Selective Serotonin Reuptake Inhibitors for Generalized Anxiety Disorder

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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 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 (Strawn et al., 2018). Serotonergic neurons are concentrated in areas of the brain associated with anxiety and studies have found that levels of a serotonin metabolite are low in GAD patients. An early study indicated that anxiety symptoms were 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 (Strawn et al., 2018). 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 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 CPGs to inform best clinical practices. In the absence of an official VA/DOD recommendation, clinicians should look to CPGs and authoritative reviews published by other recognized organizations and may rely on knowledge of the literature and clinical judgement.

Q: Do other authoritative reviews recommend SSRIs as a treatment for GAD?

A: Yes. CPGs and authoritative reviews published by other organizations recommend the use of SSRIs for GAD.

Other recognized organizations publish CPGs or conduct systematic reviews and evidence syntheses on psychological health topics using grading systems similar to the VA/DOD CPGs. These include the American Psychiatric Association, American Psychological Association, and the United Kingdom's National Institute for Health and Care Excellence. Additionally, Cochrane is an international network that conducts high-quality reviews of health care interventions.

- United Kingdom's National Institute for Health and Care Excellence (NICE): SSRIs are considered a "step 3" intervention that should be pursued if the patient is experiencing marked functional

impairment and/or has not responded to step 2 interventions (e.g., guided self-help, psychoeducational group). Sertraline was noted as a preferred SSRI due to its cost effectiveness (NICE, 2011).

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

A: Historically, systematic reviews and meta-analyses of randomized controlled trials have found SSRIs to be an effective treatment for GAD (e.g., Baldwin et al., 2011; Bandelow et al., 2015; Gomez et al., 2018). Recent research has compared the efficacy of different pharmacological interventions. Chen et al. (2019) performed a network meta-analysis, comparing different pharmacotherapies and psychological interventions for GAD. SSRIs were the third-most efficacious treatment (bupropion and mirtazapine were ranked first and second), but the authors indicated that the evidence for SSRIs was stronger due to the greater number of studies and patients represented. He et al. (2019) performed a network meta-analysis to compare the efficacy of the most common SSRIs and SNRIs to one another. Of the SSRIs, fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and escitalopram were included. All SSRIs were more efficacious than placebo, though paroxetine was worse than placebo in terms of acceptability and fluoxetine was worse than placebo in terms of response rate. Sertraline and fluoxetine were the only SSRIs associated with lower drop-out rates than placebo. Head-to-head comparisons showed no difference between individual SSRIs. Similarly, Kong et al. (2020) performed a network meta-analysis comparing the remission rates and tolerability of pharmacotherapies used in the treatment of GAD, including SSRIs, SNRIs, atypical antipsychotics, and anticonvulsants. Of the SSRIs, escitalopram and paroxetine were superior to placebo in terms of remission rate. For tolerability, sertraline was comparable to placebo but nearly all other medications were worse than placebo. In head-to-head comparisons, no differences were found between individual SSRIs. Finally, the meta-analysis completed by Gomez et al. (2018) compared the efficacy of classes of drugs – namely, SSRIs, SNRIs, and benzodiazepines – and found that SSRIs had the lowest effect size and benzodiazepines the highest. Moderator analyses indicated that these differences were not due to factors other than drug class (e.g., length of treatment, publication year). The authors acknowledged that benzodiazepines are not recommended for long-term treatment of GAD and recommended a combination of SSRIs and benzodiazepines when initiating pharmacotherapy followed by a taper of the benzodiazepine within one to two months.

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

A: The evidence continues to support SSRIs as an efficacious treatment for GAD, particularly for long-term management. Recent literature has shown that there may be some differences between SSRIs and placebo in terms of acceptability, tolerability, response rate, and remission rate, but no differences were found between individual SSRIs. Authoritative reviews support the use of either pharmacotherapy or psychological intervention as a treatment for GAD. Thus, when choosing a treatment for GAD, clinicians

should take into account several factors to enhance patient response and retention, including clinician competence, patient preference, and treatment availability.

References

Baldwin, D., Woods, R., Lawson, R., & Taylor, D. (2011). Efficacy of drug treatments for generalised anxiety disorder: Systematic review and meta-analysis. *BMJ, 342*, d1199. https://doi.org/10.1136/bmj.d1718

Bandelow, B., Reitt, M., Rover, C., Michaelis, S., Gorlich, Y., & Wedekind, D. (2015). Efficacy of treatments for anxiety disorders: A meta-analysis. *International Clinical Psychopharmacology, 30*(4), 183–192. https://doi.org/10.1097/YIC.0000000000000078

Chen, T., Huang, H., Hsu, J., Ouyang, W., & Lin, K. (2019). Pharmacological and psychological interventions for generalized anxiety disorder in adults: A network meta-analysis. *Journal of Psychiatric Research, 118*, 73-83. https://doi.org/10.1016/j.jpsychires.2019.02.014

Germine, M., Goddard, A. W., Woods, S. W., Charney, D. S., & Heninger, G. R. (1992). Anger and anxiety responses to m-Chlorophenylpiperazine in generalized anxiety disorder. *Biological Psychiatry, 32*, 457–461. https://doi.org/10.1016/0006-3223(92)90133-k

Gomez, A. F., Barthel, A. L., & Hofmann, S. G. (2018). Comparing the efficacy of benzodiazepines and serotonergic anti-depressants for adults with generalized anxiety disorder: A meta-analytic review. *Expert Opinion on Pharmacotherapy, 19*(8), 883–894. https://doi.org/10.1080/14656566.2018.1472767

Gordon, J. A., & Hen, R. (2004). The serotonergic system and anxiety. *Neuromolecular Medicine, 5*(1), 27–40. https://doi.org/10.1385/NMM:5:1:027

He, H., Yiang, Y., Gao, F., Bai, L., Gao, F., Fan, Y., Lyu, J., & Ma, X. (2019). Comparative efficacy and acceptability of first-line drugs for the acute treatment of generalized anxiety disorder in adults: A network meta-analysis. *Journal of Psychiatric Research, 118*, 21-30. https://doi.org/10.1016/j.jpsychires.2019.08.009

Kavan, M. G., & Elsasser, G. N. (2009). Generalized anxiety disorder: Practical assessment and management. *American Family Physician, 79*(9), 785–791.

Kong, W., Deng, H., Wan, J., Zhou, Y., Zhou, Y., Song, B., & Wang, X. (2020). Comparative remission rates and tolerability of drugs for generalized anxiety disorder: A systematic review and network meta-analysis of double-blind randomized controlled trials. *Frontiers in Pharmacology, 11*. https://doi.org/10.3389/fphar.2020.580858

National Institute for Health and Care Excellence (NICE). (2011). *Generalised anxiety disorder and panic disorder in adults: Management* (National clinical guideline number 113). London: The Royal College of Psychiatrists.

Nutt, D. J., Ballenger, J. C., Sheehan, D., & Wittchen, H. U. (2002). Generalized anxiety disorder: Comorbidity, comparative biology and treatment. *International Journal of Neuropsychopharmacology, 5*(4), 315–325. https://doi.org/10.1017/S1461145702003048

Strawn, J. R., Geracioti, L., Rajdev, N., Clemenza, K., & Levine, A. (2018). Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: An evidence-based treatment review. *Expert Opinion on Pharmacotherapy, 19*(10), 1057–1070. https://doi.org/10.1080/14656566.2018.1491966