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ABSTRACT

This research study aims to expand the field of knowledge of Gulf War Illness. The research may provide initial proof of the innovative hypothesis that Gulf War Illness is related to low grade neuron-inflammation, which can be down regulated, by Naltrexone and Dextromethorphan. This is untested but potentially ground breaking concept that could provide, both an enhanced understanding of, and beneficial treatment for, Gulf War Illnesses. Research at the National Institute of Environmental Health and other facilities has proven that naltrexone and dextromethorphan reduce inflammation in the brain. Clinical trials in humans with low dose naltrexone have established benefits in syndromes related to Gulf War Illness such as fibromyalgia. We have successfully enrolled 41 subjects in the study, and anticipate obtaining important data by the end of the coming year. A no cost extension has been obtained to complete the study.

15. SUBJECT TERMS

Gulf War Illness, naltrexone, dextromethorphan

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INTRODUCTION

Gulf war veterans' illnesses comprise distinct clusters of symptom-defined illnesses (Haley 1997 a, b, c) for which there are neither diagnostic tests nor effective treatments. Gulf war veterans had variable exposures to a number of chemicals (3), including organophosphate insecticides, pyrethrum-related insecticides, DEET, Pyridostimine bromide, smoke from oil well fires, and Sarin gas. Gulf war veterans' illnesses may reflect an inflammatory cycle involving the brain which may be a common mechanism of many neurological conditions, whether initiated by toxic exposures, infection, or trauma. In this theory, central nervous system inflammation initiated by toxic exposures and sometimes exacerbated by subsequent exposures is a component of illness hypothesized to explain the neurological manifestations. Substance P release at sensory nerve endings is an explanation for the peripheral pain manifestations of illness.

This theory suggests that novel anti-inflammatory drugs may be of benefit in symptom-defined illnesses related to a cycle of inflammation. Dr. J. S. Hong's laboratory at the National Institute of Environmental Health Sciences has demonstrated that Morphine-related analogs, including Naltrexone and Dextromethorphan, have great potency in anti-inflammation and neuroprotective effects. Naltrexone is a safe and readily available generic medication. Dextromethorphan is also a safe and readily available generic medication that is available without a prescription as a cough medication. Results from several clinical trials showed that Naltrexone is effective in several inflammation-related diseases, such as neurogenic pain, movement disorders, etc. In addition, there were no obvious side effects in patients taking this drug for six months. This project is a randomized double-blinded study for treating ill Gulf war veterans with Naltrexone and Dextromethorphan. Laboratory tests for markers of inflammation including neurogenic inflammation will be performed pre- and post-treatment, to see if these markers are elevated and if so, to see if treatment modulates these markers.

BODY

The major accomplishment of the past year was completion of the study except for one subject, who will finish during the six month extension from July 1, 2015 to December 31, 2015. The naltrexone protocol has been completed, with 39 subjects having successfully completely the naltrexone protocol. The dextromethorphan protocol has been successfully completed by 20 subjects, with one subject currently enrolled. We have screened 301 ill Gulf War Veterans who have responded to advertisements, but the rejection rate has been high. Reasons for not participating were not meeting the exclusion criteria, particularly those on multiple medications with potential drug interactions with study drugs, or not meeting inclusion criteria, particularly those not meeting the case definition. The rate of veterans meeting inclusion or exclusion criteria but rejecting enrollment was low. We have completed the laboratory evaluations except for the one patient. Data analysis is ongoing.

KEY RESEARCH ACCOMPLISHMENTS

The most significant accomplishment during the past year was successfully recruiting and enrolling a number of veterans with Gulf War Illness in the clinical trials. Data collection has been complete with no gaps on last data review. The level of adverse reactions to study drugs has been minimal.

