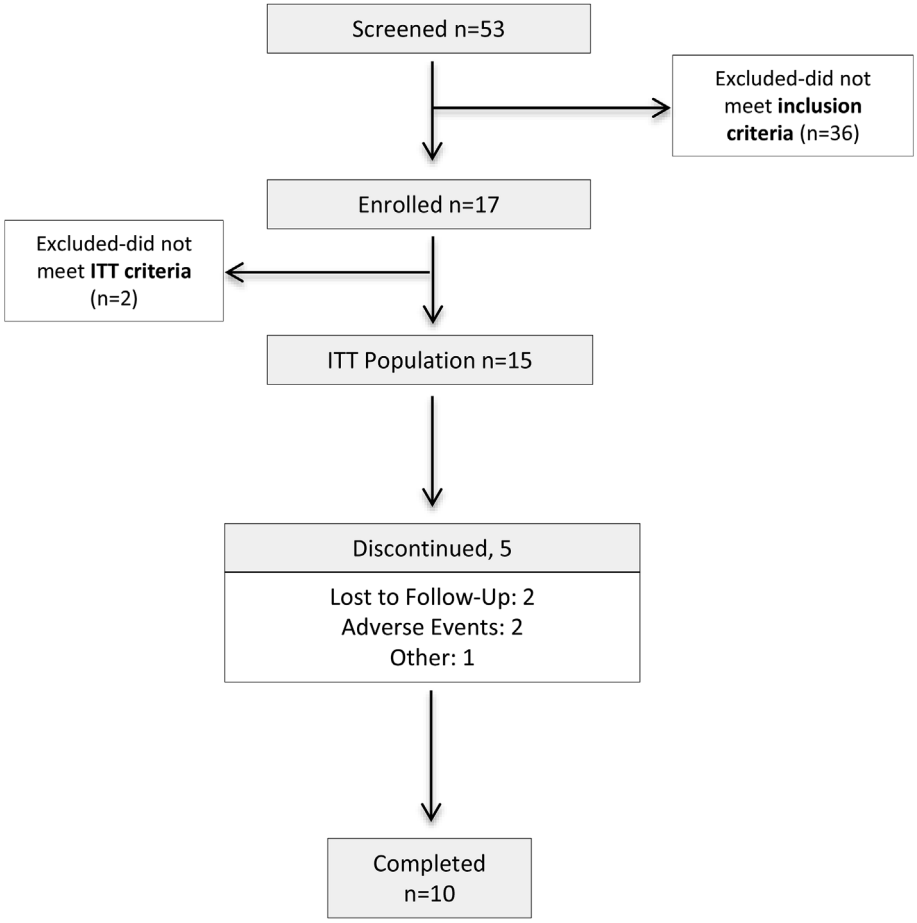

Fig. 1. Flow diagram of KPAX002-02 subject disposition.

Table 2
Baseline patient demographics (N = 17).

Age (years)	Median	52
	Mean (SD)	53.0 (6.15)
	Min, Max	46, 62
Gender	Female, n (%)	2 (11.8)
	Male, n (%)	15 (88.2)
Race	African-American, n (%)	2 (11.8)
	Hispanic, n (%)	1 (5.9)
	Native American, n (%)	1 (5.9)
	Other, n (%)	1 (5.9)
	White, n (%)	12 (70.6)
Weight (lbs.)	Mean (SD)	199.2 (30.93)
	Median	197
	Min, Max	159, 282

baseline to Week 12 was −14 (± 19.59) (95% CI, −22.3 to −5.7; $p < 0.004$). This represents a mean overall decrease in the CIS total score of 15%.

There was also a statistically significant reduction in all four VAS scales from baseline to Week 12, including fatigue ($p = 0.019$), cognitive symptoms ($p = 0.006$), pain ($p = 0.05$), and sleep problems ($p = 0.026$). The complete results of the efficacy outcomes can be found in Table 3.

The four assays used to assess the intervention's effect on antioxidant status and mitochondrial function included the change in serum levels of glutathione, SOD, glutathione peroxidase, and lipid peroxides from baseline to Week 12. Of these four indirect assays of mitochondrial health, only a reduction in the level of lipid peroxides showed a statistically significant effect. At Day 84, there was a −1.0 change from baseline in the serum lipid peroxides level ($p = 0.043$), representing a 13% mean reduction from baseline.

