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Second Generation Antipsychotics: Are these drugs effective in treating PTSD?

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The National Comorbidity Survey Replication recently estimated an increase in lifetime prevalence of Posttraumatic Stress Disorder (PTSD) among adult Americans to be 6.8% compared to the previous rate of 3.5%.[1] This rise may be due to the increasing incidence of combat-related PTSD within recent years. Studies have found a prevalence of up to 19.6% in veterans returning from service in Iraq and Afghanistan.[1,2]

Typical symptoms of PTSD include persistent re-experiencing of traumatic events (e.g., flashbacks, nightmares), and avoidance of thoughts and feelings related to the event.[3] Other symptoms include decreased concentration, insomnia, irritability and hypervigilance.[3] Psychotherapy with or without pharmacotherapy is considered standard of care to improve symptoms and daily functioning in PTSD patients.[5]

Selective serotonin reuptake inhibitors (SSRIs) or venlafaxine are recommended first line for PTSD treatment. Sertraline and paroxetine are the only SSRIs approved by the Food and Drug Administration (FDA) for PTSD.[5] Some patients, particularly combat veterans, respond poorly to this class of drugs.[6,7] Also, a majority of PTSD patients present with psychiatric comorbidities.[8] In light of this, many clinicians seek augmentation strategies with a variety of medications to enhance medication response in patients with SSRI resistant PTSD symptoms. Adjunct treatment options include tricyclic antidepressants, monoamine oxidase inhibitors, non-SSRI antidepressants (mirtazapine and nefazodone) and prazosin.[5] Second-generation antipsychotic (SGAs) are often utilized for treatment of psychotic symptoms in PTSD despite the limited amount of evidence. The purpose of this review is to explore the literature on the use of SGAs as an augmentation therapy in the management of SSRI resistant PTSD patients.

The Evidence

Use of SGAs in PTSD is strongly correlated to the presence of comorbid psychotic, bipolar or cognitive disorders and recent psychiatric hospitalization.[9] A study at a single Veterans Affairs (VA) medical center found that SGAs were most commonly prescribed for their perceived "efficacy" and the goal of "[improving] sleep or sedation" in individuals with PTSD.[10] Another study which looked at multiple VA sites reported 19.9% of PTSD patients were prescribed an antipsychotic medication with 93.6% of these prescriptions being an SGA.[11]

In clinical practice, the selection of the most appropriate SGAs has been left up to the clinician's discretion and patient preferences. According to 2004 American Psychiatric Association (APA) guidelines, risperidone, olanzapine, and quetiapine are recommended as possible adjunct treatment options for PTSD, however, the supporting evidence for this recommendation is limited.[4] On the other hand, the 2012 revised VA/Department of Defense (DoD) PTSD Clinical guidelines do not recommend any SGAs due to lack of evidence.[5]

Risperidone

The largest body of evidence for the use of SGAs as augmentation treatment for PTSD comes from trials of risperidone. A meta-analysis of seven double blind placebo controlled trials suggested that both monotherapy and augmentation therapy with olanzapine and risperidone is efficacious in improving symptoms of PTSD, measured by the Clinician Administered PTSD Scale (CAPS) (standard mean difference, SMD, -0.94; 95% CI -0.75 to -0.14).[12] However, there was no difference in responder rate. The evidence was limited based on a small number of diverse trials.

The most recent randomized trial by Krystal et al., in 2011 compared the efficacy of risperidone versus placebo for the treatment of SSRI-resistant PTSD as measured by the CAPS change in baseline.[13] The study was conducted at 23 VA medical centers from 2007 to 2010 and included 247 highly symptomatic veterans despite having received at least 2 adequate SSRI treatments (4 weeks of therapy) prior to the study enrollment.[13] They were allowed to be on other pharmacotherapy agents including prazosin, trazodone, nefazodone, quetiapine and mirtazapine.[13] Participants were randomized to either a target dose of risperidone 4 mg daily (n=133) or placebo (n=134).[13] After 6 months of therapy, no significant difference was found with change in CAPS scores from baseline between risperidone (-16.3; 95% CI, -19.7 to -12.9) and placebo (-12.5; 95% CI, -15.7 to -9.4; mean difference 3.74; 95% CI, -0.86 to 9.35; p = 0.11).[13] Both groups were also receiving a similar number of other pharmacotherapy agents (risperidone 3.09 vs. placebo 2.86) during this trial.[13] The most common side effects were self-reported weight gain (risperidone 15.3%; placebo 2.3%), fatigue (risperidone 13.7%; placebo 0%), somnolence (risperidone 9.9%; placebo 1.5%) and hypersalivation (risperidone 9.9%; placebo 0.8%).[13] This study failed to show any additional benefits when risperidone was used in combination with SSRIs in treating PTSD.[13] This RCT was higher quality of evidence and included a much larger sample size (n=247) compared to the trials used in the previous meta-analysis which most included less than 40 subjects. The Va/DoD clinical practice guidelines originally recommended off-label risperidone, olanzapine, or quetiapine for the adjunctive treatment of patients with PTSD.[5] However, based on the negative results of this recent VA study, the 2012 revised VA/DoD PTSD Clinical Practice Guideline "recommend against the use of risperidone as adjunctive therapy.", stating insufficient evidence as an adjunctive therapy for the treatment of PTSD.[5]

