Preventing migraine from taking over people's lives: Lundbeck's perspective and current research

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Lundbeck is a global biopharmaceutical company solely focused on brain disease and restoring brain health. In 2019, Lundbeck acquired Alder BioPharmaceuticals (now Lundbeck Seattle BioPharmaceuticals) and with it eptinezumab – a humanised anti-calcitonin gene-related peptide (CGRP) monoclonal antibody. Eptinezumab was approved by the United States Food and Drug Administration (FDA) for preventive treatment of migraine in adults in February 2020. It has not been approved for any other indication in the US, and it has not been approved for any indication outside the US (October 2020). Also included in the acquisition was a monoclonal antibody against pituitary adenylate cyclase-activating peptide (PACAP), putting Lundbeck on a path to deliver new therapies and solutions to people living with migraine worldwide, to support a future where migraine no longer control people's lives.

The majority of shares in Lundbeck are owned by the Lundbeck Foundation, which has supported biomedical research, including research in headache, for many years. The Lundbeck Foundation also awards The Brain Prize, the world's largest international research prize within neuroscience.

A GLOBAL HEALTH CONCERN

Recent estimates show that more than one billion people around the world are living with migraine[1]. Migraine diagnosis is defined by the third edition of the International Classification of Headache Disorders (ICHD-3)[2]. It is based on criteria related to the number (at least 5) and the duration (4–72 hours) of the attacks, as well as characteristics of the headache and the presence of accompanying symptoms (nausea/vomiting or photophobia/phonophobia). Patients who experience aura with their attacks receive an additional ICHD-3 diagnosis and are further categorised depending on the type of the aura[2].

Migraine is a chronic disease, yet it is often subtyped as episodic migraine or chronic migraine based on the frequency of headache days and migraine days. Chronic migraine is defined diagnostically by ICHD-3 criteria as migraine with 15 or more headache days per month for more than 3 months, with features of migraine headache on at least 8 days per month[2]. Episodic migraine, while technically not an ICHD-3 diagnosis, is migraine with or without aura with 14 or fewer headache days per month.

The impact of migraine can differ greatly between patients as well as for an individual patient at different stages of their life, as is evident by the wide range of headache days per month within the definitions of episodic and chronic migraine. There is a large variation in disability between patients with the same frequency of headache days per month, as assessed using the Migraine Disability Assessment (MIDAS) questionnaire[3], thus emphasising that migraine disability is based on more than the single symptom of headache.

The Global Burden of Diseases, Injuries and Risk Factors (GBD) studies have shown that headache disorders, and migraine in particular, are among the most disabling disorders worldwide and constitute a major global public health concern, not limited to high-income countries[1] (**Fig. 1**).

In the GBD studies, disease burden is estimated using years of life lived with disability (YLDs). In both sexes, the YLDs due to migraine as a percentage of all YLDs was highest in the group aged 15–49 years, but was also high in children aged 5–14 years, and in individuals aged 50–69 years[1]. The burden of migraine is thus the highest when pursuing education, and in the years when families and careers are formed.