3.3. Adverse events

Not all subjects were able to reach the maximum daily methylphenidate dose per protocol because of reported side effects. The dosage range of methylphenidate on study ranged from 2.5 mg to 10 mg twice daily. Table 4 is a list of treatment-emergent AEs. The most common side effects considered possibly or probably related to the study medication were headache, hypertension, and dizziness/lightheadedness. Two subjects discontinued due to AEs, but no AEs were classified as serious and all of them resolved. Eleven subjects had AEs of grade severity ≤2 (mild to moderate), as assessed by research investigators experienced in GWI.

4. Discussion

We have shown that veterans with GWI taking KPAX002 for 12 weeks had a statistically significant reduction in overall symptom severity as demonstrated by reductions in SAT and CIS total scores as well as statistically significant improvement in VAS scores for concentration disturbance symptoms, fatigue, sleep problems and pain. There was also a significant reduction in serum lipid peroxide levels, a marker of systemic oxidative stress, from baseline to Week 12. There were no SAEs, and AEs were generally mild, although they did cause discontinuation of the intervention in two subjects.

In 1991, Gulf War soldiers were exposed to multiple toxicant exposures, both individually and in combination. Previous research has consistently linked exposure to pesticides and pyridostigmine bromide medications (used as prophylaxis against chemical warfare attacks) to

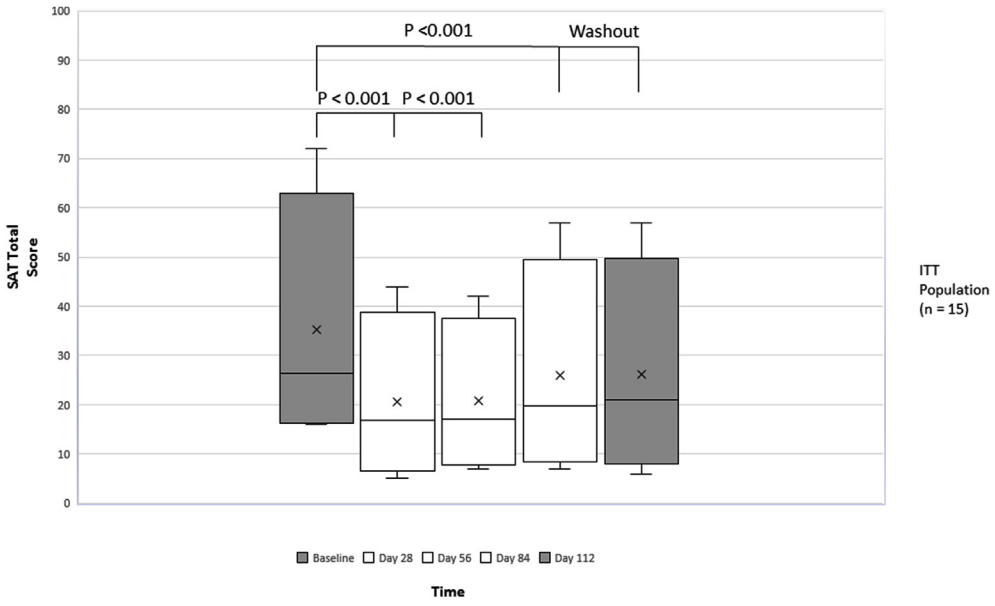

Fig. 2. Change in Symptom Assessment Tool (SAT) Total Score. Bars indicate SAT score range for each time point. Grey bars indicate baseline and washout periods not on study medication. X = mean SAT score, horizontal line = median SAT score. P values indicate significant differences in SAT scores between stated time points.

Table 3
Primary and secondary study endpoints at Day 84 (n = 15).

