# Indian Health Service
# National Pharmacy and Therapeutics Committee
## Formulary Brief: ***Selective Serotonin Reuptake Inhibitors (SSRIs)***
-July 2019-

**Background:**

In July 2019, the IHS National Pharmacy & Therapeutics Committee (NPTC) discussed the medication class of Selective Serotonin Reuptake Inhibitors (SSRIs) for the treatment of depression and anxiety. Prior to the review, the National Core Formulary (NCF) included two SSRIs, fluoxetine and sertraline. Based on the clinical data, IHS procurement and utilization trends, and pharmacoeconomic analysis, the NPTC voted to **add (1) citalopram, (2) escitalopram, and (3) paroxetine to the NCF**.

Depression and anxiety are highly prevalent mental health disorders in the United States (US), particularly among American Indians and Alaska Natives (AI/AN). Between 2009-2012, 7.6% of people 12 and older had depression during any given 2-week period, and there were 44,965 deaths by suicide in 2016 alone.[1-3] Between 2009-2013, suicide rate was higher in AI/AN than any other ethnic/racial group for both males and females, and AI/AN males were more than twice as likely to commit suicide than most other sexes, racial, and ethnic subgroups.[4] Meanwhile, the lifetime prevalence of anxiety in the US is 5.1-11.9% and is approximately 2 times more common in women than men.[5]

**Discussion:**

Depression is a mood disorder characterized by ongoing feelings of sadness and a loss of interest in activities previously found enjoyable, lasting at least 2 weeks and interfering with daily activities. It can contribute to numerous emotional, physical, and social problems. Symptoms may include reduced mood, anhedonia, fatigue, hopelessness, guilt, anger, sleep changes, poor concentration, irritability, altered appetite, thoughts of death or suicide, and suicide attempts and/or completions. Generalized Anxiety Disorder involves difficult to control, ongoing, significant worry that impairs important social responsibilities and/or daily life activities. It is experienced on more days than not over a 6 month period and often coexists with other mood or substance use disorders. Symptoms may include disproportionate worry or anxiety, indecisiveness, difficulty relaxing, poor concentration, sleep issues, unexplained pain or digestive issues, and irritability. The causes of depression and anxiety are not entirely understood, but likely include a combination of genetic predisposition, physical brain changes, changes in neurotransmitter activity in the brain, hormonal changes, as well as personality and developmental factors. In both depression and anxiety, patients often present with physical manifestations, leading to misdiagnosis and delayed treatment.[6]

Management options for depression and anxiety include both non-pharmacologic treatments (psychotherapy) and medication therapy. The SSRI class of medications (including citalopram, escitalopram, fluoxetine, sertraline, paroxetine and fluvoxamine) are generally considered first-line agents and are commonly used in treating both depression and anxiety. Other options include serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, serotonin modulators, tricyclic and tetracyclic antidepressants, monoamine oxidase inhibitors, buspirone, pregabalin, hydroxyzine, benzodiazepines, and antipsychotic medications.[1,2,6,7]

SSRIs act by increasing serotonergic activity. Serotonin (5-HT) is a neurotransmitter released by raphe nuclei in the brainstem. SSRIs have affinity for 5-HT receptors, decreasing the activity of the presynaptic (5-HT) reuptake pump by as much as 80%. This does not fully explain treatment benefits, and there tends to be a delayed response of full therapeutic effects. All SSRIs have similar efficacy overall in treating depression, though vary somewhat in treating anxiety. Treatment goals are response (at least a 50% improvement in symptoms) and remission (a depression rating scale score within the defined normal range). Possible side effects are numerous, including anticholinergic effects, drowsiness, insomnia, orthostatic hypotension, QTc prolongation, gastrointestinal issues, weight gain, and sexual dysfunction.[8,9] In 2004, the FDA required all antidepressant labeling to include a Black Box Warning regarding the risks in children and adolescents of suicidality. In 2007, the FDA expanded the warning to include adults younger than 25. Prescribers are required to counsel patients and family about this possible risk of suicidality, and patients should be given a MedGuide by pharmacy for each new prescription and refill.[10]

In 2015, the Agency for Healthcare Research and Quality conducted a network meta-analysis reviewing and comparing 2nd generation antidepressants (i.e., SSRIs, SNRIs, atypical antidepressants, serotonin modulators) to Cognitive Behavioral Therapy (CBT). Authors found that 2nd generation antidepressants and CBT are not significantly different as first-line treatment in relieving symptoms of moderate to severe Major Depressive Disorder, but that 2nd generation antidepressants tended to have a higher rate of adverse events than CBT.[11]

