# Consideration of PTSD Nosology and Pathophysiology in Targeting the Study Population, Intervention, and Outcomes

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# Posttraumatic Stress Disorder

- Lifetime Prevalence
  - 7% US population (3-5% men, 10% women)
  - 19% Vietnam veterans
  - 13% OIF/OEF veterans
  - 32% treatment seeking OIF/OEF veterans
- Chronicity and Comorbidity
  - Persistent for decades
  - Commonly comorbid with other Axis I (>50%)
- FDA-approved medications
  - Sertraline
  - Paroxetine

# Posttraumatic Stress Disorder

A. Exposure to a life-threatening event involving intense fear, helplessness, or horror
B. Re-experiencing symptoms
C. Avoidance and emotional numbing
D. Hyperarousal symptoms
E. At least one month duration (acute < 3 mo; chronic > 3 mo)
F. Social dysfunction, occupational dysfunction, or significant personal distress

# Response to Catastrophic Stress

Freeze-Flight-or-Fight

# DSM-IV Conventional 3-Factor Model

**Criterion B (≥1 REEXPERIENCING) – 40 CAPS POINTS**

1. Intrusive recollections
2. Distressing Dreams or Nightmares
3. Acting or Feeling as if events were recurring
4. Psychological distress at exposure to cues
5. Physiological reactivity on exposure to cues

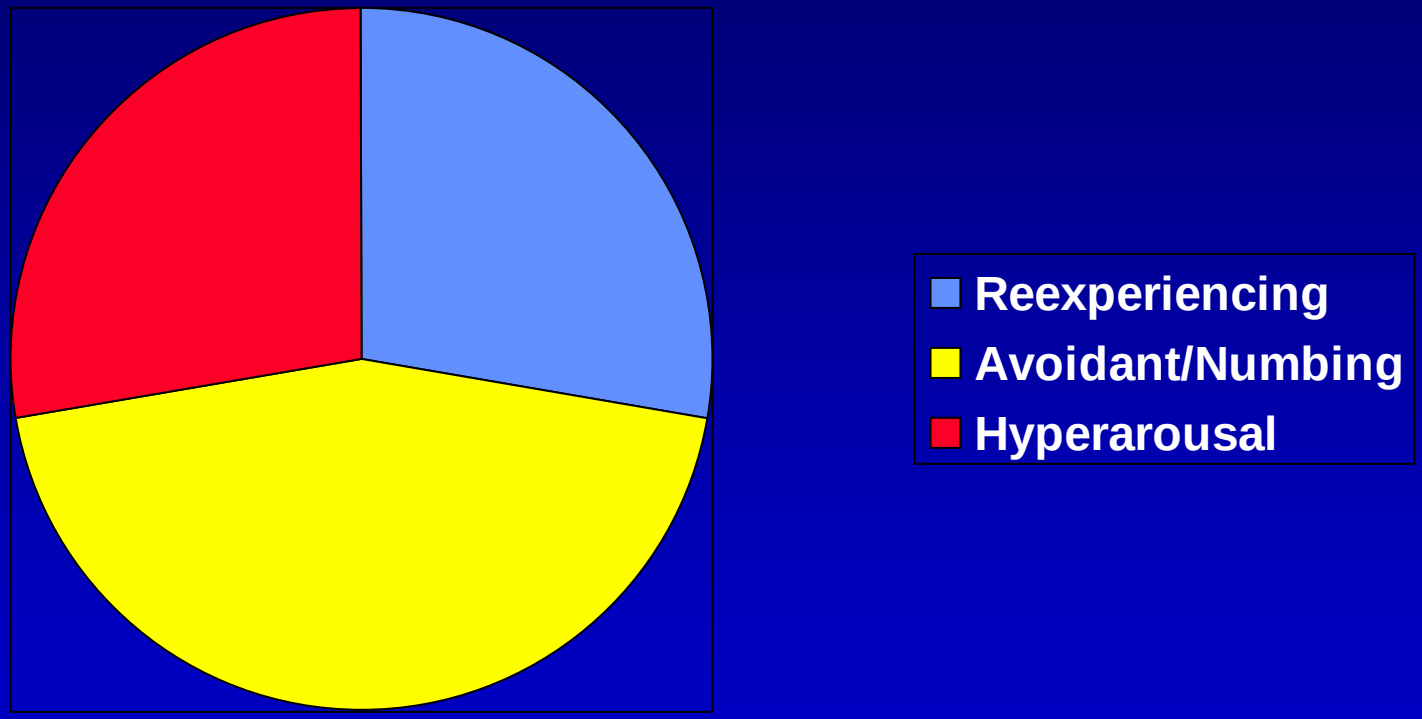
**Criterion C (≥3 AVOIDANCE/NUMBING) – 56 CAPS POINTS**

