POST-TRAUMATIC STRESS DISORDER

Comorbidity and Treatment

American Society of Clinical Psychopharmacology, Inc.
(ASCP)
Model Curriculum, 6th Edition 2010

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Major Teaching Points

• PTSD develops in a substantial minority of individuals exposed to severe trauma and is highly comorbid with other psychiatric disorders

• SSRI medications have FDA approval for PTSD and efficacy for some PTSD subpopulations

• An Alpha-1 adrenergic antagonist (prazosin) has been found beneficial in reducing PTSD symptoms which disrupt sleep

• Other antidepressants, new generation antipsychotic medications, noradrenergic antagonists, and mood stabilizers have a role in treating some PTSD cases

• Cognitive behavioral therapy is an important evidence-based intervention for PTSD
Pre-Lecture Exam

Question 1

True or False:

1. The prevalence of PTSD is higher in women than men.
True or False:

1. All individuals exposed to severely threatening trauma will develop PTSD.
Pre-Lecture Exam

Question 3

True or False:

1. Cortisol activity in chronic PTSD is similar to major depression.
Question 4

1. The psychosocial PTSD treatment with the strongest evidence for efficacy is:
   
   A. EDMR
   
   B. Breathing relaxation
   
   C. Exposure
   
   D. Thought-stopping
Question 5

1. The weakest evidence for efficacy for PTSD is for which class of pharmacological agents:
   A. SSRI’s
   B. TCA’s
   C. MAOI’s
   D. Benzodiazepines
   E. Risperidone
Overview

I. Epidemiology
II. Diagnosis
III. Psychiatric Comorbidity
IV. Treatment
Post-Traumatic Stress Disorder (PTSD)

Lifetime prevalence in community of 1% to 14%, recent estimates from NCS of 7-8%; in US citizens lifetime prevalence: 8% (1)

PTSD is associated with sexual abuse, physical assault, military combat, torture, accidental trauma, natural or man-made disasters, diagnosis of threatening illness (2)


2. American Psychiatric Association, 1994 Kessler et al., ’95, 05
POST-TRAUMATIC STRESS DISORDER

A characteristic set of symptoms following exposure to extreme traumatic stress

1. experience, witness, or confronted with actual or threatened death or injury
2. Response involves intense fear, helplessness, or horror

Duration more than one month

Significant functional impairment
POST-TRAUMATIC STRESS DISORDER

Re-experiencing symptoms (need 1)

1. intrusive recollections
2. trauma-related nightmares
3. flashbacks
4. psychological distress with reminders
5. physiologic reactivity with reminders
POST-TRAUMATIC STRESS DISORDER

Avoidance symptoms (need 3)
1. avoid thoughts/feelings/conversations
2. avoid activities, places, people
3. inability to remember
4. diminished interest
5. feelings of detachment
6. restricted affect
7. foreshortened future
POST-TRAUMATIC STRESS DISORDER

Arousal symptoms (need 2)

1. impaired sleep initiation/maintenance
2. irritability
3. concentration
4. hypervigilance
5. exaggerated startle
Associated Features

1. Alcohol/drug problems
2. Aggression/violence
3. Suicidal ideation, intent, attempts
4. Dissociation
5. Distancing
6. Problems at work
7. Marital problems
8. Homelessness
# Lifetime Prevalence of DSM-III-R Major Psychiatric Disorders

## NCS Data

<table>
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<th></th>
<th>%</th>
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<td>Major depressive episode</td>
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<td>Manic episode</td>
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<td><strong>Anxiety Disorders</strong></td>
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<td>Simple phobia</td>
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<td>Agoraphobia without panic</td>
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<td>GAD</td>
<td>5.1</td>
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<td>Panic disorder</td>
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<td><strong>Substance Use Disorders</strong></td>
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<td>Alcohol abuse/dependence</td>
<td>23.5</td>
</tr>
<tr>
<td>Drug abuse/dependence</td>
<td>11.9</td>
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</tbody>
</table>

Lifetime Prevalence of PTSD

PTSD

Risks of Specific Traumas in the US Population

PTSD

Risk Factors for PTSD

- Severity of trauma (i.e., threat, duration, injury, loss)
- Prior trauma
- Gender
- Prior mood and/or anxiety disorders
- Family history of mood or anxiety disorders
- Low Education
PTSD
Rates Related to Specific Traumas

PTSD Persistence Over Time

(Untreated Group)