Screening interview	301
Consent obtained	50
Completed naltrexone protocol	39
Completed dextromethorphan protocol	20
Withdrew	3
Loss to follow-up	8
Currently enrolled in naltrexone protocol	0
Currently enrolled in dextromethorphan protocol	1
Discontinued naltrexone due to adverse reaction (subjective dizziness)	1
Discontinued dextromethorphan due to adverse reaction	0

We have performed nerve growth factor analyses using an ELIZA assay on samples from those participants who have completed courses of either naltrexone versus placebo or naltrexone versus placebo. We are analyzing the data for correlations with symptoms, response to therapy, and other parameters.

REPORTABLE OUTCOMES

The data from the initial visit has been analyzed. The most reportable finding was the a comparison between symptoms in veterans taking standard pharmaceutical medications to treat symptoms were no different from those taking one or less medications. An article discussing characteristics of study subjects on their first visit is attached as appendix A.

The naltrexone arm of the protocol had dramatic responses in some participants, while others had no response. Responders and non-responders have similarly been reported in studies of efficacy of naltrexone in treating other conditions such as the chronic pain of fibromyalgia (Younger). Resonders were defined as those with greater than 30% improvement on pain scores on naltrexone. Our results are variable depending on symptom and modality, with 50% improving with naltrexone on the visual analogue scale for fatigue and 21% improving

on the Clinical Global Assessment scale. 6% had a dramatic improvement on the Clinical Global Assessment scale. We are currently analyzing the full data set to see if there are differences in the two groups.

Preliminary analysis of the dextromethoprhan trial to treat Gulf War Illness also shows promise. A full data analysis is underway.

The details of these evaluations will be given in the December 31, 2015 final report.

CONCLUSIONS

Naltrexone shows promise as a treatment for Gulf War Illness, but has limitations in the variability in responders, as seen in other studies. Preliminary data analysis indicates that dextromethorphan is a promising treatment for Gulf War Illness, with analysis of the full data set underway. We anticipate finishing the study over the next six months. Successful recruitment, enrollment, compliance, and data collection has been gratifying. All work is on target to be completed imminently. We anticipate a successful outcome to the study aims and objectives.

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Appendix A. Medication Use for Symptomatic Treatment of Veterans with Gulf War Illness

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Abstract

Background: 30% of veterans of the 1991 Gulf War developed a persistent illness now known as Gulf War Illness (GWI), that is treated empirically with a variety of medications of unknown efficacy.
Research Question: How effective is medication use in GWI subjects compared to those who take no medications?
Methods: An observational study of medication use was conducted. The Kansas case definition of GWI was used. Veterans meeting inclusion criteria were scheduled for a clinic visit. History, physical examination, and medication use was recorded. Symptoms were scored using a visual analogue scale. Means $\pm$ standard errors of scores were calculated and compared to medication use. Statistical analysis compared groups using t-tests. IRB approval was obtained.
Results: 50 subjects were enrolled. Symptoms included chronic fatigue, pain, and neuropsychological disabilities. Treatments included psychotropic, analgesic, and anti-flammatory medications. Mean number of medications to treat symptoms was 1.9, and ranged from 0 to 11. Symptom scores were not different for those taking 2 or more than 2 medications except for greater sinus congestion (37 ± 33 versus 54 ± 28 cm,$p=0.003$) and joint aches (56.4 ± 33 versus 73.3 ± 21,$p=0.004$) in those taking 2 or more medications.
Conclusion: Subjects taking ≥2 medications were not improved relative to those taking less. This result is consistent with anecdotal reports that empirical treatment of Gulf War Illness is not helpful and in some cases may be harmful.

Introduction

Gulf War Illness (GWI) affected between 25% and 32% of veterans of the 1991 Gulf War (1,2). Symptoms include chronic fatigue and chronic pain. Neuropsychological disabilities range from difficulty with memory, concentration, and cognition, to sleep disturbances and inappropriate anger and rage. Gastrointestinal and respiratory difficulties are common. Rashes are also reported. Treatment has been empirical with symptom directed medications. Anecdotal evidence suggests that many veterans report that medications are ineffective in relieving the symptoms of Gulf War Illness. In this paper we report an observational study of the use and efficacy of medications used by a cohort of veterans with Gulf War Illness.

