INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Anxiety Disorders*
-August 2021-

Background:

In August 2021, the Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed medications used to treat Generalized Anxiety Disorder (GAD) and Panic Disorder (PD). Based on current guidelines, the committee reviewed medication classes including the Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), second-generation antipsychotics, benzodiazepines, and hydroxyzine. Following the comprehensive clinical review, the **NPTC voted to ADD hydroxyzine to the National Core Formulary.**

The median age of onset for anxiety disorders in the United States is between 6 and 7 years old[1] with a life-time prevalence of 21%.[2] Patients with anxiety disorders have a higher prevalence of hypertension and other cardiovascular conditions, gastrointestinal disease, arthritis, thyroid disease, respiratory disease, migraine headaches, and allergic conditions compared to those without anxiety disorders.[3] Children and adolescents with anxiety disorders are more likely to experience suicidal ideation and to attempt suicide than unaffected youth.[4] However studies show that 40% of patients with an anxiety diagnosis are left untreated.[3]

The ability to detect anxiety symptoms in patients presenting in an outpatient setting offers a pathway to treatment. Assessing and treating anxiety has particular utility in pediatric patients as it can decrease chances of developing comorbidities later in life. General screening questions can be employed in an outpatient setting. For pediatric patients, the Screen for Child Anxiety Related Disorder is recommended for use in an outpatient setting.[11] In adult patients, the GAD-7 screening tool is a validated diagnostic tool and severity assessment scale useful for detecting GAD.[9,12]

Discussion:

Generalized Anxiety Disorder is characterized by extreme anxiety and apprehensive anticipation of certain events or activities causing clinically significant impairment in social, work or other activities of daily life with a duration of at least 6 months.[5] The anxiety and worry are accompanied by at least three (or more) of the following symptoms (for children, only one symptom is needed): 1) restlessness or feeling on edge, 2) being easily fatigued, 3) difficulty concentrating or mind going blank, 4) irritability, 5) muscle tension, and/or 6) sleep disturbance.[5]

First-line management of GAD includes Cognitive Behavioral Therapy (CBT) and psychopharmacotherapy.[3,6,7,8] The SSRIs, including escitalopram, paroxetine, and sertraline, are considered first-line.[3,6,7,8] The SNRIs, such as venlafaxine and duloxetine are considered alternatives to SSRIs.[3,6,7,8] Other options include buspirone[6,8], hydroxyzine[6,8], pregabalin[3,8].

Second-Generation Antipsychotics (SGA): A 2010 Cochrane review of 11 randomized, double-blind trials comparing SGA monotherapy vs. placebo, or antidepressant, or benzodiazepine in adults with a diagnosis of PD, GAD, and specific phobias concluded that efficacy of quetiapine appears similar to doses in the lower range of SSRIs, but side effects (sedation and weight gain) limited quetiapine use in GAD. With SGA vs. placebo: extrapyramidal side effects (N = 2262, OR = 1.80, 95% CI: 1.12 to 2.90); weight gain (N = 2201, Mean Difference = 0.63 kg, 95% CI: 0.40 to 0.86), more sedation (24.5% vs. 6.7%).

Benzodiazepines (BZDs): In 2018, a meta-analysis of 56 randomized, placebo-controlled trials (RCTs) spanning 3 decades examined SSRIs, SNRIs, and BZDs on improvement in anxiety scale ratings in adult patients with GAD.[15] The meta-analysis showed a significant effect size (i.e., magnitude of difference between groups) based on drug class (p=0.004). The SSRIs had slightly lower effect size compared to SNRIs whereas BZDs had the highest effect size. The author concluded that BZDs were more efficacious in decreasing GAD symptoms. However, the utility of BZDs was seen in the context as short-term adjuncts to SSRIs or SNRIs during the initial 4-8 weeks of treatment initiation; beyond this time period, BZDs should be tapered and used only as needed.

Panic Disorder (PD) is characterized by an acute surge of intense fear or discomfort that peaks in minutes of which in that period of time at least four (or more) of the following symptoms occur: 1) palpitations, 2) sweating, 3) shaking, 4) feelings of being smothered or shortness of breath, 5) choking feeling, 6) chest pain/discomfort, 7) nausea or abdominal distress, 8) dizziness, 9) chills or heat sensations, 10) numbness or tingling sensation, 11) feelings of unreality or being detached from oneself, 12) fear of losing control, 13) fear of dying.[5] In addition, at least one of the panic attacks is followed by one month or more of one or both of the following: 1) Persistent concern or worry about additional panic attacks or the consequences of a panic attack, 2) A significant maladaptive change in behavior related to the attacks that is designed to avoid incurring another panic attack.[5] Part of the diagnosis of PD is ruling out other causes to such physiological effects felt during a panic attack such as substance abuse or use (e.g., caffeine), medications (e.g., albuterol, levothyroxine) or medical conditions (e.g., cardiopulmonary disease, transient ischemic attacks).[5,9]

