**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-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.

1.0 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; Golier et al., 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., 2006 a,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; Golier et al., 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.

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 and Riondel, 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 and Luckenbaugh, 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 and Matthias, 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 x 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.

2.0 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 0800h–0830h on two consecutive mornings. Participants ingested 0.5 mg of DEX at 2300h 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 IC₅₀ 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 ($3.5\text{--}4.0 \times 10^5$) were incubated with multiple concentrations of DEX from 0 to 200 nM at 37 °C in a humidified atmosphere with 5% CO₂ 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 IC₅₀ 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-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 figure 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 definition is currently the state-of-the art approach with regard to assessing CMI.

All participants underwent a medical assessment by a single physician rater which included review of symptoms, vital sign assessment, routine laboratory assessment, review of concomitant medication, physical examination, complete medical history and an EKG. A diagnosis of CMI was not made if the participant had significant comorbid medical syndromes which might explain their symptoms or increase their risk of adverse events. Exclusions included cancer, diabetes, chronic infectious disease, liver disease, TBI or another major medical or neurologic condition likely to contribute to their symptom profile.

During both treatment phases, which were separated by a one month wash-out period, participants were evaluated in-person every two weeks (baseline, week two, week four, and endpoint) after which participants completed a one month follow-up visit. Clinical and neuroendocrine test batteries were measured at baseline, week two, and endpoint for each treatment phase and at one month follow-up. Self-report questionnaires, vital signs, adverse events, and concomitant medications were obtained at every visit.

No stopping rules were determined a priori. An independent data monitoring committee reviewed efficacy and safety data annually and deemed the study safe at each evaluation.

2.4 Measures

The primary clinical outcome measure was the change in the physical health components score (PCS) derived from the acute form of the veterans SF-36 health survey. A secondary clinical outcome measure was the change in the mental health components score (MCS) of the SF-36. Additional secondary clinical

outcome measures included self-reported symptoms of fatigue, depression, and PTSD as measured by the MFI-20, BDI, and PCL, respectively.

The neurocognitive outcome measures were baseline to endpoint changes in spatial working memory, verbal learning, and visual learning as measured by the Wechsler Memory Scale-III Spatial Span and Letter-Number Span, the Hopkins Verbal Learning Test, and the Brief Visuospatial Memory Test-Revised, respectively, using normative standards from the MATRICS Consensus Cognitive Battery. The normative composite score from this test battery was used, which is an equally weighted average of standard performance scores across all of the subtests. The MATRICS was normed on a community sample of healthy individuals who were selected for diversity in age, sex, and educational attainment (n=300) (Kern et al., 2008).

2.5 Analyses

Data are presented for 32 completers, defined as completing at least two weeks of treatment in both phases. For measures of physical and mental health, the last observation was carried forward for patients who did not complete the study, whether due to withdrawal, missed visits, or the development of side effects. Primary and secondary outcome measure change scores were calculated as the difference between the change from baseline to endpoint in each drug phase, and then calculated as mifepristone change minus placebo change. For each measure, treatment order effects were assessed using independent sample t-tests; if order effects were not present, a simple sample t-test was used on each outcome measure change score. Treatment phases were then separated, resulting in most participants contributing two observations, and a hierarchical regression was performed to evaluate whether neuroendocrine changes (cortisol, ACTH, glucocorticoid sensitivity) predict outcome. Cortisol and ACTH variables were created by subtracting 8am cortisol levels (pre-dexamethasone) on Day 1 from Day 2 (post-dexamethasone) to obtain the magnitude of suppression to DEX. This variable was tested as a mediator of significant outcomes using regression analyses, as previously described. Full mediation was ascertained if significant

relationships between drug condition and cortisol change and cortisol change and outcome were present, as well as, a non-significant association between drug condition and outcome. Years of education was added to each regression to control for group differences and baseline cortisol levels were added to the model predicting verbal learning in order to control for individual differences. All tests of significance were two-sided with statistical significance set at $p < 0.05$. No outcome measure changes were made once the study started.

