

## A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial of Mifepristone in Gulf War Veterans with Chronic Multi-symptom Illness (CMI)

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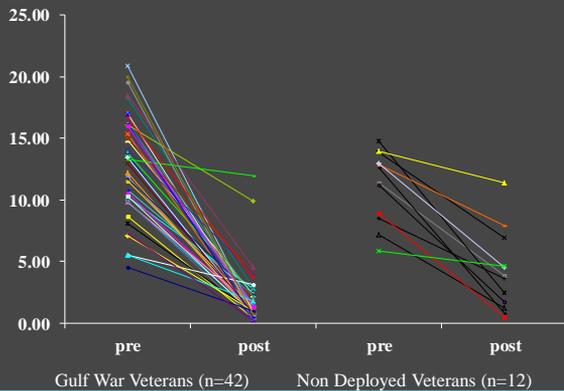
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## Rationale for studying HPA axis in GWV

- The hypothalamic-pituitary-adrenal axis (HPA) is a complex set of direct influences and feedback interactions among the hypothalamus, the pituitary gland and the adrenal gland
- Constitutes a major part of the neuroendocrine system that controls reactions to stress and regulates many processes including the immune system, mood, memory and metabolism.
- Relevance to GWV
  - Illness followed environmental exposures in combination with physical and psychological stressors
  - HPA axis has reciprocal connections with multiple systems implicated in GWI: autonomic NS, immune system, central nervous system, metabolic
  - Chronic multisymptom illness overlaps with other conditions associated with HPA axis disturbance (chronic fatigue, fibromyalgia, depression)
- Study of HPA axis does not imply that etiology is presumed to be psychological stress

## Cortisol response to low-dose DEX in Gulf War veterans and non-deployed controls

Plasma cortisol (ug/dl) before and after 0.5 mg DEX



Dexamethasone is an exogenous steroid that provides negative feedback to the pituitary to suppress the secretion of ACTH. Assess a specific part of the HPA axis. DEX binds to glucocorticoid receptors in the pituitary gland resulting in regulatory modulation.

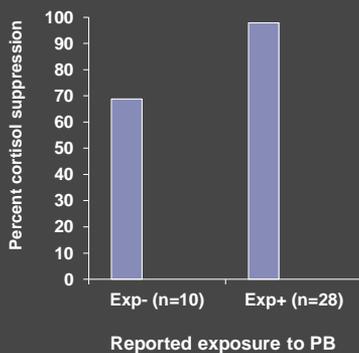
GWV had significantly greater percent cortisol suppression than non-deployed veterans controlling for weight, smoking, PTSD and MDD.

PTSD was not associated with cortisol suppression.

Golier et al., *Psychoneuroendocrinology*, 2006

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## DST associated with reported exposure to PB and some health symptoms



Gulf War veterans who reported ingestion of anti-nerve gas pills (pyridostigmine bromide) had a significantly higher percent cortisol suppression than those who did not (adjusted mean (SE) 97.9 (6.9)% vs. 68.8 (11.6);  $F(1,30)=4.66$ ,  $p=0.039$ ).

Combat exposure and other environmental exposures were not associated with DST.

Sx domains of Gulf War Illness derived from health symptom scale:

Mood-cognitive sx :  $r=0.15$ ,  $df=32$ ,  $p=0.40$

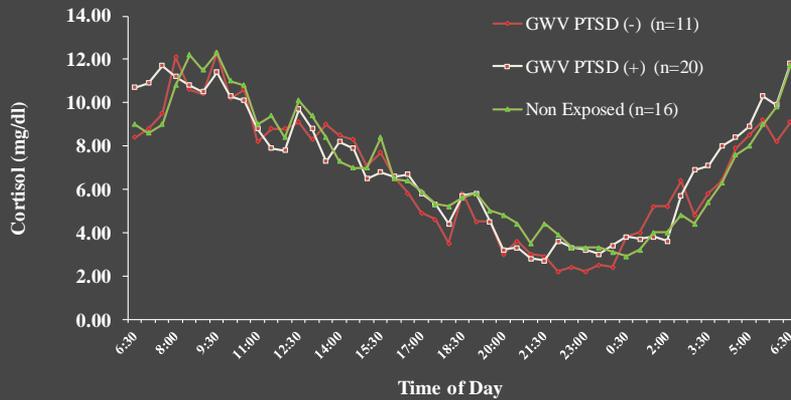
Musculoskeletal sx:  $r=0.44$ ,  $df=32$ ,  $p=0.009$