Methods

An observational study of medication use to treat symptoms of Gulf War Illness was conducted. Gulf War veterans were recruited by contacting veterans groups, mailings to Veterans Administration (VA) physicians, postings at VA clinics and hospitals, a study web site, and mailings to veterans in the Carolinas and Virginia. A phone number was given for interested veterans who served in the 1991 Gulf War to call for a screening interview. Veterans who called were consented to participate in a telephone interview and screened for Gulf War Illness using the Kansas case definition (Steele). Those who meet the case definition were invited to come to a clinic visit where written informed consent was obtained. A standardized history and physical examination were performed, medication use was recorded, and a 10 cm visual analogue scale (VAS) was used to quantitate symptoms associated with GWI. Means $\pm$ standard errors of visual analogue scores were calculated and compared according to medication use. Statistical analysis compared groups using t-tests.

Results

302 Veterans completed screening interviews. 50 veterans were enrolled. 100% reported chronic pain, chronic fatigue, and neuropsychological disabilities (difficulty with memory, cognition, concentration, sleep, anger control, mood, etc.). Many also reported gastrointestinal, respiratory, and dermal ailments. The only consistent physical finding was upper airway inflammation (100%) and decreased lower extremity vibratory sensation (4%). Medication use included multiple psychotropic, analgesic, anti-seizure, and anti-inflammatory medications to treat symptoms. The number ranged from 0 to 11, with the distribution depicted in figure one. VAS scores were not statistically different between those taking 2 or more medications, relative to those taking none or one, except that those taking two or more medications had greater sinus congestion and joint aches relative to those taking none. Symptom scores were not different for those taking ≥2 medications except for greater sinus congestion (37 ± 33 versus 54 ± 28 cm,$p=0.003$) and joint aches (56.4 ± 33 versus 73.3 ± 21,$p=0.004$) in those taking 2 or more medications. The distribution of symptoms scores for sinus congestion and joint aches are illustrated in figure 2a and 2b, respectively.

Discussion

Over 20 years after the conflict, veterans with GWI continue to suffer. Symptoms of chronic pain, chronic fatigue, and neuropsychological problems were universal. Rhinitis was evident on physical examination in 100% of the veterans with GWI reported here. Medication use was empirical and consisted of psychotropic, anti-inflammatory, analgesic, and anti-seizure medications. 17 of 50 veterans with GWI were taking no medications to treat their symptoms. These residents said they had tried a number of prescription medications but quit taking them because they found them to be of no benefit. 25 residents were taking 2 or more medications to treat their GWI symptoms. Based on symptoms scores relative to those taking 0 or 1 medications, there was no benefit from taking these medications. Patients taking 2 or medications had a significant increase in severity of sinus congestion and joint aches. One explanation could be that these veterans who were prescribed more medicaitons had worst symptoms and that increased number of medications were prescribed. Another is that the medication side effects increased their symptoms as adverse reactions, though there is no evidence for this explanation.

Controlled studies have been conducted to treat GWI with alternatives to empirical based pharmaceuticals directed at symptoms. These include antibiotic therapy, nutritional supplements, cognitive behavioral therapy, acupuncture, and exercise. A double-blinded randomized placebo controlled trial of doxycycline taken for 12 months to treat GWI demonstrated no long term efficacy (Donta). The endogenous antioxidant L-carnosine (B-alanyl-L-histidine) was considered a potential treatment since it is a free radical scavenger in nervous tissue. A randomized double blind placebo controlled 12 week dose escalation study of carnosine found no benefit for fatigue, pain, hyperalgesia, and activity. Cognitive function as measured by the WAIS-R digit symbol substitution test improved significantly, while diarrhea was also improved (Baraniuk).

