Pharmacotherapy Rounds
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Jacquelyn E. Canning, Pharm.D.
PGY-1 Pharmacy Resident
Central Texas Veterans Health Care System
The University of Texas at Austin College of Pharmacy

Learning Objectives:
1. Describe the background and pathophysiology of post traumatic stress disorder (PTSD)
2. Identify current treatment options for symptom management of PTSD
3. Compare and contrast evidence for the use of atypical antipsychotics in PTSD
4. Discuss appropriate therapeutic recommendations for atypical antipsychotics in PTSD
I. Post Traumatic Stress Disorder

A. Background

i) Definition
   (1) An anxiety disorder that can develop after direct exposure to a traumatizing event or ordeal where grave physical harm was threatened or occurred
   (2) Traumatic events that may trigger PTSD
      a) Accidents
      b) Violent personal assaults
      c) Witnessing violent events
      d) Natural or human-caused disasters
      e) Military combat

ii) Epidemiology
   (1) Lifetime exposure to traumatic events is common and reported prevalence is up to 90% in some populations
   (2) Lifetime prevalence of PTSD has been estimated at 6.8% in the United States general population
      a) May be as high as 24% in subpopulations
         i) Combat veterans
   (3) Approximately 50% of men and 60% of women are exposed to traumatic events during their lifetime
   (4) Of those exposed to traumatic events, 8.2% of men and 20% of women will develop PTSD

iii) Combat-Related Stress
   (1) PTSD related to the psychological toll of war is unique and often difficult to treat with current therapies
   (2) Traumatic events are often daily events in war zones
   (3) The pure physical demands of a war zone are unprecedented compared to civilian life and sustain the body’s alarm reaction over great periods of time
   (4) During battle, soldiers are purposely pushed to keep their fighting edge
   (5) Alertness, hypervigilance, and narrowed attention span are features that increase the rate of survival during wartime
   (6) A variety of emotional responses that also occur during war include sadness about losses, frustration, guilt, anger, or rage
   (7) An individual’s contextual and cultural aspects define how combat-related stress will affect their psychological well-being
   (8) Transition from a war-zone mindset back to civilian life is often difficult and frequently not completely achievable
iv) Diagnostic Criteria (DSM-IV-TR)\(^4\)

**Criterion A: STRESSOR**  
Both of the following must be met:
- Experienced, witnessed, or been confronted with an event or events involving actual or threatened death or serious injury, or threatening the physical integrity of oneself or others
- Response involved intense fear, helplessness, or horror

**Criterion B: INTRUSIVE RECOLLECTION**  
At least one of the following:
- Recurrent and intrusive distressing recollections of the event, including images, thoughts, and perceptions
- Recurrent distressing dreams of the event
- Acting or feeling as if the traumatic events were recurring, including reliving the experience, illusions, hallucinations, and dissociative flashbacks
- Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
- Physiologic reactivity upon exposure to internal or external cues symbolizing or resembling an aspect of the traumatic event

**Criterion C: AVOIDANCE/NUMBING**  
At least three of the following:
- Avoidance of thoughts, feelings, or conversations associated with the trauma
- Avoidance of activities, places, or people that elicit memories of the trauma
- Inability to recall important aspects of the trauma
- Markedly diminished interest or participation in significant activities
- Feeling detached or estranged from others
- Restricted range of affect
- Sense of a shortened future

**Criterion D: HYPERAROUSAL**  
At least two of the following:
- Difficulty falling or staying asleep
- Irritability or outbursts of anger
- Difficulty concentrating
- Hypervigilance
- Exaggerated startle response

**Criterion E: DURATION**
- Duration of disturbance (symptoms from criterion B, C, and D) is more than one month

**Criterion F: FUNCTIONAL SIGNIFICANCE**
- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
v) Pathophysiology

1. Attributed to the failure of the stress response system to appropriately react, adapt, and recover from the traumatic event

Table 1. Dysregulated pathways in PTSD

<table>
<thead>
<tr>
<th>Dysregulated Biological Pathway</th>
<th>Location</th>
<th>Function</th>
<th>Dysregulated Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>Amygdala Hippocampus Thalamus Prefrontal Cortex</td>
<td>“Fight or Flight” Response</td>
<td>Hyperarousal Hypervigilance Memory Formation Attention Deficits</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Amygdala Hippocampus Prefrontal Cortex</td>
<td>Regulation</td>
<td>Mood Anxiety Irritability Impulsivity Insomnia</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Amygdala Hippocampus</td>
<td>Excitation</td>
<td>Memory Formation Decreased Hippocampal Volume</td>
</tr>
<tr>
<td>Corticotropin Releasing Hormone</td>
<td>Hypothalamic-Pituitary-Adrenal Axis</td>
<td>Physiological Stress Response</td>
<td>Memory Formation Stress Response</td>
</tr>
</tbody>
</table>

