doses or with a history of cardiac disease, electrocardiograms (ECG) might be needed for monitoring. Propranolol is used to treat hypertension and certain types of tremors and might be effective for patients with these comorbid conditions.

Patient preferences vary regarding this treatment. Some patients might find propranolol less favorable than other evidence-based treatments, such as topiramate or the CGRP receptor antagonists, because of propranolol's effect on heart rate, particularly in patients who exercise frequently and are unable to maximize their heart rate during cardiovascular (CV) activity. Further, dosing multiple times a day and the risk of orthostasis and bradycardia might be burdensome and could potentially cause discontinuation. Patients with concomitant anxiety might find propranolol helpful for their headaches and anxiety.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(167) Therefore, this recommendation is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations including small sample size, limited duration of follow-up (12–16 weeks), and imprecision.(167) The benefits of propranolol slightly outweighed the potential harms and AEs. Patient values and preferences were similar because of the low side-effect profile. The Work Group also considered this recommendation's impact on patients with anxiety, tremors, or hypertension. Thus, the Work Group made the following recommendation: We suggest propranolol for the prevention of migraine.

Recommendation

11. We suggest valproate for the prevention of episodic migraine.
    (Weak for | Reviewed, New-replaced)

Discussion

Mulleners et al. (2015) performed a meta-analysis of antiepileptics in migraine prophylaxis that included 10 eligible valproate studies.(166) Active interventions included topiramate, propranolol, and flunarizine in a range of doses (400–1,500 mg per day) and study duration (8–12 weeks, average 11 weeks).(166)

In six placebo-controlled trials, valproate was found to be more effective in treating episodic migraine at all assessed time points, including 4, 8, and 12 weeks.(169-174) Four placebo-controlled divalproex sodium trials showed patients receiving active treatment were twice as likely to experience a 50% reduction in headache frequency.(172, 175-177) One trial found that sodium valproate was significantly superior to placebo for the same metric but different between treatments.(171)

Mulleners et al. (2015), which included two crossover trials of sodium valproate, showed significant headache frequency reduction in the active group compared with the placebo group of approximately four headaches per 28 days.(170, 171) Comparisons with