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14. 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: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

A recent authoritative review of GWI concluded that "studies in the U.S. and elsewhere have consistently concluded that approximately 25-32% of this population suffers from a disorder characterized by symptoms that vary somewhat among individuals and include fatigue, headaches, cognitive dysfunction, musculoskeletal pain, and respiratory, gastrointestinal and dermatologic complaints (White 2015)." Treatment for GWI has been problematic. While studied treatments have been of benefit, none has provided remission (Golomb 2014, Golier JA, Donta 2004, Baraniuk 2011, Amin 2011). Naltrexone was considered for treatment because it down-regulates neuroinflammation (Younger 2014). Exposure data indicate that organophosphate insecticides and nerve gas exposures occurred (White 2015). Neuroinflammation plays a role in organophosphate induced illness (Chen 2012). A prior study for chronic pain found that naltrexone improved symptoms in some (responders) but not others (non-responders) (Younger 2013). The purpose of the research is to find better treatments for Gulf War Illness and to determine if biomarkers of inflammation are affected by two treatments of Gulf War Illness. The scope of the research is to conduct randomized double-blinded placebo-controlled trials of two generic medications that modulate neuroinflammation, naltrexone and dextromethorphan.

KEYWORDS: Provide a brief list of keywords (limit to 20 words).

Gulf War Illness, naltrexone, dextromethorphan, treatment, biomarkers, nerve growth factor, cytokines, inflammation

OVERALL PROJECT SUMMARY: Summarize the progress during appropriate reporting period (single annual or comprehensive final). This section of the report shall be in direct alignment with respect to each task outlined in the approved SOW in a summary of Current Objectives, and a summary of Results, Progress and Accomplishments with Discussion. Key methodology used during the reporting period, including a description of any changes to originally proposed methods, shall be summarized. Data supporting research conclusions, in the form of figures and/or tables, shall be embedded in the text, appended, or referenced to appended manuscripts. Actual or anticipated problems or delays and actions or plans to resolve them shall be included. Additionally, any changes in approach and reasons for these changes shall be reported. **Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) requires review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.**

Every task ion the statement of work has been completed. Subjects were recruited. Double-blinded, placebo-controlled, randomized trials of both naltrexone and dextromethorphan were conducted. All planned laboratory tests were performed. Data was analyzed.

Institutional Review Board (IRB) approval was obtained from both the institutional and Department of Defense IRBs.

Subjects with GWI were recruited through the media, veterans groups, mailing to Gulf War era veterans and Veterans Administration physicians, and individual veteran activists. Advertisements were posted in Veterans Administration clinics. Respondents had a screening telephone interview after verbal informed consent to determine if the veterans met inclusion criteria. Eligible veterans were invited to participate. Those who accepted were invited to a clinic visit. Those who gave written informed consent were invited to participate.

A randomized placebo-controlled double-blinded study of naltrexone to treat symptoms of GWI was conducted. The Kansas Case Definition of GWI (Steele) was used as an inclusion criteria, with the modification that individuals who had developed co-morbidities such as diabetes mellitus who were excluded in the original criteria were not excluded. This definition of GWI includes six categories: fatigue/sleep problems, pain, neurological/cognitive/mood symptoms, respiratory complaints, gastrointestinal problems or skin symptoms (Steele). Moderate or severe symptoms in at least three of the six categories are required for inclusion.

Exclusion criteria included those taking opioids chronically as naltrexone can precipitate opioid withdrawal. Also excluded were potential subjects with cancer not in remission, chronic infectious diseases, liver disease, lupus, multiple sclerosis, stroke, and those under current treatment for schizophrenia, bipolar disorder and depression. Those with a history of current illicit drug use were also excluded. Institutional Review Board (IRB) approval was obtained from both the institutional and Department of Defense IRBs.

Veterans with GWI were recruited through the media, veterans groups, mailing to Gulf War era veterans and Veterans Administration physicians, and individual veteran activists. Advertisements were posted in Veterans Administration clinics. Respondents had a screening telephone interview after verbal informed consent to determine if the veterans met inclusion criteria. Eligible veterans were invited to participate. Those who accepted were invited to a clinic visit. Those who gave written informed consent were enrolled.

Subjects received blinded medications once daily in the morning (naltrexone 4.5 mg or an identical placebo pill). Each treatment course was for three months, with a one-month washout period between treatments. The order of naltrexone or placebo was randomized. Evaluations were performed at the beginning and end of each course of intervention. Study pills were dispensed by the Research Pharmacy at Vidant Medical Center. Blinded pharmaceuticals were compounded specially for this study. The pills were administered in a randomized, double-blinded fashion. The code for the blinding was held by the research pharmacist. Randomization was performed by drawing a card from a box that specified the order of administration.

The study variables included the SF-36 evaluation, a widely used and accepted measure of health status in clinical studies (Brandes 2006, Goodacre 2007, Slottje 2007). The SF-36 has been used to assess health status in ill Gulf war veterans (see for example, Eisen 2005, Hotopf 2003, Voelker 2002). The Global Clinical Impression Scale (GCI), a widely used instrument for determining global health in pharmaceutical studies (Mowla 2007, McElroy 2007, Ranuck 2007) was also used. Connors Continuous performance test was administered at each visit. Symptoms were assessed using a 10 cm visual analogue scale (VAS). Symptoms on the VAS included those characteristic of GWI plus individualized symptoms that a subject reported.