Coenzyme Q10, a cofactor for mitochrondial function, was studied in a randomized, double-blind, placebo-controlled study. Participants were 46 veterans meeting Kansas and Centers for Disease Control criteria for Gulf War illness (Golomb). General self-rated health (GSRH), the primary outcome, showed statistically significant benefit in men and approached significance in women and the combined-sex sample. showed no significant benefit in the combined-sex sample. Physical function on the summary performance score of the SPS vehicle improved on 100 mg/day of Coenzyme Q10 versus placebo. Sleep problems were not improved.

A trial of nasal continuous positive airway pressure (CPAP) significantly improved but did not eliminate self-reported pain and cognition measured on a 10 cm visual analogue scale, with improvements of 34% and 38%, respectively, relative to sham treatments. Sleep quality measured by the Pittsburgh Sleep Quality Index improved 41%. General physical and mental health measured by the SF-36 vehicle improved 34% and 16%, respectively.

A multicenter study randomly assigned veterans with Gulf War Illness to receive usual care (n = 271), cognitive behavioral therapy (CBT) plus usual care (n = 286), exercise plus usual care (n = 269), or CBT plus exercise plus usual care (n = 266). Exercise sessions were 60 minutes weekly for 12 weeks. CBT sessions were 60 or 90 minutes weekly for 12 weeks. Evaluations were performed at 0, 3, 6 and 12 months using the Physical Component Summary scale of the Veterans Short Form 36-Item Health Survey. The percentage of veterans with improvement in physical function, defined as greater than a 7 point improvement on the survey, at 1 year was 11.5% for usual care, 11.7% for exercise alone, 18.4% for CBT plus exercise, and 18.5% for CBT alone. Exercise alone or in combination with CBT significantly improved fatigue, distress, cognitive symptoms, and mental health functioning, while CBT alone significantly improved cognitive symptoms and mental health functioning. Neither treatment had a significant impact on pain. The authors concluded that CBT and/or exercise provided modest relief for some of the symptoms of GWVI.

Conclusion

Over twenty years after the 1991 Gulf War, veterans with GWI continue to suffer with chronic pain, chronic fatigue, neuropsychological disabilities, and upper airway inflammation. Controlled trials have shown that novel therapies such as carnitine, Coenzyme Q10, and CPAP improved but did not eliminate symptoms. This observational study supports anecdotal reports that empirical medication use did not relieve symptoms of Gulf War Illness, as determined by VAS symptom scores. Improved therapies for Gulf War Illness are needed.

Figure one. Distribution of number of medications used to treat symptoms of Gulf War Illness.

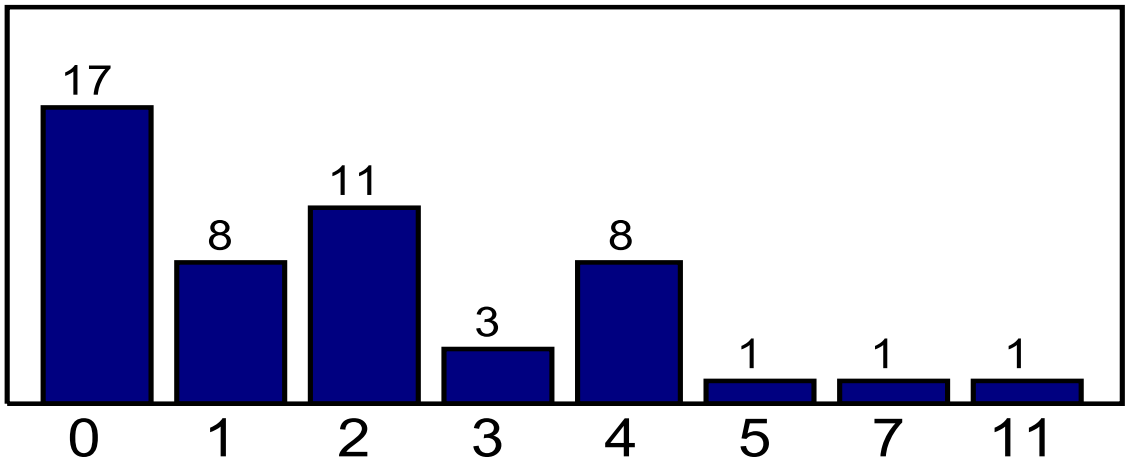

Figure 2a. Comparison of VAS scores for sinus congestion between those taking less than 2 medications to those taking ≥2 medications to treat symptoms of Gulf War Illness.