Endpoint	Baseline	Day 84	P value
Symptoms Assessment Tool (SAT)			
Mean	35.9	27.1	< 0.001
SD	15.98	12.54	
Min, Max	17, 72	7, 57	
Checklist Individual Strength (CIS)			
Mean	94.9	80.9	0.001
SD	17.43	19.59	
Min, Max	70, 128	52, 122	
VAS Cognitive Disturbance			
Mean	6.8	5.3	0.006
SD	1.8	2.45	
Min, Max	3, 9	1, 10	
VAS Fatigue			
Mean	6.8	5.5	0.019
SD	1.36	2.41	
Min, Max	5, 9	1, 9	
VAS Pain			
Mean	6.9	5.9	0.054
SD	2.08	2.62	
Min, Max	1, 10	0, 9	
VAS Sleep			
Mean	7.2	5.8	0.026
SD	1.39	2.47	
Min, Max	5, 10	0, 10	
Serum Glutathione (μmol/L)			
Mean	1041.3	979.8	0.328
SD	279.2	269.1	
Min, Max	597, 1619	698, 1465	
Serum Glutathione Peroxidase (U/g Hb)			
Mean	31.3	32.2	0.462
SD	8.68	11.2	
Min, Max	15, 45	15, 55	
Serum Superoxide Dismutase (U/g Hb)			
Mean	19,954	21,254	0.198
SD	3012	3586	
Min, Max	16,143, 25,980	14,504, 25,663	
Serum Lipid Peroxides (μmol/L)			
Mean	7.5	6.5	0.043
SD	1.88	2.04	
Min, Max	5, 11	3, 10	

VAS = visual analog scale.

the development of GWI, while exposures to low-level nerve gas agents, contaminants from oil well fires, multiple vaccinations, and significant combinations of these exposures also occurred (White et al., 2016).

Mitochondrial damage, leading to increased levels of oxidative stress, is a physiologic effect associated with many of the aforementioned toxic exposures. Evidence from several previous studies supports a role for mitochondrial dysfunction in GWI (Koslik et al., 2014). Evidence supporting mitochondrial dysfunction as a contributing factor in GWI is also supported by the fact that amyotrophic lateral sclerosis, a condition strongly linked to mitochondrial dysfunction, has been observed in several studies to have an elevated prevalence among GWI patients (Coffman et al., 2005; Haley, 2003; Horner et al., 2003).

Mitochondrial dysfunction can simultaneously affect the cells of many organ systems and is frequently associated with a waxing and waning pattern of symptoms (Morris and Maes, 2014). Emerging evidence supports the possibility that GWI may represent an acquired mitochondrial disease resulting from a multitude of toxic exposures leading to excessive oxidative stress and subsequent mitochondrial damage (Koslik et al., 2014). Secondary (acquired) mitochondrial diseases often include symptoms of fatigue, muscle weakness, neuropathic pain, neurocognitive abnormalities, and immune-related abnormalities (Niyazov et al., 2016).

Methylphenidate is well known to stimulate CNS neuronal activity by increasing dopamine and norepinephrine levels via a reuptake inhibitor mechanism. It is our hypothesis that, by augmenting methylphenidate administration with broad-spectrum antioxidant support, KPAX002 administration will be able to generate a sustained improvement in fatigue and cognitive dysfunction symptoms in GWI subjects. Without concurrent mitochondrial support, the benefit of CNS stimulation by methylphenidate is potentially blunted by a shortage of ATP generation due to compromised mitochondrial function.

The mitochondrial modulator component of KPAX002 is comprised of key antioxidants and micronutrients including several not found in most multivitamins. These nutrients were selected based on prior research study findings demonstrating their ability to produce clinical benefits in patients with mitochondrial dysfunction at these dosages (Hart et al., 2004; Herzenberg et al., 1997; Kaiser et al., 2006). The nutrients are dosed at therapeutic levels designed to address the metabolic needs of dysfunctional mitochondria.

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 (Long et al., 1982). ALCAR has been more widely utilized than L-carnitine in animal research and

Table 4
Treatment-emergent adverse events.

Adverse Event	Subjects (n)	Severity (n)	Relation to Treatment
Headache	7	Mild (5), Moderate (2)	Definitely related (1), Possibly related (6)
Hypertension	5	Moderate (5)	Possibly related (5)
Dizzy, light headed	5	Mild (5)	Possibly related (4), Unrelated (1)
Nausea	3	Moderate (2), Mild (1)	Possibly related (3)
Insomnia	3	Mild (3)	Probably related (1), Possibly related (2)
Rash	2	Mild (2)	Probably related (1), Possibly related (1)

human clinical trials. It is also better absorbed and more efficient at crossing the blood–brain barrier when compared to L-carnitine (Kido et al., 2001). Significant experimental evidence has demonstrated that ALCAR can boost mitochondrial ATP production when supplemented in pharmacologic dosages (Beal, 2003; Mazzio et al., 2003).

