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Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans

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Abstract

Migraine is a highly disabling neurovascular disorder characterized by a severe headache (associated with nausea, photophobia and/or phonophobia), and trigeminovascular system activation involving the release of calcitonin-gene related peptide (CGRP). Novel anti-migraine drugs target CGRP signaling through either stimulation of 5-HT_{1F} receptors on trigeminovascular nerves (resulting in inhibition of CGRP release) or direct blockade of CGRP or its receptor. Lasmiditan is a highly selective 5-HT_{1F} receptor agonist and, unlike the triptans, is devoid of vasoconstrictive properties, allowing its use in patients with cardiovascular risk. Since lasmiditan can actively penetrate the blood-brain barrier, central therapeutic as well as side effects mediated by 5-HT_{1F} receptor activation should be further investigated. Other novel anti-migraine drugs target CGRP signaling directly. This neuropeptide can be targeted by the monoclonal antibodies eptinezumab, fremanezumab and galcanezumab, or by CGRP-neutralizing L-aptamers called Spiegelmers. The CGRP receptor can be targeted by the monoclonal antibody erenumab, or by small-molecule antagonists called gepants. Currently, rimegepant and ubrogepant have been developed for acute migraine treatment, while atogepant is studied for migraine prophylaxis. Of these drugs targeting CGRP signaling directly, eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant and ubrogepant have been approved for clinical use, while atogepant is in the last stage before approval. Although all of these drugs seem highly promising for migraine treatment, their safety should be investigated in the long-term. Moreover, the exact mechanism(s) of action of these drugs need to be elucidated further, to increase both safety and efficacy and to increase the number of responders to the different treatments, so that all migraine patients can satisfactorily be treated.

Keywords: CGRP; Ditans; Gepants; Migraine; Monoclonal antibodies; Triptans.

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