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Minireview: Efficacy and safety of sertraline for the treatment of adult patients with PTSD

Introduction

Post-traumatic stress disorder (PTSD) is an anxiety disorder that develops in response to exposure to severe psychological trauma. Across the world, PTSD has a prevalence of 3-4%, but is as high as 15.4% in conflict-affected populations.[1] The biological mechanisms that underlie PTSD are still unclear, but are thought to reflect a dysregulated stress response that is initiated by the traumatic event.[2] There are numerous biological consequences of this initiating event, including adrenergic hyperresponsiveness, [3] alterations in the hypothalamo-pituitary-adrenal (HPA) axis, [4] limbic system sensitization, [5] and insufficient serotonin activity. [6]

PTSD is described in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) as having four main symptom clusters: intrusion, avoidance, negative alterations in cognition and mood, and alterations in arousal and reactivity.[7] The diagnosis of PTSD requires identification of symptoms from each of these four clusters that persist for more than four weeks.[7] PTSD is often comorbid with other psychiatric disorders, such as anxiety disorder, major depressive disorder and substance abuse disorder, which complicates its diagnosis and treatment.[8]

Several psychological and pharmacological treatments have been developed for PTSD, and are often used simultaneously because no single treatment has been shown to fully resolve symptoms. This review will discuss the current clinical evidence supporting the treatment of PTSD with sertraline, a selective serotonin reuptake inhibitor (SSRI).[9]

Clinical Evidence for Sertraline's Efficacy

Currently, only two SSRIs – sertraline and paroxetine – have been approved by the FDA for the treatment of PTSD.[10,11] Some guidelines recommend these drugs as first lines of treatment,[12-14] while

other guidelines recommend that they be used as second lines of treatment behind psychotherapy.[15-16] The rationale for using SSRIs such as sertraline in PTSD is two-fold. First, there is a recognized relationship between PTSD and other mood and anxiety disorders for which these medications are known to be effective.[13] Second, there is a putative role of serotonin, norepinephrine, and other neurotransmitters in the pathophysiology of PTSD.[17] In the short-term, SSRIs increase serotonin in the synaptic cleft by inhibiting its re-uptake into the presynaptic neuron. In the long-term, it has been proposed that SSRIs modulate responsiveness to external trauma-related stimuli, thereby reducing subjective feelings of fear.[18]

Sertraline Monotherapy

Results from two, 12-week, double-blind, placebo-controlled clinical trials including almost 400 patients provided the basis for the FDA approval of sertraline.[10,11] In these studies, response rates were significantly higher with sertraline (53-60%) compared with placebo (32-38%). The greatest responses were achieved for arousal and avoidance symptoms. Sertaline was generally well tolerated, with the most commonly reported side effects being gastrointestinal upset, sexual dysfunction and headaches. Adverse events that were reported more commonly in patients receiving sertraline compared with placebo included diarrhea, nausea, fatigue and decreased appetite. [10,11] Sertraline may also cause drug interactions by interfering with metabolic clearance via the cytochrome p450 system.[10,11]

Several studies have also demonstrated sertraline's ability to produce sustained improvements in PTSD symptoms.[19-21] In one open-label study, when sertraline treatment was extended by 24 weeks following a 12-week double-blind trial (N=128), PTSD remission rates increased from 30 to 55%, and 54% of patients who initially did not respond to therapy went on to respond.[19] In another double-blind, controlled trial, 96 patients who had responded to sertraline therapy were assigned to continue

sertraline treatment or switch to placebo for 28 weeks.[20] Relapse rates were significantly lower among patients receiving sertraline compared to placebo (5% versus 26%, respectively).[21] In both studies, discontinuation of sertraline treatment was associated with clinical relapse.[20,21]

The effects of sertraline are less consistent in veterans with PTSD compared with civilians, suggesting that PTSD related to combat trauma may be more refractory to sertraline treatment.[22,23] In one pilot study of 23 Israeli military veterans, sertraline only modestly improved PTSD symptoms over 10 weeks.[22] A larger, randomized, double-blind study consisting of 169 veterans found no improvement in PTSD symptoms over 12 weeks.[23] However, larger studies of longer duration are necessary to corroborate these findings. Future studies should also evaluate the confounding effects of comorbidities and PTSD chronicity on the efficacy of sertraline in veterans suffering from PTSD.

