Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Migraine Prevention***

-November 2019-

Background:

In November 2019, the IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed medications used for migraine prevention, specifically the calcitonin gene-related peptide (CGRP) antagonists and botulinum toxins. The National Core Formulary contains the following medications commonly used for migraine prophylaxis; amitriptyline, atenolol, divalproex, metoprolol, propranolol, topiramate, and venlafaxine. After evaluating current treatment guidelines, applicable literature and agency procurement/utilization data, **no modifications were made to the National Core Formulary**.

Discussion:

Migraine headache is exceedingly common, affecting approximately 12% of the U.S. adult population, with women affected at least 3 times more than men[1]. The World Health Organization in the Global Burden of Disease Study ranks migraine as the second most disabling neurologic conditions globally in terms of years lost to disability[2]. In 2018, a systematic review of three population-based U.S. government surveys found that prevalence of "migraine and severe headache" was highest in American Indian and/or Alaska Natives[3].

Migraine is characterized by an underlying state of increased responsiveness that amplifies the intensity of sensory stimuli ("sensory sensitization"). The somatosensory function of CGRP has been implicated in the development of neuronal sensitization and pain generation, most notably in migraine[4-5]. In 2018, three CGRP antagonists were FDA-approved for the use of chronic/episodic migraine. These novel migraine prophylactic medications offer the convenience of self-administering monthly (or every 12-week) subcutaneous injections and may improve medication adherence and compliance.

=CGRP antagonists=

A 2018 meta-analysis from the independent, non-partisan Institute for Clinical and Economic Review (ICER) meta-analyzed evidence of the safety, clinical effectiveness, and tolerability of the CGRP antagonists in comparison with no preventive treatment or commonly-used preventive therapies in adults with chronic or episodic migraine[6].

For *chronic* migraine, the ICER Report synthesized the individual trial results[7-9] and overall found there were greater reductions in monthly migraine days, monthly headache days, and days using acute medication per month for all interventions versus placebo. Results comparing CGRP antagonists to active therapies were not statistically different. For *episodic* migraine, the ICER Report including eight randomized, placebo-controlled trials (RCTs) of CGRP antagonists assessing erenumab, fremanezumab, and galcanezumab and 10 trials evaluating other oral preventive therapies (e.g., amitriptyline, propranolol, topiramate). The analysis synthesized individual trial results[10-16] and found that overall, there were greater reductions in monthly migraine days, higher odds of a 50% response, and greater reductions in days using acute medication per month for all CGRP antagonists versus placebo. Results comparing CGRP antagonists to oral preventive therapies were again not statistically different. Across CGRP antagonist trials, the most commonly reported adverse events were injection site-related in up to 30% of patients however, in general, CGRP antagonists have similar or improved tolerability to conventional oral anti-migraine therapies. Trial data showed that some patients developed neutralizing antibodies after administration but the rate was low and no efficacy or safety concerns were identified in these patients. In summary, the ICER Report found that the currently available trials of erenumab, fremanezumab, and galcanezumab show treatment benefits for episodic/chronic migraines with few harms. Of note, these outcome trials were limited however to 12 or 24 weeks in duration and there remains uncertainty in any durability of effect and/or adverse events from prolonged use.

Another meta-analysis published in 2018 reviewed episodic migraine in eight RCTs (n=2292) of erenumab, fremanezumab, galcanezumab and also eptinezumab (currently unapproved)[17]. The primary endpoint was reduction in monthly migraine days. Pooled mean reduction in monthly migraine days was -1.52; 95% CI: -1.92 to -1.11, $p<0.001$.

=Botulinum toxins=

Onabotulinum toxin A (Botox®) was FDA approved in 2010 for the treatment of chronic migraine, primarily based on two phase 3 placebo-controlled, multicenter studies[18]. The Cochrane Database published a meta-analysis in 2018 whereby the primary outcome assessed the reduction in number of migraine days per month[19]. Twenty-three trials were included which compared botulinum toxin type A with placebo. The authors concluded that, in chronic migraine, botulinum toxin type A may reduce the number of migraine days per month by ~2 days (95% CI: -2.8 to -1.1, 2 trials, 1384 participants; moderate-quality evidence) compared with placebo treatment. A single trial of patients with *episodic* migraine (n=418) showed no difference between groups for this outcome measure (p=0.49). Non-serious adverse events were estimated to be experienced by 60% of study participants in the treated group compared with 47% in the placebo group. For patients with *episodic* migraine, the authors remain uncertain whether this treatment is effective because the quality of the (limited) evidence is very low.

A meta-analysis published in 2019 reviewed 17 trials of botulinum toxin type A use (n=3646) in both episodic and chronic migraine patients[20]. The primary endpoint was change in number of headache episodes per month from baseline to three months. Although the mean change in migraine frequency overall (both episodic and chronic) was not different from placebo, for chronic migraine sufferers specifically, the results showed a significant reduction in migraine frequency of -1.56 (95% CI: -3.05 to -0.07, p=0.004). Improvements in quality of life at 3 months were significant (p<0.00001) for the botulinum toxin group. Adverse events were more common in the botulinum toxin group but none were severe and all were reported as mild in severity, transient and resolved without sequelae.

=Guidelines=

The American Academy of Neurology and the American Headache Society published a guideline update on botulinum neurotoxin use in 2016 which noted that onabotulinum toxin A (Botox®) should be offered as an option to patients with chronic migraine to increase the number of headache-free days (Level A); it should also be considered to reduce headache impact on health-related quality of life (Level B) [21].

Guidance from the Department of Veterans Affairs (VA) as of 2013 recommends onabotulinum toxin A (Botox®) for chronic migraine prophylaxis for patients who demonstrate no therapeutic response to other prophylactic agents[22]. Current VA guidance for CGRP antagonists require a neurologist or designated headache or TBI expert to prescribe[23]. For episodic migraine, four different medications must be trialed initially for 3 months unless intolerance occurs or contraindications exist. For chronic migraines, again unless contraindications exist, step therapy (including a trial of one beta blocker and two antiepileptic agents) is also required prior to prescribing onabotulinum toxin A.

International guidelines available for review on the use of CGRP antagonists and/or botulinum toxins include the (1) Scottish Intercollegiate Guidelines[24]; (2) the British Association for the Study of Headache Guidelines[25]; and (3) European Headache Federation Guideline[26-27].

The American Headache Society published their position statement in 2019 on the use of new migraine treatments including guidance for both CGRP antagonists and botulinum toxins[28]. The position statement offers specific criteria for identifying patients for preventive treatment (Table 2), evidence of treatment-specific efficacy in migraine prevention (Table 4) and indications for initiating treatment with CGRP antagonists (Table 5).

Findings:

In summary, migraine headache is very common and especially prevalent in American Indian/Alaskan Natives. It is estimated that ~40% of patients with episodic migraine and nearly all patients with chronic migraine could benefit from preventive treatment. Both the CGRP antagonists and botulinum toxin type A (chronic migraine only) have demonstrated limited but meaningful safety and efficacy endpoints including reduction of migraine headache days by approximately 2 per month. Although migraine guidelines generally support initial trials of traditional oral therapies (e.g., antiepileptics, beta-blockers, etc.) based around established efficacy, the emergence of the injectable CGRP antagonists and botulinum toxins suggest they may have an increasing role in migraine prophylaxis in the near future.

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