2.6 Power analyses

The intended sample size of 40 was not reached due to recruitment difficulties. Based on a sample size of 32, the adjusted power was determined to be above 0.995 and 0.78 for the single sample t-test with large and medium effect sizes, respectively.

3.0 Results

Data on sociodemographic characteristics and self-reported physical and mental health measures are shown in Tables 1 and 2, respectively. The mean age was 49.1 (7.2) years and the exclusively male sample was ethnically diverse. The mean level of education was 13.3 (1.8) years, with most participants (43.8%) having some college or vocational school education. The majority of GWV were employed full time (56.3%) and were married or had a common law marriage (53.1%). No significant group differences in baseline self-reported variables were observed. Based on the CAPS, 59.4% ($n=19$) also met criteria for PTSD, 21.9% ($n=7$) met criteria for current Major Depressive Disorder, 6.3% ($n=2$) met criteria for dysthymia and 3.1% for panic disorder ($n=1$). The CTQ results suggest that as a group the sample did not have extensive exposure to adverse early life experiences.

Participants endorsed a mean of 4.9 (1.2) out of six Gulf War symptom domains. For the SF-36, mean

PCS and MCS scores were 33.6 (10.0) and 29.9 (12.2), respectively, reflecting relatively poor health-related quality of life. These scores were significantly lower than the US population norms for individuals 45-54 years old (PCS=49.62, MCS=50.54) (Kazis, 2000) and the VA national average (PCS=35.2, MCS=43.6) (Ware, 1998). The mean PCL score was 55.8 (19.4) and the mean BDI score was 25.2 (11.0) indicating the presence of associated symptoms of posttraumatic stress and depression. The mean CEQ score (50.1 (9.6)) indicated moderate exposure to combat stress. There were no significant differences between groups for any of the sociodemographic variables.

The normed cognitive baseline data is useful to characterize the cognitive status of these veterans, which was well below average at baseline. More specifically, working memory and overall composite scores were greater than one standard deviation below the mean (37.84 (12.45) and 35.75 (12.90), respectively). Verbal learning was one standard deviation (40.60 (9.76)) and visual learning (45.53 (10.71)) was half a standard deviation lower than the normative scores previously obtained.

Change scores from baseline to endpoint for all outcome measures and neuroendocrine variables are shown in Table 2 by treatment assignment (mifepristone vs. placebo first) and treatment phase. Neurocognitive, clinical, and neuroendocrine outcomes, calculated as drug change minus placebo change are shown in Table 3.

Mifepristone treatment was not associated with improvement in the primary outcome of self-reported physical health status ($p=0.838$) or the secondary outcome of self-reported mental health status ($p=0.423$), as measured by the SF-36. Nor was it associated with changes in PTSD symptom severity ($p=0.130$) and depression severity ($p=0.595$).

Chronic administration of moderate-dose mifepristone did result in significant improvement in verbal learning ($p=0.008$, $d=0.508$); groups displayed a mean difference of 5.225 (95% CI, 1.450 – 9.002). As

shown in Figure 2, verbal learning change scores increased from baseline to endpoint in both treatment phases among those taking mifepristone, while mean scores decreased from baseline to endpoint for those on placebo. Mifepristone treatment was not associated with improvements in working memory ($p=0.914$) or visual learning ($p=0.643$) or on the overall composite score ($p=0.937$). The finding for verbal learning remains significant after controlling for multiple cognitive outcome measures (four).

Treatment with mifepristone was associated with increased levels of cortisol and ACTH typical of GR antagonists. Mifepristone treatment was associated with a 113% increase in plasma cortisol level and a 510% increase in ACTH level, both of which were significant ($p<0.001$). With the removal of one outlier, the mean increase in ACTH with active treatment was 158%. Non-significant increases were observed for lysozyme IC_{50-DEX} levels ($p=0.138$). Treatment order effects were not significant for primary or secondary outcome measures. Study cortisol fluctuations are depicted in Figure 3. One participant in the mifepristone treatment group developed a rash assessed at week two and was taken off the study drug. The rash fully resolved.