2. Norepinephrine dysregulation

   a. Physiologic studies suggest patients with PTSD have more autonomic hyperactivity at baseline when compared to healthy individuals
   b. Increases in norepinephrine activity in patients with PTSD may increase amygdala activation and intensify fear conditioning
   c. Activity in the prefrontal cortex is decreased in the presence of significantly increased levels of norepinephrine for prolonged periods of time

3. Serotonin Dysregulation

   a. Reciprocal interaction between serotonin and norepinephrine
   b. Serotonin secreting neurons are found predominately in key areas involved with fear and anxiety
   c. Symptomatic benefit from selective serotonin reuptake inhibitors may be normalization of the prefrontal cortex’s inhibition of the amygdala via the serotonin pathway
   d. Serotonin has modulating effects on the hypothalamic-pituitary-adrenal axis and corticotropin releasing hormone
(4) Glutamate Dysregulation\(^2,7\)
   (a) Modulation of corticotropin releasing hormone release from hypothalamic-pituitary-adrenal axis in response to stress
   (b) Regulation of long-term potentiation leading to learning and memory formation
   (c) N-methyl-D-aspartate (NMDA)-receptor antagonists have been used to block acquisition of fear conditioning in the amygdala and hippocampus

(5) Corticotropin Releasing Hormone\(^2,5,6\)
   (a) Hypothalamic-pituitary-adrenal axis acts as a regulatory agent of the physiological responses to stress
   (b) Elevated glucocorticoid levels work with norepinephrine activation in the amygdala to enhance the encoding process and consolidation of emotional memories

B. Pharmacotherapy for all PTSD populations
   i) Selective serotonin reuptake inhibitors\(^1,8\)
      (1) Mainstay of therapy due to efficacy during clinical practice
      (2) Has most randomized controlled trial data available
      (3) Medications with FDA approved indication for PTSD\(^1\)
         (a) Sertraline
         (b) Paroxetine
      (4) SSRIs show significant improvement in\(^1,8\)
         (a) Hyperarousal
         (b) Re-experiencing
         (c) Numbing
      (5) Response rates for patients using SSRIs are generally less than 60\(^%\)\(^9\)
      (6) 20-30\(^%\) of these patients achieve full remission\(^9\)
      (7) Effective in treating co-morbid disease states of anxiety and major depression
      (8) The length and severity of symptoms determines how effective SSRIs are at fully remitting symptoms\(^10\)
      (9) Randomized controlled trial data supporting fluoxetine also\(^1\)

   ii) Serotonin and norepinephrine reuptake inhibitors\(^1,11\)
      (1) Only venlafaxine has data published for use in PTSD
      (2) Venlafaxine showed significant improvement in\(^1\)
         (a) Avoidance
         (b) Numbing
         (c) Re-experiencing
      (3) Effective therapy for co-morbid disease states of anxiety and major depression
iii) Centrally acting selective α₁ antagonists¹,¹¹-¹⁴
   (1) Prazosin is the medication of all the centrally acting selective α₁ antagonists with randomized controlled trial data
   (a) Especially in combat veterans
   (2) α₁ receptor stimulation is linked to sleep disruption, stress-induced disruptions in prefrontal cortex cognitive processing, and increased release of corticotrophin releasing hormone¹
   (3) Improvement in sleep disruptions¹³
      (a) Difficulty falling asleep
      (b) Difficulty staying asleep
      (c) Nightmares
   (4) Prazosin seems to shift dream content from trauma-related nightmares to more normal and less distressing content increasing total sleep time¹

iv) Anticonvulsants¹,⁹,¹⁵
   (1) Lack of efficacious data to support first line use
   (2) Often used second- or third-line for mood symptoms

v) Benzodiazepines¹,⁹,¹¹
   (1) Benzodiazepines influence the central nervous system through their effects on the gamma-aminobutyric acid (GABAₐ) receptors
   (2) Effects of activated GABAₐ receptors¹
      (a) Decrease anxiety
      (b) Sedation
      (c) Muscle relaxation
      (d) Cognitive effects
      (e) Anticonvulsant properties
   (3) There is very little randomized controlled trial data available supporting the efficacy of benzodiazepines despite their widespread use

vi) Miscellaneous medications in PTSD¹,¹¹,¹²
   (1) Trazodone
      (a) First-line hypnotic in PTSD¹,¹¹,¹²
      (b) Considered to be very effective and well-tolerated for the treatment of sleep disturbances in PTSD patients¹
      (c) Shown to be effective adjunctive treatment for antidepressant-related insomnia¹
      (d) Very few randomized controlled trials for use in PTSD
   (2) Cyproheptadine
      (a) Antagonizes both serotonin 5-HT₂ and histamine H₁ receptors¹,¹²
      (b) Mixed data for its efficacy
      (c) Case reports indicate it is effective in reducing nightmares in PTSD patients¹
      (d) Randomized controlled trials indicate it may actually exacerbate sleep problems¹
vii) Atypical antipsychotics\(^1,10,11,15,28,29\)

1. The use of atypical antipsychotics as adjunctive medication for various psychiatric disorders is increasing in clinical practice, especially at VA hospitals\(^28,29\).

