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A randomized, double-blind, placebo-controlled, crossover trial of mifepristone in Gulf War veterans with chronic multisymptom illness

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ABSTRACT

No pharmacological treatments have been demonstrated to effectively treat chronic multisymptom illness (CMI) in Gulf War veterans (GWV). This study assessed the effect of the glucocorticoid receptor antagonist mifepristone in GWV with CMI. A randomized, double-blind, cross-over trial of mifepristone, with two six-week treatment phases separated by a one-month washout period, was conducted at a Veterans Affairs (VA) hospital between 2008 and 2011. Participants were randomized to receive either 200 mg of mifepristone per day or matched placebo first. The primary clinical outcome measure was change in self-reported physical health. Neurocognitive functioning and self-reported measures of depression, PTSD, and fatigue were secondary outcomes. Sixty-five participants enrolled, of whom 36 were randomized and 32 (mean age, 49.1 (7.2) years) completed the study. Physical and mental health status and neurocognitive functioning were poor at baseline. Mifepristone treatment was not associated with improvement in self-reported physical health ($p = 0.838$) or in other self-reported measures of mental health. Mifepristone treatment was significantly associated with improvements in verbal learning ($p = 0.008$, $d = 0.508$), in the absence of improvement in other cognitive measures (working memory ($p = 0.914$), visual learning ($p = 0.643$) and a global composite measure ($p = 0.937$). Baseline morning cortisol levels and lysozyme $IC_{50\text{-}DEX}$, a measure of peripheral glucocorticoid sensitivity, displayed a significant relationship with endpoint verbal learning scores ($p = 0.012$ and $p = 0.007$, respectively). The magnitude of cortisol change during treatment mediated the improvement in verbal learning.

This study was negative for the primary and secondary clinical outcomes. However, the data suggest a moderate dose of mifepristone may have circumscribed cognitive-enhancing effects in CMI. Further study is warranted to determine whether and through which mechanisms mifepristone treatment can yield clinically meaningful improvement in cognitive function in CMI or other neuropsychiatric conditions associated with HPA axis dysregulation.

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1. Introduction

Despite advances in the assessment and understanding of chronic multi-symptom illness (CMI) in Gulf War veterans (GWV), no pharmacological treatments have been demonstrated to effectively treat this medically unexplained illness. Novel treatment approaches are needed to improve the health of the 34–65% of GWV who experience CMI (Fukuda et al., 1998; Steele, 2000; Blanchard et al., 2006). Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis is a potential treatment target for CMI in GWV (Golier et al., 2006a, 2007; Broderick et al., 2013) since GWV have been shown to have greater responsivity to glucocorticoids than non-deployed veterans, as evidenced by greater dexamethasone (DEX) induced suppression of ACTH and cortisol (Golier et al., 2006a,b). GWV also show substantial reductions in both basal and metyrapone-stimulated levels of ACTH compared to healthy non-deployed veterans (Golier et al., 2007, 2009). The mechanisms responsible for this apparent reduced drive to the HPA axis in the face of excess responsivity to neuroendocrine challenge have yet to be definitively characterized. However, their possible pathophysiological relevance is supported by their associations with health symptoms and specific deployment-related environmental exposures (e.g., pyridostigmine bromide)—which have been consistently linked to Gulf War illness in epidemiological studies.

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To the extent that enhanced glucocorticoid receptor sensitivity is a molecular driver of CMI, reducing GR sensitivity or blocking GR activity may be therapeutic. Accordingly, we examined the clinical effect of mifepristone, a selective type II glucocorticoid receptor antagonist, in GWV with CMI. Mifepristone binds to the same site as the synthetic glucocorticoid dexamethasone and blocks the negative feedback control of cortisol on the pituitary (Gaillard et al., 1984). Given that glucocorticoids influence cognitive performance, a glucocorticoid-based treatment may also be warranted to address the neurocognitive symptoms and concomitant deficits in attention, executive functioning, and verbal learning and memory (Blanchard et al., 2006; Vasterling et al., 1998; Binder et al., 1999; Lange et al., 2001; Axelrod and Milner, 1997; White et al., 2001; Vythilingam et al., 2005) observed in Gulf War veterans. Mifepristone has been shown to have beneficial effects on mood and/or cognition in other neuropsychiatric disorders including psychotic depression and Alzheimer's disease (Belanoff et al., 2001; Chu et al., 2001; Pomara et al., 2002; Young et al., 2004; Simpson et al., 2005; Flores et al., 2006; Watson et al., 2012). Accordingly, we hypothesized that mifepristone would improve physical and mental health symptoms and cognitive functioning in GWV with CMI. A moderate dose strategy (200 mg/day × 6 weeks) was used to minimize side effects and allow for longer-term treatment than a high-dose strategy would permit. This dosing strategy followed the regimen outlined for the study of Alzheimer's disease (Pomara et al., 2002; Belanoff et al., 2002a). HPA axis biomarkers were also obtained before and during treatment to determine predictors of response and mechanisms of action.