Alpha lipoic acid (ALA; thioctic acid) is a highly potent antioxidant that acts as a critical cofactor in mitochondrial oxidative decarboxylation reactions (Maczurek et al., 2008; Shay et al., 2009). As a potent electron donor, ALA is capable of regenerating reduced glutathione, thus ameliorating oxidative stress (Goraca et al., 2011). Ames and colleagues have published seminal work on the benefits of combining ALA and ALCAR as an intervention for improving mitochondrial function (Ames and Liu, 2004; Hagen et al., 1998; Liu et al., 2002a, 2002b).

N-acetyl-cysteine (NAC) is a 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 recovery (Acetadote [package insert], 2016). NAC has also been shown in multiple clinical investigations to increase serum glutathione levels (Atkuri et al., 2007; De Rosa et al., 2000). 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 (Monti et al., 2016).

The National Academy of Sciences recently released a report addressing the landscape for GWI treatment (Institute of Medicine, 2013). After reviewing current literature, the researchers could not recommend any definitive treatment for GWI, although they concluded that GWI veterans might benefit from medications such as selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, as well as from cognitive behavioral therapy. However, few interventional clinical studies have been performed.

Acupuncture was evaluated as a modality to improve GWI symptoms in 104 subjects, who were randomized to either 6 months of biweekly acupuncture treatments or a 2-month delay followed by weekly acupuncture treatments for 4 months (Conboy et al., 2016). Improvements in overall health and pain scores, as measured by the Short Form physical component (SF–36P) and McGill Pain scales, respectively, were found to be significantly greater in the group that received biweekly acupuncture than in the group treated weekly.

Coenzyme Q10 (CoQ10), a potent antioxidant, was evaluated in 46 GWI patients in a randomized, double-blind, placebo-controlled study at oral doses of 100 mg/day versus 300 mg/day of CoQ10 versus placebo taken for 3.5 months (Golomb et al., 2014). The results demonstrated significant improvement on a general self-rated health questionnaire among men, and physical function as assessed by the lower-extremity Summary Performance Score (SPS), particularly in the 100-mg dose arm.

Administration of KPAX002 resulted in a significant decrease in plasma lipid peroxides, indicating an overall reduction in oxidative stress in GWI subjects. Plasma SOD activity levels were increased above the reference range in all subjects throughout the study, indicating increased oxidative stress.

Our study has some limitations, including small sample size, not being placebo-controlled and being composed predominantly of men. In addition, we were required to use imputation for missing efficacy data, which may have introduced bias in our study results. We plan to follow up this uncontrolled, open-label study with a randomized, double blind, placebo-controlled trial to determine if this evidence supports causal benefit as opposed to the natural history of disease, regression to the mean, placebo effect or social desirability bias. A standard dose of methylphenidate was also not well defined, as several subjects required dosage adjustments to maintain tolerability.

5. Conclusion

In conclusion, statistically significant improvement in multiple GWI symptoms relative to baseline occurred after 12 weeks of KPAX002 administration with an acceptable side effect profile. Lipid peroxide levels were significantly reduced, possibly linked to improved mitochondrial redox status. Since the treatment effect of KPAX002 observed in this study does not substantially exceed a possible placebo effect, additional studies are needed to assess this intervention in a randomized, double blind, placebo-controlled manner to determine if this evidence supports causal benefit and further development. Furthermore, we propose that respirometric measurement of mitochondrial function be utilized to directly assess the treatment's effects on mitochondrial functioning and to potentially identify GWI subgroups most responsive to KPAX002 administration.

Disclosure of conflicts of interest

Mark Holodniy has no conflict of interest to declare.

Jon D. Kaiser is the Chief Medical Officer of K-PAX Pharmaceuticals (Mill Valley, California).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.08.003.

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