2. Atypical antipsychotics are unique from typical antipsychotics by their effect on other neurotransmitters besides dopamine.

3. Atypical antipsychotics antagonize\(^1,15,16\)
   a. \(D_2\) receptors
   b. \(5-HT_{2A}\) receptors
   c. \(\alpha_1\) adrenergic receptors
   d. histamine receptors

4. They also agonize\(^1,15,16\)
   a. \(5-HT_{1A}\) receptors (partial)

5. Dopaminergic dysfunction has been associated with psychotic symptoms and possibly hyperarousal\(^1\).

6. However, it is the atypical antipsychotics’ effect on the serotonergic pathway that may indicate their use in PTSD.

7. This leads to the conclusion they may have added benefit in the remission of symptoms when used adjunctively with SSRIs.

8. This effect on the serotonin pathway excludes typical antipsychotics\(^16\).

9. Few randomized controlled trials exists to support the use of atypical antipsychotics for the treatment of PTSD.

C. Individual Characteristics of Atypical Antipsychotics\(^1,16\)

i) Risperidone\(^17\)

1. High affinity antagonist of serotonin \(5-HT_{2A}\) and dopamine \(D_2\) receptors.

2. Less affinity for adrenergic \(\alpha_1\), \(\alpha_2\) and histamine \(H_1\) receptors.

3. Higher incidence of extrapyramidal symptoms.

4. Only generic atypical antipsychotic available.

5. Five published randomized controlled trials available for use in PTSD.

ii) Olanzapine\(^18\)

1. High affinity for serotonin \(5-HT_{2A}, 5-HT_{2C}, 5-HT_6\), dopamine \(D_1, D_4\), histamine \(H_1\), and adrenergic \(\alpha_1\) receptors.

2. Moderate affinity for serotonin \(5-HT_3\) and muscarinic \(M_{1,5}\) receptors.

3. Low affinity for \(GABA_A\) and \(\beta\) adrenergic receptors.

4. Major metabolic side effects.

5. Approved for adjunctive treatment with fluoxetine for refractory depression.

6. Two published randomized controlled trials available for use in PTSD.

iii) Quetiapine\(^19\)

1. High affinity for serotonin \(5-HT_{1A}, 5-HT_2\), dopamine \(D_1, D_2\), histamine \(H_1\), and adrenergic \(\alpha_1\), \(\alpha_2\) receptors.

2. Highly sedating with some metabolic side effects.
(3) One unpublished randomized controlled trial for use in PTSD
(4) Several open label trials for use in PTSD

iv) Aripiprazole
   (1) High affinity for serotonin 5-HT_{1A}, 5-HT_{2A}, and dopamine D_2 receptors
   (2) Moderate affinity for adrenergic α_1 receptors
   (3) Approved for adjunctive treatment in depression
   (4) No randomized controlled trials for use in PTSD
   (5) Mostly case studies available for use in PTSD

v) Ziprasidone
   (1) High affinity for serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, dopamine D_2, D_3, and adrenergic α_1 receptors
   (2) Moderate affinity for histamine H_1 receptors
   (3) Inhibits synaptic reuptake of serotonin and norepinephrine
   (4) No randomized controlled trials for use in PTSD
   (5) Very few case reports available for use in PTSD

D. PTSD Treatment Algorithm

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First Line Treatment
   SSRIs
   Augmentation with other antidepressants

Aggression and Insomnia
   Benzodiazepines
   Trazodone
   Prazosin

Co-morbid Psychiatric Disorders
   Anticonvulsants
   Atypical Antipsychotics
Low-Dose Risperidone as Adjunctive Therapy for Irritable Aggression in Posttraumatic Stress Disorder

Reference

Design
Randomized, placebo-controlled, double-blinded, flexible dose

Objective
To determine the therapeutic role of risperidone in the treatment of aggression in PTSD

Population
Inclusion criteria:
- Adult male combat veterans
- Diagnosis of PTSD according to DSM-IV rated by the CAPS
- ≥ 20 on cluster D subscale (hyperarousal) on the PCL-M

Exclusion criteria:
- History of schizophrenia, bipolar disorder with psychotic features, or organic mental disorder
- History of antipsychotic medication use
- Diagnosed substance disorder with less than 1 year of remission

Outcome
Change in total score on the OAS-M and PCL-M

Methods
- Randomized to risperidone 0.5mg daily or placebo
- Participants were evaluated with rating scales at weeks 2, 4, and 6
- Risperidone dose could be increased at weeks 2 and 4 on the basis of clinical response and side effects up to a maximum daily dose of 2mg
- Currently prescribed psychotropic medications were continued unchanged