6. Avoidance of thoughts or feelings
7. Avoidance of activities, places, or people
8. Inability to recall important aspect of trauma
9. Diminished interest in activities
10. Detachment or estrangement (emotional numbing)
11. Restricted range of affect
12. Sense of foreshortened future

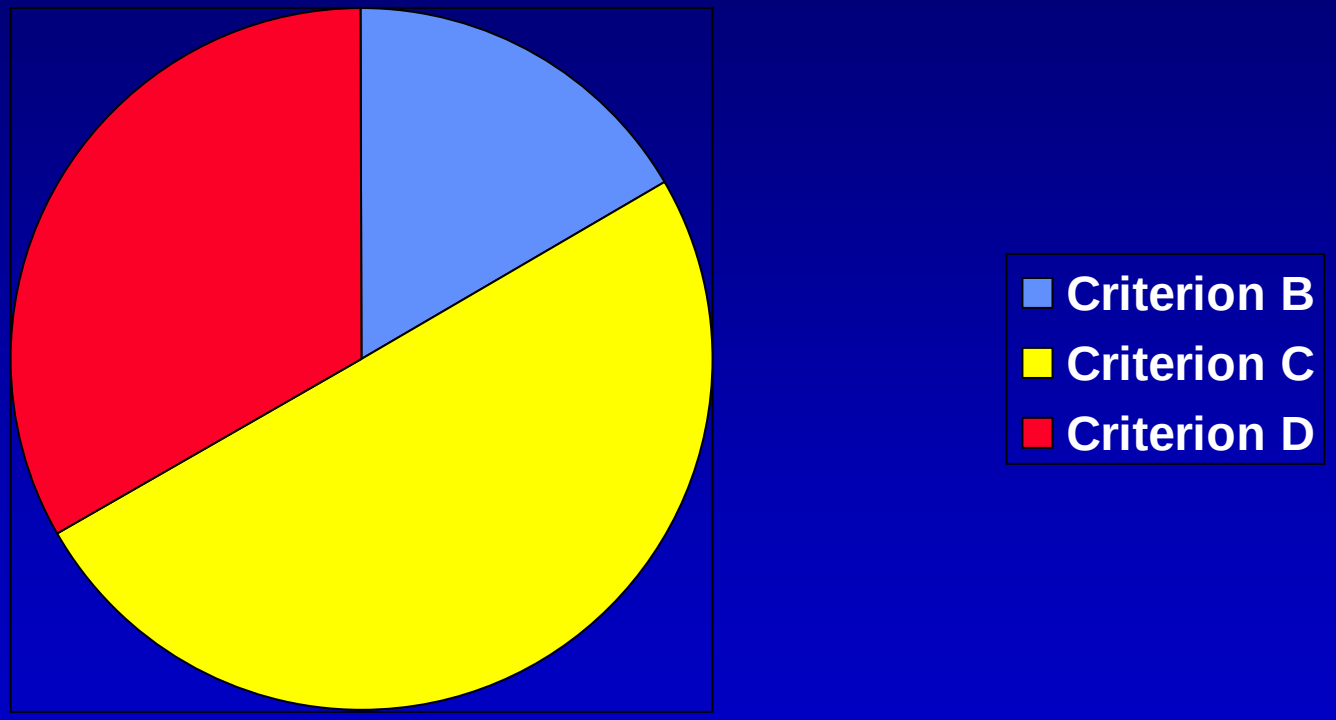
**Criterion D (≥2 HYPERAROUSAL) – 40 CAPS POINTS**

13. Insomnia
14. Irritability or Outbursts of anger
15. Difficulty Concentrating
16. Hypervigilant
17. Exaggerated Startle Response

# PTSD DSM-IV Diagnosis
# Number of Criterion



# PTSD CAPS rule of 4



# King 4-Factor Model

**REEXPERIENCING**

1. Intrusive recollections
2. Distressing Dreams or Nightmares
3. Acting or Feeling as if events were recurring
4. Psychological distress at exposure to cues
5. Physiological reactivity on exposure to cues

**AVOIDANCE**

6. Avoidance of thoughts or feelings
7. Avoidance of activities, places, or people

**NUMBING**

8. Inability to recall important aspect of trauma
9. Diminished interest in activities
10. Detachment or estrangement (emotional numbing)
11. Restricted range of affect
12. Sense of foreshortened future

