Antihypertensive Agents for the Management of Civilian Post-Traumatic Stress Disorder

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Learning Objectives

• Review the epidemiology, pathophysiology, and treatment of Post-Traumatic Stress Disorder
• Review the mechanisms of actions and potential roles for antihypertensive agents in the management of post-traumatic stress disorder
• Evaluate the literature for various antihypertensive agents in the management of civilian PTSD
• Formulate evidence-based conclusions regarding the place of antihypertensive agents in the treatment of civilian PTSD
I. Epidemiology\textsuperscript{1, 2, 3}

A. Prevalence in the general adult population of the United States
   1. Lifetime: 6.8-12.3%
   2. One year: 3.5-6%

B. Susceptibility
   1. Overall development of PTSD after any traumatic event: ~ 12%
   2. Women – four times more likely than men to develop PTSD after trauma when adjusted for trauma rates
   3. Men more likely to develop PTSD after rape, but less likely after molestation or physical assault

C. Risk factors
   1. Previous exposure to trauma with subsequent traumatic events
   2. FKBP5 Polymorphism
      a. Stress related gene
      b. One of four polymorphisms associated with higher rates of PTSD only in patients with a history of child abuse

II. Diagnostic and Statistical Manual (DSM) Diagnostic Criteria\textsuperscript{4, 5}

A. Changes in DSM-5
   1. Moved from the “Anxiety Disorders” chapter into the new “Trauma and Stress or Related Disorders” chapter
   2. PTSD may now be precipitated by learning that a traumatic event occurred to a family member or a close friend
   3. Changes in symptom classification
      a. Patient response to an event (fear, helplessness, horror) removed
      b. Added mood and cognition cluster (now four symptom clusters)
      c. Arousal now includes aggressive and self-destructive behaviors to encompass both aspects of “fight or flight” response
   4. Changes in subtypes
      a. Acute (<3 months) and chronic (>3 months) subtypes removed
      b. Preschool subtype (<6 years old) added
      c. Dissociative subtype added (symptoms predominantly consist of detachment from one’s own mind, world seems unreal, dreamlike, or distorted)
III. Pathophysiology

A. Structural Changes – decreased hippocampus, left amygdala, and anterior cingulate cortex volume
   1. Hippocampus – inhibition, memory, and spatial awareness
   2. Left amygdala – induces pleasant (happiness) or unpleasant (fear, anxiety) emotions
   3. Anterior cingulate cortex – attention, motivation, modulation of emotions

B. Neurotransmitters
   1. Increased central norepinephrine levels
   2. Down-regulated central adrenergic receptors
   3. Chronically decreased glucocorticoids with subsequent up-regulation of receptors
   4. Chronically elevated norepinephrine levels and hypersensitivity of glucocorticoid receptors may help explain exaggerated stress response

Figure 1: Areas of the brain associated with PTSD

Image from: www.cnsforum.com/content/pictures/imagebank/hirespng/Neuro_biol_PTSD.png
IV. Treatment \textsuperscript{9, 10, 11, 12}

A. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are first line agents
   1. Sertraline and paroxetine are FDA indicated
   2. SNRIs used off-label
B. Mirtazapine, nefazodone, TCAs, and phenelzine may also be effective
C. Risperidone may be used to augment antidepressant therapy if there is a partial response to treatment
D. Prazosin may help augment distressing nightmares and sleep disturbances
E. Benzodiazepines
   1. Not considered effective for avoidance or dissociation
   2. Short-term use may be beneficial for anxiety or insomnia
   3. Habit forming, may interfere with prolonged exposure therapy

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| American Psychiatric Association (APA) Acute Stress Disorder and PTSD | • SSRIs and SNRIs first line for civilian PTSD, may not be as effective for combat-related PTSD  
• SNRIs also effective for civilian PTSD  
• Mirtazapine and nefazodone potentially efficacious  
• Prazosin may be used to augment psychotropics for trauma-related nightmares and sleep disturbances  
• Risperidone may help augment partial response to an antidepressant |
| Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guideline for Post-traumatic Stress | • First line – SSRI or SNRI  
• Second line – mirtazapine  
• Third line – TCA, nefazodone, or phenelzine  
• Prazosin may be added at any time for sleep/nighmares  
• Benzodiazepines and atypical antipsychotics are not recommended |
| International Society for Traumatic Stress Studies (ISTSS) PTSD Guidelines for Adults | • First line – SSRI (sertraline, paroxetine, fluoxetine) or SNRI (venlafaxine)  
• Second line – mirtazapine, nefazodone, TCAs, phenelzine  
• Other options – trazodone, bupropion  
• Prazosin effective for traumatic nightmares, may reduce overall PTSD symptoms  
• Propranolol, may be effective as a treatment in children, may act as prophylactic agent  
• Clonidine – some open-label evidence for dissociative symptoms  
• Guanfacine – ineffective in a randomized trial |
V. Antihypertensive Agents in PTSD