Results
- Sixteen participants were enrolled with no significant difference between groups concerning age, education, or baseline rating scale measures for 6 weeks
- Mean dosage of risperidone(0.57mg) and placebo (0.62mg) were not significantly different
- One dropout due to urinary retention in risperidone group
- Side effects were characterized as none, mild, moderate, severe, or life-threatening with risperidone having scores of none (N=3) and mild (N=4) and placebo having scores of none (N=5), mild (N=2), and moderate (N=1)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Baseline</th>
<th>Point Change from Baseline</th>
<th>Baseline</th>
<th>Point Change from Baseline</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=7)</td>
<td></td>
<td></td>
<td>(N=8)</td>
<td></td>
<td></td>
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<tr>
<td>OAS-M Aggression</td>
<td>13.0</td>
<td>-12.0*</td>
<td>11.0</td>
<td>-8.0</td>
<td>0.80</td>
</tr>
<tr>
<td>OAS-M Irritability</td>
<td>7.0</td>
<td>-2.0*</td>
<td>6.0</td>
<td>-1.0</td>
<td>0.04</td>
</tr>
<tr>
<td>OAS-M Suicidality</td>
<td>0.0</td>
<td>0.0</td>
<td>1.5</td>
<td>-1.0*</td>
<td>0.08</td>
</tr>
<tr>
<td>OAS-M Total</td>
<td>19.0</td>
<td>-17.0*</td>
<td>18.5</td>
<td>-9.5</td>
<td>0.79</td>
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<tr>
<td>PCL-M Cluster B</td>
<td>23.0</td>
<td>-4.0*</td>
<td>21.5</td>
<td>0.0</td>
<td>0.001</td>
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<tr>
<td>PCL-M Cluster C</td>
<td>27.0</td>
<td>-2.0</td>
<td>26.5</td>
<td>2.0</td>
<td>0.20</td>
</tr>
<tr>
<td>PCL-M Cluster D</td>
<td>24.0</td>
<td>-2.0</td>
<td>22.5</td>
<td>0.0</td>
<td>0.20</td>
</tr>
<tr>
<td>PCL-M Total</td>
<td>73.0</td>
<td>-10.0*</td>
<td>72.0</td>
<td>-0.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Conclusions of Authors
Risperidone was significantly more effective than placebo in decreasing irritability, as measured by the OSA-M, intrusive thoughts (Cluster B) PCL-M, and total PCL-M scores in a group of combat veterans with severe PTSD.

Comments
- Small sample size with short duration (6 weeks)
- Significant differences between groups
- Every participant had a comorbid psychiatric diagnosis
- Relatively low treatment dose of risperidone
- Difficult to determine effect of risperidone when used with various other psychotropics
- No metabolic side effects noted
- Did not prove primary endpoint, no difference in total OAS-M score
- Not effective in reducing symptoms of anxiety or depression

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; CAPS, Clinician Administered PTSD Scale; PCL-M, Patient Checklist for PTSD-Military Version; OAS-M, Overt Aggression Scale-Modified for Outpatients
Adjunctive Risperidone in the Treatment of Chronic Combat-Related Posttraumatic Stress Disorder

Reference

Design
Randomized, placebo-controlled, double-blinded, parallel group

Objective
To evaluate the efficacy and safety of risperidone as adjunctive therapy in veterans with chronic combat-related PTSD

Population
Inclusion criteria:
- Adult males entering residential treatment program
- Diagnosis of PTSD determined by DSM-IV criteria
- Score of 65 or higher on CAPS
- Proof of military service

Exclusion criteria:
- Current treatment with antipsychotic medications
- Psychotropic antidepressant regimen that changed within six weeks prior to program
- Significant medical illness, physical impairment, or cognitive impairment that would affect validity of rating scales
- History of seizure disorder requiring treatment
- Alcohol or substance abuse or dependence in the past six months
- High risk of suicide or violence

Outcome
- Primary was change in total score on the CAPS (Total), CAPS-B, CAPS-C, and CAPS-D
- Secondary was change in total score on the HAM-A, HAM-D, PANSS-P

Methods
- Phase I = residential program x 5 weeks
- Phase II = outpatient x 11 weeks (for a total of 16 weeks)
- Randomized to adjunctive risperidone or placebo with current psychotropics unchanged
- Risperidone was initiated at 1mg qHS and increased to 3mg qHS over 2 weeks
- At week 5, participants were discharged home
- Evaluations occurred at baseline and weeks 1, 2, 3, 4, and 16

