

# Chronic Postconcussive Headaches in OEF/OIF/OND Service Members and Veterans: A Novel Treatment Approach

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# The Nature of an Emerging and Unprecedented Problem

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Helmand Province,  
Afghanistan. July 13,  
2009. (MSNBC)

2.4 million Service Members have been deployed to  
Iraq and Afghanistan

# Chronic Postconcussive Headache in OEF/OIF/OND Veterans

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- Estimated 19% of OEF/OIF/OND Veterans have sustained deployment-related mTBI
- Majority of mTBIs are result of blast concussion
- Prevalence of post-traumatic headaches (PTHAs) is approximately 40%

# Chronic Postconcussive Headache

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- International Classification of Headache Disorders defines PTHA:
  - Secondary HA precipitated by head trauma
  - In practice, new onset HAs within months of trauma
- Postconcussive headaches that persist for 3 months or more are considered chronic

# Chronic Postconcussive Headache

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- Tendency for PTHAs to become chronic is increased by:
  - PTSD
  - Depression
  - Sleep deprivation
  - Female gender

# Chronic Postconcussive Headache

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- In a recent cross sectional study of 978 soldiers with deployment-related concussion, 20% met criteria for chronic daily headaches (15 days or more/month)
  - 4-5-fold higher than in general population
  - 66% had headaches with migraine features

# Characteristics of Chronic Postconcussive Headache

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- Considered to be one of most disabling and difficult to treat headache syndromes
- Injudicious use of opioids or other analgesics can provoke superimposed rebound (“medication over-use”) headaches, particularly in those with frequent headaches at baseline
- “Medication over-use” headaches occur in 19-42% of patients with PTHA

# Chronic Postconcussive Headache in Iraq/Afghanistan Veterans

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- In civilian TBI population, PTHA tends to be tension-type, migraine or mixed
- In military combat population, headaches with migraine features predominate
- Migraine results in significantly more functional impairment and more sick call days than other types of headaches
  - 77% of migraine attacks interfered with duty performance on a mean of 2.4 days per month

# Treatment Outcomes of Chronic Post-Traumatic Headaches After Mild Head Trauma in US Soldiers: An Observational Study

LTC Jay Erickson, MD, et al  
(Headache 2011;51:932-944)

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- Retrospective cohort study of 100 soldiers treated with migraine prophylaxis for chronic PTHA at Madigan Army Medical Center Neurology Clinic
  - 77 had blast PTHA
  - 23 had non-blast (impact) PTHA
  - Multiple concussions significantly more common in those with blast PTHA (51% vs. 23%)

Erickson et al, Headache 51(6):932-944, 2011.

# Treatment of Blast Concussion Migraine is Challenging

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- Blast concussion migraine was usually responsive to acute abortive therapy with a triptan
  - 77% reported reliable headache relief within 2 hours
  - Triptans equally effective in blast and non-blast PTHA
- However, compared to impact postconcussive migraine, blast postconcussive migraine was poorly responsive to standard migraine prophylaxis (TCAs, propranolol, valproate, topiramate)

Erickson et al, Headache 51(6):932-944, 2011.

# Change at 3 Months in Headache Frequency in Response to Migraine Prophylaxis in Blast vs. Impact PTHA

	Headache (Days/Months)		Change Mean (%)	<i>P</i> Value	Responders*
	Baseline Mean (SD)	Follow-Up Mean (SD)			
Blast PTHA (n=77)	17.3 (9.2)	15.8 (10.4)	-1.5 (-9.1%)	0.21	22/77 (29%)
Impact PTHA (n=23)	16.5 (9.2)	9.8 (8.7)	-6.7 (-41%)	0.003	13/23 (57%)

\*Defined as  $\geq 50\%$  decline in headache frequency at follow-up compared to baseline.

Erickson et al, Headache 51(6):932-944, 2011.

# Does the PTSD Drug Prazosin Reduce Blast PTHA in OEF/OIF Veterans?

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- OEF/OIF Veterans with blast concussion PTHA have a high prevalence of comorbid PTSD trauma nightmares and sleep disturbance
- Robert Ruff, MD, VA Director of Neurology, used open label prazosin to treat comorbid PTSD in OEF/OIF Veterans with blast mTBI manifested by PTHA and other postconcussive symptoms<sup>1</sup>
- Prazosin is a CNS-active alpha-1 adrenoreceptor antagonist demonstrated effective for combat PTSD trauma nightmares, sleep disruption, and global clinical status<sup>2,3,4</sup>

<sup>1</sup>Ruff et al, J Rehabil Res Dev 46:1071-1084, 2009.

<sup>2</sup>Raskind et al, J Clin Psychiatry 63:565-568, 2002.

<sup>3</sup>Raskind et al, Biol Psychiatry 61:928-934, 2007.

<sup>4</sup>Raskind et al, Am J Psychiatry (in press).

# An Open Label Prazosin and Sleep Hygiene Trial for OIF/OEF Blast mTBI with Comorbid PTSD

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	Baseline	Week 9	p value
Headaches per month	12.4 ± 8.1	4.8 ± 2.9	< 0.001
Headache intensity	7.1 ± 1.4	4.1 ± 1.6	< 0.001
Daytime sleepiness (Epworth)	16.1 ± 2.4	7.3 ± 2.9	< 0.001
% subjects with “restful and restorative” sleep	7.0%	87.8%	< 0.001
Montreal Cognitive Assessment	24.1 ± 2.0	28.1 ± 2.2	< 0.001

Ruff et al, J Rehabil Res Dev 46:1071-1084, 2009.