% Without Recovery

Years

**PTSD**

**Function and Quality of Life In Vietnam Veterans With and Without PTSD**

## PTSD

### Psychiatric Comorbidity

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<thead>
<tr>
<th></th>
<th>Lifetime Rates (%)</th>
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<td></td>
<td></td>
<td>Men</td>
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<td>Women</td>
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<tr>
<td></td>
<td>PTSD</td>
<td>Non-PTSD</td>
<td>PTSD</td>
<td>Non-PTSD</td>
<td>PTSD</td>
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<tr>
<td>Depression</td>
<td>48</td>
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<td>48</td>
<td>19</td>
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<td>Mania</td>
<td>12</td>
<td>1</td>
<td>6</td>
<td>1</td>
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<td>Panic Disorder</td>
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<td>2</td>
<td>13</td>
<td>4</td>
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<tr>
<td>Social Phobia</td>
<td>28</td>
<td>11</td>
<td>28</td>
<td>14</td>
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<tr>
<td>GAD</td>
<td>17</td>
<td>3</td>
<td>15</td>
<td>6</td>
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<tr>
<td>Alcohol Abuse/Dependency</td>
<td>52</td>
<td>34</td>
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<td>Substance Abuse/Dependency</td>
<td>34</td>
<td>15</td>
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<td>Any Diagnosis</td>
<td>88</td>
<td>55</td>
<td>79</td>
<td>46</td>
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</table>

Comorbidity in PTSD
National Comorbidity Study

**MEN**
- 1 Other Diagnoses
- 2 Other Diagnoses
- 3 Other Diagnoses
- No Other Diagnosis

**WOMEN**
- 1 Other Diagnoses
- 2 Other Diagnoses
- 3 Other Diagnoses
- No Other Diagnosis
Impact of Comorbid PTSD in Subjects With Other Anxiety Disorders

DIAGNOSTIC SPECTRA

- PTSD
- Depression
- Personality Disorder
- Panic Disorder
- Obsessive Compulsive Disorder
- Psychosis
- Substance Use Disorders
- Somatization
- Dissociation
- Personality Disorder
- Psychosis
- Substance Use Disorders
- Somatization
- Dissociation
PTSD
Model Sequence of Comorbidity

PTSD  Substance Abuse  GAD  MDD PANIC

Age  23  24  25  30

Disability

Lifetime History of Suicidal Attempts by Anxiety Disorder

General US population lifetime rates of suicide attempts range from 2.9% to 4.6%.

Disability Weights (Rating Scale)

Sanderson K and Andrews G, Australian and New Zealand Jnl of Psych 2001
PTSD

Impact of Treatment on Recovery

(N = 459)

Treated

Untreated

Median Months to Recovery

Overview of Treatment Options

- Psychotherapy
- Pharmacotherapy
- Combined treatments
PTSD

Considerations for Psychotherapy

1. Capacity to tolerate distress with exposure
2. Motivation/preference
3. Ability to participate and follow structure
4. Problems with interpersonal adjustment
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marks et al., 1998</td>
<td>87 civilian trauma victims</td>
<td>Relaxation vs E vs cognitive restructuring (CR) vs combination</td>
<td>All superior to relaxation</td>
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<tr>
<td>Resick et al., 2002</td>
<td>120 F, sexual assault</td>
<td>Cognitive processing Tx (CPT) (elements of CR and E) vs E vs minimal contact</td>
<td>CPT = E &gt; MC</td>
</tr>
<tr>
<td>Monson et al., 2007</td>
<td>60 Male veterans</td>
<td>Cognitive processing CPT vs Present Centered (PC)</td>
<td>CPT superior to PC</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Comparison</td>
<td>Results</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------</td>
<td>---------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Keane et al., 1989</td>
<td>24 Vietnam veterans</td>
<td>E vs WL</td>
<td>Exposure group more improved, especially re-experiencing</td>
</tr>
<tr>
<td>Foa et al., 2005</td>
<td>179 Women civilian trauma</td>
<td>E vs E+CR vs WL</td>
<td>E superior effective with all Sx clusters</td>
</tr>
<tr>
<td>Schnurr et al., 2007</td>
<td>Women veterans</td>
<td>E vs PC</td>
<td>E superior to PC</td>
</tr>
</tbody>
</table>

*E = exposure-based treatment  
WL = wait list control  
SIT = stress inoculation training
PTSD