**HYPERAROUSAL**

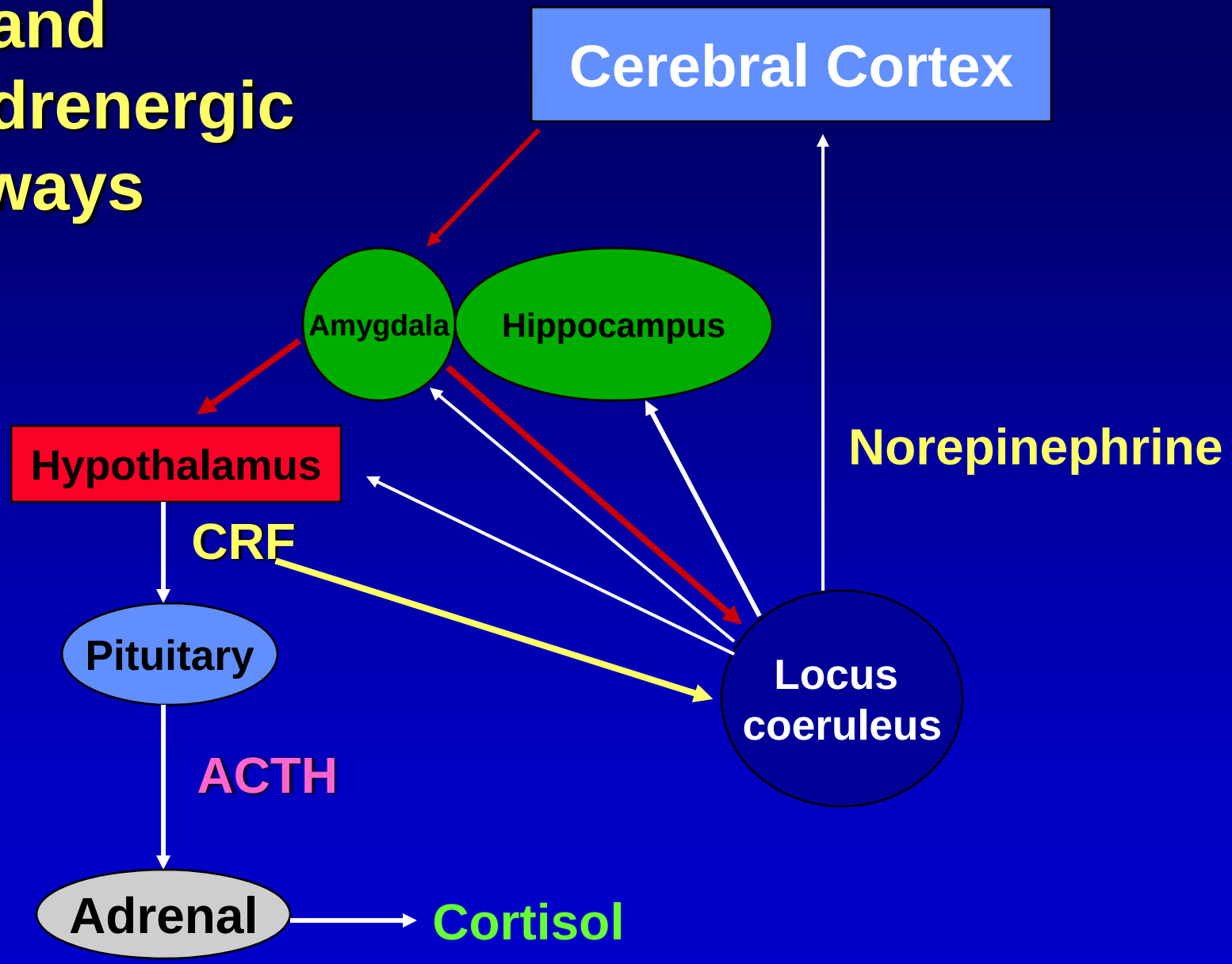
13. Insomnia
14. Irritability or Outbursts of anger
15. Difficulty Concentrating
16. Hypervigilant
17. Exaggerated Startle Response