Laboratory panels consisted of markers of inflammation, to include plasma levels of the Lincoplex human cytokine panel (IL-1β, IL-6, IL-8, IL-10, IFN-γ, TNF-α, and nerve growth

factor). In addition, a complete blood count, comprehensive chemistry profile, C-reactive protein, and urinalysis was performed at the beginning and end of each course of therapy by a routine clinical laboratory, to screen for untoward hematological, metabolic, renal, or hepatic adverse reactions to naltrexone. Interim data was collected from the patient through a patient diary. This diary was issued at the beginning of each course and provided documentation of prescribed consumption of medication by the patient and associated adverse events.
Patients were categorized as responders or non-responders based on the results of the CGI scale at the end of treatment periods. Any patient showing some improvement on this scale were categorized and responders, where patients who were unchanged or showed worsening were considered non-responders. Statistical analysis of differences between responders and non-responders were done using t-tests for continuous data and chi-square analysis for categorical data. All scores are reported as mean ± SEM.

In a second study, subjects received blinded medications of dextromethorphan sustained release 60 mg tablet twice a day oral mg or an identical placebo pill. The sustained release pills were obtained from each treatment course was for three months, with a one-month washout period between treatments. The order of dextromethorphan or placebo was randomized. Evaluations were performed at the beginning and end of each course of intervention. Study pills were dispensed by the Research Pharmacy at Vidant Medical Center. Blinded pharmaceuticals were compounded specially for this study. The pills were administered in a randomized, double-blinded fashion. The code for the blinding was held by the research pharmacist. Randomization was performed by drawing a card from a box that specified the order of administration.

Telephone interviews were conducted on 301 respondents.

Results of Naltrexone Clinical Trial

Of the 301 respondents, 37 (36 men and 1 woman) met study criteria for the naltrexone study and completed the study. Three patients who were enrolled did not complete the study. One of these withdrew for subjective dizziness while taking naltrexone. Two were non-compliant with follow-up visits. Average and mean ages were 54 and 51, with range of 43 to 76. Average body mass index (BMI) was 29.6 ± 0.7, with range of 17.2 to 39.1. Nine percent of patients were considered to be at a healthy BMI, 45% overweight, 43% obese and 2% underweight.

Clinical Global Impression Scale for for Naltrexone Clinical Trial.
The CGI-I is a 7 point scale that is completed by the examining physician at the time of patient visit and represents the physician's response to a single query: "Compared to the patient's condition prior to medication initiation, this patient's condition is: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline; 5=minimally worse; 6= much worse; 7=very much worse since the initiation of treatment."

The CGI for global improvement (CGI-I) divided subjects into two groups, individuals who responded to naltrexone therapy and a group of non-responders. A similar dichotomy has been reported in a study of low dose naltrexone for fibromyalgia (Younger 2013). The CGI-I detected improvement in symptoms in 38% (CGI=1-3; n=15) (responders), with 21% (n=7) rated as being much improved. The remaining patients had no change from baseline (n=18; 48%), minimally worse (n=5; 13%) (non-responders).

SF-36 Health Survey Results for Naltrexone Clinical Trial

Table 1 gives the results of the SF-36 Health Survey results for all participants. There were no significant differences seen with treatment. However, when scored on the SF-36 Health Survey, responders were found to have significantly less disability (i.e. higher scores) than non-responders with respect to physical limitations (65.9 ± 10.8 vs. 38.9 ± 7.6; p=0.05), fatigue (55.0 ± 6.1 vs. 35.5 ± 3.9; p=0.01) and emotional limitations (75.7 ± 11.1 vs. 48.1 ± 8.8; p=0.03) (Table 2). The responders also showed strong trends toward improvement (lower scores) on VAS compared to non-responders, including confusion, memory and fatigue. The differences between groups did not reach statistical significance due to small numbers and large variability. Figure 1 gives the distribution of SF-36 scores of responders and non-responders for the SF-36 category, emotional wellbeing.

Visual Analogue Scores for Naltrexone Clinical Trial

When all participants in the naltrexone trial were combined, the VAS scores did not show improvement while taking naltrexone relative to placebo except for the category libido, which showed improvement both when all participants were combined, as seen in Figure 4.

For responders, there was statistically significant improvement in libido, rash, nasal congestion, and runny nose (Figure 5). Trends for improvement in abdominal pain, concentration, confusion, dizziness, irritability, nausea, and sinus pain were observed (Figure 5).

Connors Continuous Performance Test for Naltrexone Clinical Trial

Hit response times were measured before and after treatment with naltrexone and placebo. The mean change from baseline in hit response time for the placebo group was -0.88 +/- 7.98 (95% CI= -15.3 - 17.09). The mean change in hit response time from baseline for naltrexone group was -7.33 +/- 6.92 (95% CI= -21.49 - 6.72) (p=0.43). The trend was for a bigger reduction in hit response with naltrexone vs. placebo, but the large variability prevented the detection of a significant difference.