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- Data from our recent positive RCT of prazosin for PTSD in active duty combat soldiers is consistent with beneficial effects of prazosin on PTHA

# Active Duty OEF/OIF Prazosin RCT

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- Parallel group RCT (1:1) at Joint Base Lewis McChord, WA
- Active duty OIF/OEF soldiers with combat operations PTSD (CAPS > 50) and distressing trauma nightmares (at least two nights/week)
- Majority of participants had comorbid mTBI

Raskind et al, Am J Psychiatry ( in press).

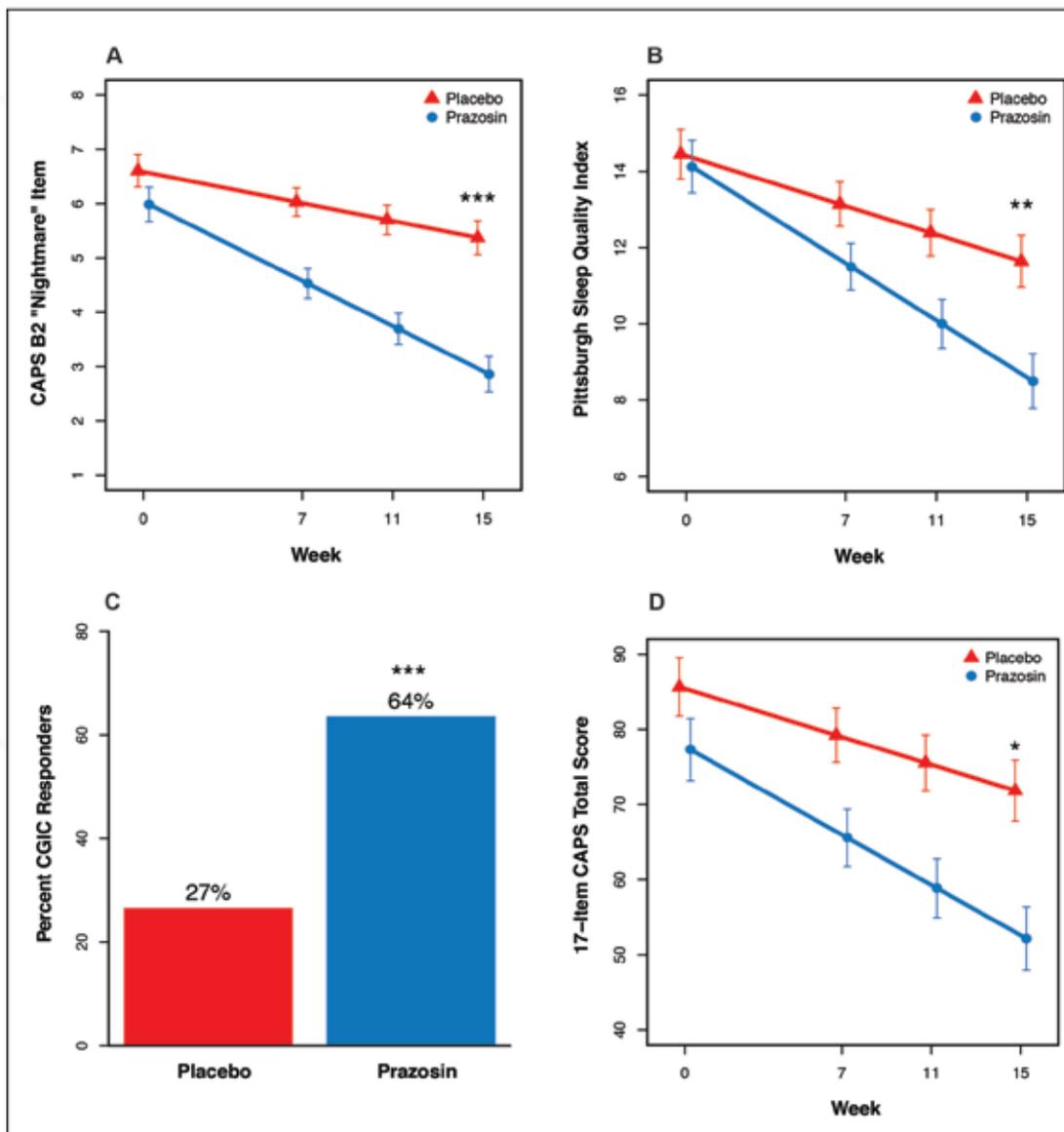
# Design Methodology

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- 6-week dose titration to maximum 20 mg qhs and 5 mg midmorning
- Study duration 15 weeks
- Outcome measures:
  - Total Clinician Administered PTSD Scale (CAPS)
  - CAPS “recurrent distressing dreams” item
  - Pittsburgh Sleep Quality Index
  - Clinical Global Impression of Change
  - Adverse Events (including headache)

Raskind et al, Am J Psychiatry ( in press).

# Effects on PTSD Outcome Parameters in Combat Soldiers Randomized to Prazosin (n=32) or Placebo (n=35)



Raskind et al, Am J Psychiatry ( in press).