The hierarchical regression examining the relationship between HPA axis biomarkers and verbal learning is shown in Table 4. The first step examines the relationship between treatment phase and drug group on verbal learning $F(4, 51)=3.282$, $p=0.018$, and accounts for 21% of endpoint verbal learning scores. Without the other variables taken into account, treatment order significantly predicted verbal learning ($\beta=-2.739$, $p=0.028$). Baseline verbal learning score was entered into the next block and this overall model was significant, $F(5, 50)=11.412$, $p<0.001$, accounting for 53% of endpoint verbal learning scores. As expected, drug group significantly predicted outcome ($\beta=2.515$, $p=0.009$). The final step, which included HPA axis biomarkers, was also significant, $F(8, 47)=10.687$, $p<0.001$ and accounted for 65% of verbal learning. In addition to drug group ($\beta=2.464$, $p=0.005$), morning cortisol difference and lysozyme IC_{50} were both significant unique predictors of endpoint verbal learning scores ($\beta=0.475$, $p=0.012$ and $\beta=-1.115$, $p=0.007$, respectively) with lysozyme IC_{50-DEX} displaying an inverse relationship. It should be noted

that treatment order was not a significant predictor in the last steps of the analysis.

The results of the mediation analysis are depicted in Table 5. The first overall model (path a) was significant, $F(5, 56)=7.743$, $p<0.001$ and account for 41% of cortisol changes. Drug condition was a significant unique predictor of cortisol change ($\beta=4.40$, $p<0.001$). Thus, for participants who were prescribed mifepristone, an almost 4.5 mcg cortisol difference was observed. The next model (path c) was also significant $F(5, 58)=13.282$, $p<0.001$ and accounted for 53% of endpoint verbal learning scores. Drug condition was a significant unique predictor ($\beta=2.139$, $p=0.012$) of verbal learning. Full mediation was shown in the final regression (path b and c), $F(7, 54)=11.698$, $p<0.001$, where it accounted for 60% of verbal learning scores, and drug condition was no longer a significant unique predictor of verbal learning ($\beta=1.014$, $p=0.301$), but cortisol change was ($\beta=0.310$, $p=0.016$). The indirect effect of drug condition on verbal learning scores is 1.365. Therefore, a 1.4 verbal learning score increase was observed through the effect of drug condition on cortisol difference for participants prescribed mifepristone even when controlling for baseline cortisol levels. A graphical depiction of the mediating effects of cortisol is shown in Figure 4.

4.0 Discussion

Chronic administration of a moderate-dose of the glucocorticoid receptor antagonist mifepristone in GWV with CMI resulted in the anticipated neuroendocrine changes (increased plasma cortisol and ACTH levels) but was not associated with improvement in the primary outcome measure of self-reported physical health status or the secondary outcome measures of self-reported mental health status, depression, fatigue and post-traumatic stress symptoms.

Treatment with mifepristone did, however, selectively improve verbal learning, which was among the cognitive domains impaired in the current sample at pre-treatment. Although there are few studies of the neuropsychological effects of mifepristone, improvement has been reported using a variety of doses and regimens. For example, a single 200 mg dose enhanced memory retrieval in healthy men (Rimmele et al.,

2013). In patients with bipolar disorder, one week of treatment with 600 mg/day improved spatial working memory (Young et al., 2004 and Watson et al., 2012). Enhancements in verbal learning and executive function were reported following chronic treatment (300 mg/day for 12 weeks) in older adults with anxiety disorder and neuroendocrine impairment (Lenze et al., 2014). In each of these studies, the positive effects were confined to circumscribed areas of cognition, primarily memory performance, rather than appearing as a global effect on all aspects of cognition studied.