A. Clonidine
   1. Centrally-acting, lipophilic
   2. Alpha-2 receptor agonist
   3. Studies in pediatric patients showed efficacy for several PTSD symptoms
      a. Aggression
      b. Hyperarousal
      c. Sleep disturbances
   4. Data lacking in adults

B. ACEIs and ARBs
   1. ACEIs – inhibit the conversion of angiotensin I to angiotensin II
   2. ARBs – antagonize the binding of angiotensin II to angiotensin receptors
   3. Reducing activity of angiotensin type-I receptors in the brain may reduce stress-related behavior and inflammation in animal models

C. Prazosin
   1. Pharmacology
      a. Alpha-1 adrenergic receptor antagonist
      b. Lipophilic, centrally active
      c. Originally for the management of hypertension and benign prostate hypertrophy
   2. Evidence in combat-associated PTSD
      a. In multiple placebo-controlled studies in veteran populations, prazosin was effective for the PTSD-associated sleep disturbances
      b. Appeared to be equally efficacious to cognitive behavioral therapies
      c. Appeared safe when titrated, even in older populations
      d. Mean doses of 9-15mg per day

D. Propranolol
   1. Non-selective, beta-adrenergic antagonist
   2. Lipophilic, able to cross the blood-brain barrier
   3. Used for hypertension, also useful in anxiety disorders
   4. Data for use in the military is limited, but is thought to have some effect on the fear response
   5. Doses of 40-80mg studied

VI. Assessment Rating Scales (See appendix B)

A. Clinical Global Impressions Scale - Improvement (CGI-I)  
B. Clinical Global Impressions Scale- Severity (CGI-S)  
C. Clinician Administered PTSD Scale (CAPS)  
D. Profile of Mood States-Anxiety (POMS)  
E. PTSD Checklist- Civilian Version (PCL-C)
### Clinical Trials

<table>
<thead>
<tr>
<th><strong>Daytime prazosin reduces psychological distress to trauma specific cues in civilian PTSD.</strong>&lt;sup&gt;25&lt;/sup&gt;</th>
</tr>
</thead>
</table>

**Design**
- Randomized, double-blind, placebo-controlled trial

**Objective**
- To investigate the effects of prazosin on trauma cues in patients with residual PTSD symptoms during the daytime despite reduction of nocturnal symptoms by prazosin

**Inclusion Criteria**
- Must meet DSM-IV criteria for PTSD caused by civilian trauma
- Persistent daytime PTSD symptoms despite nighttime prazosin therapy
- Experiencing distressing trauma-related dreams/nightmares more than twice/week for at least one month prior to nighttime prazosin
- Free of substance abuse for at least 3 months
- In good general health

**Exclusion Criteria**
- Substance abuse within the last 3 months
- Complicated comorbid medical conditions

**Intervention**
- **Pre-study phase:** Patients first participated in an open-label, pre-study phase where prazosin 1mg at bedtime was initiated and titrated to decrease night time sleep disturbances by at least one point on the PCL-C
  - Patients then maintained at least one month
  - After month, a PCL-C and CGI-S were completed by the subject
- **Study Phase:** A dose of prazosin or placebo equal to their nighttime dose was administered in the early afternoon
  - These were administered randomly, one week apart
  - Patients were asked whether they believed they had received prazosin or placebo
- **Post-study phase:** Patients could then elect to continue open-label prazosin in a post-study phase for two weeks, after which a CGIS was administered

**Assessment:**
- Patients were exposed to verbal trauma cues using the E-Stroop method two hours after administration of prazosin or placebo,
  - Blood pressure and heart rate were monitored
  - A POMS was administered after each category list

**Endpoints**
- Prazosin effects on E-Stroop test (time to completion, accuracy)
- Effect of prazosin on PCL-C, POMS, and CGI-S scales

**Statistical Analysis**
- ANOVA used to calculate the effects of prazosin vs. placebo on POMS scores and the E-Stroop

**Results**
- Patients randomized: n=11
- **POMS Score:** POMS Score significantly lower on the trauma-related word list after prazosin administration (10±10.2 vs. 20±15, p<0.05)
  - No differences observed with control word list
  - Subscale POMS components not significantly different between prazosin and placebo, but trended lower in the “emotional distress” subscale
**Taylor, et al. 2006 continued**