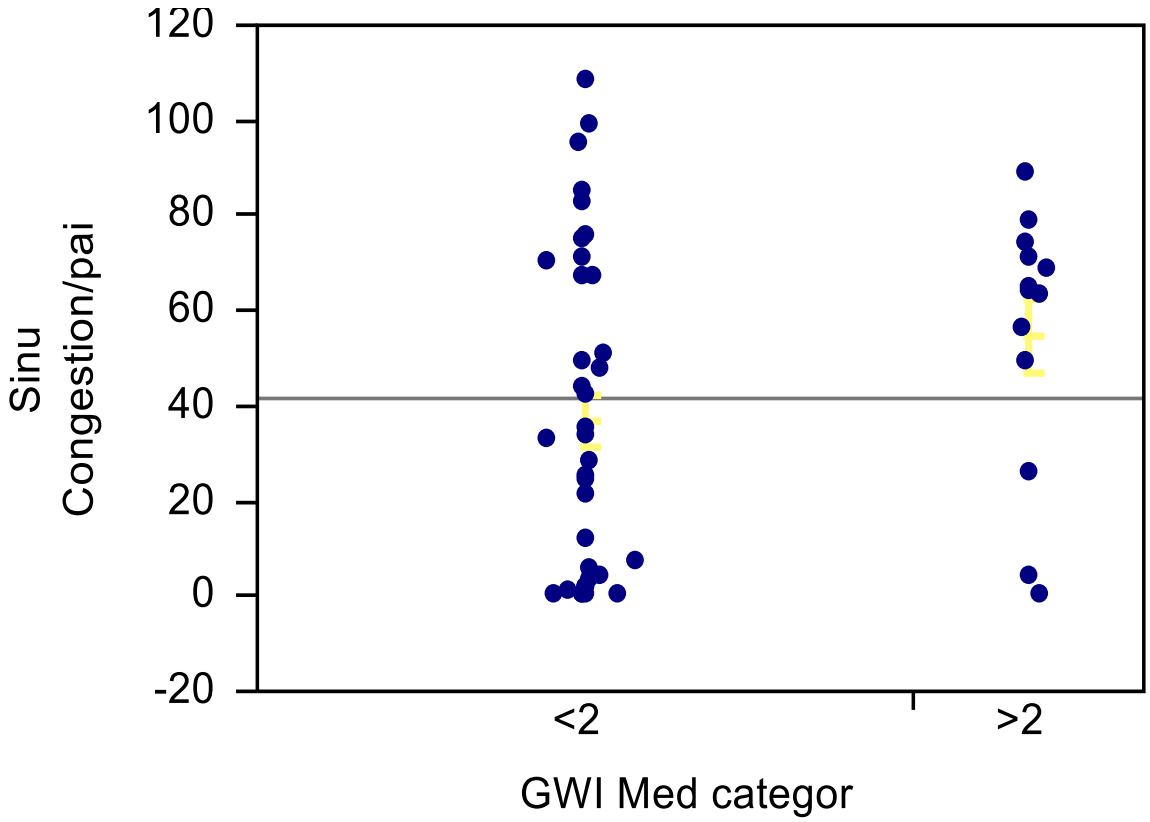

Figure 2b. Comparison of VAS scores for sinus congestion between those taking less than 2 medications to those taking ≥2 medications to treat symptoms of Gulf War Illness.