Results
- Sixty three participants were enrolled with no significant difference between groups
- Eleven participants from risperidone group discontinued study (ADEs, unrelated medical condition, lost to follow-up, alcohol abuse, and stopped taking medication)
- Six participants from placebo discontinued study (ADEs, lost to follow-up, alcohol abuse)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Risperidone (N=22)</th>
<th>Placebo (N=26)</th>
<th>Significance</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS-Total</td>
<td>102.2 (11.9)</td>
<td>102.2 (11.9)</td>
<td>98.6 (15.8)</td>
<td>98.6 (15.8)</td>
</tr>
<tr>
<td>CAPS-B</td>
<td>27.6 (4.7)</td>
<td>27.6 (4.7)</td>
<td>26.4 (6.8)</td>
<td>26.4 (6.8)</td>
</tr>
<tr>
<td>CAPS-C</td>
<td>42.2 (6.7)</td>
<td>42.2 (6.7)</td>
<td>41.3 (7.6)</td>
<td>41.3 (7.6)</td>
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<tr>
<td>CAPS-D</td>
<td>32.3 (4.5)</td>
<td>32.3 (4.5)</td>
<td>30.9 (5.2)</td>
<td>30.9 (5.2)</td>
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<tr>
<td>HAM-A</td>
<td>23.4 (4.7)</td>
<td>23.4 (4.7)</td>
<td>23.7 (6.4)</td>
<td>23.7 (6.4)</td>
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<tr>
<td>HAM-D</td>
<td>20.6 (5.1)</td>
<td>20.6 (5.1)</td>
<td>21.9 (6.4)</td>
<td>21.9 (6.4)</td>
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<tr>
<td>PANSS-P</td>
<td>16.7 (4.6)</td>
<td>16.7 (4.6)</td>
<td>15.8 (4.1)</td>
<td>15.8 (4.1)</td>
</tr>
</tbody>
</table>

Conclusions
Adjunctive treatment with risperidone improved a broad range of psychiatric symptoms in patients with combat-related PTSD in the absence of overt psychiatric disorders. Risperidone was significantly more effective than placebo in reducing total CAPS, avoidance (CAPS-C), hyperarousal (CAPS-D), anxiety (HAM-A), and positive psychosis symptoms (PANSS-P).

Comments
- Study population consisted of all males with chronic PTSD that would justify referral to residential treatment program decreasing the ability to generalize to other populations
- Participants had a mean score of 100 on CAPS despite previous medication therapy
- Long evaluation gap between week 4 and week 16

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; CAPS, Clinician Administered PTSD Scale; CAPS-B, “Re-experiencing” subscale; CAPS-C, “Avoidance” subscale; CAPS-D, “Hyperarousal” subscale; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; PANSS-P, Positive and Negative Syndrome Scale Positive Symptom subscale
Adjunctive Risperidone Treatment in Posttraumatic Stress Disorder: A Preliminary Controlled Trial of Effects on Comorbid Psychotic Symptoms

Reference

Design
Randomized, placebo-controlled, single-blind, flexible-dose

Objective
To evaluate the efficacy of risperidone as adjunctive therapy well-characterized, combat-associated PTSD patients with psychotic features

Population
Inclusion criteria:
- Adult male and female veterans aged ≥ 18 years old
- Diagnosis of PTSD determined by DSM-IV criteria
- Current psychotic features defined as hallucinations delusions, or thought disorder not occurring exclusively during a flashback re-experiencing episode
- Score of ≥ 60 on the total PANSS with a score of at least moderate (4) on the following four positive subscales: conceptual disorganization (P2), hallucinatory behavior (P3), suspiciousness (P6), or unusual thought content (P9).

Exclusion criteria:
- Medical conditions that would preclude safe administration of risperidone
- Individuals who met DSM-IV criteria for alcohol or drug dependence within 1 month
- Diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, exhibiting clinically significant suicidal or homicidal ideation or other dangers
- Participants with >20% decline in PANSS total scores during the placebo lead-in phase

Outcome
Change in total score on the CAPS and PANSS

Methods
- Participants taking antipsychotics or thymoleptics (lithium, anticonvulsants) had the medications reduced and discontinued at least 1 week before placebo lead-in phase
- Other psychotropics were allowed and had to be maintained at a constant dose for 1 month before randomization
- One week of single-blind placebo lead-in phase
- After lead-in phase, randomized to risperidone or placebo
- Risperidone was initiated at 1mg qHS and adjusted at each visit based on clinical impression of patients’ responses to a maximum daily dose of 6mg
- CAPS and PANSS were administered once weekly for the 5 weeks of treatment

Results
- Forty participants were enrolled with similar background characteristics for 5 weeks
- Two participants did not have adequate follow-up assessments and 1 participant was dropped because he was a placebo responder during the placebo lead-in phase
- Fifteen participants dropped out of the study after starting, 6 in placebo group and 9 in treatment
- No statistically significant differences were found between attrition rates and causes
- Average risperidone dose was 2.5mg daily
- No statistically significant difference was found between groups for CAPS