Fatigue:  $r=0.13$ ,  $df=32$ ,  $p=0.45$

Golier et al., *Psychoneuroendocrinology*, 2006

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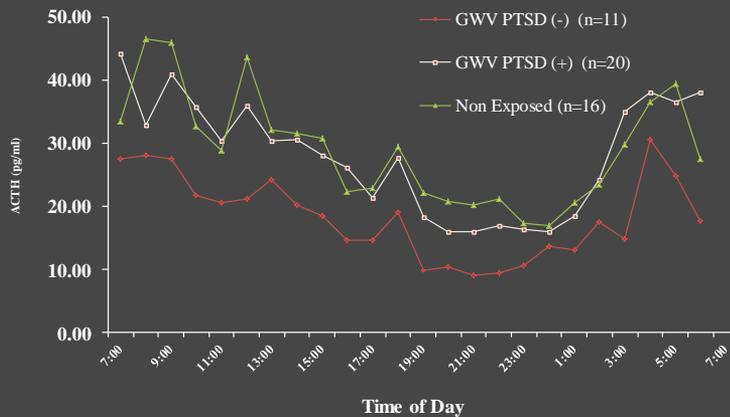
## Basal HPA axis activity: 24 hour cortisol levels in GWV and non-deployed veterans



Golier et al., Biol Psych, 2007

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## Basal HPA axis activity: 24 hour cortisol levels in GWV and non-deployed veterans



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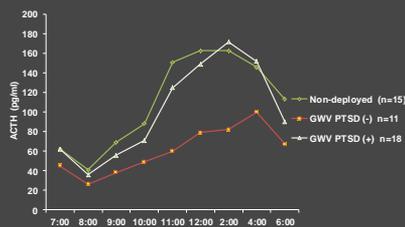
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## Why are ACTH levels significantly lower in Gulf War veterans?

- Is it due to enhanced negative feedback inhibition of cortisol on pituitary release of ACTH?
- Metyrapone stimulation test
  - Metyrapone inhibits 11-beta hydroxylase--an enzyme which converts 11-deoxycortisol into cortisol--resulting in increased 11-deoxycortisol levels and **decreased cortisol synthesis and increased ACTH secretion**

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## Metyrapone stimulation test in GWV and non-deployed subjects



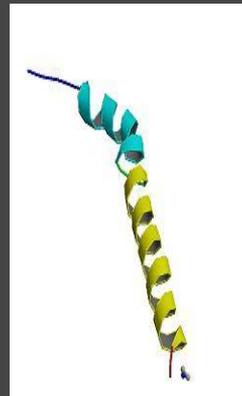
Since ACTH levels increased less in the GWV deployed group without PTSD than in the GWV group with PTSD and the healthy non-deployed group the following metyrapone stimulation, rather than normalize or increase more, suggests that enhance cortisol inhibition not driving the lower 24 hour ACTH, may be due to reduced central/hypothalamic drive to the HPA axis.

Group:  $F(1,40)=13.07, p=0.001$  controlling for basal ACTH  
PTSD- < PTSD+ ( $p=0.007$ ) and non-exposed ( $p=0.02$ )

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# Corticotropin Releasing Factor (CRF) Stimulation Test

- Corticotropin releasing factor (CRF) is a hypothalamic peptide that stimulates the release of beta-endorphin and ACTH from the anterior lobe of the pituitary gland.
- The CRF stimulation is used in the differential diagnosis of Cushing's syndrome, an endocrinologic disorder characterized by hypercortisolism, and of adrenal insufficiency
- Used in clinical research to examine the integrity of the HPA axis and provide information about the central drive to the HPA axis
- After a 90-min period of accommodation, plasma samples drawn for basal cortisol and ACTH levels
- One hundred ug of o-CRF (corticotropin ovine triflutate, Acthrel®, Pferring Laboratories, Suffern, NY) administered as an i.v. bolus at 2 pm



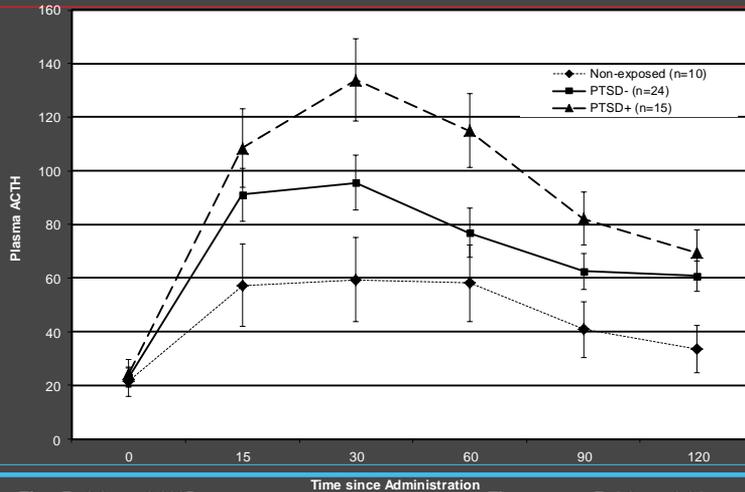
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## CRF stimulation test performed in Vietnam, Gulf War and OIF/OEF veterans