The standard deviation in hit response time was also measured, which is a measure of consistency of response. The change in standard deviation was significantly different, with a greater change for the naltrexone group relative to the placebo group. For the standard deviation Measure: Mean change from baseline for placebo group: -0.12 +/- 0.33 (95% CI= -0.80 - 0.56) Mean change from baseline for naltrexone group: -1.02 +/- 0.23 (95% CI= -1.49 - -0.55) (p=0.02). This result means that the hit response time was less chaotic at the end of the naltrexone course of therapy.

Laboratory Studies for the Naltrexone Clinical Trial

At the beginning and end of each course of therapy, subjects had phlebotomy for a complete blood count with differential (CBC), comprehensive metabolic panel (CMP) that included renal and hepatic function, and urinalysis. The purpose of these routine laboratory parameters was to screen for hematologic, hepatic, or renal toxicity. No toxicity was detected in any of these assays in any subject.

The Lincoplex® cytokine panel, nerve growth factor (NGF), and c-reactive protein (CRP) were performed on serums samples at the beginning and end of treatment courses, to see if there were improvements in the cytokine profile with treatment with naltrexone versus placebo. When all subjects were combined (Table 6), there was a statistically significant increase in IL-6 while taking active drug relative to placebo.

Naltrexone Levels

A qualitative photometric serum assay for naltrexone was obtained (Neogen Corp, Lansing, MI). The test was not marketed to quantify levels, but as qualitative test to identify presence. A standard curve of color intensity for naltrexone levels ranging from 1 to 20 mg/mL was constructed. Color intensity of color changes in subject samples were compared to the standard curve to obtain naltrexone levels in each sample. All subjects who completed the naltrexone protocol had detectable levels of naltrexone in their serum at the end of the treatment period, with values ranging from 1.5-18 ng/ml. Mean naltrexone levels was actually lower in responders vs. non-responders (4.1 ± 0.3 ng/ml vs. 5.2 ±0.3 ng/ml; p=0.02). A possible explanation of this finding is that at the 4.5 mg dose of naltrexone used in the study was too high a dose for some participants. That is, for some participants, a lower dose might be more efficacious.

Results of Dextromethorphan Clinical Trial.

Twenty-one male subjects completed the dextromethorphan study. No female subjects completed the study. Average age was 52.4 years. Median age was 54 years. Age range was 41 to 67 years. Average body mass index was 28.46 kg/m2.

The CGIS Results for the Dextromethorphan Clinical Trial

The CGIS improved on 7 subjects of the 21 subjects while on active study drug (28%). 28% of subjects reported improvement with placebo while 38% reported improvement while taking dextromethorphan.

Table 8 gives SF-36 scores comparing change of beginning to end of 3 month course of placebo to changes from beginning to end of taking active dextromethorphan. Treatment with active dextromethorphan showed no improvement on SF-36 scores for any parameter measured. However, the subjects who improved on the CGI score while taking dextromethorphan reported less disability on the SF-36 General Health parameter (p=0.01) and on the Social parameter (p=0.02).

Changes in VAS scores comparing placebo to active dextromethorphan are given in Table 9. No improvement was seen on any score while taking dextromethorphan.

Change from baseline for the mean hit response time on the Connors continuous performance test was 13.11 + 11.31 (95% confidence interval -10.47, 36.697) while taking dextromethorphan. While taking the placebo for dextromethorphan, the mean hit response time was 8.77 + 6.25 (95% confidence interval -4.32, 21.86) while taking the placebo for dextromethorphan. P-value was 0.74 that was not significant. The mean change from baseline of the mean standard error

while taking dextromethorphan was 0.43 + 0.28 (95% confidence interval -0.15,1.01). The mean change from baseline of the mean standard error while taking the placebo for dextromethorphan was -0.05 + 0.26 (95% confidence interval -0.59,0.48). The p-value was 0.21.

In summary, taking dextromethorphan had no significant effect on the mean hit response time and standard error relative to placebo.

The biggest disappointment in the research was the inability to enroll the targeted number of subjects. As enrollment began, we discovered that the Kansas Case Definition of GWI was too restrictive. The exclusion criteria excluded patients who had diabetes and other conditions that are distinct from GWI. The inclusion criteria, however, with its emphasis on neuropsychological disabilities, chronic pain, and chronic fatigue, were found to correctly identify GWI. Therefore, it was necessary to modify the protocol in order to study GWI, which is distinct from these other conditions. The reason for this inability is that the Gulf War Veterans with Gulf War Illness had developed many co-morbidities in the almost two decades since the 1991 Gulf War which were treated with multiple medications, many of which had drug interactions with study drugs. Another difficulty was the original protocol was designed as a three-arm study, with a three month course of naltrexone, a three month course of dextromethorphan, and a three month course of placebo. The number of veterans with GWI who could take both naltrexone and dextromethorphan was small so the two studies were separated into a randomized placebo-controlled cross-over trial of naltrexone and a separate randomized placebo-controlled cross-over trial of dextromethorphan.

Figure 1.