<table>
<thead>
<tr>
<th><strong>E-Stroop test:</strong></th>
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<tbody>
<tr>
<td>• Significant reduction in emotional distress mood category (p=0.01)</td>
<td></td>
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<tr>
<td>• No significant changes in somatic, autonomic, cognitive, or dissociate symptoms observed</td>
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<tr>
<td>• No difference in the number of errors during or completion time of the trauma word list between prazosin and placebo</td>
<td></td>
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</tbody>
</table>

**Safety:**

- Adverse events did not differ between groups (2 reported mild sedation on prazosin vs. 1 in placebo)
- No significant differences in blood pressure or heart rate

**Post-study period:**

- 10 of the 11 patients chose to receive open-label prazosin
- The mean afternoon dose was reduced to 1.6±1.7mg
- After 2 weeks, the mean CGI-S scores changed from 3.2±0.6 to 1.5±1.6 (p<0.01) and correlated with overall reduced POMS scores (p<0.02)

<table>
<thead>
<tr>
<th><strong>Authors’ Conclusions</strong></th>
<th>Daytime prazosin pretreatment of 2-5mg reduced psychological distress in response to trauma cues. Adjunctive therapy with prazosin may reduce overall PTSD severity and distress.</th>
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<thead>
<tr>
<th><strong>Comments and Conclusions</strong></th>
<th><strong>Strengths:</strong></th>
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<tbody>
<tr>
<td></td>
<td>• Funded by a Department of Veterans Affairs and NIMH grant</td>
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<tr>
<td></td>
<td>• Randomized, double-blinded, placebo-controlled study</td>
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<tr>
<td></td>
<td>• Uses validated rating scales</td>
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<tr>
<td></td>
<td>• High retention rate to the post-study phase may indicate patients noticed an improvement in their symptoms when exposed to trauma cues</td>
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<tr>
<td><strong>Weaknesses:</strong></td>
<td></td>
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<tr>
<td></td>
<td>• Small sample size</td>
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<tr>
<td></td>
<td>• Short duration of trial</td>
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<tr>
<td></td>
<td>• Duration on maintenance psychotropics before randomization unknown</td>
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<tr>
<td></td>
<td>• The maintenance psychotropics may have different effects on sleep</td>
</tr>
<tr>
<td></td>
<td>• The mean dose of prazosin in the post-study phase was reduced, but ADRs were not reported</td>
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</table>

**Conclusions**

- Prazosin doses of 2-5mg appear effective for managing the emotional response to trauma cues when dosed in the afternoon
- Prazosin did not appear to affect cognition symptoms
<table>
<thead>
<tr>
<th><strong>Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma PTSD</strong>&lt;sup&gt;26&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Design</strong></td>
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<tr>
<td><strong>Objective</strong></td>
</tr>
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</table>
| **Inclusion Criteria** | • Must meet DSM-IV criteria for PTSD  
• Scored at least 40 on the PTSD Checklist (civilian version) (PCL-C)  
• Scored at least 4 on the “distressing dreams” item of the Clinician administered PTSD scale (CAPS) and at least 4 on the “difficulty falling asleep/staying asleep” item |
| **Exclusion Criteria** | • Diagnosis of restless leg syndrome, narcolepsy, alcohol or substance abuse within the last 3 months  
• Failure of the prazosin test dose  
• Withdrawal of consent |
| **Intervention** | • Assessment: Baseline ratings scales were obtained then reassessed the last day of each trial arm. A “second baseline” was obtained on the last day of the washout period  
• Test dose: A 1mg test dose of prazosin was administered one week prior to randomization to assess for “first dose hypotension”  
• Intervention: Prazosin (or placebo) initiated at 1mg at bedtime, then titrated up in 1mg increments every 2-3 days to achieve benefit while minimizing ADRs  
• Duration: Three weeks using placebo or prazosin with a 1 week washout period  
• Monitoring: During the last 3 nights of each treatment, participants wore a REMView sleep monitor, patients contacted the day after dose increases to assess for ADRs |
| **Endpoints** | • Effect of prazosin on objective sleep measures, including total sleep time, REM latency, REM duration, and Sleep latency  
• Effect of prazosin on PCL-C, CAPS, and CGI-I scales |
| **Statistical Analysis** | • ANOVA used to calculate the effect of prazosin’s effect over time  
• Effect sizes calculated using Cohen’s d. |
| **Results** | Patients randomized: n=13  
• 11 women, 2 men  
• Mean age 49±10 years  
• Ongoing psychotherapy continued during the study |
| **Objective Sleep Measures** | • Total sleep time greater in prazosin group (374±86 vs. 280±105 minutes, p<0.01)  
• REM sleep time greater in prazosin group (136±63 vs. 97±70 minutes, p<0.01)  
• REM latency lower in prazosin group (85±62 vs. 30±20 minutes, p<0.05)  
• REM period duration longer in prazosin (27±9 vs. 18±9 minutes, p<0.05)  
• Sleep latency did not significantly vary between groups (p-value not reported) |
Table 2: Treatment Effects on Clinical Outcome Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo Baseline</th>
<th>Placebo End</th>
<th>Prazosin Baseline</th>
<th>Prazosin End</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS distressing dreams</td>
<td>3.9±2.3</td>
<td>3.9±1.9</td>
<td>4.8±1.7</td>
<td>3.3±2.3</td>
<td>0.04</td>
</tr>
<tr>
<td>CAPS difficulty sleeping</td>
<td>6.1±0.8</td>
<td>5.6±1.4</td>
<td>6±1</td>
<td>4.8±1.8</td>
<td>0.35</td>
</tr>
<tr>
<td>NNDI</td>
<td>3.3±3.4</td>
<td>3.2±3.8</td>
<td>4.6±3.5</td>
<td>1.8±1.7</td>
<td>0.05</td>
</tr>
<tr>
<td>CGI-I</td>
<td></td>
<td>4.1±1.1</td>
<td>2.6±0.9</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>PTSD dream rating</td>
<td>14.9±9.6</td>
<td>14.4±10</td>
<td>22±6.8</td>
<td>11.7±9.4</td>
<td>0.006</td>
</tr>
<tr>
<td>PCL-C</td>
<td>56±16</td>
<td>55±15</td>
<td>58±13</td>
<td>51±13</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Authors’ Conclusions
Prazosin displayed large improvements in objective sleep measures and sleep physiology that were consistent with the patients’ ratings of their subjective PTSD symptoms and global clinical status.