	War Zone Deployed		Non-deployed
	PTSD+ (n=15)	PTSD- (n=24)	PTSD- (n=10)
Age (yrs)	45.3 (12.9)	46.5 (12.9)	45.3 (12.9)
Education (yrs)	12.6 (2.8)	14.4 (2.5)	14.7 (2.8)
Military Rank			
Enlisted	73.3% (n=11)	41.7% (n=10)	50.0% (n=5)
NCO	20.0% (n=3)	45.8% (n=11)	40.0% (n=4)
Officer	6.7% (n=1)	12.5% (n=3)	10.0% (n=4)
Service Era			
Vietnam	46.7% (n=7)	41.7% (n=10)	40.0% (n=4)
Gulf War	33.3% (n=5)	33.3% (n=8)	30.0% (n=3)
OIF/OEF	20.0% (n=3)	25.0% (n=6)	30.0% (n=3)

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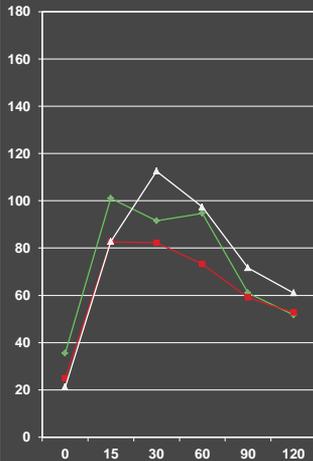
## ACTH response to o-CRF in veterans with and w/o PTSD and non-deployed veterans: 3 eras combined



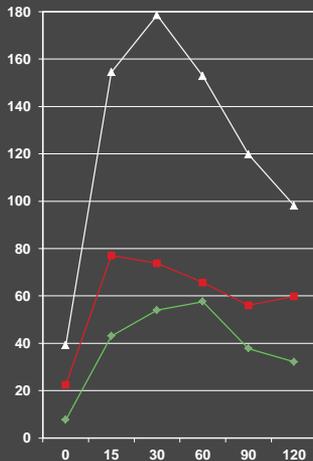
Time F =8.97, p<0.0005  
 Group =5.10, p=0.01; (PTSD+ and PTSD- > non-exposed)  
 Time x group F=1.97, p=0.04  
 Group by era: (F)=4.84, p=0.003

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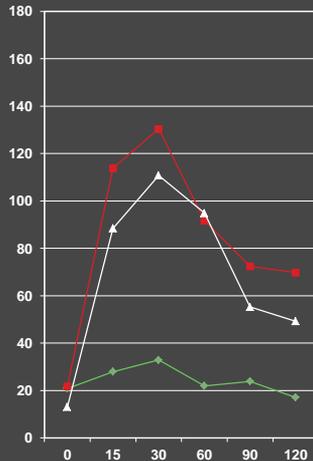
### Vietnam



### Gulf War



### OIF/OEF



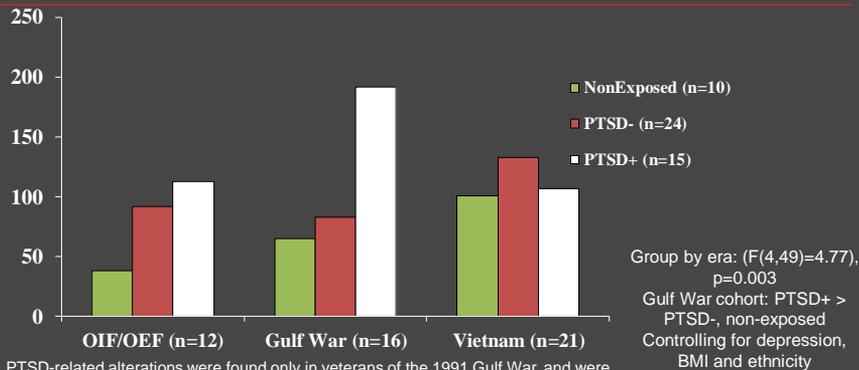
— Non-exposed  
 — PTSD-  
 — PTSD+

Gulf War Cohort:

Group x time F(10,50)=3.30, p=0.005  
 Group (F(2,10)=4.96, p=0.03)  
 PTSD+ group > non-exposed (p=0.036), PTSD- (p=0.011)

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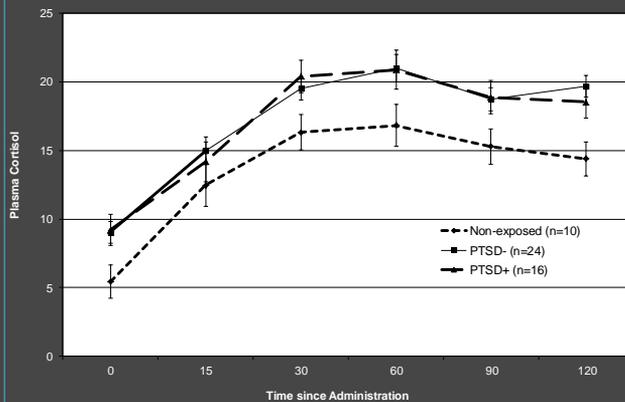
## Peak ACTH response to o-CRF by group and era



PTSD-related alterations were found only in veterans of the 1991 Gulf War, and were characterized by an enhanced pituitary response to CRF which may reflect increased sensitivity of pituitary corticotrophs or CRF hyposecretion. Suggest the HPA axis is dysregulated in symptomatic Gulf War veterans in unique ways which may reflect the long-term effects of environmental exposures in addition to disease effects.

