Preventative Therapies for Migraine

An expert interview with Uwe Reuter

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Uwe Reuter

Uwe Reuter is a neurologist and partner in the headache programme at Charité Universitätsmedizin Berlin. After finishing his residency training in Berlin he went to Harvard Medical School for a postdoctoral fellowship as a scholar for three years. During his time in Boston he focused on basic research in primary headaches and migraine aura and published several peer-reviewed publications in high-impact journals. Ever since, Dr Reuter has had a strong interest in basic and clinical headache research. He is a member of several national and international headache organisations and currently serves as board member of the European Headache Federation (EHF).

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Shortly after the 18th Congress of the International Headache Society in Vancouver, Canada, in September 2017, Uwe Reuter participated in an expert interview. Here, he shares his insights and perspective on preventative therapies for migraine, discontinuation rates on current therapies, the need for new therapies with alternate targets and most promising potential therapies currently in development.

Q: At present, what are the most effective preventative therapies for migraine?

To answer this question, we first need to differentiate between episodic migraine and chronic migraine. Chronic migraine is defined as more than or equal to 15 headache days per month for at least 3 months, of which eight days or more meet the criteria for migraine with or without aura, or which responds to migraine-specific treatment. Episodic migraine is generally defined as 14 or fewer migraine days per month.[1]

Preventative medications for migraine aim to decrease the overall clinical characteristics of migraine including the frequency of attacks and their severity, while also being aware of their response to acute medications.

In Europe, although options differ by country, the four frontline therapies that are used in preventing episodic migraine are: anti-epileptics, beta-blockers, amitriptyline and valproic acid which is used to treat bipolar disorder and epilepsy. For chronic migraine, topiramate, an anti-epileptic, may also be used. Botulinum toxin was approved for the prevention of chronic migraine in 2010 and is the second main preventative option used in patients with chronic migraine.

Physicians formulate a treatment strategy on a case-by-case basis while keeping in mind the patient's history. As such, the treatment prescribed is dependent on patient and physician preference, but will also take into account the frequency and severity of migraine and the patient's comorbidities. For example, certain anti-epileptics (e.g. topiramate) which may be prescribed for both chronic and episodic migraine, should be used with caution in patients with depression as they can further induce depression. Other comorbidities which may need consideration include vascular disease or cardiac conditions. In all cases, pharmacologic treatment should be supported by non-medical treatment, such as exercise or relaxation training.

Q: Why are new preventative therapies needed?

There are several reasons why new preventative therapies are needed. Firstly, there are no specific anti-migraine preventatives available – they have all been re-purposed from other disease areas. This is critical for the patient who would prefer to receive a therapy designed for their specific condition. Another important reason is that the preventative treatments currently available take a number

of weeks to take effect. Dose titration must be undertaken slowly to avoid adverse effects and, while the adverse effects may soon become apparent, treatment effects are often not experienced until week eight.

This leads on to the issue of side effects. All the drugs mentioned have side effects which may be intolerable to the patient. For example, many of them cause weight gain, a side effect which can be particularly undesirable. Other side effects include fatigue and drowsiness.

Further, the efficacy of current treatments is not sufficient – as a physician, I would like to aim for 50% or greater reduction in both frequency and intensity of migraine.

Additionally, current therapies often need to be taken daily. This causes dissatisfaction amongst patients who wonder why they need to take a daily tablet when they do not have migraine attacks daily. Overall, the lack of tolerability, in particular the central nervous system effects of drowsiness and fatigue, coupled with the poor efficacy and patient dissatisfaction with the current, repurposed preventative therapies all point towards the need for new and effective preventative therapies with few adverse effects for those with migraine.

Q: What is the discontinuation rate for preventative treatment?

In migraine, preventative medication is usually stopped or re-evaluated after 9–12 months in order to observe the natural evolution of the disease. However, a recent study indicated that the discontinuation rate for those with prior experience of preventative treatments, not segregated according to chronic or episodic migraine, is over 70%.[3] Notably, when asked the reasons for stopping medication for chronic migraine, up to 53% reported that they discontinued medication due to lack of tolerability and up to 48% reported that it was due to lack of efficacy, with rates depending on the class of medication prescribed. The rates of discontinuation in episodic migraine were slightly less for each of these factors (approximately 49% citing lack of tolerability and 47% citing lack of efficacy).[2] Furthermore, dependent on the indication (chronic or episodic) and on the class of medication used, the percentage of those halting treatment due to resolution of the issue of migraine was as low as 5%.[2]

Q: Which physiological pathways are potentially useful therapeutic targets in the prevention of migraine?

Within the brain, the area of interest for those studying migraine is the trigeminal nervous system. Within this, there are several molecules of interest, with calcitonin gene-related peptide (CGRP) being at the forefront amongst these. CGRP is known to be involved in migraine and has been shown to be elevated in migraine attacks; administration of CGRP to a migraine patient can cause a migraine attack.[4] Overall, there are several lines of evidence supporting the involvement of CGRP in migraine and it is an important area of research.

A second physiological pathway of interest is part of the parasympathetic nervous system, as well as receptors in the trigeminovascular system. This pathway involves the pituitary adenylate cyclase-activating polypeptide (PACAP). Initial studies have demonstrated that this peptide is involved in migraine attacks. It may act outside the blood–brain barrier in the pathogenesis of migraine; however the mechanisms involved remain unclear.[5]

A further, emerging area of research is the role of cannabinoid receptors, but this is as yet in its infancy in its relation to migraine.[6]

Q: What are the most promising preventative therapies in clinical development?

Currently, the three most promising lines of preventative therapy in clinical development are CGRP monoclonal antibodies (mAB), a CGRP receptor monoclonal antibody and some small molecule CGRP receptor antagonists. Of these, the monoclonal antibodies are the most advanced with phase III clinical trials having been completed. As such, mABs targeting CGRP or its receptor can be considered to be the most promising preventative therapies currently in the clinical development pipeline. While three of these mABs target the CGRP ligand, one, known as erenumab, targets and blocks the CGRP receptor. Phase II and III findings for this class of drugs have shown placebo-like tolerability and good efficacy to date.[7–9] There is reason to expect that these safe, effective and tolerable migraine-specific investigational drugs may be a viable new option for migraine patients in the near future. ❑

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