Comments and Conclusions
Strengths:
• No reported conflicts of interest
• Randomized, blinded, crossover study
• Uses validated rating scales and objective sleep measures
• Heterogeneity of traumas (listed as weakness by authors, but may improve generalizability)
• Titration of prazosin similar to practice

Weaknesses:
• Small sample size (only 10 for sleep measures)
• Short duration of trial
• Duration on maintenance psychotropics unknown before randomization (duloxetine may affect BP)
• The maintenance psychotropics may have different effects on sleep
• Frequent follow-up may affect PTSD symptoms
• Generalizability is limited by the small nature of the study

Conclusions
• Prazosin doses of 2-6mg at bedtime appear effective in the management of PTSD sleep disturbances in civilians, improving both objective and subjective measures
• Failure to control for confounding variables (i.e. length of times stabilized on current psychotropic) limit how much improvement may be attributed to prazosin
Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma.²⁰

<table>
<thead>
<tr>
<th>Design</th>
<th>Single blind, non-randomized, non-placebo controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To investigate the effects of propranolol on the hyperadrenergic state and PTSD symptoms/diagnosis two months post-trauma</td>
</tr>
</tbody>
</table>
| Inclusion Criteria | • Patients who presented to the emergency department, 2 to 20 hours after motor vehicle accident (MVAs) or physical attacks who met DSM-IV diagnostic stressor (A1) and response (A2) criteria for PTSD  
  • 21-30 years if age  
  • In general good health  
  • Tachycardia of at least 90bpm after 20 minute baseline period |
| Exclusion Criteria | • LOC during trauma  
  • Sustained physical or traumatic brain injuries  
  • Cardiovascular disease or active asthma  
  • Past or present PTSD at baseline |
| Intervention | • **Assessment**: Baseline PTSD signs and symptoms and trauma history taken using the Mini International Psychiatric Interview. A baseline heart rate was also recorded after 20 minutes at rest.  
  • **Intervention**: Patients received either propranolol 40mg TID for 7 days with an 8-12 day taper period (dropping 40mg every 4 days) or no treatment  
    • The patients decided whether to take propranolol or not  
    • First propranolol pill prescribed immediately after the 20 minute baseline heart rate recording period  
  • **Monitoring**: After 7 days, heart rate was measured. Two months later, the patients were seen by a blinded psychiatrist and assessed for PTSD symptoms and diagnosis |
| Endpoints | • Heart rate  
  • Frequency of PTSD diagnosis  
  • PTSD symptom scores on the Peritraumatic Distress inventory |
| Statistical Analysis | • Wilcoxon rank test used to evaluate means  
  • Fisher exact test used to evaluate rates |
| Results | Patients recruited: n=19  
  • 11 in propranolol group  
  • 8 refused propranolol, but agreed to participate in the study  
  • No significant differences between groups at baseline |
Table 3: Outcomes in Patients Receiving Propranolol vs. Refusing

<table>
<thead>
<tr>
<th>Measure</th>
<th>Propranolol (n=11)</th>
<th>No Propranolol (n=8)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD Diagnosis at 2 months</td>
<td>1</td>
<td>3</td>
<td>0.012</td>
</tr>
<tr>
<td>Mean PTSD Score at 2 months</td>
<td>6.18±7.73</td>
<td>11.75±13.13</td>
<td>0.037</td>
</tr>
<tr>
<td>Heart rate at day 7</td>
<td>61.9±5</td>
<td>79.4±9.3</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Safety
- Propranolol was well tolerated
- Three patients reported sedation/lethargy
- One patient reported increased anxiety after self-discontinuing propranolol after 7 days (did not taper)

Authors’ Conclusions
Administering propranolol to young, healthy, tachycardic patients is effective in mitigating PTSD symptoms, and may be effective in preventing PTSD from developing.