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## Cortisol response to o-CRF in veterans with and w/o PTSD and non-deployed veterans: 3 eras combined



- Significant main effect of group ( $F(2,38)=5.30$ ,  $p=0.009$ , no main effect of era or group by era interaction)
- PTSD+ group (adj. mean (S.E.) 17.01 (0.95)) and PTSD- group (17.16 (0.66)) had higher levels than the non-exposed group (13.45 (1.01)) ( $p=0.023$  and  $p=0.003$ , respectively).

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## Conclusions regarding CRF test

- Elevated ACTH response to CRF observed in Gulf War veterans with PTSD but not in Vietnam or OIF/OEF veterans and was associated with self-reported exposure to anti nerve gas pills
  - Not previously described in PTSD
  - Does not resemble previous findings of blunted ACTH response to CRF in PTSD or depression or FM
  - CSF concentration of CRF is inversely correlated with pituitary responsiveness to CRF (Newport et al., 2003); thus suggests reduced CRF drive/ levels in symptomatic GWV
  - Exaggerated response may reflect up-regulation of pituitary corticotrophs secondary to reduced hypothalamic drive

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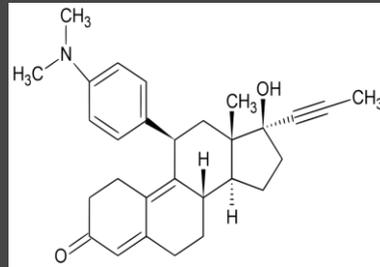
## HPA Axis in Gulf War veterans

- Data suggest the presence of overlapping/co-occurring alterations
  - Enhanced glucocorticoid sensitivity (DST) which is commonly observed in relation to deployment stress and PTSD and not unique to this population.
  - Reduced central drive to the HPA axis as suggested by low basal ACTH, blunted ACTH response to metyrapone and exaggerated ACTH response to o-CRF
    - unique to this population
    - consistent with animal model of role of neurotoxicity secondary to environmental exposures (esp. PB) contributing to poor health in GWV

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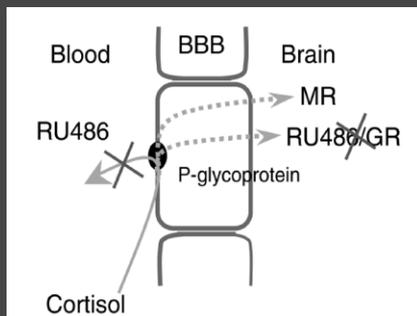
## What are the treatment implications? Rationale for Mifepristone Trial

- Selective type II glucocorticoid receptor (GR) antagonist
- Diminishes the negative feedback effects of cortisol on the HPA axis
- Compensatory increase in ACTH levels and cortisol production may increase central glucocorticoid signalling
- Net effect of mifepristone is to reset hypothalamic-pituitary-adrenal axis



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## Central Effects of Mifepristone



- Causes acute increase in cortisol in the brain due to block of cortisol pump
- Blocks GR centrally
- It is hypothesized that acute blockade of the GR centrally and the concomitant increase in cortisol level and binding to MR receptors lead to recalibration of the HPA axis and to enduring effects *after* drug discontinuation

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# Relevant observed effects of mifepristone

## Preclinical

- Protects against glucocorticoid-induced impairments in hippocampal function and neurogenesis (Haynes et al., 2001; Mayer et al., 2006)
- Reverses deleterious effects of stress on hippocampal synapses (Krugers et al., 2006)
- Improves spatial memory in stressed animals (Oitzl et al., 1998)
- Conceptualized as neuroprotective

## Clinical

- Preliminary evidence it Improves symptoms in other endocrine and neuropsychiatric conditions
  - Cushing's disease, Psychotic Major Depression. Primary insomnia

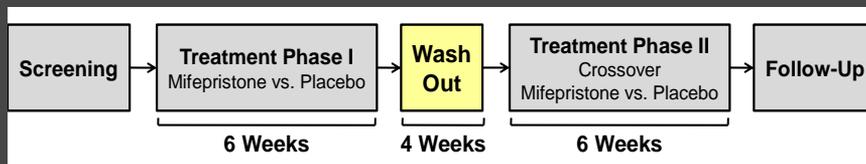
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## A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial of Mifepristone in Gulf War Veterans with Chronic Multisymptom Illness

Golier, J. A., Caramanica, K., Michaelides, A. C., Schmeidler, J., Harvey, P. D., & Yehuda, R.  
Funded by the DOD

Single site study (JJP VA Medical Center, Bronx, NY)

