

# DIMENSIONS IN DIAGNOSIS

HEADACHE FROM THE PATIENT AND EXPERT PERSPECTIVES

## ADDITIONAL RESOURCES

### LATE-STAGE EMERGING THERAPIES FOR HEADACHE PROPHYLAXIS: SUPPLEMENTARY INFORMATION (ITEMS MARKED WITH AN \*):

**Atogepant:** currently under investigation. Safety and efficacy data not publicly available.

#### Noninvasive vagal nerve stimulation (nVNS)

- U.S. Food and Drug Administration (FDA)-approved for acute treatment of cluster headache
- Under investigation for prevention of
  - Episodic and chronic migraine: in chronic migraine (from the EVENT study), the average number of headache days was decreased by 1.4 (nVNS) and 0.2 (sham), ( $\Delta=1.2$ ;  $P=.56$ );<sup>1</sup> in the open-label phase, after 8 months, the mean change from baseline headache days was  $-7.9$  (95% confidence interval  $-11.9$  to  $-3.8$ ;  $P<.01$ );<sup>1</sup> there were no safety issues<sup>1</sup>
  - Cluster headache: in the PREVA study (PREvention and Acute treatment of chronic cluster headache), nVNS added to standard of care (SoC) decreased mean weekly attack frequency compared to SoC alone<sup>2</sup>; nVNS was well-tolerated with similar rates of adverse events between groups<sup>2</sup>

#### Caloric vestibular stimulation:

- Under investigation for the prevention of episodic and vestibular migraine: in episodic migraine, migraine days decreased by more in the active group ( $-3.9\pm 0.6$  from a baseline burden of  $7.7\pm 0.5$  migraine days) compared to the control group ( $-1.1\pm 0.6$  from a baseline burden of  $6.9\pm 0.7$  migraine days) after 3 months of treatment<sup>3</sup>; the rate of expected adverse events was similar across groups<sup>3</sup>

## PRE/POSTTEST ANSWERS AND RATIONALES

### 1. Which of the following is the serotonin receptor most correlated with coronary artery vasoconstriction?

- 5-HT<sub>3</sub>
- 5-HT<sub>1F</sub>
- 5-HT<sub>2</sub>**
- 5-HT<sub>1D</sub>

#### Explanation:

In isolated human epicardial coronary arteries, application of 5-hydroxytryptamine (5-HT) led to contraction. This vasoconstriction was antagonized by ketanserin, a 5-HT<sub>2</sub> receptor antagonist, while the selective 5-HT<sub>1</sub>-like receptor agonist, GR43175 caused only small, ketanserin-resistant contractions.<sup>4</sup> These data suggest that the contractile effect of 5-HT is predominantly mediated via 5-HT<sub>2</sub> receptors. 5-HT<sub>1</sub>-like receptors additionally contribute to this response, in vitro, but to a lesser degree.<sup>4</sup> Vasoconstriction resulting from triptan medications is generally thought to result from agonist activity at the 5-HT<sub>1B</sub> receptors located postsynaptically on vascular smooth muscle cells.<sup>5</sup>

## 2. Which is NOT true of calcitonin gene-related peptide (CGRP)?

- a. Release correlates with a migraine attack
- b. **Stabilizes mast cells**
- c. Is present on trigeminal neurons
- d. Produces vasodilation

### Explanation

Both the central and peripheral nervous systems show widespread expression of CGRP, consistent with its roles in vasodilatation, nociception, motor function, secretion, and olfaction.<sup>6</sup> The  $\alpha$ CGRP isoform is prominently found in primary spinal afferent C and A $\Delta$  fibers of sensory ganglia. In the enteric nervous system, the  $\beta$ CGRP is the main isoform.<sup>6</sup> Peripheral projections contribute to neurogenic vasodilatation and inflammation. Correspondingly, central release leads to hyperalgesia.<sup>6</sup> CGRP receptor components are also localized to mast cells in rodent models are found to degranulate them.<sup>7</sup>

## 3. Fully human monoclonal CGRP antibodies

- a. Have short half-lives
- b. Easily cross the blood-brain barrier
- c. All have affinity for the CGRP receptor
- d. **Have low potential for immunogenicity**

### Explanation

Antibodies used for therapeutic purposes undergo a form of engineering by sequentially replacing mouse sequence-derived amino acids with human sequences.<sup>8</sup> This practice significantly reduces immunogenicity of the antibodies.<sup>8</sup> Chimeric antibodies were the first advancement in antibody engineering, whereby murine constant regions are replaced by human.<sup>8</sup> The humanization process was the next advancement, resulting in an antibody where the complementarity determining regions of the variable regions are the sequence remaining of mouse origin.<sup>8</sup> The current humanization process leads to antibodies with fully human amino acid sequences. The specificity of the antigen is selected either in vivo by the use of genetically modified mice or by antibody engineering processes combined with screening.<sup>8</sup> Fully human and humanized antibodies carry a lower risk for inducing immune responses in humans than mouse or chimeric antibodies.<sup>8</sup>

## 4. What percentage of patients meet the criteria for being offered a preventive treatment?

- a. 8.4%
- b. 20%
- c. **32.4%**
- d. 50%

### Explanation

In the American Migraine Prevalence and Prevention (AMPP) survey, 43.3% of migraineurs had never used a preventive medication, despite 32.4% having met criteria for considering or being offered it.<sup>9</sup> More recently, data from the Chronic Migraine Epidemiology and Outcomes (CaMEO) study found that only 4.5% of participants who met criteria for chronic migraine were receiving successful chronic migraine care.<sup>10</sup>

5. What are common factors that migraine patients experience during an attack? (Check all that apply.)

- a. Nausea
- b. Photophobia
- c. Phonophobia
- d. Disability

**Explanation**

Migraine is recognized as a major cause of disability worldwide.<sup>9</sup> The World Health Report 2001—Mental Health: New Understanding, New Hope cited migraine as the 19th leading cause of years lived with disability (YLD) among males and females of all ages. Furthermore, it listed migraine as the 12th leading cause of YLD among females of all ages.<sup>9</sup> An updated analysis of the global burden of disease listed migraine as the 7th leading cause of YLD, having increased in prevalence by 15.3% from 2005 to 2015.<sup>11</sup>

Migraine is a headache disorder associated with symptoms across systems: neurologic, gastrointestinal, and autonomic.<sup>12</sup> Gastrointestinal disturbances include nausea, vomiting, abdominal cramps, and/or diarrhea. Sensory hyperexcitability manifests as photophobia, phonophobia, and osmophobia and is frequently experienced.<sup>9</sup> Additional symptoms include blurry vision, nasal stuffiness, tenesmus, polyuria, pallor, and sweating.<sup>12</sup>

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