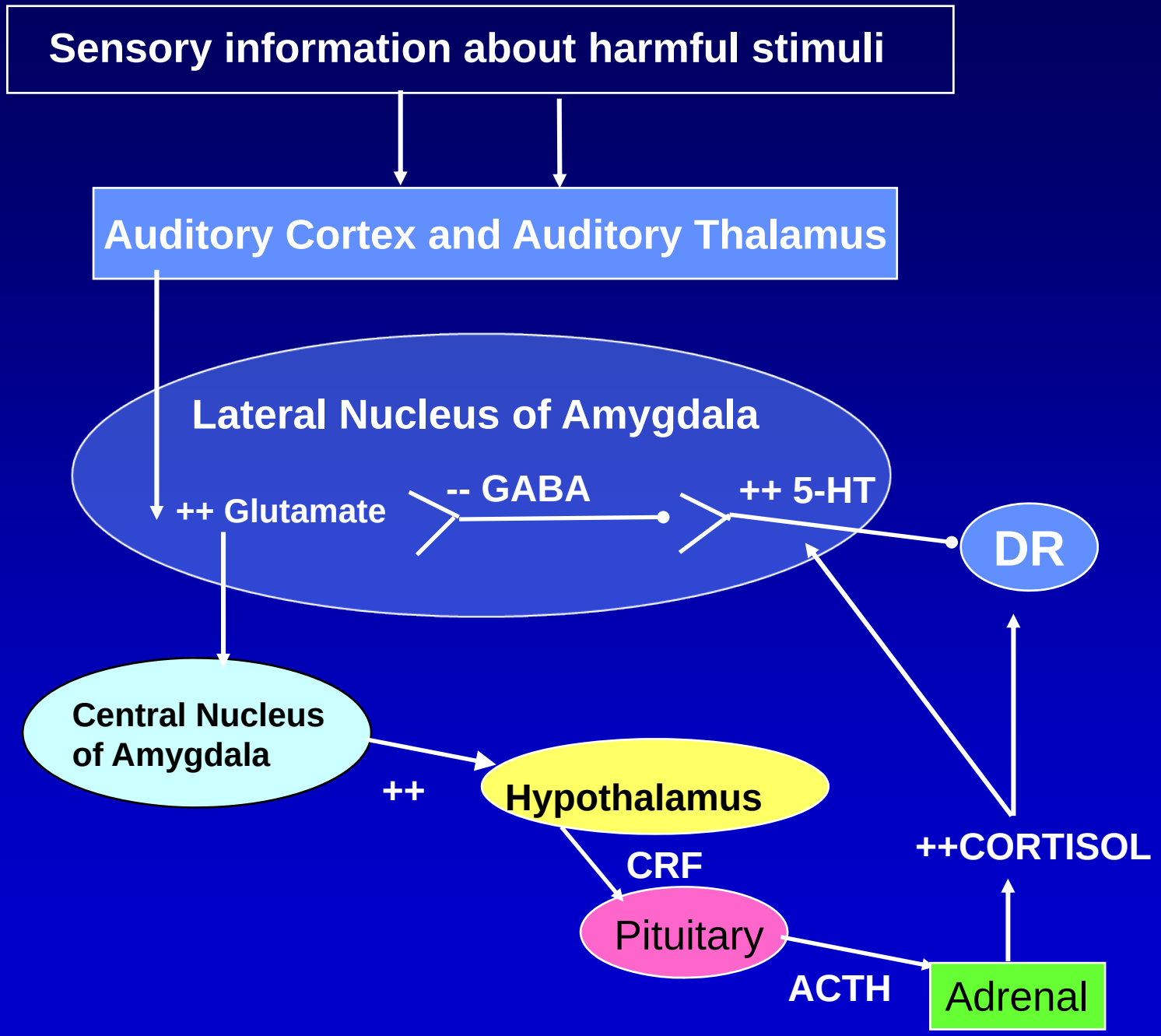
King et al Psychological Assessment 1998

# Bio-Psycho-Social Model of PTSD

- Biological Disturbances
  - Monoamines
  - Amino Acid Neurotransmitters
  - Hormones
  - Neuroanatomical
- Psychological Disturbances
  - Sense of Self and Integrity
  - Trust vs. Suspiciousness
  - Guilt and Shame
  - Difficulties with Relationships
- Behavioral Disturbances
  - Avoidance
  - Checking for Safety
  - Social and Occupational Difficulties

# HPA and Noradrenergic Pathways




Sensory information about harmful stimuli
Auditory Cortex and Auditory Thalamus
Lateral Nucleus of Amygdala
++ Glutamate
-- GABA
++ 5-HT
DR
Central Nucleus of Amygdala
++
Hypothalamus
CRF
Pituitary
ACTH
Adrenal
++CORTISOL

