Evolving Pharmacologic Strategies in the Treatment of PTSD

John J. Miller, M.D.
Medical Director
Brain Health
Exeter, NH

In Memory of the American Tragedy

September 11, 2001

Overview

- Historical perspective on PTSD
- Definition of PTSD
- Epidemiology of PTSD
- Neurobiology of PTSD
- Current Pharmacotherapy of PTSD
- Future Medication Development for PTSD

Historical Perspective on PTSD

Hysteria and Sexual Abuse

- Sigmund Freud – patients told him of sexual abuse and incest
- 1896 Freud published "The Aetiology of Hysteria" – 18 case studies
- Privately repudiated by Freud within one year due to criticism and ostracism from his medical and psychiatric colleagues

"Shell Shock" during World War I

- 8 million men died in 4 years
- Brutal trench warfare
- Combat soldiers acted like "hysterical woman"
- Soldiers lost their memory and ability to feel
- "Mental breakdowns" accounted for 40% of British battle casualties
- Medical interest in psychological trauma faded a few years after the war ended

Lessons from World War II

- "It was recognized for the first time that any man could break down under fire and that psychiatric casualties could be predicted in direct proportion to the severity of combat exposure"
- Shortly after the war: "the lasting effects of war trauma were once again forgotten"

Herman, J.; Trauma and Recovery; BasicBooks; 1992.

Vietnam War

- Traumatized veterans, often decorated war heroes, wouldn't let us forget
- 1970 – Psychiatrists met with a veteran formed group "Vietnam Veterans Against the War"
- Vietnam Veterans self-organized "rap groups"

1980

American Psychiatric Association created a new diagnostic entity which was listed in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III):

Posttraumatic Stress Disorder (PTSD)

Definition of PTSD

PTSD *DSM-IV* Diagnostic Criteria

A. The person has been exposed to a traumatic event
B. The traumatic event is persistently reexperienced
C. Persistent avoidance of stimuli associated with the traumatic event and numbing of general responsiveness
D. Persistent symptoms of hyperarousal not present before the traumatic event
E. Symptom's duration of criteria B,C, and D is more than 1 month
F. Symptoms cause clinically significant distress or impairment at home, work, or in other areas of functioning

Traumatic Event

The person has been exposed to a traumatic event in which *both* of the following occurred:

- The person experienced, witnessed, or was confronted with event(s) involving actual or threatened death or serious injury, or a threat to the physical integrity of self or others
- The person's response involved intense fear, helplessness, or horror

Reexperiencing

The traumatic event is persistently reexperienced (as manifested by one or more of the following):

- **Recurrent, intrusive distressing memories**
- **Recurrent distressing dreams**
- **Illusions, hallucinations, dissociative flashback episodes**
- **Intense psychological distress when exposed to reminiscent cues**
- **Physiological reactivity on exposure to internal or external cues**

Avoidance/Numbing

Persistent avoidance of stimuli associated with the traumatic event and numbing of general responsiveness not present before the traumatic event (as manifested by three or more of the following):

- **Avoiding thoughts, feelings, or conversations connected to the event**
- **Avoiding activities, places, or people connected to the event**
- **Amnesia about certain important aspects of the event**
- **Decreased interest in once-enjoyed activities**
- **Feeling detached from others**
- **Emotional numbing/restricted range of affect**
- **A sense of foreshortened future**

Hyperarousal

Persistent symptoms of hyperarousal not present before the traumatic event (as manifested by two or more of the following):

- **Difficulty falling or staying asleep**
- **Irritability or outbursts of anger**
- **Problems concentrating**
- **Hypervigilance**
- **Exaggerated startle response**

"Complex" PTSD Subtype??

- **Common among individuals exposed at an early age to severe and chronic trauma**
- **More disabling**
- **Chronic symptoms are common**
- **More Comorbidity**
- **More severe dissociation**

PTSD as part of a Spectrum?