# Emergent and Clinically Worsening Adverse Events

	Prazosin (n=32)	Placebo (n=35)
Syncope	2	0
Dizziness	6	6
Drowsiness	1	2
Depressed mood	0	2
Headache*	1	7
Nasal congestion	5	2
Nausea	2	5
Palpitations	4	1

\*more frequent in placebo condition,  $p < 0.05$

Raskind et al, Am J Psychiatry ( in press).

# Participants with Chronic Headaches at Baseline

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- Of participants who had headaches prior to randomization:
  - 20% in placebo group had improvement or resolution of headache
  - 50% in prazosin group had improvement or resolution of headaches

Raskind et al, Am J Psychiatry ( in press).

# Conclusion

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- Results of these studies provide rationale for a placebo-controlled trial of prazosin for blast concussion PTHA

# TBI: Screening and Evaluation of Headaches and Endocrine Disorders



## Part II: Endocrine Disorders

**Charles W. Wilkinson, PhD**

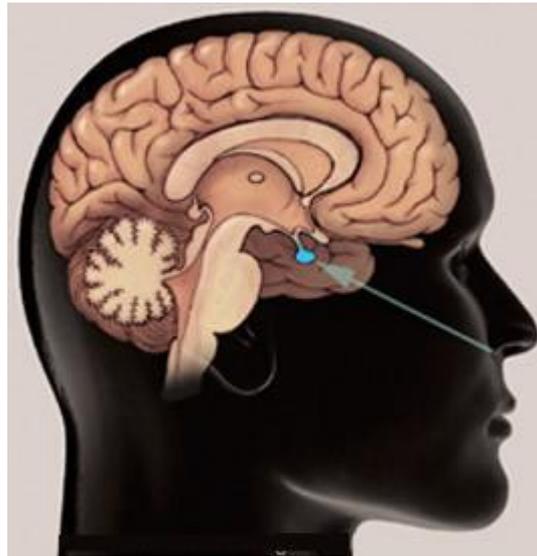
**Geriatric Research, Education and Clinical  
Center**

**VA Puget Sound Health Care System  
Seattle, Washington**

# Poll

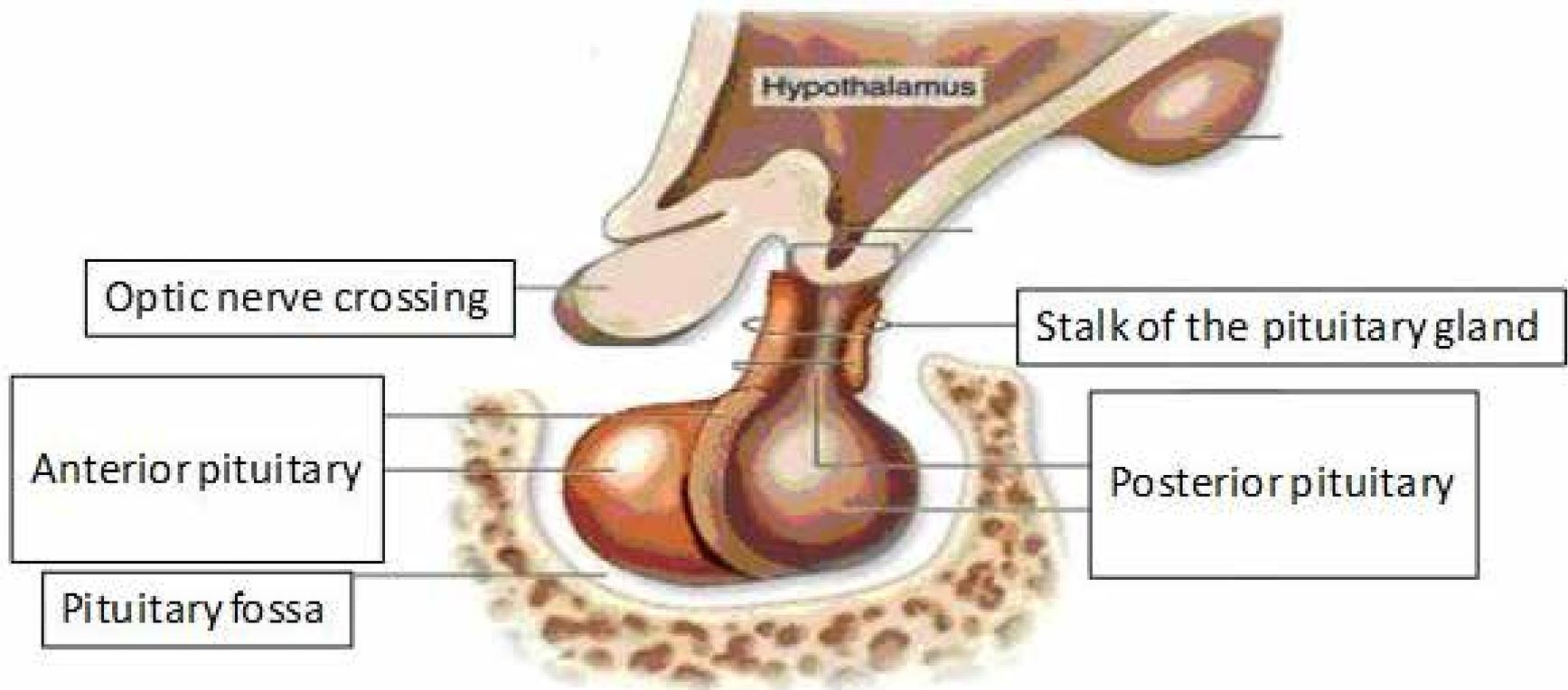
- How knowledgeable are you about endocrinology?
  - a) World expert
  - b) Well versed
  - c) Basic understanding
  - d) Endo what?