# Pharmacologic Treatment for PTSD

- Antidepressants
  - SSRI, TCA, mirtazapine, nefazodone, venlafaxine, MAOIs
- Alpha-Adrenergic Blockers
- Atypical Neuroleptics
- Anticonvulsants
- Benzodiazepines
- Other
  - D-cycloserine
  - Inositol

**37 RCT of pharmacotherapy and 22 individual drugs Reviewed by the IOM in 2007**

# Institute of Medicine

*Treatment of PTSD: An Assessment of the Evidence*

- The evidence for all classes of drugs was inadequate to determine efficacy for PTSD

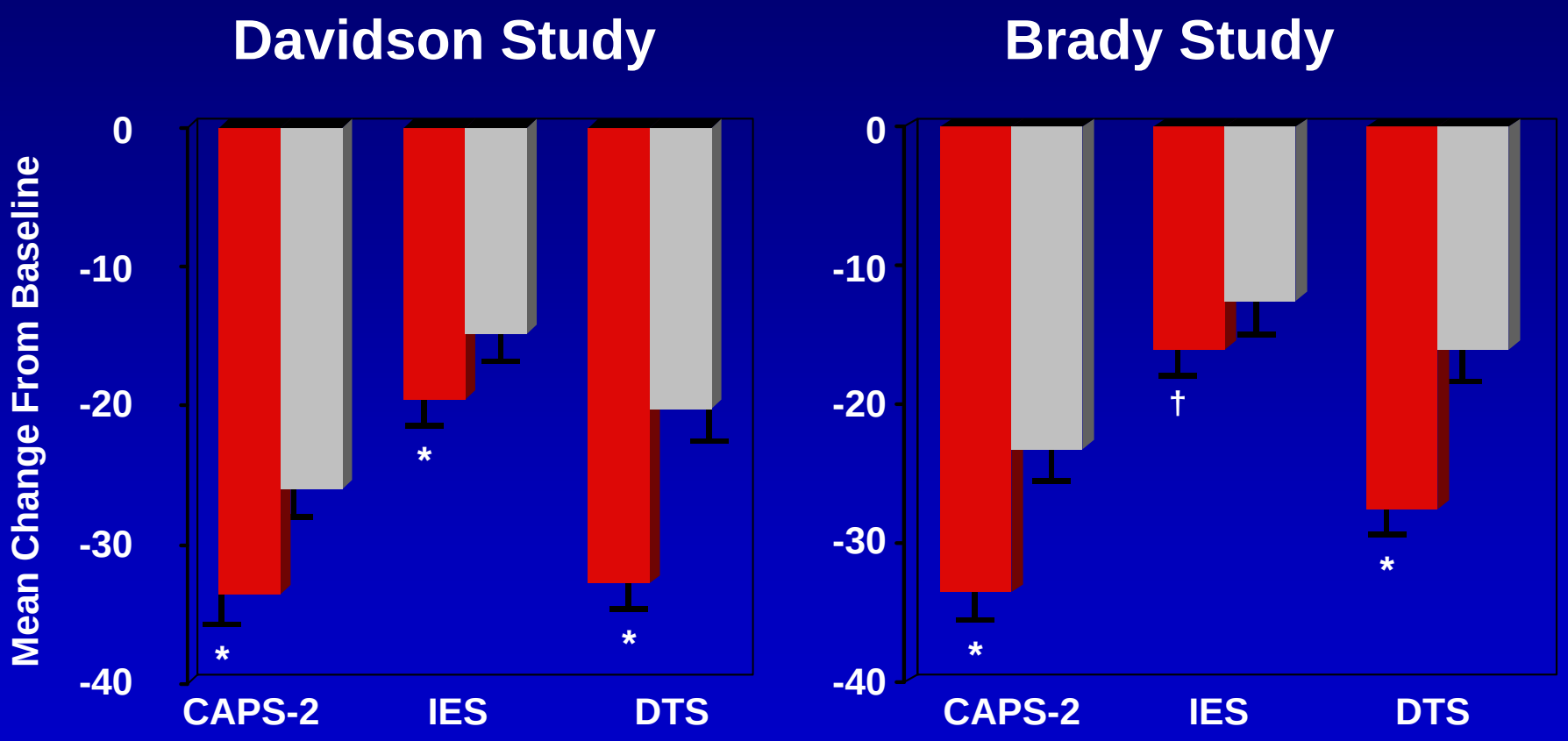
- Thomas Mellman, MD did not concur:
  - Evidence is suggestive but not sufficient to conclude efficacy of SSRIs in general population with PTSD
  - Evidence is suggestive that SSRIs are not effective in populations consisting of predominantly male veterans with chronic PTSD
  - Evidence is suggestive but not sufficient to conclude the efficacy of new generation antipsychotic medications as adjunctive treatment for PTSD