Comments and Conclusions

Strengths
- Psychiatrist blinded at two month follow up
- Validated rating scale
- Treatment groups similar at baseline

Weaknesses
- Small sample size
- Conducted through a French school of psychiatry (non-U.S. population)
- Short duration of trial
- Did not investigate whether the response is sustained beyond two months, or if maintenance propranolol is required
- The dose of propranolol was not titrated, so the required dose is unknown
- Adherence to propranolol inferred by resting heart rate, though baseline heart rates prior to trauma were unknown
- Not placebo controlled – potentially large placebo effect in psych trials
- Patients not randomized

Conclusion
- Propranolol may be effective to limit the symptoms and diagnosis of PTSD two months post-trauma
- Unclear if the effects displayed by propranolol in this study were due to the drug or due to placebo effect
<table>
<thead>
<tr>
<th>Effect of post-retrieval propranolol on psychophysiological responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. 27</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Design</th>
<th>Randomized, double-blind, placebo-controlled study at Massachusetts General Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To investigate the effects of propranolol on physiologic responses after post-reactivation of PTSD symptoms through scripted accounts of trauma</td>
</tr>
</tbody>
</table>

**Inclusion Criteria**
- Diagnosis of PTSD based on DSM-IV criteria

**Exclusion Criteria**
- SBP<100 mmHg
- Asthma, heart failure, heart block, certain cardiac arrhythmias, insulin-requiring diabetes
- Previous adverse reaction to β-blocker
- Use of another β-blocker
- Potentially dangerous drug interactions with propranolol
- Pregnant or breast feeding
- “Recovered” memory of traumatic event
- Dissociative experiences scale score > 20

**Intervention**
- **Exposure**: After randomization, patients explained the traumatic event that led to their PTSD in detail to a study investigator
- **Intervention**: Immediately after describing their trauma, the patients received either propranolol IR 40mg or placebo
  - Two hours later, this was followed by a propranolol LA 60mg or placebo
  - Propranolol LA administered if SBP had not fallen by ≥30% or below 100 mmHg, propranolol IR had to be well tolerated
- **Monitoring**: A week later, the patients listened to recorded scripts portraying their trauma and physiologic responses were measured

**Endpoints**
- Heart rate (HR)
- Skin conductance (SC)
- Corrugator EMG after listening to a script describing the traumatic event

**Statistical Analysis**
- MANOVA to evaluate propranolol’s effect on HR, SC, and EMG
- PTSD cutoffs determined from previous patients using discriminant function analysis

**Results**
- **Patients recruited**: n=19
- **Efficacy**
  - Overall physiologic response was reduced in the propranolol group compared to placebo (p=0.007)
  - HR (p=0.03) and SC (p=0.01) responses were significantly smaller in the propranolol group, and were below threshold for PTSD (placebo remained above threshold)
  - No significant difference between groups with regard to EMG (p=0.28)

**Authors’ Conclusions**
- Propranolol given after the reactivation of past traumatic memories reduces physiological response to mental imagery of the trauma in a similar manner to propranolol given shortly after the occurrence of a traumatic event.
**Brunet, et al. 2008 continued**

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<tr>
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<td>• Randomized, double-blinded, placebo controlled study</td>
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<td>• Uses validated rating scale for physiologic responses</td>
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<td></td>
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<td>Conclusion</td>
<td>• Propranolol may be effective to limit the physiologic response of PTSD in reaction to reactivation of traumatic memories</td>
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<tr>
<td></td>
<td>• Unclear if the effects of propranolol are sustained beyond one week</td>
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<thead>
<tr>
<th>Effect of acute posttrauma propranolol on PTSD outcome and physiological responses during script-driven imagery. 28</th>
</tr>
</thead>
</table>

| Design | Randomized, doubled-blind, placebo-controlled study |
| Objective | To investigate the effects of propranolol on physiologic responses and PTSD symptoms after acute trauma exposure |