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Risperidone (N=19)</th>
<th>Placebo (N=18)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean (SD)</td>
<td>Endpoint Mean (SD)</td>
<td>Baseline Mean (SD)</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>85.6 (14.3)</td>
<td>75.6 (17.2)</td>
<td>82.1 (7.9)</td>
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<tr>
<td>PANSS-P</td>
<td>20.3 (4.5)</td>
<td>16.6 (4.1)</td>
<td>21.2 (3.5)</td>
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<td>PANSS-N</td>
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<td>21.2 (5.6)</td>
<td>21.6 (3.0)</td>
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<td>GPS</td>
<td>42.1 (7.9)</td>
<td>37.8 (9.2)</td>
<td>39.3 (4.8)</td>
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<td>CAPS Total</td>
<td>90.3 (23.0)</td>
<td>81.3 (24.3)</td>
<td>89.1 (12.2)</td>
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<tr>
<td>CAPS-B</td>
<td>19.9 (7.7)</td>
<td>15.3 (8.5)</td>
<td>18.8 (6.7)</td>
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<tr>
<td>CAPS-C</td>
<td>39.3 (10.1)</td>
<td>38.0 (8.5)</td>
<td>38.8 (6.7)</td>
</tr>
<tr>
<td>CAPS-D</td>
<td>31.1 (8.6)</td>
<td>28.0 (10.5)</td>
<td>31.4 (6.7)</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Global psychotic symptoms associated with chronic PTSD were improved modestly with risperidone treatment. There was no difference in efficacy between risperidone and placebo for symptoms of PTSD as measured by CAPS.</td>
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</table>
| Comments                                                                                             | • Small sample size and short treatment duration (5 weeks)  
• Participants were previously treated with psychotropics and still had a moderate to severe level of illness indicating treatment resistance  
• All patients experienced psychotic symptoms but none met criteria for a primary psychotic diagnosis  
• Relatively low risperidone dose compared to treatment doses for schizophrenia  
• Risperidone treated the psychosis as expected by no difference was observed in PTSD symptoms |

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; PANSS, Positive and Negative Syndrome Scale; CAPS, Clinician Administered PTSD Scale; PANSS-P, Positive and Negative Syndrome Scale Positive subscale; PANSS-N, Positive and Negative Syndrome Scale Negative subscale; GPS, Positive and Negative Syndrome Scale general psychopathology subscale; CAPS, Clinician Administered PTSD Scale; CAPS-B, “Re-experiencing” subscale; CAPS-C, “Avoidance” subscale; CAPS-D, “Hyperarousal” subscale
Adjunctive Olanzapine for SSRI-Resistant Combat-Related PTSD: A Double-Blind, Placebo-Controlled Study

| Design | Randomized, placebo-controlled, double-blinded  
| Objective | To evaluate the efficacy and safety of olanzapine as an adjunctive therapy in SSRI treatment-resistant combat-related PTSD  
| Population | Inclusion criteria:  
| | • Adult male patients from VA San Diego Health Care System  
| | • Diagnosis of PTSD determined by DSM-IV criteria  
| | • Optimized dose and duration of SSRI  
| | • Chronic military-related PTSD  
| | Exclusion criteria:  
| | • Use of psychotropic medications other than current SSRI treatment regimens  
| Outcome | • Change in 3 symptom domains: posttraumatic stress using CAPS, depression using self-rated CES-D, and sleep using self-rated PSQI  
| | • Change in CGI was also compared  
| Methods | • Patients continued to take their maximally tolerated, stable dose of SSRI  
| | • Randomized to olanzapine or placebo  
| | • Olanzapine initiated at 10mg at qHS and could be increased to 20mg at next visit if needed  
| | • Evaluations occurred at baseline and weekly for 1 month, then at weeks 4, 6, 8, and 10  
| Results | • Nineteen participants were enrolled for 10 weeks  
| | • Fluoxetine N=5 with median dose of 40mg daily  
| | • Paroxetine N=7 with median dose of 40mg daily  
| | • Sertraline N=7 with median dose of 200mg daily  
| | • Four participants dropped out  
| | • Mean dosage of olanzapine was 15mg and 20mg for placebo  
| | • Weight gain was significantly higher in the olanzapine group compared to the placebo (p < 0.001) with the mean weight gain being 13 pounds  
| | • Three out of 10 (30%) in olanzapine group and 1 out of 9 (11%) in placebo group were deemed responders on CGI (p=0.58)  
| | • No statistically significant difference was found between groups for CGI  

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Placebo (N=9)</th>
<th>Endpoint (SD)</th>
<th>Olanzapine (N=10)</th>
<th>Endpoint (SD)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS</td>
<td>84.0 (16.2)</td>
<td>-2.7 (10.6)</td>
<td>86.1 (22.1)</td>
<td>-14.8 (14.2)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>CES-D</td>
<td>35.9 (13.9)</td>
<td>4.9 (9.7)</td>
<td>36.6 (12.7)</td>
<td>-5.3 (6.27)</td>
<td>&lt; 0.03</td>
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<tr>
<td>PSQI</td>
<td>15.9 (3.4)</td>
<td>1.6 (2.8)</td>
<td>16.1 (2.9)</td>
<td>-3.29 (3.2)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Conclusions | Olanzapine demonstrated superiority of treatment efficacy compared to placebo in the areas of sleep and depressive symptoms, but failed to demonstrate a clear improvement in overall symptoms.  