A 2019 Cochrane Review evaluated the relapse and recurrence rates of depression in patients treated with placebo or an alternative (most commonly, an antidepressant). Some studies were very small, but participants on antidepressants had significantly fewer relapses or recurrences compared to placebo (Number Needed to Treat = 6), and there were no significant differences in dropout rates.[12]

A 2018 meta-analysis compared SSRIs, SNRIs, or benzodiazepines with placebo for improvement on the Hamilton Anxiety Scale. Pharmacotherapy was found to be significantly more effective than placebo in reducing symptoms, but efficacy results decreased significantly over time.[13]

=*Guidelines*=
The 2016 VA/DoD Guidelines for depression recommend either psychotherapy or pharmacotherapy (SSRIs, SNRIs, mirtazapine, or bupropion) depending on patient preference, history of prior response, comorbidities, safety/side effect profile, and cost.[14] Similarly, the 2016 American College of Physicians guideline also recommends treating depression with either CBT or a second-generation antidepressant.[15] The 2018 British National Institute for Health and Care Excellence (NICE) guideline suggests a combination of pharmacotherapy and psychotherapy to treat moderate or severe depression.[16]

For the treatment of anxiety, the 2011 NICE Guidelines (updated in 2018) recommend that if pharmacologic treatment is chosen, a SSRI should be considered as first-line therapy and that benzodiazepines should only be utilized for short crisis periods.[17]

**Findings:**
Depression and anxiety are highly prevalent conditions with numerous pharmacological options available in addition to psychotherapy. SSRIs are reasonable first-line treatment options for both depression and anxiety. While individual SSRIs are generally considered equivalent in treating depression, treatment response may vary significantly depending on the individual. Based on these considerations and current IHS procurement/usage patterns, the NPTC voted to **add (1) citalopram, (2) escitalopram, and (3) paroxetine to the NCF**.

---

*If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.*

**References:**


1. Depression (major depressive disorder).” MayoClinic.com, Feb 3, 2018.
2. Unipolar depression in adults: Antidepressant doses.” UpToDate, Dec 2018
3. US Centers for Disease Control and Prevention. Depression. Available at CDC.gov, Oct 6, 2016.
4. US Centers for Disease Control and Prevention. Racial and Gender Disparities in Suicide Among Young Adults Aged 18–24: United States, 2009–2013.Available at CDC.gov, Sept 30, 2015.
5. Pharmacotherapy for generalized anxiety disorder in adults. UpToDate, Aug 31, 2018
6. Depression Overview Slideshow.” WebMD, Reviewed by Ratini, Melinda, July 03, 2018.
7. Generalized anxiety disorder.” MayoClinic.com, Oct 13, 2017.
8. Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects. UpToDate, Jan 31, 2018,
9. Unipolar major depression in adults: Choosing initial treatment.” UpToDate, Nov 12, 2017.
10. Effect of antidepressants on suicide risk in children and adolescents.” UpToDate, Nov 20, 2018
11. Gartlehner G, Gaynes BN, Amick HR, et al. Non-pharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder. *Agency for Healthcare Research and Quality*, Publication No. 15(16)-EHC031-EF, Dec 2015.
12. Machmutow K, Meister R, Jansen A, et al. Comparative effectiveness of continuation and maintenance treatments for persistent depressive disorder in adults (Review). *Cochrane Database Syst Rev* 2019, Issue 5. Art. No.: CD012855.
13. Gomez A, Barthel A, Hofmann S. Comparing the efficacy of benzodiazepines and serotonergic anti-depressants for adults with generalized anxiety disorder: a meta-analytic review. *Expert Opinion on Pharmacotherapy*. 2018; 19(8):883-894.
14. Department of Veterans Affairs/Department of Defense. Clinical Practice Guideline for the Management of Major Depressive Disorder. Version 3.0, April 2016.
15. Qaseem A, Barry MJ, Kansagara D. Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With Major Depressive Disorder. *Ann Intern Med* 2016; 164(5):350-359.
16. National Institute for Health and Care Excellence. Depression in adults: recognition and management. Clinical Guideline, 2018.
17. National Institute for Health and Care Excellence. Generalized anxiety disorder and panic disorder in adults: management. Clinical Guideline, updated 2018.