PTSD

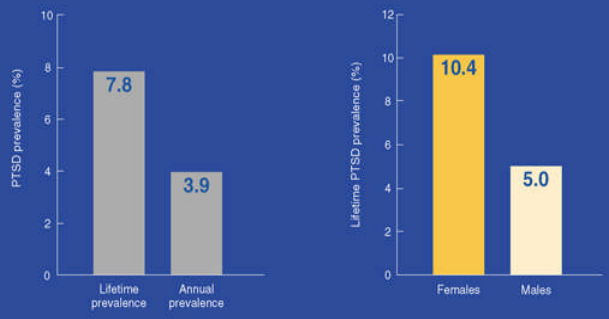
Dissociative Disorders

Dissociative Identity Disorder

Epidemiology of PTSD

PTSD—Prevalence

A common condition—PTSD is the 5th most prevalent major psychiatric illness*



Kessler 1995; Kessler 1999.

*From Part 2 of the National Comorbidity Survey (NCS). A total of 5877 respondents participated in the survey, which was conducted among individuals aged 15 to 54, from September 1990 to February 1992.

PTSD – Risk Factors

Characteristics of the traumatic event

- **Severity**
- **Duration**
- **Proximity of exposure**

PTSD – Risk Factors

Characteristics of the individual

- Family history
- Social supports
- Childhood events
- Preexisting psychiatric disorders
- Individual personality traits

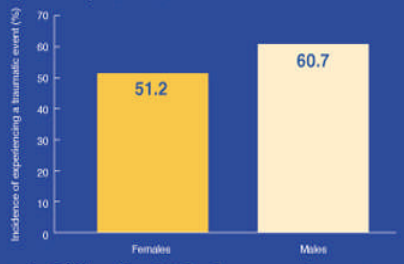
Common Traumatic Events

Some common traumatic events in the National Comorbidity Survey included:

- Witnessing injury/death
- Sexual molestation/rape
- Natural disaster/fire
- Physical attack or abuse/threatened with a weapon
- Life-threatening accident
- Combat
- Shock

Prevalence of Traumatic Events Is High

The lifetime incidence of experiencing a traumatic event severe enough to cause PTSD is more than 50%, according to the National Comorbidity Survey (NCS)*



Approximately 20% of individuals exposed to a traumatic event may develop PTSD

Kessler 1995; Breslau 1991; Resnick 1993.

*From Part 2 of the NCS. A total of 5877 respondents participated in the survey, which was conducted among individuals aged 15 to 54, from September 1990 to February 1992.

PTSD – Clinical Course

PTSD symptoms usually present within first 3 months following the traumatic event

- **Less frequently, symptom onset may be delayed for months or years after the traumatic event**
- **Symptoms of PTSD may persist for months or years following the traumatic event**

Approximately 50% of all cases of PTSD are chronic

- **Acute: Duration of symptoms is less than 3 months**
- **Chronic: Duration of symptoms is 3 months or more**

PTSD – Impact on Society

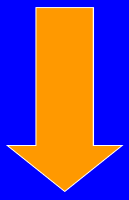
Patients with PTSD often exhibit:

- **A greater number of health problems**
- **Greater functional impairment**

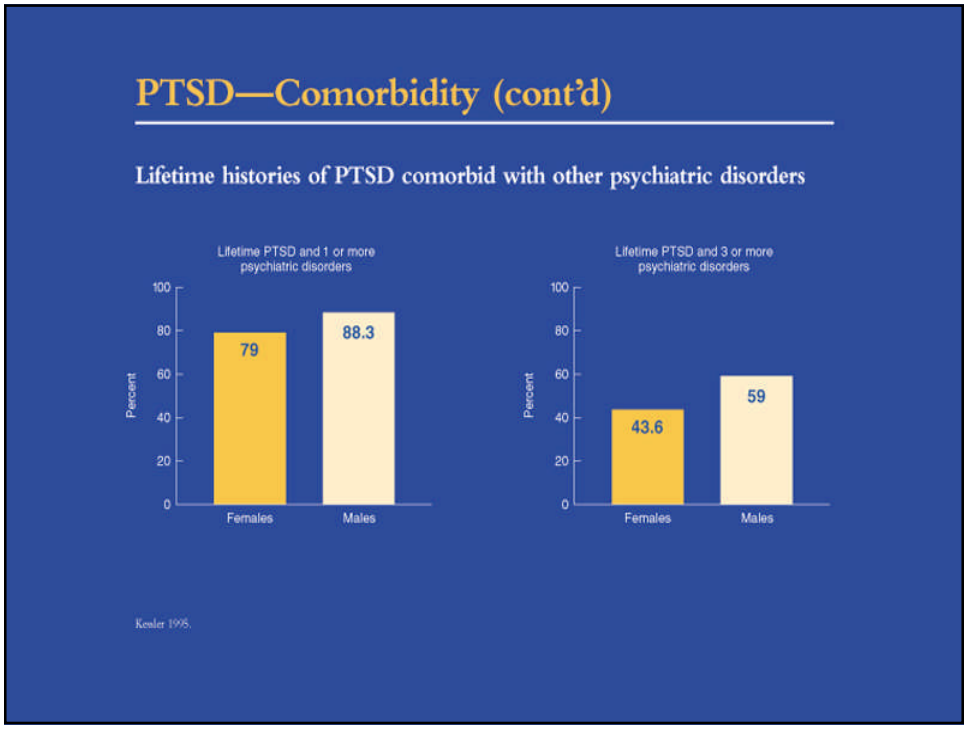
The incidence of suicide attempts in patients with PTSD has been found to be as high as 20%

- PTSD patients without comorbid depression were 8.2 times more likely to attempt suicide

In PTSD – Comorbidity is the Rule



Comorbid diagnoses can help design a pharmacologic strategy



Neurobiology of PTSD

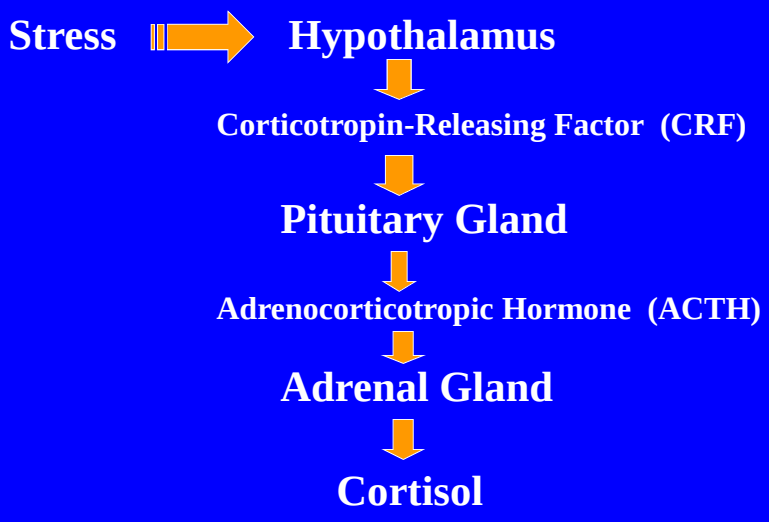
Brain Regions Activated by Fear and Life-Threatening Situations

- Amygdala
  - Activates the neurochemical/neuroanatomical circuitry of fear in milliseconds
- Hippocampus
- Locus Coeruleus
- Prefrontal Cortex

Systems Activated by Stress

- Adrenergic
- Noradrenergic
- Dopaminergic
- Serotonergic
- Opiate
- Benzodiazepine
- Hypothalamic-Pituitary-Adrenal (HPA)
- Hypothalamic-Pituitary-Thyroid (HPT)