| Inclusion Criteria | • Aged 18-65 |
|                    | • Met A1 and A2 criteria as defined in the DSM-IV |
|                    | • Originally, a minimum heart rate of 80bpm and trauma no earlier than 4 hours prior to study medication administration were required for inclusion |
|                    | • Due to difficulty recruiting, the minimum heart rate was dropped and the maximum time after trauma was changed to 12 hours |

| Exclusion Criteria | • Physical injury that would complicate participation |
|                   | • Hospital stay longer than overnight |
|                   | • Head injury with LOC |
|                   | • Contraindication to propranolol (medical conditions, drug interactions) |
|                   | • Previous adverse reaction to β-blocker |
|                   | • BAC > 0.02% or presence of substances of abuse on saliva testing |
|                   | • Pregnancy |
|                   | • Traumatic event is ongoing victimization |
|                   | • Diagnosis of psychotic, mood, or PTSD disorders from another event |
|                   | • Suicidality or homicidality |
|                   | • Inability for follow up in Boston or treating physician did not agree with enrollment |

| Intervention | • **Exposure**: Patients presented to the emergency department and were randomized immediately |
|             | • **Intervention**: Initial dose of propranolol IR 40mg IR or placebo |
|             |   o If SBP did not fall below 100mmHg or had not dropped by 10mmHg or more, another propranolol LA 60mg or placebo was given |
|             |   o Propranolol dose tapered by 60mg every three days |
Monitoring: Patients called semi-weekly by research nurses to assess tolerance of propranolol/placebo and overall well being
  - Adherence assessed via patient log and pill count (patients given a slight excess of medication), and the Medication Event Monitoring System (records when patients opened their bottles)
  - CAPS scale assessed at 4 and 12 week visits

Endpoints
- Heart rate
- Skin conductance
- Frontalis EMG
- CAPS score

Statistical Analysis
- Outcome measures evaluated via ANOVA
- Pearson correlation coefficients used to describe relationship between physiologic probability and CAPS score

Results
- Patients randomized: n=43
  - Two dropped out immediately, 41 included in ITT analysis
  - 30 patients at 13 week psychodiagnostic testing

Table 4: Outcomes at One and Three Months

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo (n=20)</th>
<th>Propranolol (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One-month post-trauma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological PTSD Probability (%)</td>
<td>40.7±17</td>
<td>33.7±10.2</td>
<td>0.15</td>
</tr>
<tr>
<td>HR response (BPM)</td>
<td>1.7±4.1</td>
<td>0.2±4.5</td>
<td>0.3</td>
</tr>
<tr>
<td>SC response</td>
<td>0.55±1.08</td>
<td>0.14±0.57</td>
<td>0.17</td>
</tr>
<tr>
<td>EMG Response</td>
<td>0.5±1.5</td>
<td>0.4±0.8</td>
<td>0.77</td>
</tr>
<tr>
<td>CAPS Score</td>
<td>28.5±27.1</td>
<td>28.5±21.5</td>
<td>0.99</td>
</tr>
<tr>
<td>PTSD Diagnosis (Y/N)</td>
<td>5/15</td>
<td>5/16</td>
<td>1</td>
</tr>
<tr>
<td><strong>Three-months post-trauma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological PTSD Probability (%)</td>
<td>34.9±13.1</td>
<td>32±5.8</td>
<td>0.44</td>
</tr>
<tr>
<td>HR response (BPM)</td>
<td>1.8±3.8</td>
<td>1.2±3.4</td>
<td>0.68</td>
</tr>
<tr>
<td>SC response</td>
<td>0.18±0.8</td>
<td>-0.08±0.29</td>
<td>0.33</td>
</tr>
<tr>
<td>EMG Response</td>
<td>0.2±0.5</td>
<td>0.4±0.7</td>
<td>0.23</td>
</tr>
<tr>
<td>CAPS Score</td>
<td>19±25.8</td>
<td>21.2±26.1</td>
<td>0.81</td>
</tr>
<tr>
<td>PTSD Diagnosis (Y/N)</td>
<td>4/14</td>
<td>2/14</td>
<td>0.66</td>
</tr>
</tbody>
</table>
**Authors’ Conclusions**

Propranolol had a limited effect on the physiologic response of PTSD, but the results do not support the prophylactic use of propranolol in the acute aftermath of trauma.