In the current study, the treatment-related improvements in verbal learning suggest the possibility of hippocampal involvement (Milner, 1965; Smith & Milner, 1981; Maki, 2009). Alterations reflecting hippocampal dysfunction have previously found to be associated with GWV CMI in neuroimaging studies (Menon et al., 2004; Li et al., 2011, Chao et al, 2010, Li et. al, 2011; Yehuda et al., 2010). Animal models of Gulf War illness, in which rodents are exposed to stress and specific neurotoxins implicated in the disorder (e.g., pyridostigmine bromide, DEET, and permethrin), have confirmed reduced neurogenesis, partial neuron loss and mild inflammation in the hippocampus (Parihar et al., 2013; Abdel-Rahman et al., 2002, Li et al., 2011). Moreover, stressed or cognitively-impaired rodents demonstrated improved performance on hippocampal-dependent learning following exposure to mifepristone (Oitzl et al., 1998; Aisa et al., 2007; Zuo et al., 2011), likely resulting from reversal of corticosterone-induced reductions in hippocampal neurogenesis (Oomen et al., 2007; Mayer et al., 2006). It is therefore possible that mifepristone yields a similar neuroprotective effect on hippocampal function in Gulf War CMI, contributing to the observed finding.

The exact mechanism through which mifepristone acted to alter memory performance in this study cannot be known due to limitations of the current design, but it is possible to generate explanations based on knowledge of mifepristone actions on glucocorticoids, as well as the complex effects of glucocorticoids on cognition. Mifepristone blocks central glucocorticoid receptors and the efflux of cortisol from the brain, which is hypothesized to recalibrate the HPA axis through an up-regulation of mineralocorticoid receptors and down-regulation of glucocorticoid receptors (Belanoff et al., 2002b). Therefore, the

enhanced glucocorticoid responsivity observed in symptomatic GWV (Golier et al., 2007) might have been attenuated by mifepristone through blockade of central glucocorticoid receptors. Several observations support the view that mifepristone's effects may have resulted from its actions on and through a disrupted HPA axis system. There was an exaggerated response to glucocorticoids at pre-treatment, reflected by an enhanced cortisol suppression following the low-dose dexamethasone suppression test (mean level 85.17% is higher than what has been observed in healthy non-deployed veterans (Gaillard and Riondel, 1984)), and similar to that previously observed (Golier et al., 2006 a,b). Additionally, the verbal learning improvement was mediated by the magnitude of neuroendocrine response, and the lower baseline cortisol level and enhanced peripheral glucocorticoid sensitivity (as measured by the lysozyme IC_{50-DEX}) were associated with improved cognitive outcomes. While correlative, that pre-treatment neuroendocrine status is a relevant predictor of mifepristone's effects on verbal memory offers the possibility that individualized treatment approaches utilizing glucocorticoid receptor antagonists could be realized in the future.

The controlled nature of this study allows us to generalize findings to other GWV with CMI. Using a crossover design allowed us to utilize each participant group as their own control. This study had a low attrition rate, providing us with a good data set. While this is a strong benefit, some disadvantages must be considered. For example, each neuropsychological measure was administered multiple times. Alternate forms were utilized to assess three of the domains studied in order to prevent practice effects, including verbal learning. However, it is not known whether these multiple administrations affected the ability to detect changes in cognition.

Future studies are needed to further explore neuroendocrine approaches to treating CMI with a focus on cognitive outcomes. These may include using a broader range of doses of mifepristone, administering it over a longer period of time, or exploring other glucocorticoid receptor antagonists. The potentially beneficial properties of mifepristone or other glucocorticoid receptor antagonists and their mechanisms of

action should be explored for the treatment of neuropsychiatric impairments in CMI and overlapping conditions associated with HPA axis dysregulation.