Several studies have directly compared the efficacy of sertraline to other proposed PTSD treatments that vary in their mechanism of action. In a small 12-week, randomized, double-blind study (N=37), both nefazodone (a 5-HT_{2A} receptor antagonist) and sertaline were found to significantly improve PTSD symptoms, depression, sleep and quality of life over time, with similar efficacy.[24] Larger trials may be warranted; however, nefazodone's clinical use may be limited because this drug can, in rare cases, induce life-threatening hepatotoxicity. In a 12-week, double-blind, multicenter trial (N=538), an extended release formulation of venlafaxine (a selective serotonin and norepinephrine reuptake inhibitor) was found to have similar efficacy and tolerability to sertraline, and was superior to placebo, for the short-term treatment of PTSD.[25] When sertraline was compared with mirtazapine (a 5-$HT_{2/3}$ receptor antagonist) in a 6-week, randomized, double-blind trial of Korean war veterans (N=113), both drugs were found to be effective and well-tolerated for the management of PTSD.[26] Mirtazapine was superior to sertraline in its effect on sleep, and may be advantageous due to its lower potential for drug interactions.[26] Because mirtazapine and venlafaxine have different

mechanisms of action from sertraline, and some studies have shown that sertraline may be less effective for combat-related PTSD, further exploration of their use in sertraline-refractory PTSD populations is warranted. Mirtazapine and venlafaxine may also be useful in cases where drug interactions prohibit sertraline treatment.

Combination Therapies

Because sertraline treatment alone does not fully resolve PTSD symptoms, several studies have examined the combined efficacy of sertraline and other drugs. In one recent double-blind study, sertraline plus mirtazapine resulted in greater remission rates and improved depressive symptoms compared with sertraline plus placebo over 24 weeks.[27] Although this study is encouraging, it did not evaluate whether combined mirtazapine/sertraline therapy can improve PTSD symptoms in the short-term compared with sertraline alone. Future studies should assess whether specific subgroups of patients, such as those who are initially refractory to sertraline treatment, might benefit from this combined therapy.

Studies have also evaluated the efficacy of sertraline in combination with psychotherapy. In a pilot study (N=10), significantly greater reductions in PTSD symptoms were observed when cognitive behavioural therapy was added to sertraline treatment in pharmacotherapy-resistant Cambodian refugees.[28] Another study found that treatment of PTSD patients (N=31) with prolonged exposure therapy plus sertraline, after they had received 10 weeks of sertraline treatment alone, led to a further reduction in symptom severity. This augmentation was observed only for patients who were partial rather than full responders to initial sertraline treatment.[29] These studies suggest that combining pharmacotherapy and psychotherapy for the treatment of PTSD may be advantageous, particularly for patients who are resistant to pharmacotherapy alone. Larger clinical trials are warranted.

Systematic Reviews and Meta-Analyses – Is Sertraline Really Best?

Although SSRIs including sertraline remain a recommended first line treatment for PTSD,[12-14] several systematic reviews and meta-analyses have generated mixed opinions about its efficacy. In response, the World Health Organization (WHO) commissioned an update based on information obtained from the most methodologically robust systematic reviews.[12,15,16] A systematic review and meta-analysis of 51 randomized controlled trials assessed the efficacy of sertraline and other pharmacological treatments compared with placebo at reducing traumatic stress symptoms in individuals experiencing PTSD.[1] This analysis found that the effect sizes for pharmacological treatments of PTSD compared with placebo were low and inferior to those reported for psychological treatments.[30] When considered together, SSRIs were found to perform better than placebo at reducing PTSD symptoms, but sertraline efficacy alone was on par with placebo.[1] WHO and other organizations now recommend antidepressants, including sertraline, as a second line of treatment for PTSD when psychological interventions with known efficacy are ineffective or unavailable.[15,16]

Although the WHO-commissioned review[1] does not support the use of sertraline as a first-line treatment for PTSD, the potential benefits of sertraline should not be disregarded. More clinical trials are required that directly compare specific psychological and pharmacological treatments for PTSD to give a better picture of which treatments work best. It is also important to recognize that different therapies may be more effective in different subpopulations of PTSD patients (e.g. veterans versus civilians); future clinical trials should make this distinction. The relative efficacy of therapies in patients with comorbid conditions should also be examined.

Conclusions

Sertraline remains a recommended first- or second-line treatment for PTSD,[12-14] and is considered to be well tolerated and safe. However, a critical review of the literature provides a muddy

picture of its merits. Although numerous trials demonstrate sertraline's efficacy in PTSD patients, clinical trial results are not uniformly applicable to the entire PTSD patient population, and many studies suffer from restrictive sample sizes. The strength of the response to sertraline appears to vary with the complexity of the study population, with the chronicity of PTSD, with previous treatment history, and with the presence of comorbid conditions. Moreover, the maximum benefit from sertraline treatment may depend upon adequate dosages and treatment duration, as well as co-treatment with other therapies. Gene polymorphisms, such as those in the serotonin transporter gene promoter-region, may also influence the therapeutic efficacy of sertraline.[31] All of these factors should be considered in clinical trials going forward if they are to provide a clear picture of sertraline's efficacy for the treatment of PTSD. A better understanding of how to match an individual to a specific treatment will help to maximize the likelihood of treatment success.

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