# Human Pituitary: Miniature Master Gland



# Pituitary Vulnerability to TBI

Anatomy of Pituitary



# Posttraumatic Hypopituitarism (PTHP): Acute and Chronic Stages

- ❖ Multiple transient endocrine abnormalities in the initial (~ 3-month) period following TBI
- ❖ Some problems resolve in the following months
- ❖ Smaller proportion of new dysfunctions emerge during the same period
- ❖ After 6-12 months, PTHP is generally considered permanent

# Growing Awareness of PTHP

- ❖ Hypopituitarism: deficient production of one or more pituitary hormones
- ❖ Chronic post-traumatic hypopituitarism (PTHP) from TBI was first reported in 1918
- ❖ Until 12 years ago, only scattered reports existed and the condition was considered rare
- ❖ A significant burst of studies has appeared since 2000
- ❖ Those studies have found the prevalence of chronic TBI-related hypopituitarism to be 25-50%

# Chronic Hypopituitarism After TBI from All Causes

1 <sup>st</sup> Author	Year	#Pts	%HP	1 <sup>st</sup> Author	Year	#Pts	%HP
Kelly	2000	22	37	Tanriverdi	2008	30	30
Lieberman	2001	70	69	Wachter	2009	55	25
Bondanelli	2004	50	54	Srinivasan	2009	18	56
Agha	2004	102	28	Berg	2010	246	21
Popovic	2004	67	34	Englander	2010	119	65
Aimaretti	2005	70	23	High	2010	83	51
Leal-Cerro	2005	99	25	Krahulik	2010	89	21
Schneider	2006	70	36	Park	2010	45	31
Tanriverdi	2006	52	51	Pavlovic	2010	61	33
Herrmann	2006	76	24	Kokshoorn	2011	112	5
Bushnik	2007	64	90	Reimunde	2011	19	58
Klose	2007	104	15	Schneider	2011	825	37
Bavisetty	2008	70	43				

# Consequences of PTHP for Psychological Health

- ❖ Pituitary abnormalities have been associated with behavioral and cognitive deficits, reductions in quality of life (QoL), and increased mortality
- ❖ The symptoms are similar in many respects to those of postconcussive syndrome and PTSD
- ❖ PTHP is generally responsive to treatment with replacement hormones
- ❖ Failure to screen for PTHP may result in inappropriate and ineffective treatment of these symptoms

# Poll

- Would you consider consulting an endocrinologist about chronic post-concussive symptoms?
  - a) Yes
  - b) Maybe; it would depend on the symptoms
  - c) No