Comments | • Small sample size and short duration of treatment (10 weeks)  
| • Weight gain was a major side effect and may lead to more metabolic side effects  
| • Sedation is a major side effect of olanzapine and getting more sleep may alleviate
### Olanzapine in the Treatment of Post-Traumatic Stress Disorder: a Pilot Study

**Reference**

**Design**
Randomized, placebo-controlled, double-blinded

**Objective**
To evaluate the efficacy and safety of olanzapine as monotherapy treatment for PTSD

**Population**
Inclusion criteria:
- Adult aged 18-70 years from Duke University Medical Center Outpatient Psychiatry Service and Durham Women Veteran’s Comprehensive Health Center
- Diagnosis of PTSD determined by DSM-IV criteria

Exclusion criteria:
- History of bipolar disorder, any psychotic disorder, or mental retardation
- Recent history of alcohol or substance use disorder
- High risk of suicide or violence

**Outcome**
Change in total score on the SIP, TOP-8, SPRINT, and DTS

**Methods**
- Randomized to olanzapine or placebo at a ratio of 2:1
- Olanzapine initiated at 5mg daily and increased to 10mg, 15mg, and 20mg at weeks 1, 4, and 6 respectively
- Evaluations occurred at baseline and weekly for 1 month, then at weeks 4, 6, 8, and 10

**Results**
- Fifteen participants were enrolled, 14 females and 1 male for 10 weeks
- Four patients dropped out
- Mean dosage of olanzapine was 14.1mg and 13.9 for placebo
- Olanzapine group had significantly more complaints of thirst and weight gain than placebo ($p < 0.05$)
- No statistical difference found between groups for any rating scale

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Placebo (N=5)</th>
<th>Olanzapine (N=10)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIP</td>
<td>Baseline Mean (SD)</td>
<td>Endpoint (SD)</td>
<td>Baseline Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>45.9 (8.2)</td>
<td>17.0 (17.5)</td>
<td>39.7 (9.7)</td>
</tr>
<tr>
<td>TOP-8</td>
<td>21.8 (3.3)</td>
<td>10.5 (8.7)</td>
<td>19.3 (4.2)</td>
</tr>
<tr>
<td>SPRINT</td>
<td>34.8 (2.1)</td>
<td>20.5 (11.1)</td>
<td>31.5 (5.7)</td>
</tr>
<tr>
<td>DTS</td>
<td>95.8 (16.7)</td>
<td>56.0 (36.6)</td>
<td>91.6 (25.4)</td>
</tr>
</tbody>
</table>

**Conclusions**
Olanzapine failed to demonstrate treatment efficacy superior to placebo.

**Comments**
- Small sample size and short duration of treatment (10 weeks)
- Predominately female and trauma type decrease ability to generalize to other populations
- Increase in primary outcomes may be due to vigorous assessment protocol

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; SIP, Structured Interview for PTSD; TOP-8, Treatment Outcomes PTSD Scale; SPRINT, Short PTSD Rating Interview; DTS, Davidson Trauma Scale
A. Quetiapine Randomize Controlled Trial (unpublished)\(^{30}\)
   ii) Randomized, double-blinded, placebo-controlled trial
   iii) Eighty patients with PTSD randomized to get 50-800mg of quetiapine or placebo for 12 weeks
   iv) No mention of other psychotropic medications
   v) CAPS scores significantly declined in quetiapine group when compared to placebo
   vi) Re-experiencing and hyperarousal subscales were significantly improved compared to placebo
   vii) Secondary outcomes also improved significantly compared to placebo group
       (1) CGI-Severity of Illness scale
       (2) CGI-Improvement scale
       (3) HAM-D
       (4) HAM-A
       (5) PANSS
   viii) Authors’ concluded quetiapine helped improve symptoms of PTSD and may benefit in this indication