Subjects randomized into two 6-week treatment phases (mifepristone (200 mg/day) vs. placebo), separated by a one month wash-out period



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## Inclusion Criteria

- Veteran of the 1991 Gulf War
- Meets criteria for multisymptom illness, based on definition from the Kansas Gulf War Health project

## Exclusion Criteria

- Lack of capacity to provide consent
- Major medical or neurological disorder or traumatic brain injury
- Morning plasma cortisol level less than 5 mcg/dl or history of adrenal insufficiency
- Taking oral corticosteroids
- Lifetime diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder
- Psychiatrically hospitalized or attempted suicide within the previous 2 years
- Current suicidal ideation
- Pregnant or breastfeeding or plans to become pregnant within the year
- Not willing to use appropriate forms of contraception during the study and for at least 90 days post treatment (male or female)
- Female veterans with diseases of the uterus by history or a family history of uterine cancer
- Known allergy to mifepristone

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## Primary Outcomes

- Clinical outcomes
  - Improvement in physical health components score (PCS) as measured by the Veterans Rand 36-item health survey (SF-36)
- Neurocognitive outcomes
  - Improvement in objective cognitive functioning as measured by the working memory, verbal memory, and visual learning domains of the MATRICS neuropsychological test battery
- Neuroendocrine outcomes
  - Cortisol and ACTH levels and measures of glucocorticoid sensitivity

## Secondary Outcomes

- Clinical Outcomes
  - Improvement in mental health components score (MCS) as measured by the Veterans Rand 36-item health survey (SF-36)
- Neurocognitive outcomes
  - Improvement in objective cognitive functioning as measured by the MATRICS overall score

## Descriptive Outcomes

- Clinical Outcomes
  - Improvement in symptoms associated with CMI (fatigue, cognitive impairment, depression and post-traumatic stress) as measured by self-report

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## Statistical Analysis

- Change scores calculated as difference between the change from baseline to endpoint in the mifepristone and placebo phases
  - For GWV who did not complete the study, provided the participant completed at least two weeks of treatment in both phases, the last observation was carried forward
- Outcome measures calculated as mifepristone change minus placebo change calculated separately according to the treatment ordering
- Single sample t-tests ( $H_0$ : mean = 0) performed for all primary, secondary, and descriptive outcomes

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## Study Sample

- 65 GWV enrolled
  - 13 lost to follow-up, 9 medically ineligible; 5 did not meet criteria for CMI, 2 withdrew due to time commitment involved
- 36 GWV randomized
  - 1 did not initiate treatment phase I
  - 1 withdrew in treatment phase I due to time commitment involved
  - 1 terminated from study during treatment phase I due to elevated blood glucose
  - 1 lost to follow-up after treatment phase II baseline
- 32 GWV completed study procedures

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## Demographic Characteristics at Baseline

	Overall Sample (n=32)	Treatment Phase I / Treatment Phase II	
		Mifepristone/Placebo (n=14)	Placebo/Mifepristone (n=18)
<b>Age (years)*</b>	49.1 (7.2)	51.3 (7.6)	47.4 (6.6)
<b>Education (years)*</b>	13.3 (1.7)	13.3 (1.9)	13.3 (1.5)
<b>Race*</b>			
American Indian or Alaska Native	3.1% (n=1)	7.1% (n=1)	0.0% (n=0)
Asian	3.1% (n=1)	0.0% (n=0)	5.6% (n=1)
African American	50.0% (n=16)	64.3% (n=9)	38.9% (n=7)
Caucasian	40.6% (n=13)	28.6% (n=4)	50.0% (n=9)
No response	3.1% (n=1)	0.0% (n=0)	5.6% (n=1)
<b>Employment Status*</b>			
Full-time	56.3% (n=18)	35.7% (n=5)	72.2% (n=13)
Part-time	3.1% (n=1)	0.0% (n=0)	5.6% (n=1)
Seeking employment	6.3% (n=2)	7.1% (n=1)	5.6% (n=1)
Unemployed	18.8% (n=6)	21.4% (n=3)	16.7% (n=3)
Student	3.1% (n=1)	7.1% (n=1)	0.0% (n=0)
Retired	9.4% (n=3)	21.4% (n=3)	0.0% (n=0)
CWT	3.1% (n=1)	7.1% (n=1)	0.0% (n=0)
<b>Comorbid Disorders*</b>			
PTSD current	59.4% (n=19)	64.3% (n=9)	55.6% (n=10)
Major Depression current	21.9% (n=7)	21.4% (n=3)	22.2% (n=4)

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\* No significant differences between groups