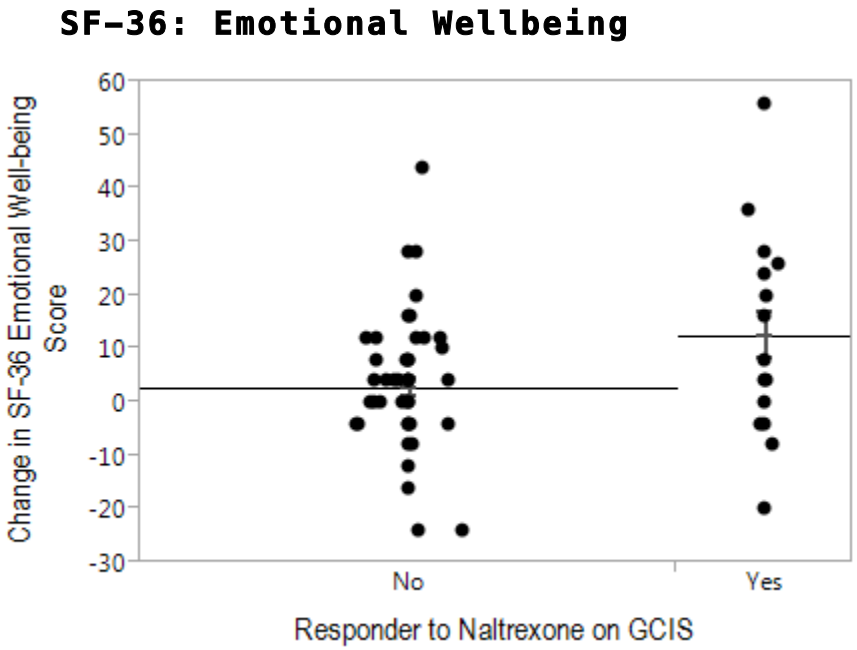

Figure 2. Comparison of the SF-36 scores on change in wellness among responders to active naltrexone based on the CGIS to those who did not respond on the CGIS. Those patients categorized as responders reported significantly less disability (i.e. higher scores) than non-responders (p=0.01).

Table 1. comparison of SF-36 scores during placebo trial to scores during active naltrexone for all partitipates.

SF-36 Category	Change from Baseline: Placebo Mean±SEM (95% CI)	Change from Baseline: Naltrexone Mean±SEM (95% CI)	p-value
Physical Limitations	5.4 ±5.5 (-5.9-16.7)	5.8 ±8.1 (-4.9-33.9)	0.52
Physical Wellbeing	2.8 ±2.6 (-2.3-8.0)	3.3 ±2.7 (-2.2-8.9)	0.55
Emotional Limitations	0.92 ±7.4 (-14.2-16.0)	5.5±8.8 (-12.2-23.3)	0.65
Emotional Wellbeing	4.3 ±2.4 (-0.6-9.1)	6.2 ±2.4 (1.2-11.1)	0.70
Energy/Fatigue	2.9 ±2.8 (-2.9-8.6)	5.7 ±3.4 (-1.3-12.6)	0.73
Social Function	4.7 ±4.7 (-4.8-14.2)	3.4±3.6 (-3.8-10.8)	0.42
Pain	6.1 ±2.7 (0.6-11.6)	6.0 ±3.2 (-0.5-12.4)	0.49
General Health	3.0 ±2.5 (-2.0-8.1)	2.1 ±2.6 (-3.1-7.3)	0.39

Table 2. Comparison of changes in SF-36 Scores from beginning to end of a course of therapy for subjects who responded to naltrexone based on the CGIS to those who had no improvement on the CGIS.

SF-36 Category	Change from Baseline: Non-Responder Mean±SEM (95% CI)	Change from Baseline: Responder Mean±SEM (95% CI)	p-value
Physical Limitations	2.9 ±5.6 (-8.3-14.2)	13.9 ±9.7 (-6.6-34.49)	0.83
Physical Wellbeing	1.7 ±1.8 (-2.0-5.4)	7.2 ±4.9 (-3.2-17.6)	0.84
Emotional Limitations	-3.1 ±6.2 (-15.5-9.3)	22.2±12.6 (-4.5-48.9)	0.08
Emotional Wellbeing	2.8±1.7 (-0.6-6.2)	12.6 ±4.3 (3.4-21.7)	0.05
Energy/Fatigue	1.4 ±2.0 (-2.7-5.5)	13.0 ±6.2 (0.0-26.0)	0.05
Social Function	2.5 ±3.1 (-3.6-8.7)	9.0±7.4 (-6.6-24.7)	0.78
Pain	4.3 ±2.3 (-0.3-8.9)	11.3 ±4.5 (1.8-20.7)	0.09
General Health	0.6 ±1.8 (-3.2-4.3)	8.6 ±4.2 (-0.2-17.4)	0.09

Table 3. SF-36 scores upon completion of a three month trial of naltrexone, comparing scores of responders based on the CGIS to non-responders based on the CGIS.