**Comments and Conclusions**

**Strengths**
- Funded by and NIMH grant
- Randomized, double-blinded, placebo controlled study
- Uses validated rating scales
- Heterogeneity of traumas

**Weaknesses**
- Small sample size
- Short duration of trial
- Did not have patients specifically diagnosed with PTSD, only trauma that could possibly result in PTSD
- Potential ethical concerns to force patients to re-experience their trauma

**Conclusion**
- Propranolol was not effective in reducing PTSD symptoms and physiologic response to trauma

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**Khoury NM, Marvar PJ, Gillespie CF, et al. The renin-angiotensin pathway in posttraumatic stress disorder: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with fewer traumatic stress symptoms.**


**Design**
Cross-sectional, observational study analyzed from a larger study

**Objective**
To investigate the effects of ACEIs and ARBs on PTSD symptom severity within a highly traumatized civilian medical population

**Inclusion Criteria**
- Reports 1 or more traumatic events on the Childhood Trauma Questionnaire or the Traumatic Event Inventory

**Exclusion Criteria**
- Missing information on blood pressure medications
- Missing information on the PSS scale
- No trauma history or missing trauma history information

**Intervention**
- **Intervention:** Presence or absence of ACEI or ARB
  - **Monitoring:** Subjects were randomly contacted by a blinded scheduler for follow up
    - Subjects then medically assessed by a physician, underwent structured clinical interviews, filled out self-report measures, and assessed with the CAPS scale
  - **Setting:** Patients included from 2006-November 2010 at an inner city Atlanta hospital
    - Recruitment was from outpatient clinics or pharmacy within the hospital

**Endpoints**
- PSS scores (overall and subscales)
- CAPS scores
- PTSD diagnosis

**Statistical Analysis**
- Descriptive analysis used $\chi^2$
- Multi-variable linear regression models utilized to calculate the effects of antihypertensives
### Results

**Patients recruited:** n=663  
- n= 505 patients remained after inclusion/exclusion criteria applied  
- 180 had a diagnosis of PTSD (325 w/o diagnosis of PTSD)  
- PTSD group vs. not PTSD  
- The no PTSD group has significantly more use of ACEIs/ARBs, CCBs, and had higher employment rate  

#### Antihypertensive agents and PSS

- ACEIs/ARBs patients had significantly reduced PSS total scores (p<0.05), the hyperarousal subscale scores (p<0.05), and the intrusive subscale scores (p<0.01)  
- Beta blocker patients had significantly reduced PSS hyperarousal subscale scores (p<0.05)  
- CCBs and diuretics patients did not significantly affect PSS scores  

#### Multi-variable Linear Regression of PSS and CAPS scores

- Beta blockers and age acted as confounders to ACE/ARB use  
- ACEI/ARB therapy still associated with a significantly decreased PSS total score (p=0.044), hyperarousal score (p=0.028), and intrusive score (0.029)  
- ACEI/ARBs also associated with lower lifetime CAPS scores (p=0.028) and current CAPS scores (p=0.01)

### Authors’ Conclusions

ACEIs and ARBs help regulate the stress response in PTSD. Further studies are needed to assess the role of ACEIs/ARBs for future treatment and potential protection from PTSD.

### Comments and Conclusions

**Strengths**

- Attempted to account for potential confounding variables  
- Financed by an NIMH grant and the Atlanta hospital  
- Compared the effects of ACEIs/ARBs to other antihypertensive classes  

**Weaknesses**

- Not a randomized or placebo controlled trial  
- Did not compare to alpha-1 antagonists (like prazosin)  
- A majority of patients did not have PTSD  
- Did not distinguish between ACEIs or ARBs and did not provide information on specific agents  
- Small number of patients were on ARBs, but given equal weight in conclusions  
- Psychiatric meds were not specified  

**Conclusion**

- ACEIs/ARBs may decrease PTSD symptoms and protect against the development of PTSD, however randomized, placebo controlled data is needed  
- If patients have a compelling indication for an ACEI or ARB (e.g. diabetes) and have comorbid PTSD, there may be a potential for improved PTSD symptoms
Conclusions

- Of the antihypertensive agents, prazosin has the most compelling evidence for the adjunctive management of PTSD symptoms in the civilian population, requiring lower doses than when used in the military.
- Propranolol, may effectively reduce the physiologic signs and symptoms of PTSD, but its ability to prevent PTSD after trauma or re-exposure requires further study.
- Although data is lacking for ACE inhibitors or ARBs, they may have some benefit for PTSD symptoms in patients with other indications (e.g. hypertension), but are not recommended for routine use.
- Antihypertensive agents should be used to augment existing psychotropic therapy for PTSD as data supporting monotherapy is limited.
References


