

# Selective Serotonin Reuptake Inhibitors for Generalized Anxiety Disorder

## **Q.** What are selective serotonin reuptake inhibitors?

**A.** Selective serotonin reuptake inhibitors (SSRIs) are a class of medications used to treat anxiety, depression, and other mood disorders. Two SSRIs are Food and Drug Administration (FDA) approved for the treatment of generalized anxiety disorder (GAD), escitalopram (Lexapro) and paroxetine (Paxil; Kavan & Elsasser, 2009). Other SSRIs, such as sertraline (Zoloft) and fluoxetine (Prozac), are commonly used off-label.

## **Q.** What are the potential mechanisms of action underlying SSRIs?

**A.** The biological basis of GAD is not fully understood, but it is thought that disturbances in neurotransmission of serotonin play a role (Baldwin & Polkinghorn, 2004). Serotonergic neurons are concentrated in areas of the brain associated with anxiety (Nutt, Ballenger, Sheehan, & Wittchen, 2002). Studies have found that levels of a serotonin metabolite are low in GAD patients (Brewerton, Lydiard, & Johnson, 1995), and that anxiety symptoms are exacerbated by administration of a serotonin receptor agonist (Germine et al., 1992). SSRIs bind with high affinity to the serotonin transporter, inhibiting the reuptake of serotonin into the releasing neuron, thus allowing serotonin molecules to remain in the synapse and exert their effects for a longer period of time. The therapeutic effects of SSRIs result from long-term neurochemical adaptations in the brain that lead to increased serotonin-mediated neurotransmission (Blier & Abbott, 2001). Desensitization of serotonin receptors in limbic areas may be responsible for the anxiolytic effects of SSRIs (Gordon & Hen, 2004).

## **Q.** Are SSRIs recommended as a front-line treatment for GAD in the Military Health System (MHS)?

**A.** There is no VA/DoD clinical practice guideline (CPG) on the treatment of GAD.

*The MHS relies on the VA/DoD clinical practice guidelines (CPGs) to inform best clinical practices. However, in the absence of an official VA/DoD recommendation, clinicians should look to CPGs published by other recognized organizations, and may rely on knowledge of the literature and clinical judgement.*

## **Q.** Do other organizations with CPGs for the treatment of GAD recommend SSRIs?

**A.** Yes. CPGs published by other organizations recommend the use of SSRIs for GAD.

- The United Kingdom's National Institute for Health and Care Excellence (NICE) recommends SSRIs as a "Step 3" intervention for GAD (for patients diagnosed with GAD who have not improved after education and active monitoring in primary care, or with marked functional impairment; NICE, 2011).
- The Canadian Psychiatric Association recommends SSRIs as first-line pharmacological agents in the treatment of GAD, rating the level of evidence as "1" for paroxetine and escitalopram, and "2" for sertraline (Canadian Psychiatric Association, 2006).

## **Q.** Do other authoritative reviews recommend SSRIs as a front-line treatment for GAD?

**A.** No. Other authoritative reviews have not substantiated the use of SSRIs for GAD.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- AHRQ: No reports on GAD were identified.
- Cochrane: A 2003 systematic review of antidepressants for GAD was identified, but is out of date (Kapczinski, Lima, Souza, & Schmitt), and its 2016 update was withdrawn (Kapczinski, dos Santos Souza, Batista Miralha de Cunha, & Schmitt). Currently, there is a published protocol for a Cochrane

systematic review on antidepressants versus placebo for GAD (Guaiana, Barbui, & Abouhassan, 2018), but the review has not yet been completed.

**Q.** **Is there any recent research on SSRIs as a treatment for GAD?**

**A.** A number of systematic reviews and meta-analyses of randomized controlled trials have found SSRIs to be an effective treatment for GAD (e.g., Baldwin, Woods, Lawson, & Taylor, 2011; Bandelow et al., 2015; Gomez, Barthel, & Hofmann, 2018). Recent research has focused on the comparative efficacy and tolerability of SSRIs and other treatments for GAD, with mixed findings. A 2011 systematic review and meta-analysis comparing a number of drug treatments for GAD included 27 trials in their analyses, and found that fluoxetine performed most favorably in terms of response and remission, and sertraline ranked first for tolerability (Baldwin et al., 2011). A recent meta-analytic review comparing the efficacy of commonly used pharmacological treatments for GAD included 56 trials and found that, while efficacious, SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) had significantly lower effect sizes than benzodiazepines (Gomez et al., 2018). Potentially biasing these results, a higher proportion of the benzodiazepine trials were published prior to the requirement of company-sponsored drug trials to make negative or null findings public. It is also important to note that benzodiazepines are not recommended for long-term treatment, due to the potential for dependence. Additionally, benzodiazepines do not treat depression, which is commonly comorbid with GAD (Gorman, 2003).

**Q.** **What conclusions can be drawn about the use of SSRIs as a treatment for GAD in the MHS?**

**A.** Based on an established evidence base, SSRIs should be considered a front-line treatment for the treatment of GAD. However, it is unclear which front-line treatments for GAD, including psychotherapy and medications, are more effective for which patients, under which circumstances, and in which combinations. Clinicians should consider several factors when choosing a front-line treatment for their patients. Treatment decisions should take into account practical considerations such as availability and patient preference that might influence treatment engagement and retention.

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