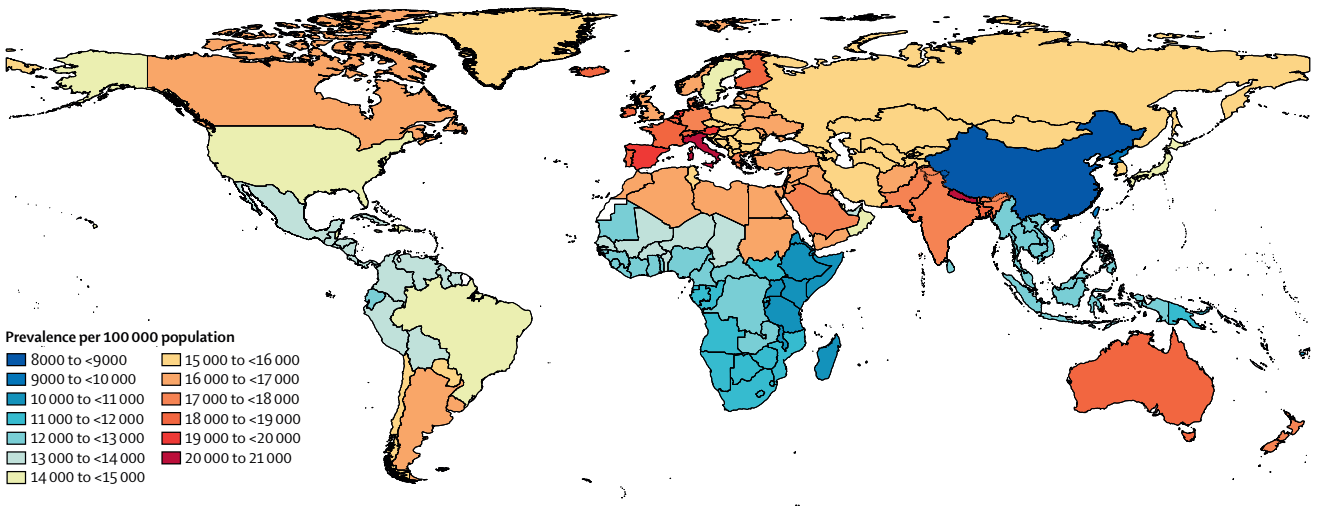

Figure 1. Age-standardised prevalence of migraine per 100,000 population, 2016. *Reproduced and adapted from reference 1 under a CC BY 4.0 licence.*

Despite its prevalence and significant burden, the impact of migraine is often underestimated by healthcare policy makers, clinicians and the people living with the disease, which contributes to underdiagnosis and undertreatment[4]. Furthermore, people with migraine are more likely to experience comorbidities such as insomnia, depression, anxiety, gastric ulcers and gastro-intestinal bleeding than people without migraine, with both monthly headache days and pain intensity associated with increased risk for many conditions[5].

Compared with episodic migraine, people who have developed chronic migraine report more severe disability, lower health-related quality of life, higher levels of anxiety and depression and greater use of health care resources[3]. Individuals with chronic migraine also have more comorbidities than those with episodic migraine[5]. Depression, along with high frequency headache and, notably, medication overuse have emerged as risk factors for progression from episodic to chronic migraine[5,6].

Medication overuse headache (MOH) is a secondary headache disorder associated with overuse of medication taken for acute and/or symptomatic treatment[2]. MOH is highly prevalent and constitutes an extra burden on many of the most ill patients with migraine[7]. Compared to migraine without medication overuse, MOH is associated with increased depression, greater disability and lower quality of life[8].

In summary, migraine is a common, but underdiagnosed and undertreated chronic disease that leads to significant disability and lost productivity, often accompanied by comorbidities and MOH. By taking a leading role in the migraine disease area, Lundbeck aims to change lives by bringing our long-standing expertise in neuroscience to unravel many of the unmet needs impacting patients and medical practitioners.

NEW TREATMENTS AND EVOLVING TREATMENT GOALS

Therapies developed specifically for the prevention of migraine have only recently become available. These treatments are targeting CGRP or the CGRP receptor, and all four of them have demonstrated a reduction in the frequency of migraine days in both episodic and chronic migraine, while also being generally well tolerated. Three of the new treatments (erenumab, galcanezumab and fremanezumab) are administered by subcutaneous injection, whereas eptinezumab is given quarterly as a 30-minute intravenous (IV) infusion. Eptinezumab reduces the frequency of migraine days not only in patients with episodic[9] and chronic migraine[10]. In preliminary findings, presented as a poster[11] at the 6th Congress of the European Academy of Neurology in May 2020, eptinezumab was reported to reduce the frequency of migraine days in patients with a dual diagnosis of chronic migraine and MOH. In all these patient populations, eptinezumab onset of efficacy was demonstrated on the first day after administration[9-11].

At Lundbeck, we are eager to continuously learn about patients' expectations of treatment. To optimise the drug development process, we need input from patients on what is relevant to measure in clinical trials, and we support shared decision-making between patient and treating physician with regards to treatment options and goal setting.

A reduction of 50% in monthly days with headache or migraine has traditionally been viewed as a benchmark for therapeutic success in migraine prevention in both clinical trials and clinical practice[12]. However, as evident from the variation in disability between patients with similar frequency of headache days[3], a successful therapeutic outcome depends not only on a reduction in monthly headache-day frequency but also on the duration and intensity of pain and other symptoms. People living with migraine experience symptoms beyond pain, and effectively treating the symptoms that are most troublesome to them could have a large impact on their quality of life.

Therefore, measures like the MIDAS and the 6-item Headache Impact Test, which measures the impact and effect on the ability to function normally in daily life when a headache occurs, emerge as important tools for obtaining patient input to setting goals for and evaluating their treatment plan[12].