**www.IOM.edu**

# IOM Review of RCTs in PTSD
## Methodological Issues

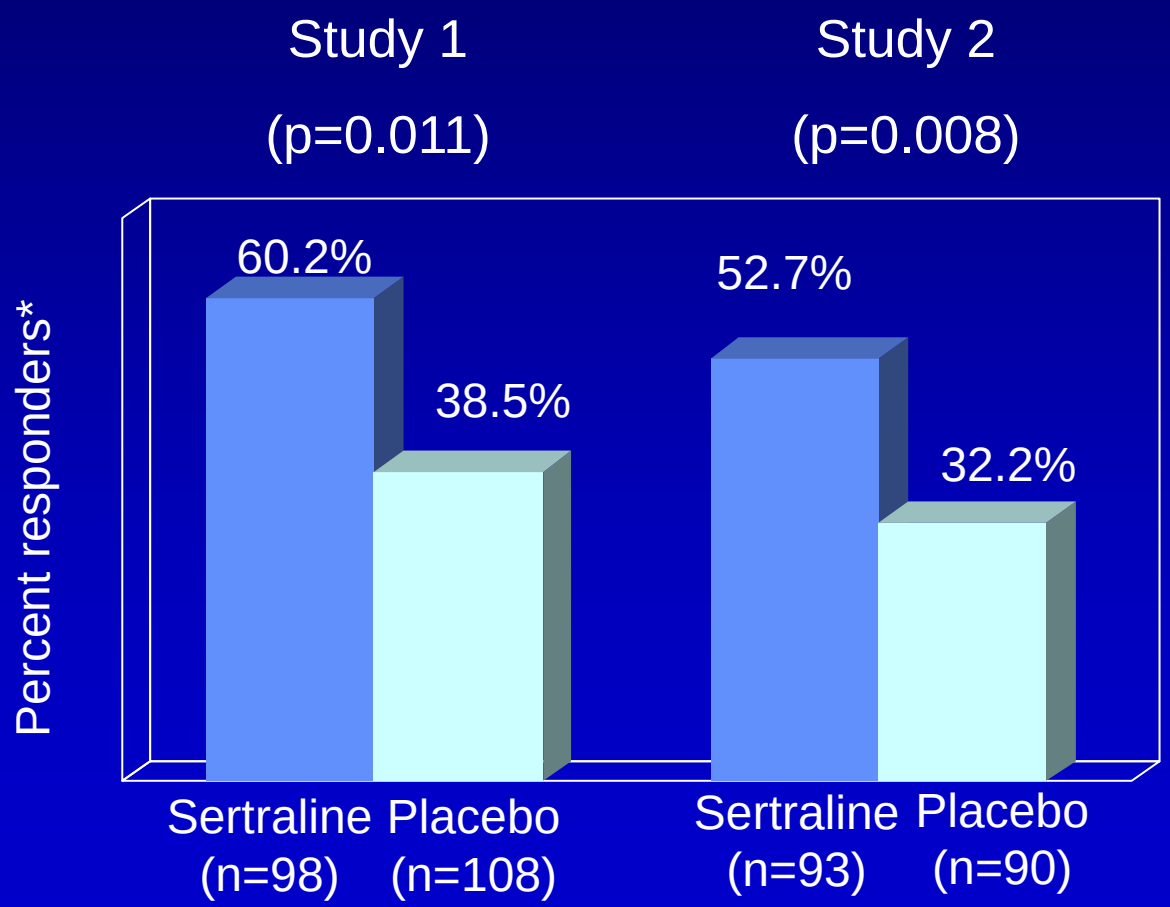
- Challenges to Internal Validity
  - Standardization of treatment and outcome measures
  - Attrition
  - Missing Data (LOCF vs MMRM)
  - Multiplicity
  - Credible Control Group
- Investigator Independence
- Special Veteran Populations
  - PTSD+TBI; PTSD+MDD; PTSD+SUD
- Applicability to VA and Veteran Populations
- Recovery and Remission inconsistent definitions
- Early intervention, length of treatment, length of follow-up

# Sertraline for Civilian PTSD




** p<0.05 sertraline vs. placebo*
*† p=0.07 sertraline vs. placebo*

# Sertaline PTSD Positive Studies:
## Analysis of Responders




*Response is defined as a CAPS-2 Total Severity Score improvement of ≥ 30% and a CGI-I score of 1 (very much improved) or 2 (much improved) at endpoint