SF-36 Category	Non-Responder Mean±SEM (95% CI)	Responder Mean±SEM (95% CI)	p-value
Physical Limitations	41.6 ±7.3 (38.5-76.5)	58.3 ±15.0 (29.5-70.5)	0.83
Physical Wellbeing	64.6 ±4.1 (56.2-73.0)	75.1 ±5.3 (62.9-87.3)	0.93
Emotional Limitations	61.5 ±3.6 (54.0-69.0)	55.1 ±4.2 (46.4-63.9)	0.13
Emotional Wellbeing	46.9 ±8.4 (29.6-64.2)	85.2±11.3 (59.2-100)	0.01*
Energy/Fatigue	37.0 ±3.5 (29.8-44.3)	50.4±8.9 (29.9-70.9)	0.90
Social Function	56.5 ±4.3 (47.6-65.3)	65.3±9.5 (43.4-87.2)	0.79
Pain	57.2 ±4.0 (49.0-65.4)	66.9 ±7.8 (48.9-85.0)	0.85
General Health	47.2±3.7 (39.4-55.0)	52.2 ±6.1 (38.1-66.4)	0.75

Table 4. Comparison of VAS scores while taking placebo to taking active naltrexone for subjects enrolled in the randomized double-blinded placebo-controlled trial of naltrexone.

Outcome	Change from Baseline: Placebo for naltrexone (mean ± SEM)	Change from Baseline: Active naltrexone (mean ± SEM)	p-value: Placebo v Active change from baseline
Abdominal Pain	-7.7 ± 4.1	-2.3 ± 3.8	.09
Anger	-10.8 ± 5.6	-9.6 ± 5.8	.88
Confusion	-8.5 ± 4.5	-2.2 ± 3.2	.27
Depression	-12.3 ± 4.4	-11.6 ± 4.3	.92
Diarrhea	-4.8 ± 3.9	-5.3 ± 4.8	.93
Dizziness	-1.2 ± 3.3	-5.3 ± 4.4	.46
Fatigue	-5.5 ± 4.6	-12.2 ± 4.4	.29
Hallucinations	0.76± 0.6	1.2± 1.1	.75
Headache	-14.3 ± 4.0	-8.2 ± 4.0	.28
Irritability	-16.6 ± 4.3	-6.7 ± 4.4	.11
Joint Aches	-5.2 ± 4.5	-3.9 ± 4.9	.84
Libido	3.9 ± 4.6	-7.7 ± 3.4	.05*
Memory	-3.6 ± 3.6	-7.0 ± 3.7	.51
Muscle Aches	-5.3 ± 4.6	-5.6 ± 4.2	.96
Nasal Congestion	2.4 ± 5.5	-11.3 ± 5.5	.08
Nausea	-6.1 ± 4.0	0.31 ± 2.5	.17
Concentration	-6.2 ± 3.8	-0.9 ± 2.9	.27
Rash	-8.5 ± 4.5	-2.2 ± 3.3	.27
Runny Nose	-4.5 ± 4.9	-6.7 ± 4.1	.08
Sinus Pain	-3.4 ± 5.3	-7.8 ± 4.8	.54
Sleep	-14.2 ± 5.7	-13.2 ± 4.0	.89
Vertigo	-1.4 ± 3.9	-9.0 ± 4.4	.20
Vomiting	-1.4 ± 4.1	-0.8 ± 1.7	.46
Weight Gain	-3.3 ± 5.8	-9.3 ± 4.0	.40
Weight Loss	-0.5 ± 3.4	1.4 ± 3.9	.72

Table 5. Comparison of VAS scores between responders to active naltrexone, based on the CGIS, to non-responders to active naltrexone.

Outcome	Change from Baseline: Placebo (mean ± SEM)	Change from Baseline: Active naltrexone (mean ± SEM)	p-value: Placebo v Active change from baseline
Abdominal Pain	-9.6 ± 4.8	1.4 ± 4.4	.09
Anger	-13.9 ± 6.2	-10.7 ± 6.3	.71
Concentration	-6.9 ± 3.9	-0.5 ± 3.1	.20
Confusion	-7.0 ± 4.5	-0.8 ± 3.4	.28
Depression	-13.9 ± 4.7	-11.7 ± 4.8	.74
Diarrhea	-6.0 ± 4.5	-7.1 ± 5.8	.88
Dizziness	-1.3 ± 3.6	-6.7 ± 5.4	.40
Fatigue	-7.4± 5.3	-12.7± 4.9	.46
Hallucinations	1.2 ± 1.0	1.4 ± 1.6	.92
Headache	-14.4 ± 3.9	-6.7 ± 4.1	.18
Irritability	-19.0 ± 4.4	-7.2 ± 4.8	.07
Joint Aches	-6.1 ± 4.4	-5.1 ± 4.8	.88
Libido	3.4 ± 5.7	-12.0 ± 4.0	.03*
Memory	-4.1 ± 3.8	-5.4 ± 3.9	.80
Muscle Aches	-6.5 ± 4.5	-5.5 ± 4.0	.87
Nasal Congestion	2.3 ± 5.6	-12.5 ± 4.8	.04*
Nausea	-7.7 ± 4.8	3.0 ± 3.1	.06
Rash	-20.9 ± 5.7	-2.6 ± 3.7	.01*
Runny Nose	4.9 ± 5.3	-8.0 ± 3.9	.05*
Sinus Pain	-7.1 ± 4.0	-0.5 ± 3.1	.20
Sleep	-16.8 ± 6.0	-12.7 ± 4.3	.58
Vertigo	-2.6 ± 4.4	-8.2 ± 5.5	.43
Vomiting	-5.6 ± 5.2	-0.73 ± 2.1	.39
Weight Gain	-4.2 ± 6.5	-12.0 ± 4.4	.32
Weight Loss	-0.2 ± 4.0	-0.6 ± 4.4	.94

Table 6. Cytokine panel, NGF, and CRP comparing changes from baseline to end of treatment for placebo versus naltrexone.

