Medication Treatment for Acute Stress Disorder and PTSD

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Most People Who Develop PTSD Recover from It

Shalev & Yehuda, 1999

Longitudinal Course of PTSD

% with PTSD Symptoms

W 3m 9m

94% 47% 42% ?

30%

Years

CME plus extras, slide 2
## Early Intervention After Trauma

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Trauma</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines¹</td>
<td>MVA/terrorism</td>
<td>Negative</td>
</tr>
<tr>
<td>Propranolol²,³</td>
<td>ER Presentation</td>
<td>Possibly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effective</td>
</tr>
</tbody>
</table>

Treatment of Acute Stress Disorder

- Pediatric Burn Survivors
- Imipramine$^1$
  1) 25 children – double blind
  2) imipramine vs chloral hydrate
- Imipramine or fluoxetine$^2$
  1) 128 children – retrospective chart review
  2) Medications increased or switched at 7 days if no significant improvement
  3) 89% responded to either imipramine or fluoxetine

Treatment of Acute PTSD

- Medication may provide sedation and relieve agitation
- Early psychosocial and psychopharmacologic intervention may reduce chronicity
- Medications to consider:
  - Beta-adrenergic blockers (propanolol)\textsuperscript{1}
  - Alpha-2 adrenergic agonists (clonidine or guanfacine)?
  - Antidepressants ?
  - Benzodiazepine hypnotic?\textsuperscript{2}
  - Mood stabilizers?

Chronic Posttraumatic Stress Disorder
Goals of Pharmacotherapy

• Reduction/amelioration of target symptoms
  - Reduce re-experiencing and intrusive symptoms
  - Improve mood and numbing
  - Reduce phasic and tonic hyperarousal
  - Improve sleep;
  - Reduce impulsivity
  - Reduce psychotic and/or dissociative symptoms

• Treat co-occurring psychiatric disorders

Davidson and van der Kolk, 1996.
### Potentially Beneficial Drugs Studied in Chronic PTSD

<table>
<thead>
<tr>
<th>Double-blind</th>
<th>Open-label</th>
</tr>
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<tbody>
<tr>
<td>- Amitriptyline&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Nefazodone&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Imipramine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Trazodone&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Phenelzine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Fluvoxamine&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Fluoxetine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Carbamazepine&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Sertraline&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Lithium&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Paroxetine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Depakote&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Citalopram&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Topiramate&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Mirtazapine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Clonidine&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>- Venlafaxine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Propranolol&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>- Lamotrigine&lt;sup&gt;2&lt;/sup&gt;</td>
<td>- Quetiapine&lt;sup&gt;4&lt;/sup&gt;</td>
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<tr>
<td>- Prazosin&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>- Olanzapine&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>- Risperidone&lt;sup&gt;4&lt;/sup&gt;</td>
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</tbody>
</table>

1) Antidepressant 2) Mood stabilizer 3) Adrenergic inhibitor 4) Antipsychotic
### Randomized Placebo Controlled Clinical Antidepressant Trials for PTSD

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Subjects</th>
<th>Effect Size</th>
<th>Rating</th>
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<tbody>
<tr>
<td>Amitriptyline</td>
<td>46</td>
<td>Mil</td>
<td>.64</td>
<td>A</td>
</tr>
<tr>
<td>Imipramine</td>
<td>60</td>
<td>Mil</td>
<td>.25</td>
<td>A</td>
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<tr>
<td>Desipramine</td>
<td>18</td>
<td>Mil</td>
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<td>A</td>
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<tr>
<td>Phentolamine</td>
<td>60</td>
<td>Mil</td>
<td>1.08</td>
<td>A</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>23</td>
<td>Civ</td>
<td>1.12</td>
<td>A</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>53</td>
<td>Civ</td>
<td>.92</td>
<td>A</td>
</tr>
<tr>
<td>Sertraline</td>
<td>208</td>
<td>Civ</td>
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<td>A</td>
</tr>
<tr>
<td>Sertraline</td>
<td>187</td>
<td>Civ</td>
<td>.30</td>
<td>A</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>551</td>
<td>Civ/Mil</td>
<td>.50</td>
<td>A</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>29</td>
<td>Civ</td>
<td>.49</td>
<td>A</td>
</tr>
<tr>
<td>Venlafaxine ER</td>
<td>329</td>
<td>Civ/Mil</td>
<td>.31</td>
<td>A</td>
</tr>
</tbody>
</table>

Adapted from Friedman et al: Effective Treatments for PTSD
Antidepressants: **SSRIs**

- Fluoxetine 20-80 mg/day, sertraline 50-200 mg/day, paroxetine 20-50 mg/day, fluvoxamine 100-250 mg/day, citalopram 20-60 mg/day
- 5-HT involved in regulation of: sleep, appetite, sexual activity, aggression, mood
- 5-HT helps to moderate excessive stimuli and ward off feelings of fear and helplessness
- Chronic administration of SSRI down regulates brain norepinephrine receptors
- Decreased intrusions, avoidance, and arousal
- Effects at 4-6 weeks; 12-24 weeks for full response
- Adverse reactions: nausea, headache, somnolence, ejaculatory delay, anorgasmia
Sertraline vs Placebo

CAPS-2

DTS

* p < .05 Sertraline vs Placebo  Visit Week
Paroxetine Fixed-Dose PTSD Study

Mean Change in CAPS-2 Total Score

Adjusted Mean Change in CAPS-2 Total Score

Paroxetine 40 mg
Paroxetine 20 mg
Placebo

Week
4
8
12

LOCF dataset; *p<0.001 vs placebo; Marshall et al. Am J Psychiatry. (2001)
SSRIs: 24-Week, Open-Label, Sertraline Extension Study