B. Summary and Conclusions
   i) Combat-related PTSD is a particular subpopulation in PTSD that is often treatment-resistant
   ii) First-line medications with the most randomized controlled trial data are SSRIs
   iii) Atypical antipsychotics are often used to augment SSRIs in treatment resistant PTSD
   iv) Atypical antipsychotics come with serious side effect profiles and higher costs
   v) Very little data exists to support the use of atypical antipsychotics for this indication
   vi) Risperidone has weak evidence to support its use in the treatment of PTSD at this time
   vii) Minor improvement has been suggested in hyperarousal symptoms (criterion D) with the adjunctive use of risperidone
   viii) The benefit of atypical antipsychotics does not outweigh the risks or cost according to existing research
   ix) Atypical antipsychotics should be used when there are co-morbid disease states such as psychosis
   x) Further research is warranted for all atypical antipsychotics for their use in PTSD
      (1) Suggested design
          (a) Adjunctive atypical antipsychotic vs. placebo
          (b) Only sertraline or paroxetine as primary medication (stable for > 2 weeks)
          (c) Primary outcome would be reduction in CAPS total score and subscales
          (d) Flexible dosing for atypical antipsychotics to titrate up to effect
          (e) At least 16 weeks in length
          (f) Suggested sample size of > 35 participants for each group (power=93%)
### Psychiatric Rating Scales

<table>
<thead>
<tr>
<th>Scale Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinician Administered PTSD Scale (CAPS)</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>A clinician completed, 17-item, structured interview that corresponds to the DSM-IV criteria for PTSD. Questions are rated on a 5-point scale and target the impact of symptoms on social and occupational functioning, overall PTSD severity, and frequency and intensity of five associated symptoms (guilt over acts, survivor guilt, gaps in awareness, depersonalization, and derealization).</td>
</tr>
<tr>
<td><strong>Patient Checklist for PTSD-Military Version (PCL-M)</strong>&lt;sup&gt;25&lt;/sup&gt;</td>
<td>A standardized self-report rating scale for PTSD comprising 17 items rated on a 5-point scale with a higher score indicating greater severity. Corresponds to the key symptoms of PTSD related to military experiences. Divided into 3 subscales measuring criterion B, C, and D.</td>
</tr>
<tr>
<td><strong>Overt Aggression Scale-Modified for Outpatients (OAS-M)</strong>&lt;sup&gt;25&lt;/sup&gt;</td>
<td>A clinician rated interview divided into 3 subscales that measure aggression, irritability, and suicidality. Aggression subscale is scores frequency and severity assessments of overt aggression with no ceiling and is weighted to increase with the seriousness of the aggression.</td>
</tr>
<tr>
<td><strong>Hamilton Anxiety Scale (HAM-A)</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>A 14 item rating scale developed to quantify the severity of anxiety. Measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety).</td>
</tr>
<tr>
<td><strong>Hamilton Depression Scale (HAM-D)</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>A 21-question multiple choice questionnaire rating the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety and weight loss.</td>
</tr>
<tr>
<td><strong>Positive and Negative Syndrome Scale (PANSS)</strong>&lt;sup&gt;27&lt;/sup&gt;</td>
<td>A 30-item clinician-administered rating scale that evaluates positive, negative, and other symptoms of schizophrenia. Items are rated from 1-7 during a 30-40 minute interview.</td>
</tr>
<tr>
<td><strong>Center for Epidemiologic Studies Depression Scale (CES-D)</strong>&lt;sup&gt;28&lt;/sup&gt;</td>
<td>A 20-item self-rated assessment measuring depressive feelings and behaviors from the preceding week.</td>
</tr>
<tr>
<td><strong>Pittsburgh Sleep Quality Index (PSQI)</strong>&lt;sup&gt;28&lt;/sup&gt;</td>
<td>A 19-item self-rated assessment of sleep quality and disturbances over a 1-month time interval.</td>
</tr>
<tr>
<td><strong>Clinical Global Impression Scale (CGI)</strong>&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Clinical scale measuring the change in function as “much improved” or very much improved” relative to the start of treatment.</td>
</tr>
<tr>
<td><strong>Structured Interview for PTSD (SIP)</strong>&lt;sup&gt;29&lt;/sup&gt;</td>
<td>A 17-item scale assessment of diagnosis, treatment effect, and symptom severity of PTSD, as well as measuring survival and behavior guilt.</td>
</tr>
<tr>
<td>Measure</td>
<td>Description</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Treatment Outcomes PTSD Scale (TOP-8)²⁹     | • An 8-item scale with each item ranked from 0-4  
• Measures PTSD symptom groups of intrusion, avoidance, numbing and hyperarousal as well as somatic distress and impairment in work and social functioning 
• Recently developed simplified version of the Clinician Administered PTSD Scale |
| Short PTSD Rating Interview (SPRINT)²⁹     | • A 7-item self-report measure that assesses the core symptoms of PTSD (intrusion, avoidance, numbing, arousal), somatic malaise, stress vulnerability, and role and social functional impairment |
| Davidson Trauma Scale (DTS)²⁹              | • A 17-item self report measure that assess the symptoms of PTSD using a 0-5 rating range                                                    |
References