Hypothalamic-Pituitary-Adrenal Axis



Cortisol

- Shuts down sympathetic activation
- Suppresses HPA Axis
- Suppresses Hypothalamus
- Suppresses Pituitary Gland
- Creates a negative feedback loop
- Suppresses further cortisol release
- Restores homeostasis

Neuroimaging Findings in PTSD

- Four MRI studies have examined hippocampal (involved in learning & memory) volume in individuals with PTSD
- Right hippocampal volume was decreased 8% in Vietnam veterans with combat-related PTSD compared to controls
- Left hippocampal volume was decreased 5% in 21 sexually abused women compared with 21 non-abused women controls

Etiology to decreased Hippocampal volume

- Patients with Cushing's Disease have elevated levels of serum cortisol and demonstrate hippocampal atrophy as well as decreased memory
- Trauma related hippocampal damage may be secondary to cortisol toxicity
- NMDA-Glutamate excitotoxicity may also contribute to hippocampal toxicity

Sympathetic Overactivity in PTSD

- Increased sensitivity of the sympathetic nervous system
- Yohimbine is an alpha-2-adrenergic receptor antagonist which activates noradrenergic neurons
- In PTSD patients, Yohimbine increases flashbacks, intrusive memories, panic attacks, cardiovascular excitation, levels of the noradrenergic metabolite MHPG

Observations in PTSD

- Plasma cortisol levels in the immediate aftermath of a MVA or rape who later develop PTSD are lower than in trauma survivors who do not develop PTSD
- Significantly lower urinary cortisol levels in Holocaust survivors with PTSD than in Holocaust survivors without PTSD and in a control group