Appendix A

## DSM-IV-TR Diagnostic Criteria for PTSD

<table>
<thead>
<tr>
<th>Symptom Cluster</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Exposed to trauma where each of the following occurred:</td>
</tr>
<tr>
<td></td>
<td>1. Experienced, witnessed, or confronted with actual/threatened death, serious injury, or a threat to the physical integrity of self or others</td>
</tr>
<tr>
<td></td>
<td>2. Response included intense fear, helplessness, or horror</td>
</tr>
<tr>
<td>B</td>
<td>Traumatic event is persistently re-experienced:</td>
</tr>
<tr>
<td></td>
<td>1. Recurrent and Intrusive recollections</td>
</tr>
<tr>
<td></td>
<td>2. Recurrent distressing dreams</td>
</tr>
<tr>
<td></td>
<td>3. Feelings the trauma were recurring</td>
</tr>
<tr>
<td></td>
<td>4. Intense psychological distress when exposed to cues</td>
</tr>
<tr>
<td></td>
<td>5. Physiological reaction in response to cues</td>
</tr>
<tr>
<td>C</td>
<td>Avoidance of stimuli associated with the trauma and numbing of general responsiveness:</td>
</tr>
<tr>
<td></td>
<td>1. Avoidance of thoughts, feelings, and conversations</td>
</tr>
<tr>
<td></td>
<td>2. Avoidance of activities, places, or people</td>
</tr>
<tr>
<td></td>
<td>3. Inability to recall important aspects of the trauma</td>
</tr>
<tr>
<td></td>
<td>4. Diminished interest in activities</td>
</tr>
<tr>
<td></td>
<td>5. Feeling detached/estranged from others</td>
</tr>
<tr>
<td></td>
<td>6. Restricted range of affect</td>
</tr>
<tr>
<td></td>
<td>7. Sense of foreshortened future</td>
</tr>
<tr>
<td>D</td>
<td>Persistent hyperarousal:</td>
</tr>
<tr>
<td></td>
<td>1. Difficulty sleeping</td>
</tr>
<tr>
<td></td>
<td>2. Irritability</td>
</tr>
<tr>
<td></td>
<td>3. Poor concentration</td>
</tr>
<tr>
<td></td>
<td>4. Hypervigilance</td>
</tr>
<tr>
<td></td>
<td>5. Exaggerated startle response</td>
</tr>
<tr>
<td>E</td>
<td>Duration of symptoms &gt; 1 month</td>
</tr>
<tr>
<td>F</td>
<td>Significant distress in social, occupational, or other important areas of functioning</td>
</tr>
</tbody>
</table>

Appendix B

## Assessment Rating Scales

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>Description</th>
</tr>
</thead>
</table>
| Clinical Global Impressions Scale    | • Three items on a seven point scale  
| Improvement (CGI-I)                   | • Used to assess how much a patient or subject has improved over time                                                                                                                                 |
| Clinical Global Impressions Scale    | • Three items on a seven point scale  
| Severity (CGI-S)                      | • Used to assess symptom severity                                                                                                                                                                          |
| Clinician Administered PTSD Scale    | • Thirty-item structured interview  
| (CAPS)                                | • May be used to make diagnosis of PTSD or to assess symptoms of PTSD over the last week                                                                                                                                 |
| Profile of Mood States (POMS)        | • 65 adjectives rated on a 5 point scale  
|                                       | • 0 = not at all; 4 = extremely  
|                                       | • Six subscales (tension/anxiety, depression, anger/hostility, vigor/activity, fatigue, confusion/bewilderment)                                                                                               |
| PTSD Checklist- Civilian Version (PCL-C) | • Self- administered, seventeen-item checklist of PTSD symptoms on a five point scale  
|                                        | • 1 = not at all; 5 = extremely                                                                                                                                                                             |
## Appendix C

### Definitions of Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ACEI</td>
<td>Angiotensin Converting Enzyme Inhibitor</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis Of Variance</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin Receptor Blocker</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>BPM</td>
<td>Beats Per Minute</td>
</tr>
<tr>
<td>CCB</td>
<td>Calcium Channel Blocker</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>GSW</td>
<td>Gun Shot Wound</td>
</tr>
<tr>
<td>HI</td>
<td>Homicidal Ideation</td>
</tr>
<tr>
<td>IR</td>
<td>Immediate Release</td>
</tr>
<tr>
<td>LA</td>
<td>Long Acting</td>
</tr>
<tr>
<td>LOC</td>
<td>Loss Of Consciousness</td>
</tr>
<tr>
<td>MANOVA</td>
<td>Multiple Analyses of Variance</td>
</tr>
<tr>
<td>MMHG</td>
<td>Millimeters of Mercury</td>
</tr>
<tr>
<td>MVA</td>
<td>Motor Vehicle Accident</td>
</tr>
<tr>
<td>PTSD</td>
<td>Post-Traumatic Stress Disorder</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid Eye Movement</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
</tr>
<tr>
<td>SC</td>
<td>Skin Conductance</td>
</tr>
<tr>
<td>SI</td>
<td>Suicidal Ideation</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin-Norepinephrine Reuptake Inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic Antidepressant</td>
</tr>
<tr>
<td>TID</td>
<td>“Ter In Die” (Latin for three times daily)</td>
</tr>
</tbody>
</table>