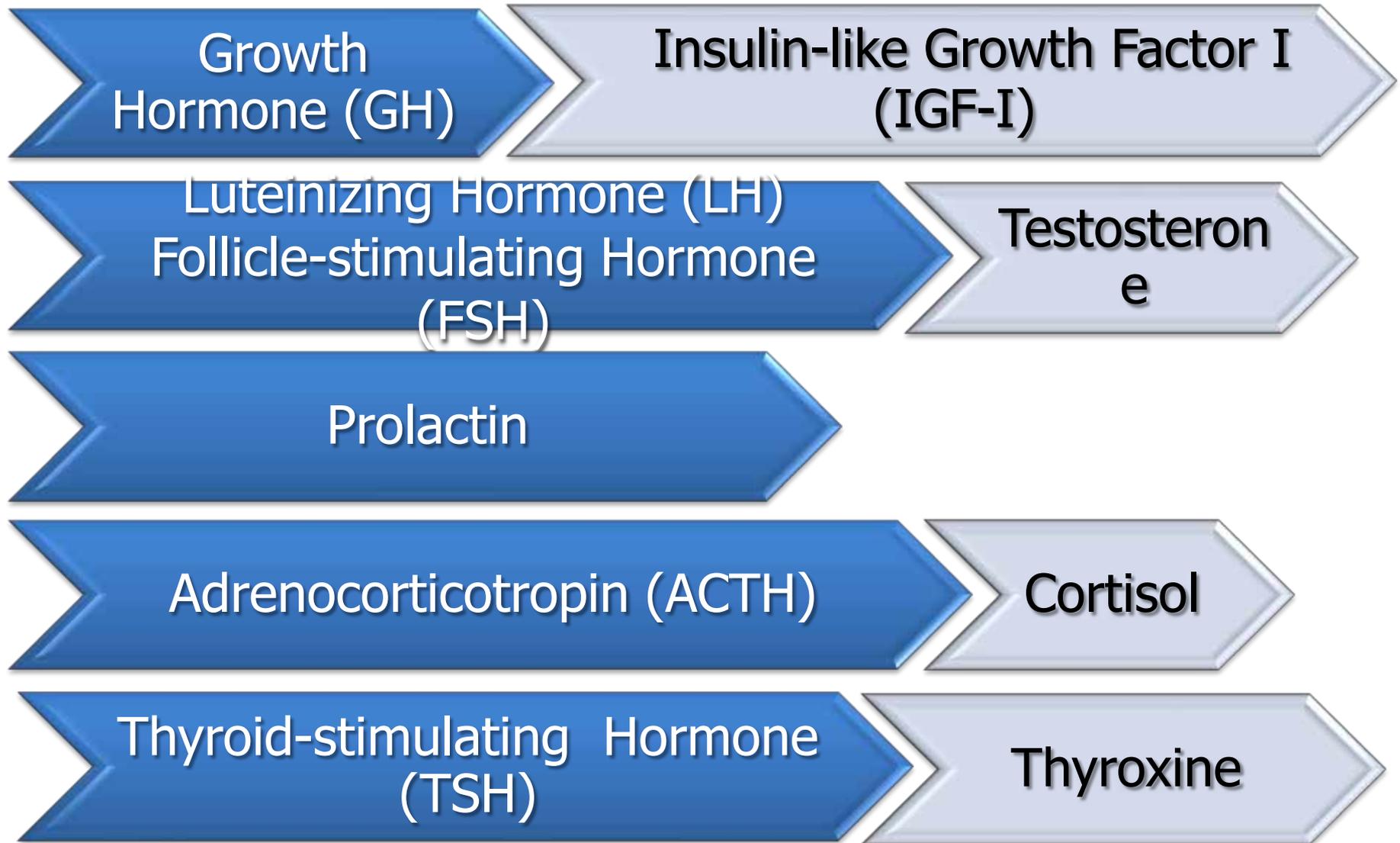
# Study Rationale & Questions

- ❖ High PTHP prevalence after TBI from other causes
- ❖ Absence of studies of the effects of blast mTBI on pituitary function
- ❖ Lack of routine hormonal screening after TBI
- ❖ Considerable overlap in symptoms between PTHP and PTSD
- ❖ Question 1: Does blast mTBI result in rates of PTHP comparable to those after TBI from other causes?
- ❖ Question 2: What pituitary hormone axes are most frequently affected?

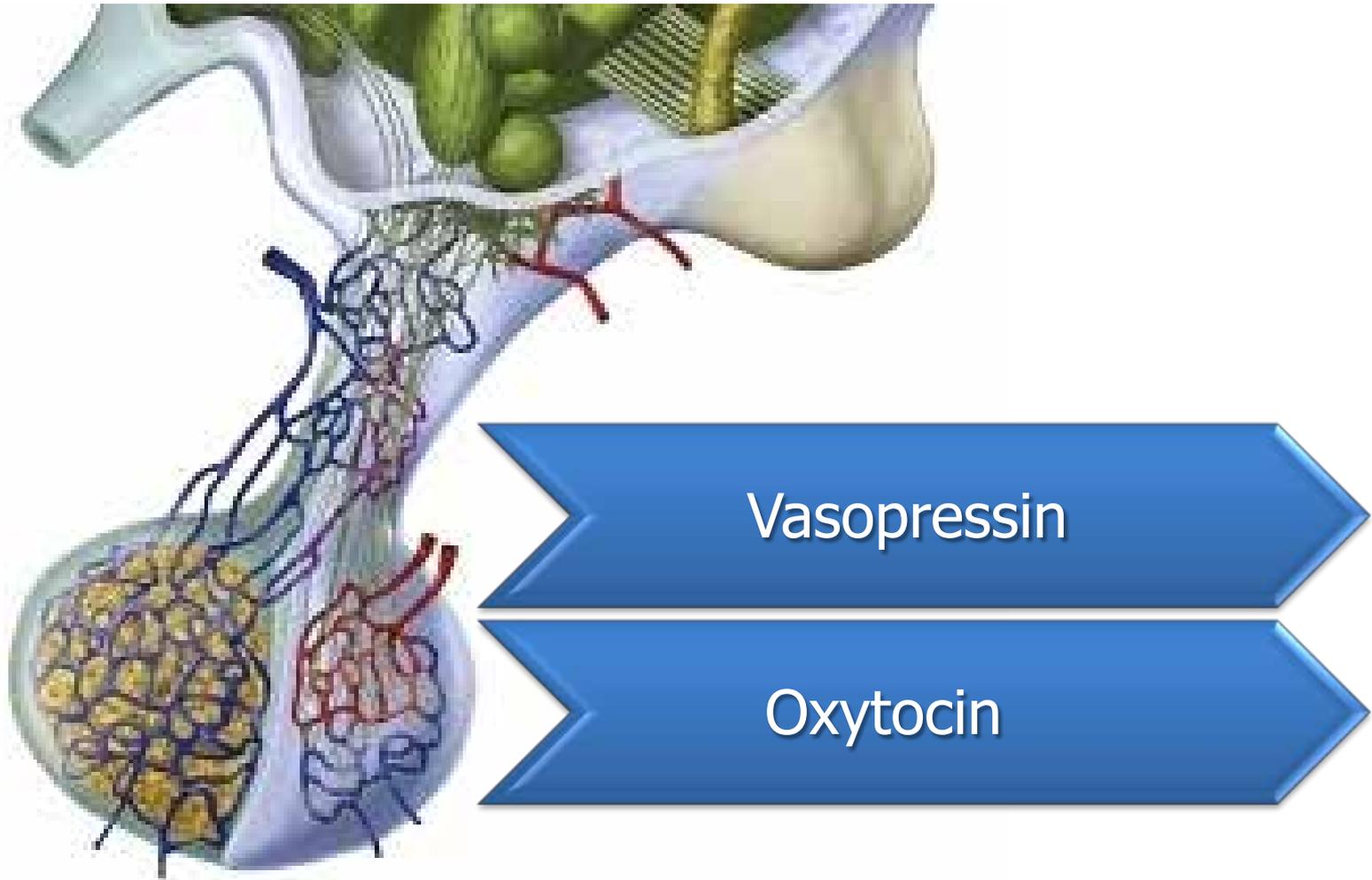
# Experimental Design

- ❖ Acquisition of blood samples from two groups of Veterans of deployment to Iraq/Afghanistan
  - Veterans diagnosed with blast mTBI – **T** group (N = 26)
  - Deployed Veterans not blast exposed – **DC** group (N = 7)
- ❖ Establishment of normal hormone reference ranges using samples from age-matched community controls
- ❖ Measurement of basal levels of 12 pituitary and target-organ hormones in serum or plasma
- ❖ Determination of prevalence of abnormalities in each pituitary hormone axis in each group