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Table 1. Sociodemographic characteristics of Gulf War veterans in overall sample

	Overall Sample (n=32)	Range
Age (years)	49.1 (7.2)	39 – 65 years old
Education (years)	13.3 (1.8)	11 – 18 years
Race		
African American	50.0% (n=16)	
Caucasian	40.6% (n=13)	
Other	9.4% (n=3)	
Ethnicity		
Hispanic	50.0% (n=16)	
Non-Hispanic	50.0% (n=16)	
Marital Status		
Married/common law marriage	53.1% (n=17)	
Single/Separated/Divorced/Widowed	46.9% (n=15)	
Employment Status		
Full-time	56.3% (n=18)	
Part-time/Unemployed/Student/Retired/Disabled	43.8% (n=14)	
Education		
High school degree or GED	40.6% (n=13)	
Some college or vocational school	43.8% (n=14)	
4 year college degree/Master's Degree	15.6% (n=5)	
Current Military Status		
Reserve	32.2% (n=10)	
Retired	67.7% (n=21)	
Childhood Trauma Questionnaire (CTQ)		
Sexual Abuse	6.56(4.17)	
Physical Abuse	8.03(3.75)	
Emotional Abuse	8.31(4.55)	
Physical Neglect	9.34(8.82)	
Emotional Neglect	9.63(4.29)	
Total Score	8.06(2.61)	

Table 2. Primary, secondary and descriptive clinical, neurocognitive and neuroendocrine change scores for Gulf War veterans in overall sample

Treatment Phase I						Treatment Phase II			
			Baseline	Endpoint	Change		Baseline	Endpoint	Change
n			Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)
Primary Clinical									
SF-36 PCS	14	Drug	34.60 (8.10)	34.10 (10.80)	-0.50 (6.50)	Placebo	35.00 (8.80)	35.30 (10.30)	0.20 (4.80)
	18	Placebo	37.90 (9.90)	38.30 (8.80)	0.40 (5.00)	Drug	39.30 (9.30)	39.40 (9.10)	0.10 (4.90)
Secondary Clinical									
SF-36 MCS	14	Drug	30.30 (14.60)	31.20 (13.80)	0.90 (8.60)	Placebo	29.50 (15.90)	31.40 (13.00)	1.80 (8.50)
	18	Placebo	31.10 (13.90)	34.20 (12.00)	3.10 (8.50)	Drug	31.50 (13.60)	32.10 (11.30)	0.60 (10.80)
Secondary Neurocognitive									
MATRICS Working Memory	14	Drug	34.50 (11.55)	36.00 (11.07)	1.50 (6.30)	Placebo	36.29 (11.16)	37.5 (12.21)	1.21 (6.47)
	17	Placebo	40.47 (13.20)	41.06 (11.87)	0.59 (7.40)	Drug	43.06 (11.83)	43.71 (10.82)	0.65 (5.09)
MATRICS Verbal Learning	14	Drug	36.64 (4.33)	39.00 (6.49)	2.36 (5.73)	Placebo	38.50 (7.98)	37.86 (7.65)	-0.64 (4.72)
	17	Placebo	44.18 (11.84)	41.59 (6.89)	-2.59 (8.99)	Drug	44.24 (10.43)	48.71 (11.38)	4.47 (8.80)
MATRICS Visual Learning	14	Drug	42.86 (6.95)	47.00 (6.01)	4.14 (6.49)	Placebo	46.00 (9.97)	49.64 (9.59)	3.64 (7.19)
	17	Placebo	48.76 (12.11)	52.94 (8.90)	4.18 (9.74)	Drug	52.41 (9.26)	54.47 (8.98)	2.06 (5.18)
MATRICS Overall	14	Drug	31.36 (9.38)	34.21 (9.17)	2.86 (4.54)	Placebo	34.71 (10.82)	36.36 (11.11)	1.64 (6.77)
	17	Placebo	40.41 (13.81)	42.71 (11.72)	2.29 (5.10)	Drug	44.53 (12.57)	46.00 (14.04)	1.47 (1.47)
Neuroendocrine									
Cortisol	13	Drug	15.72 (7.01)	24.68 (10.85)	8.97 (8.29)	Placebo	16.71 (6.11)	11.86 (4.39)	-4.85 (7.11)
	17	Placebo	13.81 (4.00)	13.14 (4.09)	-0.66 (4.01)	Drug	13.67 (6.34)	28.77 (9.33)	15.10 (11.13)
ACTH	13	Drug	61.17 (64.19)	81.81 (64.33)	20.64 (36.57)	Placebo	67.91 (91.44)	43.47 (30.80)	-24.44 (70.09)
	17	Placebo	45.85 (59.29)	40.13 (42.81)	-5.72 (20.33)	Drug	28.75 (15.31)	75.62 (36.73)	46.88 (31.46)
Lysozyme IC ₅₀ -DEX	12	Drug	5.03 (2.02)	5.56 (3.23)	0.53 (2.09)	Placebo	4.65 (3.37)	5.44 (3.18)	0.79 (1.66)
	14	Placebo	4.20 (2.38)	3.88 (2.41)	-0.32 (2.87)	Drug	3.79 (2.08)	4.85 (3.22)	1.06 (3.16)
Descriptive Clinical									
PCL total	14	Drug	53.40 (20.30)	48.60 (20.40)	-4.90 (14.50)	Placebo	52.00 (20.80)	52.00 (21.60)	0.00 (4.90)
	18	Placebo	52.90 (19.10)	49.60 (16.80)	-3.30 (9.10)	Drug	50.50 (16.80)	44.90 (17.40)	-5.60 (8.10)
BDI total	14	Drug	24.10 (12.80)	19.40 (12.00)	-4.60 (8.80)	Placebo	20.40 (13.40)	19.20 (11.60)	-1.20 (6.10)
	18	Placebo	24.90 (14.40)	20.40 (11.60)	-4.50 (9.00)	Drug	21.20 (10.10)	20.90 (11.40)	-0.30 (4.50)