Treatment of PTSD by Exposure and/or Cognitive Restructuring

IES Scores

Treatment

Follow Up

1 mo 3 mos 6 mos

r = relaxation
c = cognitive restructuring
e = prolonged exposure
ec = e + c

Conclusions of the IOM report on the Treatment of PTSD (2007)

“The evidence is sufficient to conclude the efficacy of (psychotherapy that utilize) exposure therapies in the treatment of PTSD” (PE, CPT)
PHARMACOTHERAPY

Neurobiological factors

Evidence of efficacy

What responds
PTSD related pathology

Who responds
Type of trauma
comorbidity
gender
PTSD

Biological Evidence Update

High-resolution MRI brain imaging at 4T: (2010): first time in humans that PTSD associated with selective volume loss of CA3/dentate gyrus subfields of hippocampus

Neurobiological evidence (1980 – 2006) for PTSD with Secondary Psychotic features (PTSD-SP)

- Cortisol
- Corticotrophin releasing hormone
- Dopamine beta-hydroxylase
- Smooth pursuit eye movements
- Psychopharmacological and pathophysiological mechanisms for PTSD-SP
PTSD: Neurobiological Alterations of Memory Processing

Greater physiologic reactivity to trauma-related stimuli

Selective attention to trauma stimuli

Fragmentary trauma narratives

Deficits in standard tests of verbal memory

Suggested abnormalities from structural and functional brain imaging
PTSD: Hormones and Neurotransmitters

Cortisol: reduced secretion and increased sensitivity to feedback inhibition with PTSD (Yehuda et al., 1993)

Role of noradrenergic activity in fear-enhanced learning (Cahill, 1997)

Noradrenergic and serotonergic probes stimulate panic and flashback symptoms in combat-related PTSD (Southwick et al., 1997)
PTSD: Dysregulated sleep

**Subjective**
- Trauma-related nightmares
- Insomnia/nonrestorative sleep

**Objective (EEG findings)**
- Mixed findings regarding sleep maintenance and duration
- Increased REM density/ Disrupted REM sleep continuity
- Increased motor activity

Ross et al., 1994; Mellman et al., 1997, 2002, Breslau et al., 2004
AIMS OF PHARMACOTHERAPY

Reduce core symptoms
Reduce associated symptoms
Facilitate non-pharmacologic therapies
Medication Treatment for PTSD: Nature of the Evidence

At least 7 published RCTs supporting efficacy of SSRIs for acute Rx of PTSD

Mean N participants = 236.3 (range: 47-551)

FDA approval for sertraline (’99), paroxetine (’01)

Maintenance efficacy established for sertraline for up to 52 weeks (Davidson et al. ‘01)

Improvement in all 3 sx clusters and QOL measures, treatments safe
Medication Treatment for PTSD: Nature of the Evidence

Additional RCTs not demonstrating benefit for SSRIs. Some are underpowered. The one large and well designed negative study featured male combat veterans with chronic PTSD treated in VA settings (Friedman et al., 2007)
Medication Treatment for PTSD: Nature of the Evidence

Efficacy supported by smaller RCTs
TCAs, MAOIs, lamotrigine; adjunctive olanzapine and risperidone, prazosin for sleep disturbances

Efficacy not supported by trials
benzodiazepines

Benefits suggested in open trials
Other SSRIs, Novel APs, AEDs, trazodone, nefazodone, noradrenergic suppressor/antagonists (eg prazocin)
Medication Treatment for PTSD: Recommendations

1\textsuperscript{st} Line

SSRIs (sertraline, paroxetine, fluoxetine)

2\textsuperscript{nd} Line

Noradrenergic agents; anticonvulsant/mood stabilizers; novel AP medications

Not recommended

Conventional APs, benzodiazepines

Friedman et al., 2000
DOES COMORBID PERSONALITY DISORDER AFFECT THE RESPONSE TO AN SSRI?

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>No PD</th>
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<tr>
<td>FLU</td>
<td>75</td>
<td>50</td>
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<tr>
<td>PBO</td>
<td>25</td>
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</tbody>
</table>

\[ p = 0.002 \] ns
DOES COMORBID DEPRESSION AFFECT THE RESPONSE TO AN SSRI?

