Brief Report

Adjunctive Olanzapine for SSRI-Resistant Combat-Related PTSD: A Double-Blind, Placebo-Controlled Study

Murray B. Stein, M.D.
Neal A. Kline, M.D.
Jeffrey L. Matloff, Ph.D.

Objective: Posttraumatic stress disorder (PTSD), particularly in combat veterans with chronic illness, is often refractory to standard pharmacological interventions. There is a need to test adjunctive treatments to boost response.

Method: Subjects were 19 patients with PTSD who were minimally responsive to 12 weeks of treatment with a selective serotonin reuptake inhibitor (SSRI) at maximum tolerated dose. Outcomes were compared among subjects whose treatment was augmented with 8 weeks of double-blind olanzapine or placebo administration.

Results: Olanzapine augmentation was associated with statistically significantly greater reduction than placebo in specific measures of posttraumatic stress, depressive, and sleep disorder symptoms. Clinician-rated global response rates did not, however, significantly differ between groups.

Conclusions: This is most likely the first double-blind, placebo-controlled study of an adjunct to SSRIs for PTSD. Despite the small group size, the findings suggest a role for olanzapine or other atypical antipsychotics in treating SSRI-resistant PTSD. Sleep symptoms may especially benefit.

(Psychiatry 2002; 159:1777–1779)
at bedtime for the first 2 weeks. This could then be increased to 20 mg at the next visit, if needed and tolerated. No other concurrent psychotropic medications were permitted.

Primary outcome measures were chosen to portray change in three symptom domains: posttraumatic stress (using theClinician-Administered PTSD Scale for DSM-IV [15]), depressive (using the self-rated Center for Epidemiologic Studies Depression Scale [CES-D Scale] [16]), and sleep (using the self-report Pittsburgh Sleep Quality Index [17]) symptoms. Changes in these measures were compared across treatments, as were the numbers of responders in each period that were defined by the Clinical Global Impression scale of severity (r=0.66, df=15, p=0.01), suggesting that related with change in Clinician-Administered PTSD Scale score (r=0.66, df=15, p=0.01). The observation fits with emerging data in which olanzapine has been noted to successfully augment SSRI effects in two other conditions, even in the absence of psychotic symptoms (13, 14). These patients seem to have a more severe variant of PTSD and may benefit from olanzapine as a co-medicant agent in conjunction with an SSRI in the treatment of PTSD.

Results

Mean scores at random assignment are shown in Table 1. Patients had severe PTSD and depressive symptoms and pronounced sleep problems. Olanzapine was associated with a significantly greater reduction than placebo in PTSD symptoms, as measured by total score on the Clinician-Administered PTSD Scale for DSM-IV: mean=–14.80 (SD=14.16) versus mean=–2.67 (SD=10.55), respectively (t=2.21, df=17, p<0.05). It was also associated with a significantly greater reduction than placebo in sleep disturbance, as measured by the global score on the Pittsburgh Sleep Quality Index: mean=–3.29 (SD=3.15) versus mean=1.57 (SD=2.76) (t=–3.07, df=12, p=0.01). Change in Pittsburgh Sleep Quality Inventory score was moderately correlated with change in Clinician-Administered PTSD Scale for DSM-IV score (r=0.66, df=15, p=0.01), suggesting that enhanced sleep accounted for much of the reported improvement.

Olanzapine was also associated with a significantly greater reduction than placebo in depressive symptoms, as measured by the CES-D Scale: mean=–5.25 (SD=6.27) versus mean=4.88 (SD=9.66) (t=–2.49, df=14, p<0.03). The two treatments did not significantly differ in the percentage of subjects deemed responders on the CGI scale of change: three of 10 (30%) taking olanzapine versus one of nine (11%) taking placebo (p=0.58, Fisher’s exact test).

The mean dose of olanzapine was 15.00 mg/day (SD=0.00) (t=2.83, df=17, p<0.02). Weight gain was significantly greater with olanzapine than placebo: mean=13.2 lb (SD=5.9) versus mean=–3.0 lb (SD=6.5) (t=4.32, df=11, p=0.001). Early protocol terminations occurred for three patients taking olanzapine (two for somnolence; one for unspecified reasons) and for two patients taking placebo (both for lack of efficacy).