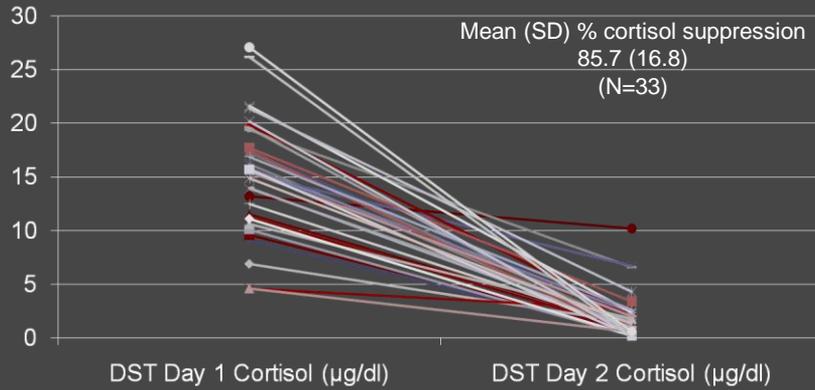
## Self-Reported Characteristics at Baseline

	Overall Sample (n=32)	Treatment Phase I / Treatment Phase II	
		Mifepristone/Placebo (n=14)	Placebo/Mifepristone (n=18)
<b>Kansas Gulf War Questionnaire</b>			
Fatigue	8.4 (2.8)	8.7 (2.8)	8.2 (2.9)
Pain	6.2 (3.0)	6.9 (2.8)	5.6 (3.0)
Neurological/cognitive/mood	24.3 (10.4)	24.9 (11.8)	23.8 (9.4)
Skin	2.2 (2.0)	1.6 (2.1)	2.6 (1.8)
Gastrointestinal	3.2 (2.5)	3.4 (3.1)	3.0 (2.1)
Respiratory	3.5 (2.7)	3.7 (2.8)	3.4 (2.8)
Number of symptom domains	4.9 (1.2)	4.8 (1.2)	5.0 (1.2)
<b>SF-36*</b>			
Physical component summary (PCS)	33.6 (10.0)	31.0 (8.8)	35.6 (10.7)
Mental component summary (MCS)	29.9 (12.2)	30.2 (10.7)	29.6 (13.6)
<b>CTQ*</b>			
Total	8.1 (2.6)	7.6 (2.3)	8.4 (2.8)
<b>CEQ*</b>			
Total	50.1 (9.6)	50.6 (10.1)	49.7 (9.4)
<b>PCL*</b>			
Total	55.7 (19.4)	57.1 (20.7)	54.6 (18.8)
<b>BDI*</b>			
Total	25.2 (11.0)	25.1 (11.8)	25.2 (10.8)

\* No significant differences between groups

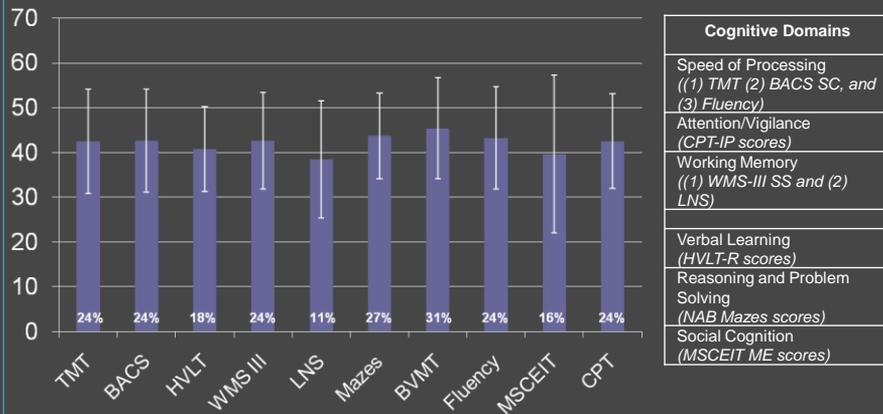
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## DST Results in GWV with CMI



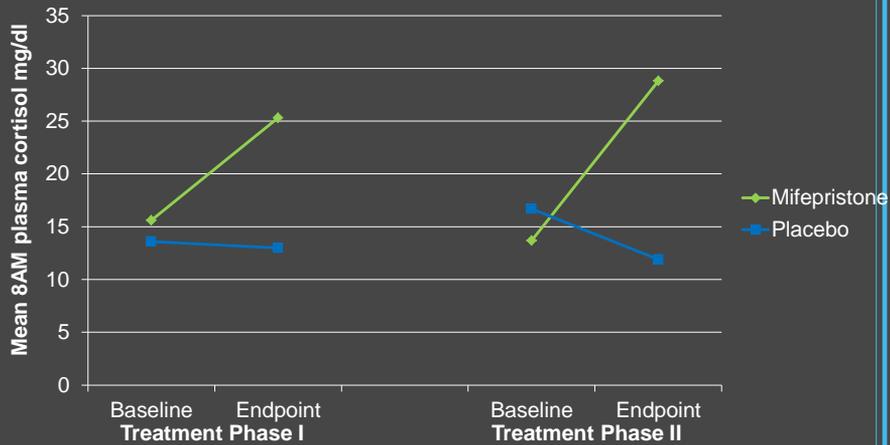
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## Mean MATRICS Scores in GWV with CMI (T Scores)