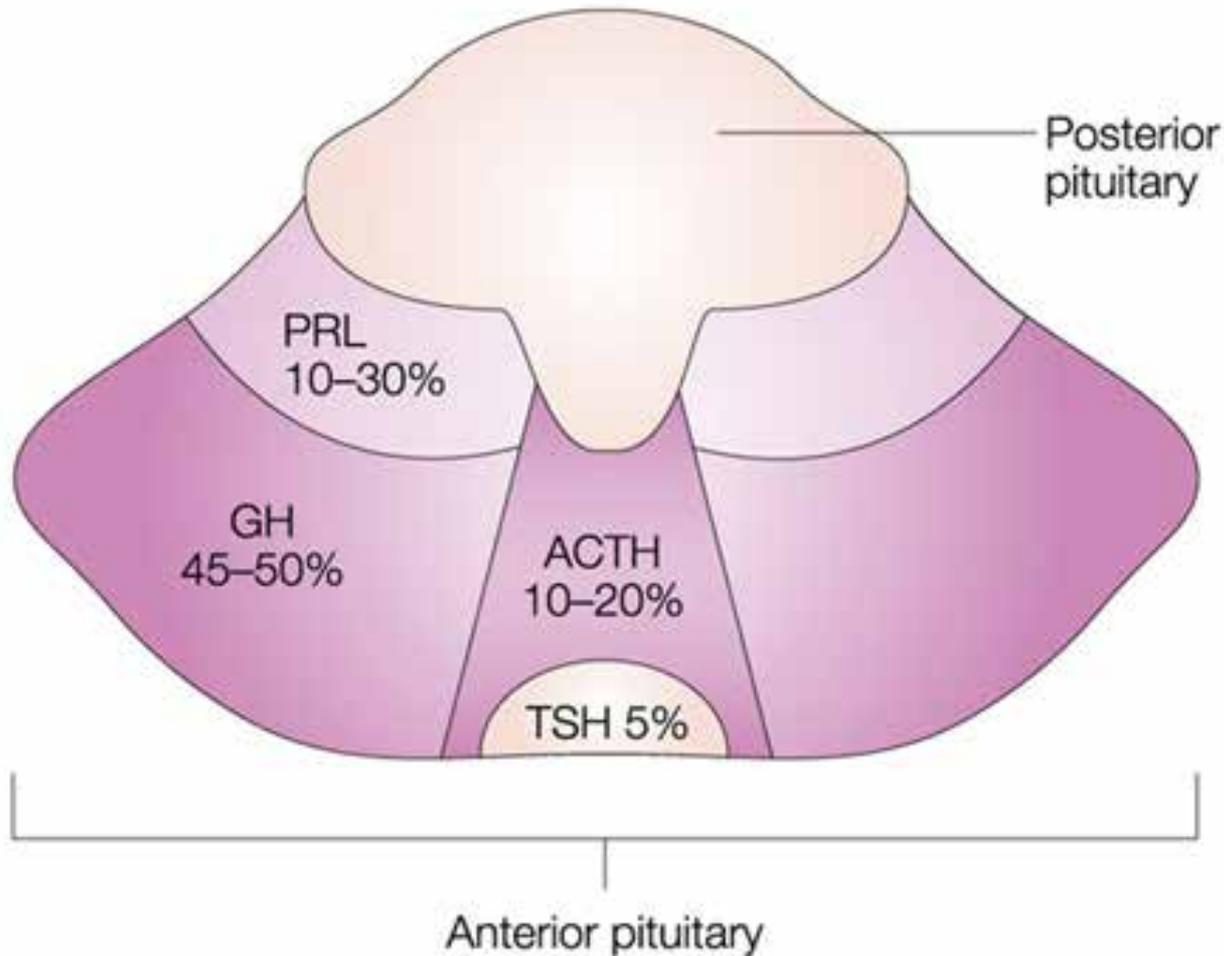
# Anterior Pituitary & Target Organ Hormones



