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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. Multiple SSRIs are Food and Drug Administration (FDA) approved for the treatment of depression and are marketed under various brand and generic drug names, including fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), escitalopram (Lexapro), and paroxetine (Paxil and Pexeva; 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 treatment for MDD in the Military Health System (MHS)?

A: Yes. The 2022 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder gives a “weak for” strength of recommendation for SSRIs as treatment for uncomplicated mild to moderate major depressive disorder (MDD).

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. Recommendations for or against a treatment may be characterized as strong or weak based on a variety of factors (e.g., confidence in the quality of the evidence, weight of treatment benefits versus risks, feasibility). The CPGs also state if there is insufficient evidence to develop a 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 treatment for MDD?

A: Yes. Other authoritative reviews have substantiated the use of SSRIs for MDD. SSRIs have been established as a treatment, so more recent authoritative reports have focused on comparative effectiveness.

Other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using grading systems similar to the VA/DoD CPGs. Notable among these is Cochrane, an international network that conducts high-quality reviews of healthcare interventions.

- Cochrane: Multiple systematic reviews have been published on the comparative effectiveness of different SSRIs versus other anti-depressive agents for depression (Cipriani et al., 2010; Cipriani et al., 2012; Cipriani et al., 2018; Guaiiana et al., 2013; 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 2022 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder suggests SSRIs for the treatment of MDD. It remains unclear if certain SSRIs are more efficacious than others, and, if so, under what circumstances. 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 an evidence-based treatment for their patients. Treatment decisions should incorporate clinical judgment and expertise, patient characteristics and treatment history, and patient preferences that might influence treatment engagement and retention. For additional guidance on selecting a treatment for MDD, please visit the PHCoE Clinician Resources section of the intranet and navigate to clinical support tools.

References

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., Leucht, S., Ruhe, H. G., Turner, E. H., Higgins, J., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J., & Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet (London, England)*, 391(10128), 1357–1366. [https://doi.org/10.1016/S0140-6736\(17\)32802-7](https://doi.org/10.1016/S0140-6736(17)32802-7)

Cipriani, A., La Ferla, T., Furukawa, T. A., Signoretti, A., Nakagawa, A., Churchill, R., McGuire, H., & Barbui, C. (2009). Sertraline versus other antidepressive agents for depression. *The Cochrane database of systematic reviews*, (2), CD006117. <https://doi.org/10.1002/14651858.CD006117.pub2>

Cipriani, A., Purgato, M., Furukawa, T. A., Trespidi, C., Imperadore, G., Signoretti, A., Churchill, R., Watanabe, N., & Barbui, C. (2012). Citalopram versus other anti-depressive agents for depression. *The Cochrane database of systematic reviews*, 7(7), CD006534. <https://doi.org/10.1002/14651858.CD006534.pub2>

Department of Veterans Affairs/Department of Defense. (2022). VA/DoD clinical practice guideline for management of major depressive disorder. Version 4.0. Washington (DC): Department of Veterans Affairs/Department of Defense.

Guaiana, G., Gupta, S., Chiodo, D., Davies, S. J., Haederle, K., Koesters, M. Agomelatine versus other antidepressive agents for major depression. *Cochrane Database Syst Rev.* 2013 Dec 17;(12):CD008851. doi: 10.1002/14651858.CD008851.pub2. PMID: 24343836.

Magni, L. R., Purgato, M., Gastaldon, C., Papola, D., Furukawa, T. A., Cipriani, A., & Barbui, C. (2013). Fluoxetine versus other types of pharmacotherapy for depression. *Cochrane Database of Systematic Reviews*, 4, CD004185.

Owens, M. J., & Nemeroff, C. B. (1994). Role of serotonin in the pathophysiology of depression: Focus on the serotonin transporter. *Clinical Chemistry*, 40(2), 288–295.

Purgato, M., Papola, D., Gastaldon, C., Trespidi, C., Magni, L. R., Rizzo, C., Furukawa, T. A., Watanabe, N., Cipriani, A., & Barbui, C. (2014). Paroxetine versus other anti-depressive agents for depression. *The Cochrane database of systematic reviews*, 2014(4), CD006531. <https://doi.org/10.1002/14651858.CD006531.pub2>

U.S. Food and Drug Administration. (2009). Medicines to help you: Depression. Retrieved from <https://www.fda.gov/downloads/forconsumers/byaudience/forwomen/freepublications/ucm182083.pdf>

Vaswani, M., Linda, F. K., & Ramesh, S. (2003). Role of selective serotonin reuptake inhibitors in psychiatric disorders: A comprehensive review. *Progress in Neuropsychopharmacology & Biological Psychiatry*, 27(1), 85–102.