# Individual PTSD Item Response to Sertraline:Placebo Pooled Analysis

- **Week 1**
  - **Anger**
- **Week 6**
  - **Psychological distress at cues/triggers**
  - **Anhedonia**
  - **Detachment**
  - **Numbness**
  - **Hypervigilance**
- **Week 10**
  - **Avoidance of activities**
  - **Foreshortened future**

Davidson et al Psychol Medicine 2002

# Sertraline for PTSD in Veterans

METHODS

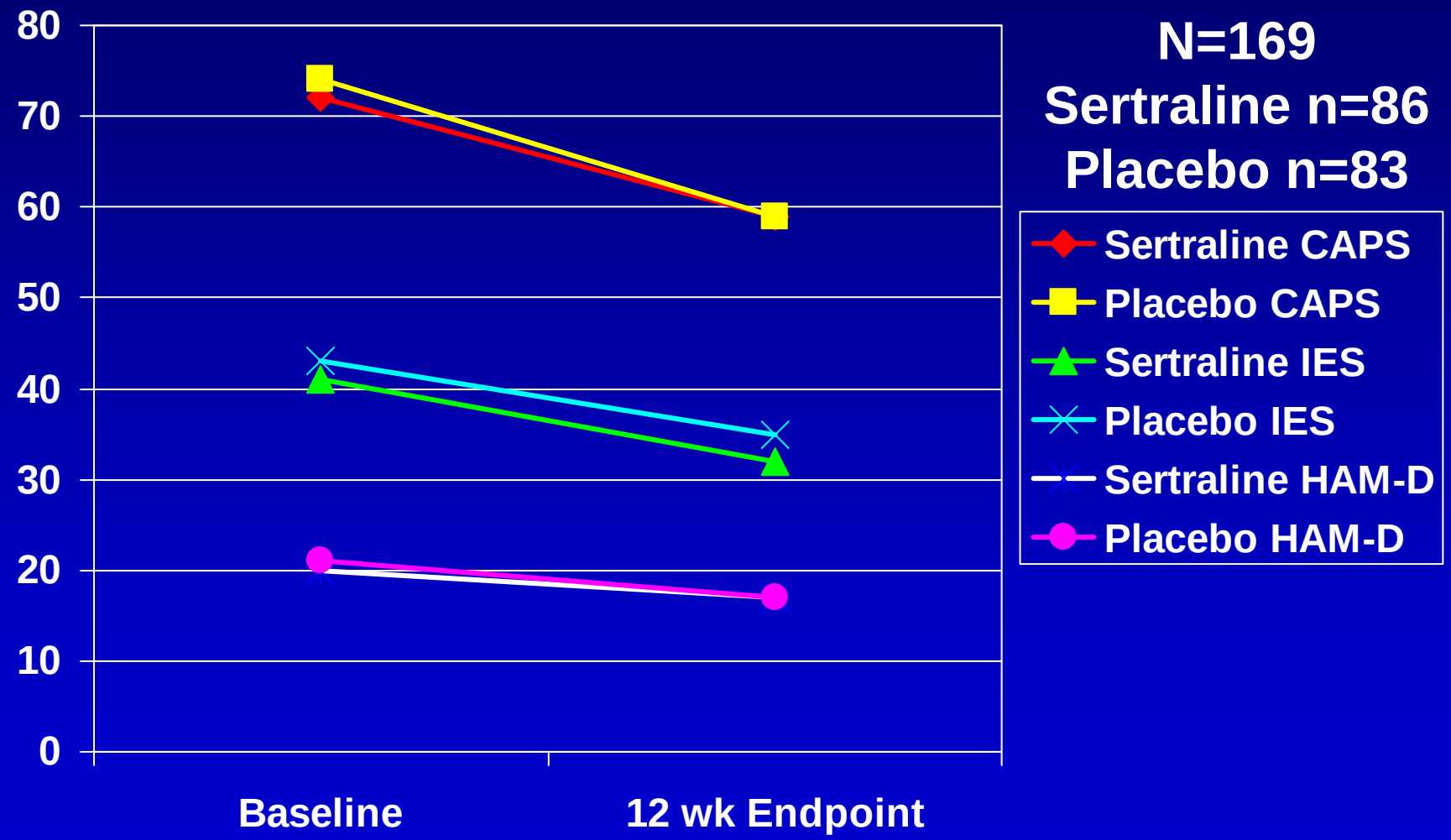
- 10 VA medical centers(1994-1996); N=169
- One week placebo run-in period
- Double-blind RCT 12-week sertaline trial (70%/72% combat-related PTSD & 79/81% male for drug/PLC)