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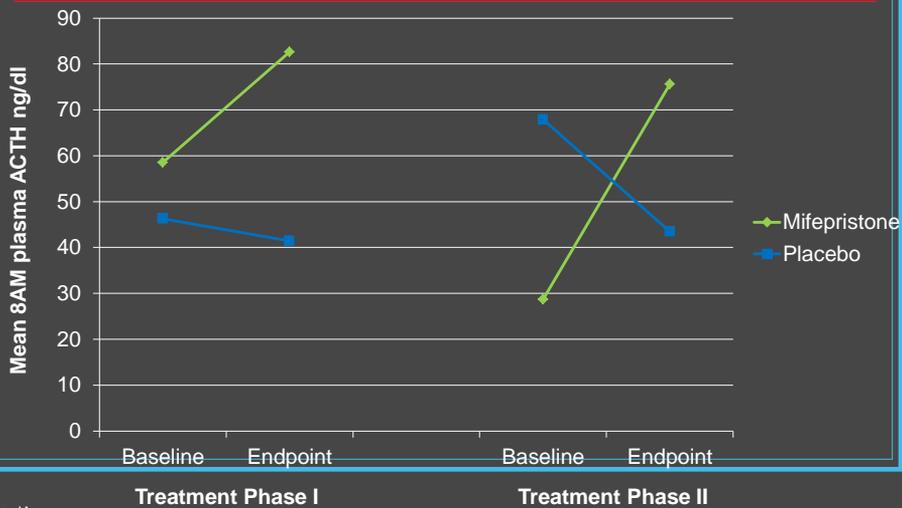
## Results: Neuroendocrine Response to Mifepristone: Plasma Cortisol



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n=30, mean (SD) change 14.92 (12.65), t=6.46, p<0.001

## Results: Neuroendocrine Response to Mifepristone: Plasma ACTH



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n=30, mean (SD)=49.53 (54.4), t=4.97, p<0.001

# Results: Clinical Outcomes (n=32)

		Treatment Phase I			Treatment Phase II			Statistics		
		Baseline	Endpoint	Change	Baseline	Endpoint	Change	Drug Δ - PBO Δ	t	p
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
<b>Primary</b>										
SF-36 PCS	Drug	34.6 (8.1)	34.1 (10.8)	-0.5 (6.5)	39.3 (9.3)	39.4 (9.1)	0.1 (4.9)	-0.46 (7.76)	-0.34	0.738
	PBO	37.9 (9.9)	38.3 (8.8)	0.4 (5.0)	35.0 (8.8)	35.3 (10.3)	0.2 (4.8)			
<b>Secondary</b>										
SF-36 MCS	Drug	30.3 (14.6)	31.2 (13.8)	0.9 (8.6)	31.5 (13.6)	32.1 (11.3)	0.6 (10.7)	-1.79 (12.49)	-0.81	0.423
	PBO	31.1 (13.9)	34.2 (12.0)	3.1 (8.5)	29.5 (15.9)	31.4 (13.0)	1.8 (8.5)			
PCL total	Drug	53.4 (20.3)	48.6 (20.4)	-4.9 (14.5)	50.5 (16.8)	44.9 (17.4)	-5.6 (8.1)	-3.38 (12.26)	-1.56	0.130
	PBO	52.9 (19.1)	49.6 (16.8)	-3.3 (9.1)	52.0 (20.8)	52.0 (21.6)	0.0 (4.9)			
BDI total	Drug	24.1 (12.8)	19.4 (12.0)	-4.6 (8.7)	21.2 (10.1)	20.9 (11.4)	-0.3 (4.5)	0.88 (9.22)	0.54	0.595
	PBO	24.9 (14.4)	20.4 (11.6)	-4.5 (9.0)	20.4 (13.4)	19.2 (11.6)	-1.2 (6.1)			

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# Results: Neuropsychological Outcomes (n=31)

		Treatment Phase I			Treatment Phase II			Statistics		
		Baseline	Endpoint	Change	Baseline	Endpoint	Change	Drug Δ - PBO Δ	t	p
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
<b>Primary</b>										
Working Memory	Drug	34.5 (11.6)	36.0 (11.1)	1.5 (6.3)	42.8 (11.5)	43.4 (10.6)	0.6 (5.1)	0.16 (8.26)	0.11	0.914
	PBO	40.4 (12.8)	40.7 (11.6)	0.2 (7.3)	36.3 (11.2)	37.5 (12.2)	1.2 (6.5)			
Verbal learning	Drug	36.6 (4.3)	39.0 (6.5)	2.4 (5.7)	44.2 (10.4)	48.7 (11.4)	4.5 (8.8)	5.23 (10.29)	2.83	0.008
	PBO	44.2 (11.8)	41.6 (6.9)	-2.6 (9.0)	38.5 (8.0)	37.9 (7.7)	-0.6 (4.7)			
<b>Secondary</b>										
Overall	Drug	31.4 (9.4)	34.2 (9.2)	2.9 (4.5)	43.3 (13.3)	44.7 (14.7)	1.5 (4.4)	0.10 (6.73)	0.08	0.937
	PBO	39.2 (14.4)	41.7 (12.1)	2.6 (5.1)	34.7 (10.8)	36.4 (11.1)	1.6 (6.8)			