Lab Value	Change from Baseline: Placebo (mean ± SEM)	Change from Baseline: Active naltrexone (mean ± SEM)	p-value: Placebo v Active change from baseline
IL-10	0.10 ± 47.9	-2.1 ± 2.2	.14
IL-6	-0.23± 0.34	0.77 ± 0.51	.02*
IL-1β	-1.55± 1.2	-1.67± 1.42	.85
IL-8	-1.7 ± 1.4	-.057 ± 0.10	.52
TNF-α	0.22 ± 0.54	-.22 ± 4.6	.10
NGF	-1.0± 0.61	0.01 ± 0.20	.27
IFN-γ	-1.1 ± 0.45	-1.2 ± 0.82	.79
CRP	0.20± 0.95	-1.29± 0.72	.22

Table 7. Comparison of laboratory values for non-reponders to responders to naltrexone therapy.

Lab Value	Change from Baseline: Non-Responders (mean ± SEM)	Change from Baseline: Responders (mean ± SEM)	p-value: Responder vs. Non-Responder change from baseline
IL-10	-2.55 ± 1.22	-0.63 ± 0.38	.38
IL-6	1.42± 2.86	-0.86 ± 1.44	.04*
IL-1β	-2.23± 8.6	0.84± 0.92	.50
IL-8	0.29 ± 5.3	-3.02 ± 4.19	.15
TNF-α	-0.36 ± 0.57	0.17 ± 0.75	.62
NGF	0.24± 7.56	-0.61 ± 1.36	.27
IFN-γ	-1.3 ± 4.93	-0.79 ± 2.95	.75
CRP	0.35± 0.95	-0.28± 0.28	.72

Table 8. SF-36 scores comparing change of beginning to end of 3 month course of placebo to changes from beginning to end of taking active dextromethorphan.

SF-36 Category	Change from Baseline: Placebo Mean±SEM (95% CI)	Change from Baseline: Dextromethorphan Mean±SEM (95% CI)	p-value
Physical Limitations	13.8 ±8.2 (-3.4-30.9)	14.5 ±9.2 (-4.9-33.9)	0.52
Physical Wellbeing	5.6 ±3.3 (-0.94-12.8)	2.6 ±3.2 (-4.0-9.3)	0.23
Emotional Limitations	16.2 ±10.1 (-4.8-37.3)	-7.9±10.7 (-30.4-14.5)	0.05
Emotional Wellbeing	2.7 ±4.0 (-5.7-11.1)	2.7 ±3.2 (-3.9-9.3)	0.50
Energy/Fatigue	7.6 ±2.8 (1.7-13.5)	4.3 ±3.5 (-3.0-11.6)	0.23
Social Function	21.0 ±3.9 (12.7-29.3)	4.7±4.4 (-4.5-14.0)	0.005*
Pain	13.4 ±3.5 (6.1-20.8)	7.0 ±3.4 (-0.1-14.3)	0.09
General Health	4.5 ±2.0 (0.3-8.8)	3.4 ±3.3 (-3.5-10.4)	0.39

Table 9. Comparisons of changes in VAS scores for subjects beginning active dextromethorphan for three months to scores at the end of therapy, and also change from beginning to end of a three month course of placebo

Outcome	Change from Baseline: Placebo (mean ± SEM)	Change from Baseline: Active (mean ± SEM)	p-value: Placebo v Active change from baseline
Abdominal Pain	-8.6 ± 4.2	-7.3 ± 7.0	.87
Anger	-9.6 ± 4.7	-9.8 ± 5.6	.98
Concentration	-6.2 ± 3.7	-12.0 ± 3.9	.29
Confusion	3.0 ± 4.1	-7.0 ± 3.3	.06
Depression	-3.4 ± 6.5	-4.2 ± 3.6	.92
Diarrhea	-3.4 ± 4.8	-7.3 ± 6.5	.64
Dizziness	-15.8 ± 7.0	-.94 ± 5.0	.08
Fatigue	-10.1 ± 3.5	-11.2 ± 5.8	.87
Hallucinations	-1.7 ± 2.9	-2.3 ± 2.1	.87
Headache	-3.7 ± 4.4	-7.0 ± 6.7	.69
Irritability	-20.6 ± 5.9	-9.4 ± 4.4	.13
Joint Aches	-3.3 ± 7.6	-4.6 ± 5.2	.88
Libido	-15.5 ± 5.5	-3.4 ± 4.3	.08
Memory	-4.1 ± 2.9	-9.7 ± 4.1	.28
Muscle Aches	-10.3 ± 4.5	-4.3 ± 5.7	.41
Nasal Congestion	1.9 ± 3.9	-4.6 ± 5.6	.35
Nausea	-5.4 ± 2.6	2.3 ± 3.6	.11
Rash	-13.6 ± 6.9	-4.2 ± 3.4	.22
Runny Nose	-2.8 ± 4.2	-7.0 ± 6.7	.60
Sinus Pain	-2.5 ± 5.4	-2.8 ± 7.0	.97
Sleep	.71 ± 5.8	-14.9 ± 5.4	.05
Vertigo	-9.4 ± 6.9	-4.2 ± 5.2	.54
Vomiting	.37 ± 2.4	-1.3 ± 1.5	.55
Weight Gain	2.8 ± 7.7	-7.4 ± 4.7	.25
Weight Loss	3.4 ± 3.9	-1.0 ± 5.0	.49