2. Materials and methods

This was a randomized, placebo-controlled, crossover trial that took place at a Veterans Affairs (VA) hospital between 2008 and 2011. Participants, research coordinators, and assessors were blind to treatment condition. GWV outpatients who met the Kansas case definition of CMI (qualifying symptoms in three of six symptom domains: fatigue, pain, neuro-cognitive-mood, dermatologic, gastrointestinal, and respiratory) (Steele, 2000) were eligible. A GWV was defined as a veteran who was deployed by the U.S. military to the Persian Gulf between August 1, 1990 and December 30, 1991. Participants with a major medical or neurological disorder or traumatic brain injury, which could explain their health symptoms, were ineligible. GWV with a lifetime diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder, current suicidal ideation, psychiatric hospitalization or attempted suicide within the previous two years, a known allergy to mifepristone, current oral corticosteroids usage, or an unwillingness to use effective forms of contraception during the study were also excluded. Participants receiving psychiatric medications were eligible to participate if they had been stabilized at a therapeutic dose for a minimum of four weeks prior to randomization. The protocol was approved by the Institutional Review Board of the James J. Peters VA Medical Center. Written informed consent and HIPAA authorization were obtained from all participants prior to the initiation of any study procedures. No changes were made to the trial design once it began.

For assessment of biomarkers, fasting blood was obtained between 0800 and 830 h on two consecutive mornings. Participants ingested 0.5 mg of DEX at 2300 h at home before the second blood draw. Plasma cortisol levels were determined using a commercially available radioimmunoassay (RIA) kit (DiaSorin Inc. Stillwater, Minnesota). ACTH levels were determined on hourly samples using an immuno-radiometric assay kit from Nichols Institute Diagnostics (San Juan Capistrano, California) based on the binding of antibodies with high affinity and specificity for defined amino acid regions of the ACTH molecule.

The lysozyme IC-50 test was calculated from the day 1 blood sample as the concentration of DEX required to inhibit lysozyme activity by 50% (Panarelli et al., 1994). Cells ($3.5–4.0 \times 10^5$) were incubated with multiple concentrations of DEX from 0 to 200 nM at 37 °C in a humidified atmosphere with 5% CO_2 for three days. Each concentration of DEX was incubated in triplicate. After centrifugation, supernatant was removed and samples were stored at −70 °C until analysis. The supernatant (50 μl) was incubated with 150 μl of substrate in 96 well plates at 37 °C for 30 min with shaking. The density was read at 450 nm on microplate spectrophotometer. Samples were run in triplicate and the results were expressed as the average. The standard was pure lysozyme from chicken egg white (Sigma Chemical Co.) dissolved in RPMI-1640 as the same as used for cell culture. The inhibition curve was drawn as concentration of DEX vs. relative activity of lysozyme. The results were expressed as IC_{50} DEX [nM] based on the concentration of DEX at which 50% of lysozyme activity was inhibited. The intra- and inter-assay coefficients of variation were 6.9 and 9.8%, respectively.

Morning plasma cortisol and ACTH levels were measured to assess the magnitude of mifepristone's neuroendocrine effects. The lysozyme $IC_{50\text{-DEX}}$ was used as a measure of mifepristone's antagonism of peripheral GR sensitivity longitudinally. The change in cortisol and ACTH in response to low-dose DEX was used as a measure of GR responsivity at baseline.

2.1. Participants

Of the 65 GWV enrolled into the study, 13 were lost to follow-up prior to the initial evaluation, nine were medically ineligible, five did not meet CMI criteria, and two withdrew consent. 36 eligible GWV were randomized to receive either 200 mg of mifepristone or matched placebo first; one did not initiate treatment, one withdrew in treatment phase I due to the time commitment, one was terminated from the study during treatment phase I due to elevated blood glucose, and one was lost to follow-up after the treatment phase II baseline visit. The final study sample consisted of 32 GWV with CMI (see Fig. 1).

2.2. Randomization

Participants were enrolled by a research coordinator. Randomization was performed by the pharmacy using a computer generated randomization list, which assigned an equal number of participants to mifepristone and placebo first. Identically matched drug and placebo pills were obtained from Danco Laboratories, LLC. The medication was electronically ordered and only the pharmacist knew whether mifepristone was being dispensed first or second.

2.3. Procedure

The diagnostic assessment included a complete medical evaluation, the Clinician Administered PTSD Scale (CAPS), and the Structured Clinical Interview for DSM-IV (SCID). Self-report questionnaires were administered to assess CMI case status (Kansas Gulf War Questionnaire), physical and mental health (SF-36), combat exposure severity and characteristics of deployment (Combat Exposure Questionnaire [CEQ]), childhood trauma (Childhood Trauma Questionnaire [CTQ]), cognitive impairment (Cognitive Failures Questionnaire [CFQ]), fatigue (Multidimensional Fatigue Inventory [MFI-20]), and symptoms of depression (Beck Depression Inventory [BDI]) and posttraumatic stress (PTSD Checklist [PCL]).

The Kansas Gulf War Questionnaire is a self-report measure used to identify symptoms in veterans across six symptom domains: fatigue, pain, neurological-cognitive, skin, gastrointestinal, and respiratory. Veterans meet criteria if they have qualifying symptoms in three of the six domains and no excluding medical diagnoses. This