- Londborg, 2000: N = 249 completers from randomized controlled trial (RCT) of sertraline vs. placebo
- Following RCT, a 24-week, open trial continuation on sertraline 50-200 mg/day
- RCT on placebo: 40% decrease in CAPS-2
- RCT on sertraline: 31% decrease in CAPS-2

The Effect of Continuation Treatment with Sertraline on Core Symptoms of PTSD

24-Week, Open-Label, Sertraline Extension Study

Sertraline in PTSD Relapse Prevention

Kaplan-Meier survival probability

Log-rank test $P<0.001$

12 Weeks 24 Weeks

Acute Phase Open-Label Continuation

Weeks of Double-Blind Treatment

Relapse-Prevention

Increased Hippocampal Volume With Paxil in PTSD

Effects of Paroxetine on Hippocampal-Based Verbal Declarative Memory in PTSD

Effects of 9-12 months of treatment with 10-40 mg paroxetine.
**Antidepressants: Other**

- **Trazodone**: 5-HT2A antagonist; helped sleep disturbances in all patients; reduced intrusions and avoidance in 2/3 patients\(^1\)
- **Bupropion**: no significant effect upon PTSD symptoms compared to placebo\(^2\)
- **Venlafaxine (6 month, double blind placebo controlled)**: significant improvement in PTSD Sxs\(^3\)
- **Mirtazapine**: improved PTSD Sxs and anxiety\(^4\)

3. Davidson et al. Arch Gen Psychiatry 2006
Anti-Anxiety Agents

• Benzodiazepines
  – Help prevent learned helplessness in animals
  – In one study of chronic PTSD - worked as an anxiolytic but had no impact on core PTSD symptoms

• Buspirone
  - High affinity for 5-HT1A receptors
  - Alleviates some behavioral effects of inescapable shock in animal studies

PTSD

Treatment With Benzodiazepines

Effect of Alprazolam

Adrenergic Inhibiting Agents

- Beta-Adrenergic Blockers
  - propranolol
- Alpha$_2$-Adrenergic Agonists
  - clonidine
  - guanfacine
- Alpha$_1$-Adrenergic Blockers
  - prazosin
**Alpha$_1$-Adrenergic Blockers**

- Prazosin 3-10 mg daily
- Alpha$_1$- post-synaptic adrenoceptor receptor antagonist
- Alpha$_1$ receptors widely distributed in the brain, including the amygdala and hippocampus
- Alpha$_1$ receptors modulate sleep and startle responses
- Adverse reactions: syncope, dizziness, drowsiness, decreased energy, headache
**Prazosin Studies**

- Prazosin ~10 mg daily
- 10 Vietnam veterans in a double blind crossover study\(^1\)
- Robust improvement in sleep quality (d=1.6) and distressing dreams (d=1.9)
- Medium to large effect size in each PTSD Sx cluster
- 34 veterans: double-blind placebo control sleep study\(^2\)
  - significant improvement in sleep quality (d=1.0) and nightmares (d=.94)
  - significant improvement in global clinical status (d=1.08)
  - no significant change in blood pressure

Atypical Antipsychotic Agents

- Not routinely used
- Reduce disorganizing hyperarousal, severe dissociation, paranoid ideation, and aggressive impulsivity
- Comorbid psychotic disorder
- Low doses are often effective
- Agents Studied
  - olanzapine\(^1\)
  - risperidone\(^2\)
  - quetiapine\(^3,4\)

Kindling Model

- Repeated sub-threshold stimuli may sensitize limbic circuits
- Chronic sympathetic hyperarousal may result in stable limbic sensitization and kindling
- Temporolimbic stimulation and discharge may be a possible cause of “flashbacks” and nightmares
Antikindling Agents and Mood Stabilizers

- Carbamazepine
- Valproate
- Topiramate
- Lamotrigine
- Gabapentin
- Lithium carbonate
Comorbidity of PTSD With Other Psychiatric Disorders


Patients With and Without a Lifetime History of PTSD (%)

- Drug abuse
- Major depression
- Social phobia
- Agoraphobia
- Gen anxiety disorder
- Panic disorder
- ≥3 Diagnoses

With PTSD
Without PTSD

Treatment of PTSD Co-morbid with other Psychiatric Disorders

- **Affective Disorders**
  - Major Depressive Disorder
  - Bipolar Disorder

- **Anxiety Disorders**
  - Phobias
  - Panic Disorder
  - Generalized Anxiety Disorder
  - Obsessive-Compulsive Disorder

- **Substance Use Disorders**

- **Psychosis**

- **Rapid Escalation to Anger and Impulsive Aggression**
Stage-Based Pharmacotherapy for PTSD: Shalev

- First hours: reduce terror, neuronal imprinting
  - Adrenergic blockers
- First days: reduce sensitization, memory consolidation
  - Adrenergic blockers, mood stabilizers
- First months: reduce symptoms
  - SSRIs and low dose trazodone for sleep
- After first year: reduce symptoms and comorbidity
  - SSRIs, adrenergic blockers, mood stabilizers

Future Directions

- Adrenergic antagonists at time of exposure
- Corticotropin releasing factor antagonists
- Neuropeptide Y enhancers
- Substance P antagonists
- NMDA facilitators
- Reversible MAOIs
- Mixed adrenergic and serotonergic agents