Table 9. VAS scores for dextromethorphan, comparing changes from beginning to end of a course of therapy for those who showed improvement on the GCIS to those that did not.

Outcome	Change from Baseline: Subjects whose CGIS improved on dextromethorphan (mean ± SEM)	Change from Baseline: Subjects whose CGIS did not improve on dextromethorphan (mean ± SEM)	p-value: Responder v. Non-Responder change from baseline
Abdominal Pain	-8.8 ± 18.1	-6.5 ± 5.7	.88
Anger	7.8 ± 7.7	-16.6 ± 6.3	.04
Concentration	-2.5 ± 5.9	-16.7 ± 4.7	.08
Confusion	.50 ± 6.0	-10.2 ± 3.7	.13
Depression	4.3 ± 2.9	-7.8 ± 4.7	.12
Diarrhea	-22.1 ± 20.1	-.92 ± 3.2	.13
Dizziness	5.8 ± 11.3	-4.0 ± 5.3	.37
Fatigue	-.42 ± 7.4	-16.6 ± 7.7	.20
Hallucinations	-8.5 ± 5.2	-.33 ± 2.1	.10
Headache	-2.8 ± 13.9	-9.2 ± 7.5	.66
Irritability	4.8 ± 6.0	-16.0 ± 5.0	.02
Joint Aches	-7.2 ± 9.7	-3.3 ± 6.4	.73
Libido	5.1 ± 8.6	-7.4 ± 4.7	.18
Memory	3.5 ± 6.0	-16.4 ± 4.6	.01
Muscle Aches	-2.7 ± 9.9	-5.3 ± 7.3	.83
Nasal Congestion	-9.7 ± 8.6	-1.9 ± 7.5	.52
Nausea	-.14 ± 3.4	3.6 ± 5.4	.63
Rash	-3.1 ± 3.0	-4.9 ± 5.4	.81
Runny Nose	-2.8 ± 13.9	-9.2 ± 7.5	.66
Sinus Pain	4.0 ± 12.3	-6.9 ± 8.8	.47
Sleep	-5.8 ± 6.0	-19.5 ± 7.4	.24
Vertigo	6.2 ± 13.0	-8.2 ± 5.1	.22
Vomiting	.40 ± 3.6	-2.0 ± 1.6	.49
Weight Gain	-12.4 ± 10.4	-4.9 ± 4.9	.46
Weight Loss	-3.2 ± 15.9	-.16 ± 3.7	.79

Table 10. Changes in laboratory panel (Lincoplex neuroinflammation panel, c-reactive protein, and nerve growth factor) for subjects enrolled in the randomized double-blinded cross-over trial of dextromethorphan from the beginning to end of the course of therapy.

Lab Value	Change from Baseline: Placebo for dextromethorphan (mean ± SEM)	Change from Baseline: Active dextromethorphan (mean ± SEM)	p-value: Placebo v Active change from baseline
IL-10	-0.17 ± 2.3	-2.6 ± 1.0	.15
IL-6	-0.40± 0.51	-0.10 ± 0.50	.58
IL-1β	-0.72± 0.28	0.13± 0.18	.06
IL-8	-1.50 ± 1.60	-0.37 ± 1.7	.63
TNF-α	0.05 ± 0.68	1.24 ± 0.82	.27
NGF	-0.95± 1.06	-1.53 ± 1.34	.72
IFN-γ	-1.41 ± 0.50	-1.2 ± 0.91	.71
CRP	1.04± 1.5	0.32± 0.54	.66

1. **KEY RESEARCH ACCOMPLISHMENTS:** Bulleted list of key research accomplishments emanating from this research. Project milestones, such as simply completing proposed experiments, are not acceptable as key research accomplishments. Key research accomplishments are those that have contributed to the major goals and objectives and that have potential impact on the research field.

   a. A randomized double-blinded placebo-controlled trial of low-dose naltrexone for symptomatic treatment of GWI was completed. 37 completed the trial. A subgroup had benefit from taking naltrexone relative to placebo. These were classified as responders. Subgroup analysis showed benefit on the SF-36 but not on the VAS. One subject withdrew from the naltrexone trial for the subjective symptom of dizziness. Laboratory evaluations found no abnormalities in CBC, CMP, and UA from taking naltrexone 4.5 mg/day. Naltrexone did not change values of cytokine panel, NGF, or CRP. Naltrexone may be of benefit for some patients with GWI. In those who had benefit from naltrexone therapy, the benefit ended within two or three days of discontinuing the medication.
   b. A randomized double-blinded placebo-controlled trial of dextromethorphan for symptomatic treatment of GWI was completed. 19 completed the trial. Dextromethorphan was not found to be of benefit in VAS, CGIS, nor SF-36. Laboratory evaluations found no abnormalities in CBC, CMP, and UA from taking dextromethorphan 50 mg twice a day. Dextromethorphan did not change values of cytokine panel, NGF, or CRP. Taking dextromethorphan was not found to be of benefit for subjects with GWI.