Table 3. Primary, secondary and descriptive clinical, neurocognitive and neuroendocrine outcomes for Gulf War veterans in overall sample

Overall						Examination of Treatment Order Effects				
	n	Mean (SD)	T	df	p-value	Order	Mean (SD)	t	df	p-value
Primary Clinical										
SF-36 PCS	32	-0.46 (7.76)	-0.34	31	0.738	M (n=14)	-0.71 (7.83)	-0.16	30	0.877
						P (n=18)	-0.27 (7.93)			
SF-36 MCS	32	-1.89 (12.49)	-0.81	31	0.423	M (n=14)	-0.96 (14.15)	0.33	30	0.744
						P (n=18)	-2.45 (11.42)			
Secondary Neurocognitive										
MATRICES working memory	31	0.16 (8.26)	0.11	30	0.914	M (n=14)	0.29 (9.19)	0.07	29	0.941
						P (n=17)	0.06 (7.7)			
MATRICES verbal learning	31	5.23(10.29)	2.83	30	0.008	M (n=14)	3 (8.36)	-1.10	29	0.282
						P (n=17)	7.06 (11.58)			
MATRICES visual learning	31	-0.94 (11.12)	-0.47	30	0.643	M (n=14)	0.5 (12.11)	0.65	29	0.524
						P (n=17)	-2.12 (10.46)			
MATRICES overall	31	0.10 (6.83)	0.08	30	0.937	M (n=14)	1.21 (8.71)	0.83	29	0.411
						P (n=17)	-0.82 (4.63)			
Neuroendocrine										
Cortisol	30	14.92 (12.65)	6.46	29	<0.001	M (n=13)	13.82 (13)	-0.41	28	0.683
						P (n=17)	15.76 (12.7)			
ACTH	30	49.34 (54.40)	4.97	29	<0.001	M (n=13)	45.08 (70.02)	-0.37	28	0.714
						P (n=17)	52.6 (40.76)			
Lysozyme IC ₅₀ -DEX	29	1.21 (4.28)	1.53	28	0.138	M (n=12)	-0.26 (2.18)	-1.20	24	0.243
						P (n=17)	1.39 (4.3)			
Descriptive Clinical										
PCL total	32	-3.38 (12.26)	-1.56	31	0.130	M (n=14)	-4.86 (14.93)	-0.60	30	0.555
						P (n=18)	-2.22 (10.03)			
BDI total	32	0.88 (9.22)	0.54	31	0.595	M (n=14)	-3.43 (10.38)	-2.52	30	0.017
						P (n=18)	4.22 (6.75)			
CFQ total	32	1.06 (15.46)	0.39	31	0.700	M (n=14)	-0.64 (13.93)	-0.54	30	0.590
						P (n=18)	2.39 (16.82)			
MFI-20 general fatigue (GF)	32	0.63 (3.37)	1.05	31	0.302	M (n=14)	-0.14 (4.22)	-1.14	30	0.262
						P (n=18)	1.22 (2.49)			

