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Adding Atypical to SSRIs of No Benefit for PTSD

No Evidence to Support Growing 'Ad hoc' Practice

Fran Lowry

August 29, 2011 — Adding the antipsychotic risperidone to a selective serotonin reuptake-inhibitor (SSRI) does not reduce the symptoms of military-related posttraumatic stress disorder (PTSD), new research suggests.

However, this does not mean that risperidone is without benefit for some individuals whose PTSD includes psychotic symptoms, lead author John H. Krystal, MD, the Robert L. McNeil Jr professor of psychiatry and chair of the Department of Psychiatry at Yale–New Haven Hospital in Connecticut, told *Medscape Medical News*.

Dr. John H. Krystal

At this time, SSRIs are the only FDA-approved pharmacotherapies for the treatment of PTSD. Within the Department of Veterans Affairs, 89% of veterans diagnosed with PTSD are prescribed SSRIs. The 2 SSRIs that have been approved for PTSD treatment are sertraline and paroxetine.

Second-generation antipsychotic medications are increasingly being added to PTSD treatment when symptoms do not respond to antidepressant therapy.

"There has been a proliferation of what you might call 'ad hoc' treatments for these patients," Dr. Krystal said. "This is the first study to test, on a large scale, if one of those treatments, developed from the art of medicine rather than the science of medicine, actually works."

The study was published in the August 3 issue of *JAMA*.

Conducted between February 2007 and February 2010 at 23 Veterans Administration outpatient medical centers, the study included 247 patients diagnosed with military-related PTSD who had ongoing symptoms despite at least 2 adequate SSRI treatments.

Participants were randomly assigned to receive either risperidone, up to 4 mg once daily, or placebo, in addition to antidepressant medication.

The main outcome measure was the Clinical-Administered PTSD Scale; other measures included the Montgomery-Asberg Depression Rating Scale, the Hamilton Anxiety Scale, the Clinical Global Impression Scale, and the Veterans RAND 36-item Health Survey.

After analysis of the data, the study showed no statistically significant difference between risperidone and placebo in reducing measures of PTSD symptoms after 6 months of treatment.

The change in Clinical-Administered PTSD Scale scores (range, 1 - 136) was −16.3 (95% confidence interval [CI], −19.7 to −12.9) in the risperidone group and −12.5 (95% CI, −15.7 to −9.4) in the placebo group, for a mean difference of 3.74 (95% CI, −0.86 to 8.35; $P = .11$).

In addition, risperidone was not statistically superior to placebo on any of the other outcomes, including improvement on measures of quality of life, depression, anxiety, paranoia, or psychosis.

Adverse Events More Common

Adverse events also were more common with risperidone compared with placebo. Patients receiving risperidone reported more weight gain (15.3% vs 2.3% on placebo), fatigue (13.7% vs 0.0%), somnolence (9.9% vs 1.5%), and hypersalivation (9.9% vs 0.8%).

"We would like our study to help clinicians think about the reasons they are using the second-generation antipsychotic medications to treat PTSD," Dr. Krystal said.

He reiterated that patients who really need an antipsychotic medication should not be deprived of risperidone or other similar drugs.

"In our study, we did not have many people who had symptoms of psychosis. It is quite possible that risperidone is an excellent medication to treat psychosis that can be associated with PTSD, but that was not the question we tested," he said.

"We wouldn't want people who are benefiting from risperidone because they are no longer hearing voices, or experiencing relief from other psychotic symptoms, to abruptly have it stopped. In these cases, risperidone might actually be very good for those symptoms, but they are not the typical core symptoms of PTSD," Dr. Krystal said.

Unrealistic Expectation

In an accompanying editorial, Charles W. Hoge, MD, from the Walter Reed Army Medical Center, Silver Spring, Maryland, writes that the results of this study "seriously call into question the use of atypical antipsychotics in PTSD treatment." He adds that more studies are needed to identify more effective treatments.

One area that has broad clinical implications for veterans that should be given priority is to learn more about the relationship between PTSD and the normal physiology of combat, Dr. Hoge suggests.

"PTSD is associated with dysregulation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis, compounded in the combat environment by prolonged extreme stress and chronic sleep restriction," he writes. "The expectation that this level of dysregulation will reset easily upon return home is unrealistic."

Finally, Dr. Hoge calls for research to better understand the perceptions of war veterans about existing mental healthcare, the acceptability of care, their willingness to continue with treatment, and ways to communicate with veterans "that validate their experiences as warriors."

Dr. Krystal reports financial relationships with Janssen Research Foundation, Abbott, Aisling Capital, AstraZeneca, Brintnall and Nicolini, Bristol-Myers Squibb, Easton and Associates, Easi, Eli Lily, F. Hoffman LaRoche, Forest Laboratories, Gilead Sciences, GlaxoSmithKline, Janssen, Lohocla Research Corporation, Lundbeck Research USA, Medivation, Merz Pharmaceuticals, MK Medical Communications, Mnemosyne Pharmaceuticals, Naurex, Pfizer, Shire, SK Holdings, Sunovion Pharmaceuticals, Takeda Industries, Tetragenex, and Teva Pharmaceuticals. He also reports having patents for glutamatergic treatment of neuropsychiatric disorders and intranasal administration of ketamine to treat depression (pending). He is also the editor of Biological Psychiatry*, and is president elect of the American College of Neuropsychopharmacology. Dr. Hoge reports receiving royalties from his book* Once a Warrior Always a Warrior *and from book-related speaking engagements.*

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