2. **CONCLUSION:** Summarize the importance and/or implications with respect to medical and /or military significance of the completed research including distinctive contributions, innovations, or changes in practice or behavior that has come about as a result of the project. A brief description of future plans to accomplish the goals and objectives shall also be included.

   Low dose naltrexone at 4.5 mg/day was found to be well tolerated and of benefit for some veterans with GWI. There was no response for other veterans. Based on our results, a trial of low dose naltrexone is a safe and reasonable approach to treating GWI. The drug should not be continued in those veterans for whom naltrexone is found to be unhelpful. Future directions for research are to determine differences in responders to naltrexone relative to non-responders. Avenues of investigation include differences in metabolism, pharmacokinetics, metabolomics, and entry across the blood brain barrier. Dose ranging experiments could be conducted because some veterans may require lower or higher doses to benefit from naltrexone therapy.

   Dextromethorphan 60 mg sustained released pills administered twice a day was well tolerated by the study population but was not found to benefit veterans with Gulf War Illness. It was well tolerated without significant clinical or laboratory adverse effects.

Further study of dextromethorphan for GWI are not planned for the future due to the disappointing results of our study.

3. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

a. List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts. Each entry shall include the author(s), article title, journal name, book title, editors(s), publisher, volume number, page number(s), date, DOI, PMID, and/or ISBN.

(1) Lay Press:

Michael Abramowitz. Vets sought for gulf War study. The Daily Reflector. August 2, 2012. http://www.reflector.com/news/veterans-sought-gulf-war-medical-study-1158117 (accessed December 15, 2015).

Michael Abramowitz. Effort targets Gulf War Illness. The Daily Reflector. Mary 11, 2014. http://www.reflector.com/news/seeking-treatment-gulf-war-syndrome-2416815 (accessed December 13, 2015).

(2) Peer-Reviewed Scientific Journals:

Brewer KL, Mainhart A, Meggs WJ. Double-Blinded Placebo-Controlled Cross-over Trial of Naltrexone to Treat Gulf War Illness. (submitted for publication).

Brewer KL, Mainhart A, Meggs WJ. Double-Blinded Placebo-Controlled Cross-over Trial of Dextromethorphan to Treat Gulf War Illness. (prepared for publication).

(3) Invited Articles:

Nothing to report

(4) Abstracts:

Meggs WJ, Brewer KL, Mainhart A. Medication use of chronically ill Gulf War Veterans presenting to a medical toxicology clinical over 20 years after the conflict. Jour Med Tox 2015;11:32.

Meggs WJ, Brewer KL, Mainhart A. Double-Blinded Placebo-Controlled Cross-over Pilot Trial of Naltrexone to Treat Gulf War Illness. Clin Tox (In Review).

b. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

Meggs WJ. Naltrexone and dextromethorphan in the treatment of Gulf War Illness. Department of Veteran Affairs Research Advisory Committee on Gulf War Illness. Washington, DC. September 22, 2014.(*)

Naltrexone and dextromethorphan in the treatment of Gulf War Illness. Department of Veteran Affairs Research Advisory Committee on Gulf War Illness. Washington, DC. September 22, 2014.(*)

Meggs WJ, Brewer KL, Mainhart A. Double-Blinded Placebo-Controlled Cross-over Pilot Trial of Naltrexone to Treat Gulf War Illness. 36th Congress of the European Association of Poison Centres and Clinical Toxicologist. Madrid, May 24-27, 2016. (In Review) (*).

(*) manuscripts prepared for submission.

4. **INVENTIONS, PATENTS AND LICENSES:** Not spplicable.

5. **REPORTABLE OUTCOMES:** Provide a list of reportable outcomes that have resulted from this research. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. This list may include development of prototypes, computer programs and/or software (such as databases and animal models, etc.) or similar products that may be commercialized.

   Naltrexone is of benefit for some veterans with GWI and is well tolerated. Dextromethorphan was not found to be of benefit.

6. **OTHER ACHIEVEMENTS:**

Based on this work, a CDMRP grant titled Naltrexone for Symptoms of Gulf War Illness: Determinants of Response versus Non-Response was submitted (Log # GW150059). The purpose of this grant is to investigate determinates of responders versus non-responders to naltrexone in Gulf War Illness. The pre-application was approved. The grant is in review.

7. **REFERENCES:** List all references pertinent to the report using a standard journal format (i.e., format used in *Science*, *Military Medicine*, etc.).

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8. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

NOTE:

TRAINING OR FELLOWSHIP AWARDS:

Not applicable.

COLLABORATIVE AWARDS:

Not applicable.

QUAD CHARTS:

Not applicable.

MARKING OF PROPRIETARY INFORMATION:

Not applicable.