Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***SNRIs in Depression and Anxiety***
-July 2019-

Background:

In July 2019, the National Pharmacy and Therapeutics Committee (NPTC) reviewed the currently available Serotonin/Norepinephrine Reuptake Inhibitors (SNRI) for the treatment of depression and/or anxiety to determine if changes to the National Core Formulary were warranted. The IHS National Core Formulary currently lists both duloxetine and venlafaxine as available SNRI formulary agents. Following the NPTC clinical and pharmacoeconomic analyses, **no modifications were made to the National Core Formulary.**

Discussion:

Depression is categorized as a mood disorder lasting ≥ 2 weeks with changes in feelings, thoughts, and daily activities. Nearly half of individuals diagnosed with depression are also diagnosed with some form of anxiety. Risk factors for depression include a prior personal or family history of depression, major life changes, illness, or use of certain medications.[1] According to the National Institute of Mental Health, an estimated 17.3 million adults in the United States (7.1% of all US adults) had a least one major depressive episode in 2017. The prevalence of major depressive episodes was highest among American Indian/Alaska Native individuals (8%) and those persons reporting two or more races (11.3%).[2] Similar to other causes, American Indians and Alaska Natives (AI/AN) experience higher rates of mortality due to suicide than other Americans. The AI/AN mortality rate between 2009 – 2011 was 20.4 per 100,000 people as compared to 12.1 per 100,000 people for all United States race rates in 2010 (ratio – AI/AN to US all races: 1.7).[3]

Pharmacotherapy is the main intervention for patients with major depressive disorder (MDD) in primary care settings, as well as one of two first line treatment options (along with psychotherapy) for the management of anxiety.[4] The selection of a second generation antidepressant is largely based on side effects, cost, tolerability, safety, potential drug interactions, and the pharmacodynamics of the drug.[5] The goal of therapy is a ≥ 50% reduction in depression severity using a validated rating scale as well as remission associated with better functioning and a lower likelihood of relapse.[6,7]

There are currently four FDA approved SNRI agents for the treatment of depression. These agents include venlafaxine, desvenlafaxine, duloxetine and levomilnacipran. Of these agents, venlafaxine and duloxetine are also FDA approved for the treatment of anxiety. While duloxetine has a FDA indication for use in Generalized Anxiety Disorder, venlafaxine is the only SNRI currently approved for use in multiple types of anxiety disorders, including panic disorder and social anxiety disorder. Of note, duloxetine is the only approved SNRI indicated for use in the pediatric population.[8]

A 2009 meta-analysis compared the efficacy and acceptability of 12 new-generation antidepressants.[9] The evaluation reviewed 117 randomized clinical trials with antidepressants at therapeutic doses (N=25,928) and included clinical trials of the specific SNRI agents, venlafaxine and duloxetine. Outcomes included either a ≥50% symptom reduction following 8 weeks of treatment as demonstrated using either the Hamilton Rating Scale for Depression or the Montgomery-Asberg Depression Rating Scale, or improved score rankings on the Clinical Global Impression Scale. Acceptability (treatment discontinuation) was also included as a primary outcome studied. When directly comparing the two SNRIs, venlafaxine was found to be statistically more efficacious than duloxetine (OR: 0.77, 0.60-0.99). Acceptability favored venlafaxine, although these results were not statistically significant (OR: 1.12, 0.84-1.50). The authors concluded that venlafaxine was among the four most efficacious treatments studied.

A 2018 meta-analysis compared the efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with MDD.[10] This study reviewed 522 double-blind, parallel, randomized controlled trials and included clinical trials evaluating the SNRI agents- venlafaxine, desvenlafaxine, levomilnacipran, and duloxetine. Study outcomes included a ≥50% reduction in score for adult patients with primary diagnosis of MDD according to either the Feighner criteria, the Research Diagnostic Criteria,

the Diagnostic and Statistical Manual of Mental Disorders 3-5, or the International Classification of Disease-10 and ranged from 4 to 12 weeks of treatment. The authors concluded that all four SNRIs were significantly more efficacious than placebo (venlafaxine OR: 1.78, 1.61 to 1.96; desvenlafaxine OR: 1.49, 1.24 to 1.79; duloxetine OR: 1.85, 1.66 to 2.07; and levomilnacipran OR: 1.59, 1.24 to 2.05) with no differences noted in patients tolerating any of the active treatments over placebo (venlafaxine OR: 1.04, 0.93 to 1.15; desvenlafaxine OR: 1.08, 0.88 to 1.33; duloxetine 1.09, 0.96 to 1.23 and levomilnacipran 1.19, 0.93 to 1.53). Direct comparisons of duloxetine to venlafaxine found no differences in efficacy (OR: 0.96, 0.77 to 1.20). Acceptability findings also showed no difference in patients tolerating either venlafaxine or duloxetine (OR: 1.18, 0.92 to 1.49). Desvenlafaxine and levomilnacipran were not included due to lack of available head-to-head trials that met inclusion criteria.

The 2018 clinical practice review for Generalized Anxiety Disorder from the Anxiety and Depression Association of America recommends the SNRI agents, venlafaxine or duloxetine, as possible first-line pharmacotherapy (equally along with paroxetine or escitalopram) for anxiety.[11] The 2016 joint clinical practice guidelines from the Department of Veterans Affairs and Department of Defense recommend evidence-based pharmacotherapy, including SNRIs (although no specific SNRI agents were named), for the treatment of mild to moderate major depressive disorder.[12]

Findings:

Serotonin/Norepinephrine Reuptake Inhibitor agents remain a guideline-supported, first-line staple in the management of both depression and anxiety. Evidence from published literature, guidelines and internal pharmacoeconomic analyses offers a value-based decisional opportunity which supports the retention of the currently named SNRI agents, duloxetine and venlafaxine, on the IHS National Core Formulary.

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.

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