Note. M=Mifepristone first, P=Placebo First

Table 4. Hierarchical regression of HPA axis biomarkers predicting verbal learning sres.

Predictor	β	$SE \beta$	p -value	Δr^2
Step 1				
Treatment Phase	-1.59	1.20	0.189	0.028
Treatment Order	-2.74	1.21	0.028	0.080
Drug Condition	2.22	1.20	0.070	0.053
Education	0.86	0.81	0.294	0.017
Step 2				
Verbal Learning Baseline	0.59	0.10	0.000	0.328
Treatment Phase	-1.15	0.93	0.222	0.014
Treatment Order	-1.41	0.96	0.149	0.020
Drug Condition	2.52	0.93	0.009	0.069
Education	-0.05	0.65	0.934	0.000
Step 3				
Verbal Learning Baseline	0.49	0.10	0.000	0.199
Treatment Phase	-1.23	0.84	0.149	0.016
Treatment Order	-1.39	0.96	0.152	0.016
Drug Condition	2.46	0.83	0.005	0.066
Education	0.66	0.63	0.302	0.008
Lysozyme IC ₅₀ -DEX	-1.12	0.40	0.007	0.060
DST Cortisol Difference	0.48	0.18	0.012	0.051
DST ACTH Difference	0.02	0.02	0.315	0.008

Note. For Drug Condition, those who received Mifepristone are coded “1” and Placebo as “-1.” For Treatment Phase, Phase 1 is coded as “-1” and Phase 2 as “1.” For Treatment Group, Mifepristone first is coded as “1” and Placebo first as “-1.”

Table 5. Multiple regression testing for cortisol change as a mediator of verbal learning.

Predictor	β	$SE \beta$	p -value	Δr^2
Step 1- outcome: cortisol change				
Verbal Learning Baseline	-0.09	0.10	0.367	0.009
Education	0.17	0.57	0.765	0.001
Treatment Phase	-2.27	0.86	0.011	0.073
Treatment Order	-0.23	0.90	0.798	0.001
Drug Condition (path a)	4.40	0.85	0.000	0.280
Step 2 - outcome: endpoint verbal learning				
Verbal Learning Baseline	0.59	0.09	0.000	0.330
Education	0.18	0.50	0.714	0.001
Treatment Phase	-1.02	0.82	0.220	0.012
Treatment Order	-1.39	0.87	0.116	0.020
Drug Condition (path c')	2.14	0.82	0.012	0.054
Step 3 - outcome: endpoint verbal learning				
Verbal Learning Baseline	0.59	0.09	0.000	0.311
Education	0.27	0.55	0.622	0.002
Treatment Phase	0.71	1.71	0.679	0.001
Treatment Order	-1.79	0.87	0.045	0.031
Cortisol Baseline	0.15	0.14	0.318	0.008
Drug Condition (path c)	1.01	0.97	0.301	0.008
Cortisol Change (path b)	0.31	0.13	0.016	0.045

Note. For Drug Condition, those who received Mifepristone are coded "1" and Placebo as "-1." For Treatment Phase, Phase 1 is coded as "-1" and Phase 2 as "1." For Treatment Group, Mifepristone first is coded as "1" and Placebo first as "-1."

Figure 1. Participant flow chart.

Figure 2. MATRICS Verbal Learning Score Change.

Note. Error bars= $\pm$ standard error of the mean

Figure 3. Study Cortisol Fluctuations.

Figure 4. Cortisol mediation of drug on verbal learning.

Note. Control variables are omitted from graphical depiction. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$