MDD

No MDD

Fluoxetine
Placebo

$p=0.003$

ns
PTSD Treatment With SSRIs
Open-Label Sertraline in Comorbid PTSD and Alcoholism

IES Score

Pre Post

IEP

Pre Post

Alcohol Use

Standard Drinks/Week

PTSD Treatment With SSRIs

Effect of Fluoxetine in Symptom Clusters


- Intrusive: Fluoxetine 6.7, Placebo 13.5, $P = 0.02$
- Avoidant: Fluoxetine 3.0, Placebo 6.3, $P = 0.08$
- Numbing: Fluoxetine 6.2, Placebo 15.1, $P = 0.01$
- Hyperarousal: Fluoxetine 9.0, Placebo 17.3, $P = 0.01$

Total (N = 53)
EFFECT OF FLUOXETINE ON QUALITY OF LIFE (SF36) IN PTSD: Pre- to Post-Treatment

Davidson et al., 1997

p=0.006 ns
IMPROVEMENT IN DISABILITY: Fluoxetine vs Placebo

Davidson et al., 1997

- Total: Fluoxetine vs Placebo, p=0.02
- Work: Fluoxetine vs Placebo, p=0.02
- Family: Fluoxetine vs Placebo, p=0.02
- Social/Leisure: Fluoxetine vs Placebo, p=0.01
WHICH SYMPTOMS RESPOND TO AN SSRI?

- RIR: $P=0.006$
- Phys Distress: $P=0.01$
- Detach: $P=0.02$
- Numbing: $P=0.02$
- Concnc: $P=0.005$
- Startle: $P=0.002$

Davidson et al., 1997
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
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<tr>
<td>Startle</td>
<td>**</td>
<td>*</td>
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<tr>
<td>Concentration</td>
<td>**</td>
<td>**</td>
<td>**</td>
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<tr>
<td>Intrusive recollections</td>
<td>**</td>
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<tr>
<td>Physiological symptoms</td>
<td>**</td>
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<tr>
<td>Estrangement</td>
<td></td>
<td>*</td>
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<tr>
<td>Numbing</td>
<td></td>
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*p<0.05  *p<0.01
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<th>Symptom</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 10</th>
<th>Week 12</th>
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<td>Hypervigilance</td>
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<td>***</td>
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<tr>
<td>Poor concentration</td>
<td>**</td>
<td>***</td>
<td>***</td>
<td>*</td>
<td>***</td>
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<tr>
<td>Upset by reminders</td>
<td>*</td>
<td>*</td>
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<td>*</td>
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<td>Estrangement</td>
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<td>Anhedonia</td>
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<td>Avoid thoughts</td>
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<td>Foreshortened future</td>
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<td>*</td>
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*p<0.05  **p<0.01  ***p<0.001
PTSD Treatment With SSRIs

Effect of Fluoxetine


Effect of Trauma Population

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<thead>
<tr>
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<th>Pre</th>
<th>Post</th>
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<tr>
<td><strong>Trauma Clinic (n = 23)</strong></td>
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<tr>
<td>Fluoxetine</td>
<td>80</td>
<td>60</td>
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<tr>
<td>Placebo</td>
<td>40</td>
<td>60</td>
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<td><strong>VA (n = 24)</strong></td>
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<tr>
<td>Fluoxetine</td>
<td>90</td>
<td>80</td>
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<tr>
<td>Placebo</td>
<td>40</td>
<td>80</td>
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</table>
Paroxetine in PTSD

Efficacy of paroxetine in non-combat-related PTSD

Sertraline vs Placebo in Non-Combat-related PTSD

Week

Brady et al., JAMA 2000
# ADVANTAGES AND DISADVANTAGES OF SSRIs

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>Effective on all PTSD symptoms</td>
<td>Unproven in Combat Veterans</td>
</tr>
<tr>
<td>Abuse-free</td>
<td>GI, sexual, activating side effects</td>
</tr>
<tr>
<td>Once daily</td>
<td>Medication interactions</td>
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</table>
PTSD
Treatment With Benzodiazepines

Effect of Alprazolam

## ADVANTAGES AND DISADVANTAGES OF BZDs

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute relief of non-specific anxiety</td>
<td>No evidence of efficacy for PTSD</td>
</tr>
<tr>
<td></td>
<td>Possible disinhibition</td>
</tr>
<tr>
<td></td>
<td>Possible dependence</td>
</tr>
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</table>
Studies Comparing Amitriptyline and Imipramine With Placebo