RESULTS

- No significant differences b/w sertaline and PLC in mean change CAPS-2, Impact of Event Scale, CGI-S, CGI-I
- 13% discontinued due to adverse events
- No effect of gender, duration of PTSD, severity of PTSD, type of trauma, history of SUD

Friedman et al J Clin Psychiatry 2007

# Sertraline vs. Placebo for PTSD in Veterans




Friedman et al J Clin Psych 2007

# Venlafaxine ER for PTSD

6-mo placebo-controlled RCT; N=329

- Mean change CAPS
  - -51.7 drug and -43.9 placebo (p=0.006)
- Drug better than plc in reducing B and C, but not D
- Remission 50.9% venlafaxine and 37.5% placebo

12-wk RCT venlafaxine, PLC and sertraline; N-538

- Mean change CAPS
  - -41.8 venlafaxine, -39.4 sertraline, -33.9 Plc ($p<0.05$ active vs plc)
- Remission 30.2% venlafaxine ($p<0.05$), 24.3% sertraline, 19.6% placebo

Davidson et al Arch Gen Psychiatry. 2006

# Early Onset of Action and Time to Response on CAPS Items

## Venlafaxine:Placebo Pooled PTSD Studies

- **Wk 2**
  - **Physiological reactivity (#5B)**
  - **Irritability or anger outbursts (#14D)**
- **Wk 4**
  - **Intrusive recollections (#1B)**
  - **Psych distress at exposure to cues (#4B)**

Stein et al International J Neuropsychpharmacol 2008

# Late Onset of Action and Time to Response on CAPS Items

## Venlafaxine:Placebo Pooled PTSD Studies

- **Wk 6-12**
  - Avoidance of thoughts/feelings or conversations (#6 C)
  - Diminished interest (#9C)
  - Detachment or estrangement (#10C)
  - Restricted range of affect (#11C)
  - Sense of foreshortened future (#12C)
  - Difficulty concentrating (#15 D)
  - Hypervigilance (#16D)
  - Exaggerated startle response (#17D)

# Onset of Action and Time to Response on CAPS Items

## Venlafaxine:Placebo Pooled PTSD Studies

- **ABSENT**
  - Distressing Dreams (#2B)
  - Avoidance of activities, places, people (#7C)
  - Inability to recall important aspect of trauma (#8C)
  - Difficulty falling/staying asleep (#13C)

# PTSD Clinical Associations

- Anger and Treatment Outcome
- Numbing and Hyperarousal
- Fear and Avoidance

# Study Population Issues

- Civilian or Veterans
- Gender
- Number of Lifetime Traumatic Events
- Type of Traumatic Index Event
- Chronicity of Exposure to Trauma
- Subtypes of PTSD
- Chronicity of PTSD Illness
- Comorbidities
- Prior Treatment Resistant or Refractory
- Genetic Polymorphisms or Markers

# Alternatives for Intervention

- Novel Antidepressants
- Modulators of Norepinephrine
- Atypical Neuroleptics
- CRF antagonists
- Modulators of GABA and glutamate
- Combination Psychopharmacology
- Combination with Psychotherapy

# Design Issues

- Monotherapy  vs. Placebo
- Combination Drug A+B vs. Double Matching Placebo
- Monotherapy vs. Combination
- Combination Drug A +Psychotherapy vs. Placebo +Control therapy
- Augmentation Designs

# Targeted Outcomes

- Full PTSD CAPS score
- PTSD Symptom Clusters (subdimensions)
- Response
- Remission
- Quality of Life and Reintegration

Also consideration of frequency of assessments, length of trial, adherence to protocol and treatment, retention

# New Study Drug Nepicastat

- Dopamine-beta-hydroxylase inhibitor
- 120 OIF/OEF veterans with PTSD
- 5 clinical sites (Tuscaloosa, Charleston, Houston, Bronx, San Diego VAMC)
- 6 week placebo-controlled study
- 8 week extension phase (open+paroxetine)
- Primary outcome CAPS-D hyperarousal

- Funded by DOD 2008-2012
- Drug and placebo by Synosia Therapeutics
- Biostatistical services UAB and Weill Cornell

# Conclusions

- PTSD is common and chronic
- PTSD is complex
- To date, RCT are limited by
  - Small number of RTCs
  - Small sample sizes
  - Modest effect sizes
  - Methods
- Innovative treatments are needed
- Sound study designs are essential