# Posterior Pituitary Hormones



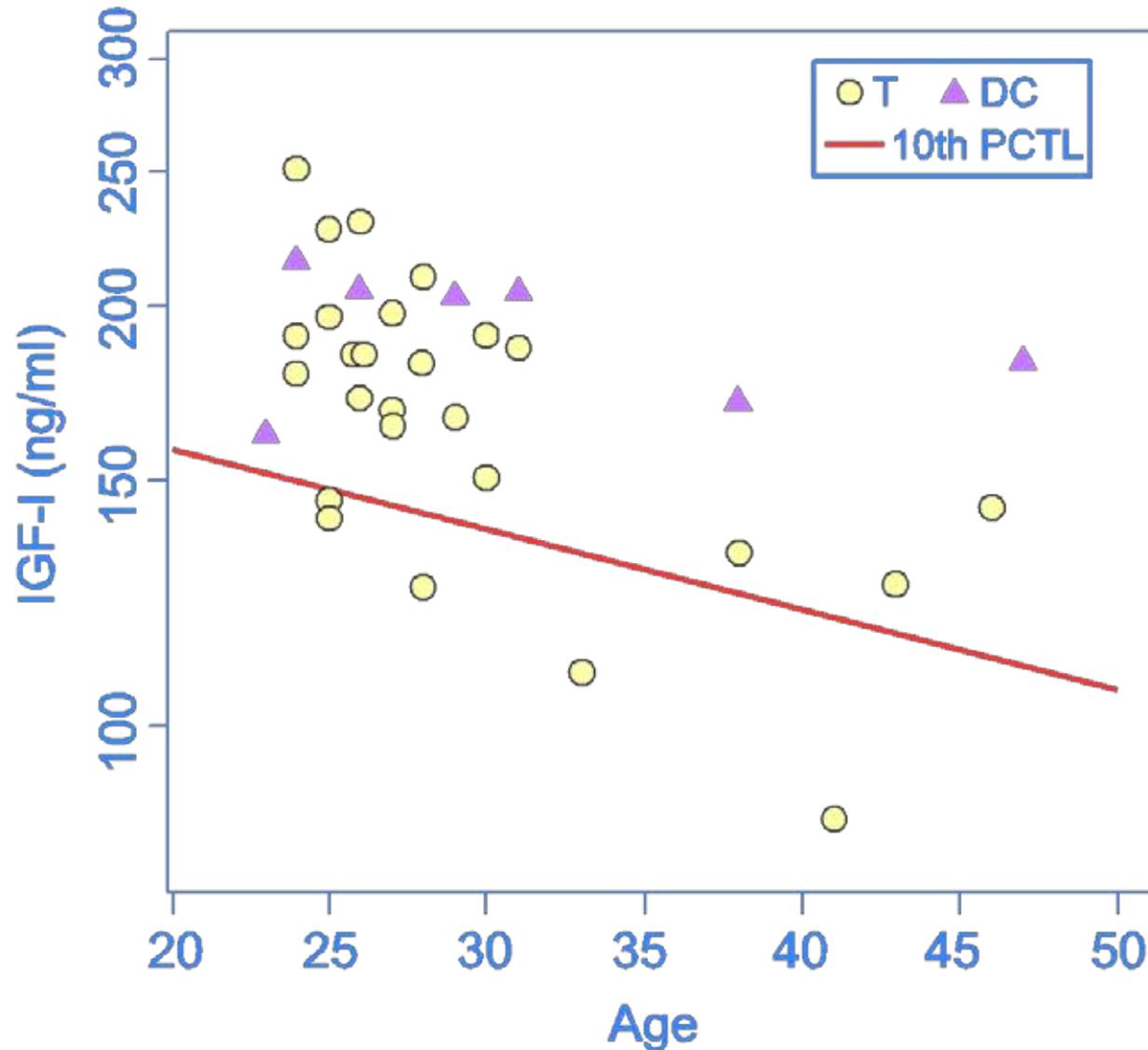
# Schematic of Pituitary Cell Types



# Consequences of Adult GH Deficiency

- ❖ Increased incidence of depression, irritability, aggressiveness, social isolation, pain, physical mobility, sexual dysfunction, and sleep disorders
- ❖ Cognitive impairment in multiple domains
- ❖ Detrimental effects on metabolism including high plasma triglycerides and low HDL cholesterol
- ❖ Negative effects on body composition (reduced lean body mass, increased adiposity)
- ❖ Low scores on quality of life assessments
- ❖ Increased hypertension & cardiovascular mortality

# Insulin-like Growth Factor-I





# OT and Human Social Behavior

- ❖ Release elicited by socially relevant challenges resulting in attenuation of stress responses
- ❖ Released in positive social interactions and may mediate stress-protective effect of social support
- ❖ Linked to reduction of limbic reactivity and autonomic arousal to social stimuli
- ❖ Implicated in promotion of social cognition and interpretation of social signals
- ❖ Altered in mental disorders characterized by severe social disturbances

# Abnormal AVP Secretion

- ❖ Diabetes insipidus (DI): very low values with plasma hyperosmolality and low urine specific gravity
- ❖ Syndrome of inappropriate antidiuretic hormone secretion (SIADH): abnormally high values accompanied by hypoosmolality and hyponatremia
- ❖ Large body of work demonstrates increased anxiety and depression in animal models
- ❖ High plasma and/or CSF levels are associated with personality disorder, depression, obsessive-compulsive disorder, schizophrenia, and PTSD

# Abnormal Hormone Levels in Veterans with TBI

<b>Subj.</b>	<b>LH</b>	<b>FSH</b>	<b>tTest</b>	<b>PRL</b>	<b>IGF-I</b>	<b>AVP</b>	<b>OT</b>
	<b>mIU/ml</b>	<b>U/L</b>	<b>ng/dl</b>	<b>ng/ml</b>	<b>ng/ml</b>	<b>pg/ml</b>	<b>pg/ml</b>
T-2	2.03	---	669	9.6	185	12.3	181
T-4	2.03	2.06	252	54.9	110	8.0	88
T-8	2.72	4.02	401	11.9	141	0.2	44
T-10	1.97	2.43	520	12.3	230	0.2	22
T-12	7.27	5.70	715	13.0	198	12.0	55
T-13	1.92	1.18	253	6.3	187	6.4	50
T-14	2.66	2.51	390	12.0	151	0.5	19
T-16	2.64	4.01	380	21.5	126	0.9	190
T-21	4.00	4.48	588	12.8	227	0.0	21
T-23	2.24	4.34	463	7.2	146	2.1	25
T-26	2.11	2.64	264	15.3	86	8.4	0