- Amitriptyline: % Responders 47 (n = 22) vs Placebo: % Responders 19 (n = 18)
- Imipramine: % Responders 65 (n = 23) vs Placebo: % Responders 28 (n = 18)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>Effective in PTSD</td>
<td>Numerous side effects</td>
</tr>
<tr>
<td>Abuse-free</td>
<td>Poorly tolerated</td>
</tr>
<tr>
<td>Once daily</td>
<td>Dangerous in overdose</td>
</tr>
<tr>
<td>Hypnotic effects</td>
<td>Wide dose range</td>
</tr>
</tbody>
</table>
PTSD Treatment With MAOIs

Studies Comparing Phenelzine and Brofaromine With Placebo

- **Phenelzine vs. Placebo**
  - Kosten TR et al.
  - % Responders: 68 vs. 28
  - Participants: n = 19 vs. n = 18

- **Brofaromine vs. Placebo**
  - Baker DG et al.
  - % Responders: 60 vs. 39
  - Participants: n = 55 vs. n = 58

- **Brofaromine vs. Placebo**
  - Katz RJ et al.
  - % Responders: 55 vs. 26
  - Participants: n = 22 vs. n = 23

*Note: The diagram includes data from three separate studies comparing the efficacy of MAOIs (Phenelzine and Brofaromine) with Placebo in the treatment of PTSD.*
<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective in PTSD</td>
<td>Numerous side effects</td>
</tr>
<tr>
<td>May be particularly useful in complex cases</td>
<td>Poor tolerance</td>
</tr>
<tr>
<td></td>
<td>Dietary &amp; other restrictions</td>
</tr>
<tr>
<td></td>
<td>Dangerous in overdose</td>
</tr>
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</table>
Antipsychotic Medications

• **Support for risperidone as add on Rx** (Bartzokis et al., 2005; Reich et al., 2004)

• **olanzapine 1 small study supporting adjunct efficacy, benefit to sleep** (Stein et al., 2002)

• **Traditional Antipsychotic medications “not recommended”**
  – (Friedman et al. ISTSS Treatment Guidelines, 2000)
Mood Stabilizers

• **Carbamazepine**
  – Open clinical trial: decreased intrusions, flashbacks, insomnia, irritability, impulsivity, and violent behavior (Lipper et al., Psychosomatics, 1986)

• **Valproic acid**
  – Open trial: decreased hyperarousal and avoidance (Stein, J Clin Psych, 1995)

• **Lamotrigine**
  – Small controlled trial: decreased re-experiencing, numbing and avoidance (Hertzberg et al., Biol Psychiatry, 1999)
Alpha 1 Antagonist (Prazosin)

At Doses of 1-20 mg/day, Prazosin reduced:

- Combat-related nightmares
- Recurrent distressing dreams
- Re-experiencing traumatic event in sleep
1. Persistence of traumatic memories in World War II prisoners of war.

2. Traumatic memories and clinical levels of PTSD persist for WWII POWs as long as 65 years after their captivity.

3. Rumination about these experiences, including flashbacks and persistent nightmares, may increase after retirement, particularly for those held in the Pacific theater.
1. PTSD is common, usually chronic, Presentation varies, comorbidity is the rule

2. Comprehensive assessment of patients is critical to develop an individualized treatment plan

3. Treatment often involves multiple modalities
PTSD Treatment Recommendations

CBT effective

Antidepressant agents can be effective

SSRI, MAOI, TCA

Combine CBT & pharmacotherapy

Treat sleep-disruptive symptomatology
PTSD: Unmet Medical Need

Few Are Treated

% Lifetime Prevalence

- Depression: 50% untreated, 90% treated
- Social phobia: 50% untreated, 90% treated
- PTSD: 75% untreated, 80% treated
- GAD: 50% untreated, 50% treated
- Panic disorder: 30% untreated, 50% treated
- OCD: 30% untreated, 30% treated

Untreated vs. Treated
Question 1

True or False:

1. The prevalence of PTSD is higher in women than men.
1. All individuals exposed to severely threatening trauma will develop PTSD.
Question 3

True or False:

1. Cortisol activity in chronic PTSD is similar to major depression.
Question 4

1. The psychosocial PTSD treatment with the strongest evidence for efficacy is:

A. EDMR
B. Breathing relaxation
C. Exposure
D. Thought-stopping
Question 5

1. The weakest evidence for efficacy for PTSD is for which class of pharmacological agents:

A. SSRI’s
B. TCA’s
C. MAOI’s
D. Benzodiazepines
E. Risperidone
Answers to Pre & Post Competency Exams

1. True
2. False
3. False
4. C
5. D