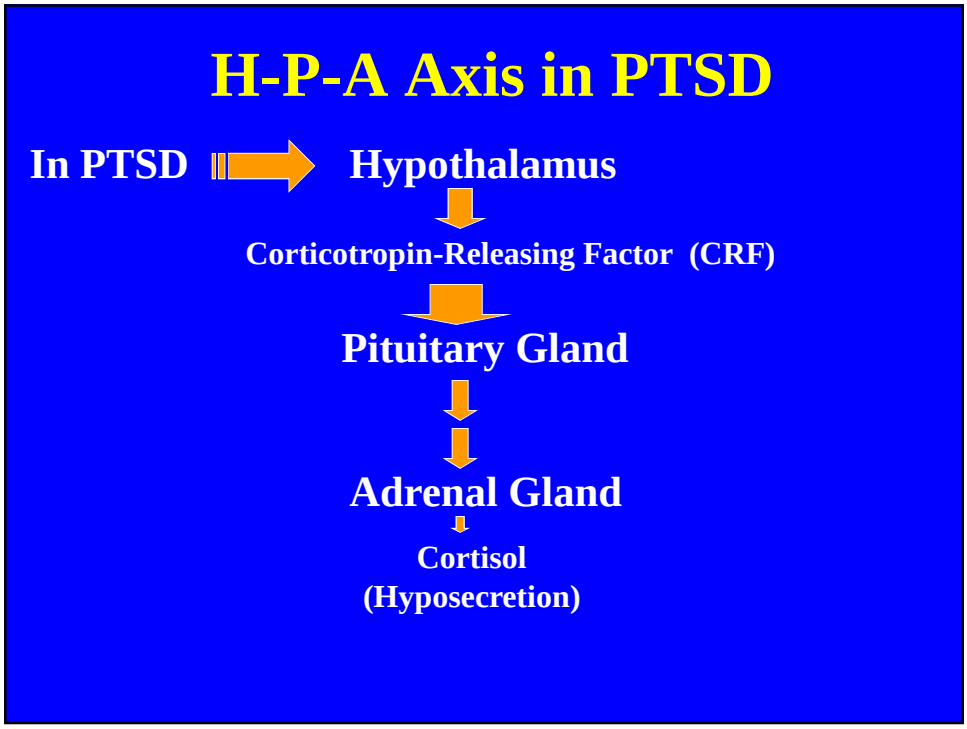
CRF is increased in PTSD

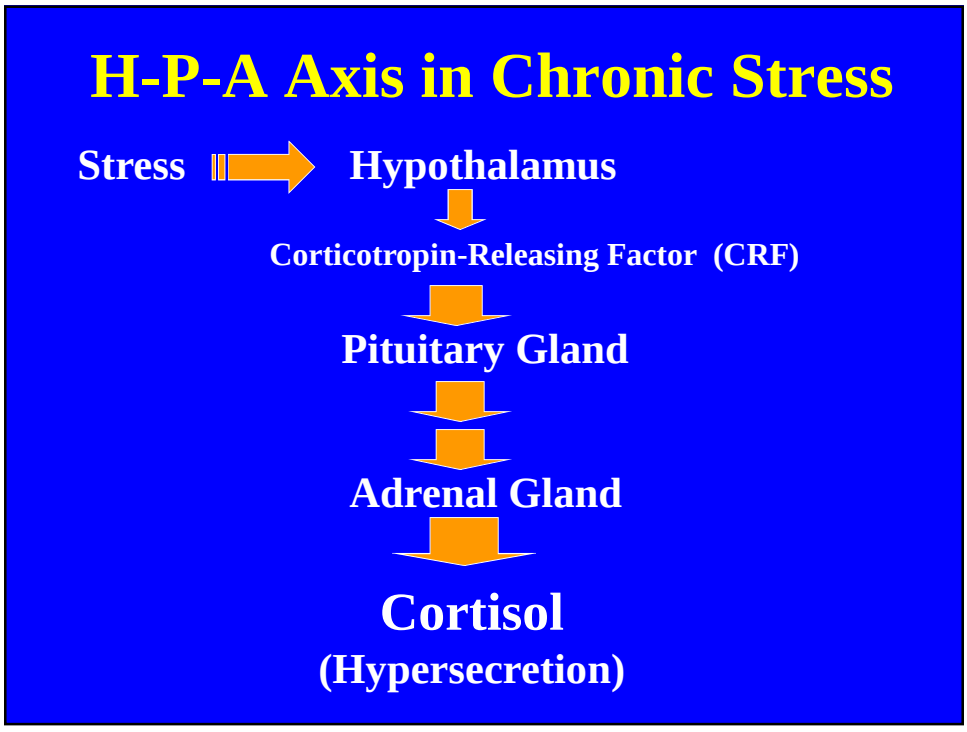
- Cerebrospinal Fluid concentrations of CRF are increased in patients with PTSD compared to controls
- Blunting of ACTH and cortisol response to CRF is consistent with downregulation of pituitary CRF receptors secondary to chronic hypothalamic CRF hypersecretion
- PTSD patients have a greater number of lymphocyte glucocorticoid receptors than normal controls or patients with MDE, PD, Bipolar Disorder or Schizophrenia
- This implies an upregulation in response to low circulating levels of cortisol

PTSD versus Stress/Depression

PTSD	Chronic Stress and Depression
• Increased CRF release	• Increased CRF release
• Decreased Levels of cortisol	• Increased levels of cortisol
• Increased glucocorticoid receptor responsiveness	• Decreased glucocorticoid receptor responsiveness
• Stronger negative feedback inhibition of HPA	• Weaker negative feedback inhibition of HPA

Yehuda, R.; CNS Spectrums; Volume 3; Number 7; Supplement 2; page 24; July/August 1998


H-P-A Axis in PTSD
In PTSD
Hypothalamus
Corticotropin-Releasing Factor (CRF)
Pituitary Gland
Adrenal Gland
Cortisol
(Hyposecretion)


H-P-A Axis in Chronic Stress
Stress
Hypothalamus
Corticotropin-Releasing Factor (CRF)
Pituitary Gland
Adrenal Gland
Cortisol
(Hypersecretion)