Quetiapine

Of the SGAs, quetiapine has the largest proportion of off-label use (42.9%) for treatment of PTSD in the VA system.[11] However, supporting evidence is low quality, with mostly open-label, small studies. A six-week open-label trial (n=20) by Hamner et al., was the first to show a significant reduction in PTSD symptoms when quetiapine was used as an adjunct treatment.[14] Another open-label, 8 week study (n=15) by Ahearn et al., reported a 42% overall improvement in PTSD symptoms in patients with refractory symptoms on background SSRI therapy,. as measured by CAPS scores and significant improvement in each symptom cluster including re-experiencing, hyperarousal and avoidance.[15] The use of quetiapine has also been studied as an adjunctive treatment to reduce PTSD-related nightmares. In 2010, a prospective cohort trial and the first comparative study examined the long-term efficacy and safety of quetiapine versus prazosin for treatment of nighttime symptoms in combat veterans with PTSD.[16] Patients in this study (n=237) received either prazosin (n=62) or quetiapine (n=175).[16] Efficacy of the drug was identified through physician notation that "patient's nighttime symptoms improved" or "frequency of nightmares decreased."[16] The prazosin and quetiapine groups had similar short-term efficacy (61.3% vs 61.7%; p= 0.54) with symptomatic improvement within 6 months.[16] However, the prazosin group had significantly greater long-term efficacy (48.4%) compared with those receiving quetiapine therapy (24%; P <0.001; OR 3.0; 95% CI, 1.62-5.45) as therapy continued for approximately 3 to 6 years.[16] In terms of concurrent therapies, there were more patients in the prazosin group than the quetiapine group who were receiving sleep agents (32% vs. 18%; P = 0.02) such as diphenhydramine, trazodone, mirtazapine, zolpidem, and/or a benzodiazepine.[16] Patients in the quetiapine group were more likely to have been on an SSRI at baseline (69% vs. 53%; p = 0.02) or had an SSRI added on at baseline (80% vs. 61%; p = 0.005).[16] The prazosin group was less likely to discontinue therapy due to adverse events compared to

those receiving quetiapine (17.7% vs. 34.9%; p = 0.008).[16] The most frequent adverse effect resulting in therapy discontinuation in the quetiapine group was sedation (21% vs. prazosin 1.6%; p < 0.001).[16] There were also significantly more patients in the quetiapine group that discontinued therapy due to metabolic effects (9.1% vs. prazosin 0%; p = 0.014).[16] At the end of the study, 25% of quetiapine patients were switched to prazosin; whereas only 8% of prazosin patients were switched to quetiapine.[16] Based on the results of this study the authors concluded that prazosin should be used as the first line adjunctive treatment for PTSD-related sleep disturbances due to its superior long-term efficacy and safety.[16] The American Academy of Sleep Medicine as well as VA/DoD guidelines highly recommended the adjunctive use of prazosin for treatment of resistant sleep problems and nightmares in PTSD patients.[5,17]

Olanzapine

Previously, the evidence supporting the role of olanzapine in treating PTSD symptoms was limited to only case reports and small studies, as emphasized in the meta-analysis by Pae et al.[12] One of these small randomized, double-blind placebo controlled study examined the effect of adjunctive use of olanzapine (mean dose: 15 mg/day) versus placebo in 19 male veterans with SSRI resistant PTSD.[18] Olanzapine was associated with a significant improvement in CAPS score (14.80 vs placebo 2.67; p < 0.05).[18] In particular, sleep disturbances as measured by self-report Pittsburgh Sleep Quality Index (PSQI -3.29 vs 1.57; p = 0.01) and depressive symptoms as measured by self-rated Center for Epidemiologic Studies Depression Scale (CES-D 5.25 vs 4.88; p < 0.03) were significantly reduced in olanzapine group versus placebo.[18] However, participants receiving adjunctive treatment with olanzapine exhibited a significantly greater weight gain (13.2 lb vs -3.0 lb; p = 0.001).[18]The authors concluded that adjunctive use of olanzapine was superior compared to placebo in reducing PTSD symptoms particularly sleep disturbances and depressive symptoms.[18] However, this clinical benefit may come at the cost of weight gain and other metabolic disturbances.[18]

Aripiprazole

In 2005, Lambert et al published a case series examining the efficacy of aripiprazole in addition to ongoing treatment with cognitive behavioral therapy or with sertraline in five PTSD patients.[19] The authors reported that adding aripiprazole 15 or 30 mg at bedtime significantly improved symptoms in four out of five patients.[19] One patient reported agitation and inability to sleep on aripiprazole 15 mg and thus discontinued therapy.[19] The authors did not report the duration of follow-up for patients.[19] Recently, a 12-week, open-label trial conducted in veterans with severe PTSD demonstrated that using aripiprazole as adjunct treatment significantly reduced symptoms in 53% of the 17 subjects leading to a 20% reduction in total CAPS scores.[20] Another recent 12-week retrospective chart review examined PTSD symptom improvement in 27 military veterans as measured by total PTSD Checklist-Military Version (PCL-M) scores: a 17-item self-report measure completed by participants.[5] This study demonstrated that the addition of aripiprazole (average dose of 12.40 mg daily) to standard PTSD treatment decreased total PCL scores from 56.11 at baseline to 46.85 ($p < 0.0001$).[21]

Conclusion

Off-label use of antipsychotics for the treatment of PTSD remains controversial based on low quality evidence, including very small studies of limited duration. Most studies have focused on war veterans with PTSD and therefore it is challenging to extrapolate the results to the general population (e.g. civilians and women). Furthermore, combat related PTSD may be more resistant to SSRI treatment. All SGAs can cause significant side effects and therefore routine monitoring is required to safely use these medications. More robust evidence is needed to clarify the potential utility of these medications in the treatment of PTSD. Risks and benefits should be carefully considered before prescribing SGAs.

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