First-line management of PD includes CBT and psychopharmacotherapy.[3,6] SSRIs are considered first-line medications. The SNRI, venlafaxine XR, is an alternative to SSRIs.[3,6] The British Association for Psychopharmacology also considers BZDs (alprazolam, clonazepam, diazepam, lorazepam), tricyclic antidepressants (TCAs) such as clomipramine and imipramine, buspirone and hydroxyzine as therapeutic alternatives if patients are not responsive to SSRIs and SNRIs.[6] In a 2016 Cochrane review, 35 RCTs were profiled to determine if adults with a primary diagnosis of PD with or without agoraphobia improved after 2-6 months with treatment of either an antidepressant or BZD vs. an antidepressant or BZD.[16] Agoraphobia is the fear of certain situations such as open or enclosed spaces, as well as crowds which may cause the person to feel overwhelmed or unable to escape leading to a panic attack.[6] Authors concluded that there was low quality evidence which failed to find any difference between antidepressants and BZDs on efficacy. There was no difference between antidepressants and BZD on efficacy on panic symptoms or frequency of panic attacks. However, BZDs were better tolerated than SSRIs and TCAs.

In a 2010 Cochrane review, Guaiana et al. performed a meta-analysis of five RCTs of hydroxyzine for GAD.[17] Authors found insufficient data to recommend hydroxyzine as a first-line treatment. Psychiatric field subject matter experts however suggest there may be potential utility as a short-term adjunct therapy for insomnia in patients starting SSRIs.

Considerations for Special Populations:

- **Elderly-** Consider avoiding citalopram in the elderly especially those with a history of cardiovascular disease due to its ability to prolong QTc intervals in doses >40 mg/day. Escitalopram has a much lesser effect on QTc than citalopram.[8] Paroxetine should be avoided as well due to its anticholinergic, sedating, and orthostatic hypotension adverse effects.[8] Hydroxyzine meets BEERS criteria and its use should be avoided in elderly.
- **Pregnancy-** According to experts in the field of reproductive psychiatry, treatment consideration is a collaborative effort between clinician and patient.[13] SSRIs with the most data in pregnant women are sertraline, escitalopram and citalopram.[8] The general consensus is to avoid using paroxetine in women who are pregnant as it has been associated with fetal heart defects and has a Category D pregnancy classification.[8]
- **Pediatrics-** In pediatric patients, depending on the severity of the anxiety disorder, CBT is considered first-line therapy.[10] Low dose SSRIs such as fluoxetine or sertraline can be considered in severe cases of anxiety.[10] A 2016 RCT by Dobson et al. reported that SSRIs and SNRIs were efficacious and well-tolerated overall.[4] When SSRIs were compared, sertraline showed a lower risk of GI side effects (NNH = 29) than fluoxetine (NNH = 4). For the SNRIs, venlafaxine XR (NNH = 11) had lower GI side effects than duloxetine (NNH = 7). Sertraline also had lower risk of being activating (NNH = 24) compared to fluoxetine (NNH = 13). The Numbers Needed to Treat (NNT) for fluoxetine (NNT = 6) and sertraline (NNT = 6) were similar in remission as shown by a Pediatric Anxiety Rating Scale after 4 to 12 weeks of treatment. When compared to placebo, duloxetine (NNT= 3) had a better remission rates than venlafaxine XR (NNT = 9). When CBT was added, the Clinical Global Impression-Improvement score improved greatly compared to SSRI monotherapy. Of special interest to clinicians, the Anxiety Algorithm for Pediatrics (page 34) may be useful for outpatient providers in treating anxiety in young patients.[10]

Findings:

- SSRIs remain a guideline supported, first-line treatment in the management of anxiety.
- Evidence from published literature and guidelines supports the retention of the currently named SSRI agents (i.e., citalopram, escitalopram, fluoxetine, paroxetine, sertraline) and SNRI agents duloxetine and venlafaxine on the IHS National Core Formulary.
- **Benzodiazepines are not first-line treatment for anxiety**. However, short-term use as an adjunct to SSRI or SNRI therapies may be useful in patients without a history of substance abuse.
- Hydroxyzine may have utility in mitigating the activating side effects of SSRIs and may be considered as adjunct therapy for anxiety.

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