Hypothalamic-Pituitary-Thyroid Axis

- 1927 Bram described a history of traumatic stress in 85% of over 3000 cases of thyrotoxicosis
- A high level of fear for survival was a common feature
- Increases in T3 are seen in PTSD
- Hyperthyroidism is clinically similar to a hyperarousal syndrome
- Shared symptoms: irritability, insomnia, poor concentration, increased startle response, outbursts of anger

Effects of Severe Trauma During Childhood

- Effects the Neurobiological Development of the Brain (Especially the HPA Axis)?
- Creates Brain Neurophysiology that requires a unique pharmacological strategy?

Current Psychotherapies for PTSD

Current Psychotherapies for PTSD

- Prolonged Exposure (PE)
- Stress-Inoculation Training (SIT)
- Cognitive Restructuring
- Dialectic Behavioral Therapy
- Eye Movement Desensitization and Reprocessing (EMDR)
  - Are eye movements necessary?
  - Controversial

Current Pharmacotherapy of PTSD

"Make things as simple as possible … never simpler."

-Albert Einstein-

Current Pharmacological Options

- Antidepressants
- Alpha 1 antagonism
- Anxiolytics
- Atypical Antipsychotics
- Alpha-2-agonists
- Beta-adrenergic antagonists
- Mood stabilizers
- Opiate receptor antagonists

"Antidepressants"

Serotonin Reuptake Inhibitors (SRIs)

- Sertraline
- Paroxetine
- Fluvoxamine
- Fluoxetine
- Citalopram
- Escitalopram
- Venlafaxine
- Duloxetine
- Desvenlafaxine

SSRIs

- Sertraline was the first medication FDA approved for PTSD (December 7, 1999)
  - Dosage range is 50-200mg per day
- Paroxetine is the only other FDA approved medication
  - Dosage range is 20-60mg per day
- Efficacious in three core symptom clusters of PTSD: reexperiencing, avoidance/numbing, and hyperarousal
- Maintain treatment for *at least* one year
- Fluoxetine and fluvoxamine seem efficacious as well (several published studies)
- case reports for venlafaxine & nefazodone

Other Antidepresants

- Tricyclic Antidepressants
- Monoamine Oxidase Inhibitors
- nefazodone, trazodone
- bupropion
- mirtazapine
- venlafaxine, duloxetine, desvenlafaxine
- vilazodone

Alpha 1 antagonism

- prazosin

Anxiolytics

- Benzodiazepines
- Buspirone
- Gabapentin
- Trazodone
- Pregabalin
- Hydroxyzine

Atypical Antipsychotics

- Clozapine
- Risperidone
- Olanzapine
- Quetiapine
- Ziprasidone
- Aripiprazole
- Paliperidone
- Iloperidone
- Asenapine
- Lurasidone

Alpha-2-agonists

- Clonidine
- Guanfacine

Beta-adrenergic antagonists

- Propranolol
- Atenolol
- Metoprolol
- And Others

Mood stabilizers

- Divalproate/valproic acid
- Carbamazepine
- Gabapentin
- Lamotrigine
- Topiramate

Opiate receptor antagonists

- Naltrexone

Civilian versus Combat Trauma

- Civilians seem to respond better to SSRIs than do Veterans with combat exposure
- Is childhood onset of trauma (affecting brain development) a factor?
- Is type of trauma a factor?
- Is PTSD a symptom complex with divergent etiologies/neuropathologies?

Future Medication Development for PTSD

Pharmacotherapy based on Neurobiology

- Corticotropin-Releasing Factor Antagonists
- Neuropeptide Y enhancers
- Anti-adrenergic Drugs
- Glucocorticoids
- Specific 5-HT Receptor Agonists/Antagonists
- Opioid Agonists/Antagonists
- Substance P Antagonist
- NMDA-Glutamate Receptor Function