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## Verbal Learning

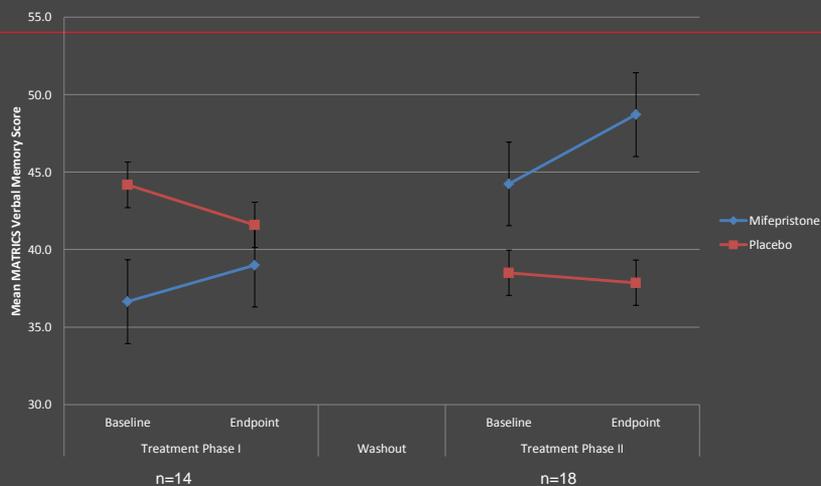
- Measured using the Hopkins Verbal Learning Test™ - Revised subtest of the MCCB
- Participants were read a list of 12 words across three consecutive trials. They had to recall as many words as they could following each trial.
- Alternate forms were used to eliminate practice effects.

Word List	Learning Trials		
	Trial 1	Trial 2	Trial 3
TEACHER			
BASKETBALL			
LETTUCE			
DENTIST			

- The verbal memory score is based on the sum of correctly repeated words across each of the three trials.

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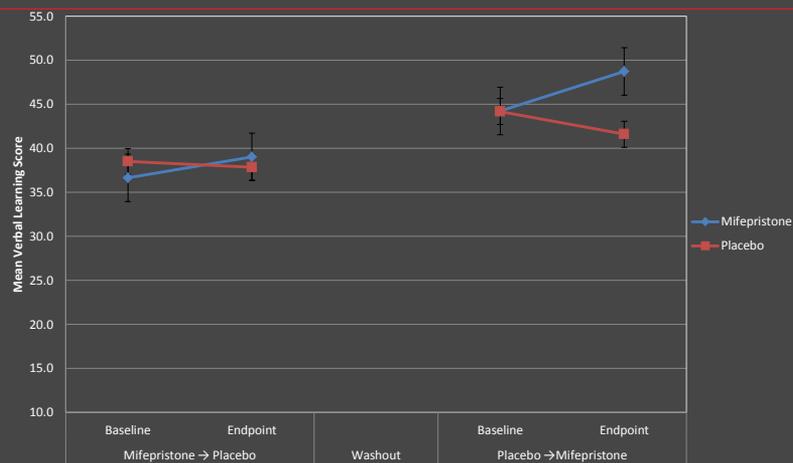
## MATRICS Verbal Learning



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Condition:  $F=2.24$ ,  $p=0.15$  Condition by Time:  $F=7.38$ ,  $p=0.01$   
Time: ns Effect of order:  $F=6.07$ ,  $p=0.02$

## Verbal Learning by Treatment Order



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## Summary

- Chronic administration of moderate-dose mifepristone was well-tolerated with few side effects.
- Improvement in a primary cognitive outcome measure, verbal learning, was observed.
- A weak trend toward improvement in a secondary clinical outcome measure, PTSD hyperarousal sx was also observed with time.
- Improvements were more evident when the drug was administered 2<sup>nd</sup>, suggesting a run-in phase may be advantageous for future trials.

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# Summary

- Circumscribed improvement in cognitive functioning was detected in the area of verbal learning
- Improvements in cognition have previously been described using a higher dose (600 mg/day x 7 days in bipolar disorder patients)
  - These data suggest that cognitive enhancing effects may be observed at lower, easily-tolerated doses of mifepristone
- Suggests a signal that targeting of the HPA axis may provide some benefits in cognitive functioning and associated symptoms; further understanding of mechanism of action of this drug in relation to Gulf War Illness is indicated.

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# Verbal Learning Last Trial Differences

Mean Words Recalled at Last Trial

	Treatment Phase 1	Treatment Phase 2
Mifepristone	8.5	9.9
Placebo	9.5	8
Difference:	-1.0 (ns)	1.9 (p=0.011)

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