# Poll

- NOW would you consider consulting an endocrinologist about chronic post-concussive symptoms?
  - a) Yes
  - b) Maybe; it would depend on the symptoms
  - c) No

# Summary and Conclusions

- ❖ In this preliminary study, 42% of Veterans with blast mTBI were found to have chronic hormonal abnormalities
- ❖ As in studies of civilian TBI, deficiencies indicative of GHD and hypogonadism were most frequent
- ❖ PTHP is associated with neuropsychiatric symptoms and reduced quality of life similar to PTSD
- ❖ Screening for hypopituitarism after blast mTBI shows promise for appropriately directing diagnostic and therapeutic alternatives that may otherwise remain unconsidered and for markedly facilitating recovery and rehabilitation.

# This Work Was Made Possible by

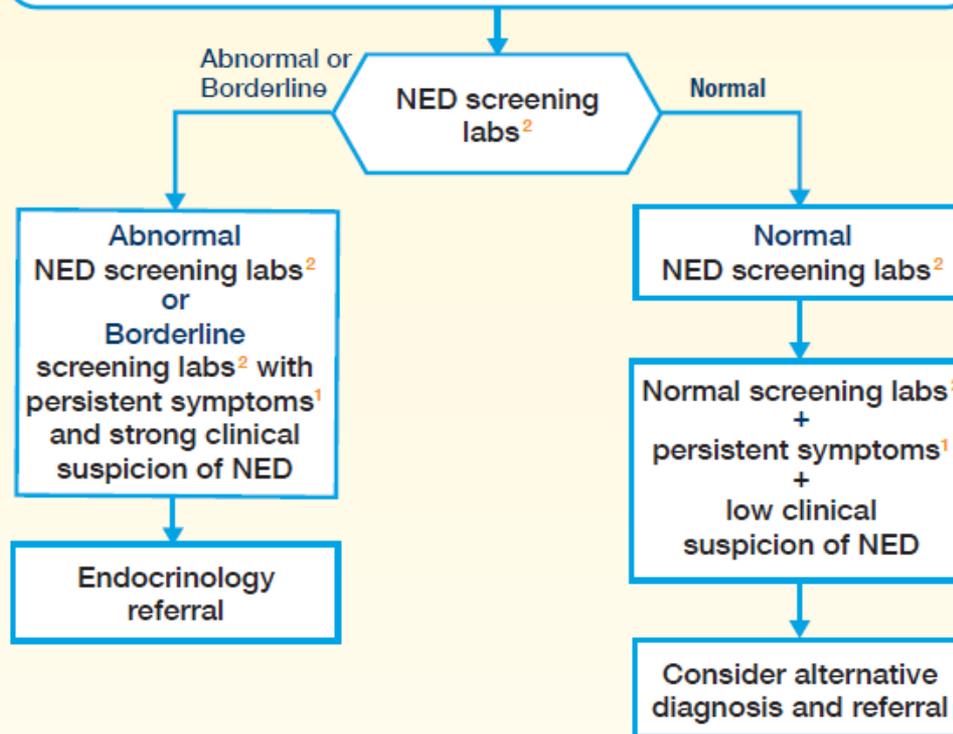
- ❖ Co-authors/collaborators Elaine Peskind, Kathleen Pagulayan, Eric Petrie, Cindy Mayer, Elizabeth Colasurdo, Jane Shofer, Kim Hart, David Hoff, Matthew Tarabochia
- ❖ Essential staff members Carl Sikkema, Natalia Czajkiewicz, Alka Goyal, Molly Chinn, Rebecca Walker, Carol Xiang, Daniel Morelli, Rebekah Rein
- ❖ Support from Department of Defense Congressionally Directed Medical Research Program in Psychological Health/Traumatic Brain Injury and the Department of Veterans Affairs



# Neuroendocrine Dysfunction Screening Post Mild TBI



Neuroendocrine testing should be considered if there is a history of mild TBI (in accordance with the VA/DoD 2009 Evidence Based Clinical Practice Guideline: Management of Concussion/mild Traumatic Brain Injury) and the patient is experiencing continuing symptoms that are suggestive of NED<sup>1</sup> for greater than three months duration; or there is a new onset of symptoms suggestive of NED<sup>1</sup> up to 36 months following mild TBI.



# For More Information:

Wilkinson CW, Pagulayan KF, Petrie EC, Mayer CL, Colasurdo EA, Shofer JB, Hart KL, Hoff D, Tarabochia MA, Peskind ER: High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury. *Front Neurol* 3:11, 2012.

<http://www.frontiersin.org/Neurotrauma/10.3389/fneur.2012.00011/abstract>

Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) Neuroendocrine Dysfunction Post mTBI Clinical Recommendations, Reference Card, and Training Slides

[http://www.dcoe.health.mil/TraumaticBrainInjury/TBI\\_Information.aspx](http://www.dcoe.health.mil/TraumaticBrainInjury/TBI_Information.aspx)