Discussion

We found the atypical antipsychotic olanzapine to be superior to placebo as an adjunct in the treatment of SSRI-resistant PTSD. Beneficial effects on sleep and depressive symptoms, in particular, were noted. Still, when global clinical improvement was considered, response rates to adjunctive olanzapine were fairly low (30%) and not statistically superior to placebo (11%). This suggests that although improvement in symptoms was attained with olanzapine, the overall magnitude of effects was modest for most patients (but clinically meaningful for some). Given the typical chronicity and severity of combat-related PTSD, even small gains (such as those seen in this study) must be cherished.

There is a subgroup of combat-related PTSD patients with psychotic symptoms (13, 14). These patients seem to have a more severe variant of PTSD and may benefit from the addition of antipsychotic agents to their treatment regimens. None of the patients in our study had psychotic symptoms, yet olanzapine was still helpful for some. This observation fits with emerging data in which olanzapine has been noted to successfully augment SSRI effects in two other conditions, even in the absence of psychotic symptoms: obsessive-compulsive disorder and major depressive disorder (18, 19).

Mean weight gain in subjects receiving olanzapine was approximately 13 lb. The benefits of using this antipsychotic agent in conjunction with an SSRI for treating PTSD must be balanced against the potential detrimental health effects associated with this magnitude of weight gain. Effects on glucose regulation should also be systematically evaluated (20).

We cannot rule out the possibility that more prolonged treatment with an SSRI would have resulted in additional improvement. Indeed, in one study in which sertraline

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**TABLE 1. Characteristics (Before Random Assignment to 8 Weeks of Olanzapine or Placebo) of Patients With Resistant Combat-Related PTSD at End of SSRI-Only Treatment Period**

<table>
<thead>
<tr>
<th>Age and Measure</th>
<th>Patients Taking Placebo (N=9)</th>
<th>Patients Taking Olanzapine (N=10)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SD</td>
<td>Mean SD</td>
<td>t</td>
<td>df</td>
</tr>
<tr>
<td>Age (years)a</td>
<td>51.1 8.1</td>
<td>55.2 6.6</td>
<td>–1.21</td>
</tr>
<tr>
<td>Total score on Clinician-Administered PTSD Scale for DSM-IV</td>
<td>84.0 16.2</td>
<td>86.1 22.1</td>
<td>–0.23</td>
</tr>
<tr>
<td>Score on Center for Epidemiologic Studies Depression Scaleb</td>
<td>35.9 13.9</td>
<td>36.6 12.7</td>
<td>–0.11</td>
</tr>
<tr>
<td>Global score on Pittsburgh Sleep Quality Index</td>
<td>15.9 3.4</td>
<td>16.1 2.9</td>
<td>–0.15</td>
</tr>
<tr>
<td>Score on Clinical Global Impression scale of severityc</td>
<td>5.4 0.5</td>
<td>5.1 0.9</td>
<td>1.02</td>
</tr>
</tbody>
</table>

a Range=34–69.  
b For both groups, N=8.  
c Mode=6.
treatment was continued up to 36 weeks (21), 20%–25% of
the improvement in scores on the Clinician-Administered
PTSD Scale for DSM-IV occurred between weeks 12 and
36. Practically, however, it is doubtful that most patients
(or clinicians) would be willing to persist with a treatment
that had negligible effects after 12 weeks in the hope that
additional gains would accrue with prolonged treatment.
There thus remains a clear need for interventions that can
potentiate the effects of SSRIs for PTSD. Pharmacological
(including olanzapine and other atypical antipsychotic
agents) and psychological therapies should be systemati-
cally tested for this purpose under controlled conditions.

Received Aug. 3, 2001; revisions received March 20 and April 25,
2002; accepted May 8, 2002. From the Anxiety and Traumatic Stress
Disorders Programs, Psychiatry Service, VA San Diego Healthcare Sys-
tem, San Diego, Calif. Address reprint requests to Dr. Stein, Depart-
ment of Psychiatry (0985), 9500 Gilman Dr., La Jolla, CA 92093-0985;
mstein@ucsd.edu (e-mail).

Supported by a investigator-initiated research grant from Eli Lilly.
The authors thank Traci Berghold, Rebecca Lenox, and the staff of
the posttraumatic stress disorder clinical team at the VA San Diego
Healthcare System outpatient clinic for help with patient care and
recruitment.

Dr. Stein is a paid consultant for Eli Lilly.

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