

Q. What are selective serotonin reuptake inhibitors?

A. Selective serotonin reuptake inhibitors (SSRIs) are a class of medications used to treat depression, anxiety, and other mood disorders. A number of SSRIs are Food and Drug Administration (FDA) approved for the treatment of depression, and are marketed as various brand and generic drug names, including fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), escitalopram (Lexapro), and paroxetine (Paxil and Pevea; FDA, 2009).

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

A. Serotonin is a neurotransmitter in the brain that plays an important role in regulating mood. Alterations in serotonin levels have been implicated in depression (Owens & Nemeroff, 1994). 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. This inhibition of serotonin reuptake does not lead to acute antidepressant effects, but instead causes more long-term neurochemical adaptations in the brain (Vaswani, Linda, & Ramesh, 2003).

Q. Are SSRIs recommended as a front-line treatment for major depressive disorder in the Military Health System (MHS)?

A. Yes. The 2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder gives a “Strong For” strength of recommendation for SSRIs as first-line treatment for uncomplicated mild to moderate major depressive disorder (MDD), except fluvoxamine, which has not received FDA approval for the treatment of depression.

The MHS relies on the VA/DoD clinical practice guidelines (CPGs) to inform best clinical practices. The CPGs are developed under the purview of clinical experts and are derived through a transparent and systematic approach that includes, but is not limited to, systematic reviews of the literature on a given topic and development of recommendations using a graded system that takes into account the overall quality of the evidence and the magnitude of the net benefit of the recommendation. A further description of this process and CPGs on specific topics can be found on the VA clinical practice guidelines website.

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

A. Yes. Other authoritative reviews have substantiated the use of SSRIs for MDD. With the status of SSRIs as first-line treatments established, authoritative reports have focused on comparative effectiveness.

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: A 2015 comparative effectiveness review of second-generation antidepressants (SGAs) versus nonpharmacological treatment for depression found that SGAs and cognitive behavioral therapy (CBT) do not differ significantly in their effects on depression symptoms, though they did not report separately on SSRIs (Gartlehner et al., 2015).
- Cochrane: A number of systematic reviews on the comparative effectiveness of different SSRIs versus other anti-depressive agents for depression have been published (Cipriani et al., 2010; Cipriani et al., 2012; Magni et al., 2013; Purgato et al., 2014). Overall, these reviews are conservative in their conclusions, finding that there may be some differences in efficacy between the SSRIs under investigation and other antidepressants, but that methodological issues and potential bias in the included studies limit confidence in these findings.

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

A. The 2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder strongly recommends SSRIs for the treatment of MDD. It remains unclear if certain SSRIs are more efficacious than others, and, if so, for whom. It is also unclear if SSRIs are more effective than evidence-based psychotherapy or other evidence-based pharmacotherapy options for uncomplicated mild to moderate MDD. Clinicians should consider several factors when choosing a front-line treatment for their patient. 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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