With the introduction of the new treatments developed specifically for migraine prevention, patients' and

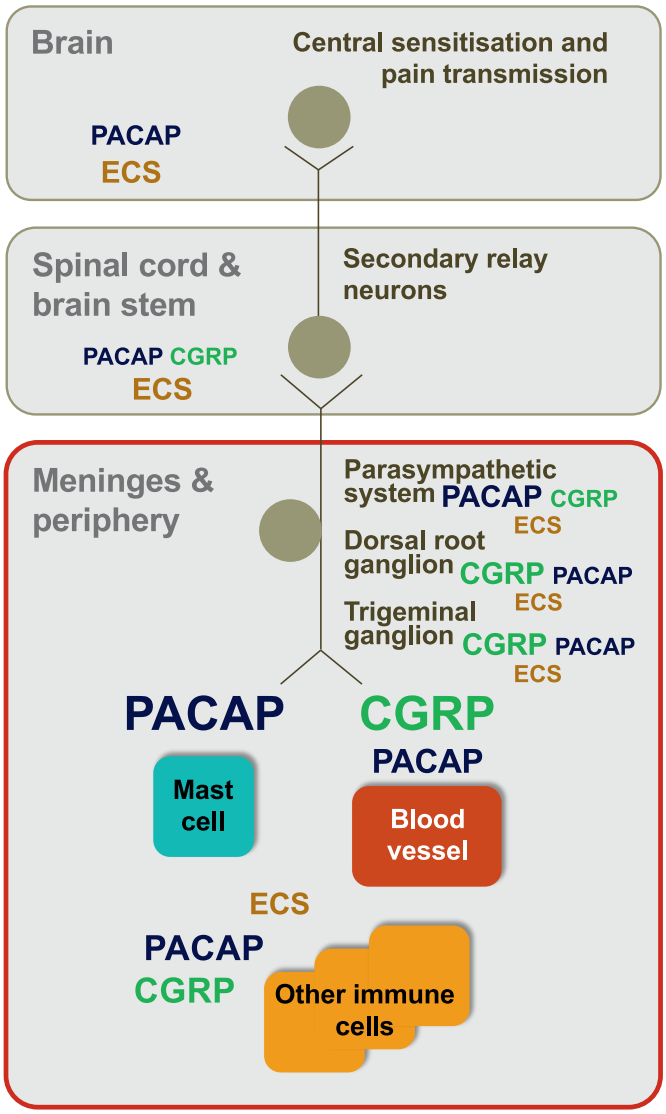

Figure 2. Involvement of calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP) and endocannabinoid system (ECS) in migraine and headache pain. Both CGRP and PACAP signalling pathways may contribute directly to central sensitisation and the generation of pain. Cranial trigeminal nerve and autonomic mechanisms are believed to be involved, with trigeminal driven vascular activation and neurogenic inflammation in the dura as the most prominent consequences. Clinical and experimental evidence suggests that the ECS is centrally and peripherally involved in the processing of pain. CGRP and PACAP may also directly impact ascending pain transmission, although this is less well understood.

physicians' expectations to treatment outcomes may increase. The 50% reduction in headache or migraine days will remain an important initial and general goal. However, the expectation of how fast this goal can be achieved is changing, as improvements with the new treatments becomes apparent within a day to a few weeks for those who respond well. Further is the realisation that significant migraine burden may remain for many patients experiencing more frequent migraine even after achievement of a 50% reduction in migraine days. Aiming for a 75% or greater reduction in migraine days is today a realistic possibility for many patients[13]. Lundbeck was the first to include this as a prespecified key secondary endpoint in the pivotal trials of eptinezumab, in which ≥30% of patients with episodic or chronic migraine experienced a ≥75% reduction in migraine days in the first 4 weeks after treatment initiation[9,10].

Even with a reduction in migraine days of 75%, patients may still be impacted by their migraine. Supplementing response based on reduction of days with headache with assessment of the most troublesome residual symptoms or specific aspects of functioning could be a way forward for defining the ultimate treatment goal between a patient and the treating physician.

REMAINING UNMET NEED

The need for more people to reach their treatment goals, and earlier than at present, remains despite the availability of the new treatments developed specifically for migraine prevention.

First, we need to overcome the limited access to the new, effective and well-tolerated anti-CGRP treatments. In 2014, more than two-thirds of people living with migraine had either never consulted a physician or had stopped doing so, in part due to low expectations of treatment and/or poor experiences with traditional preventive treatments[14].

Second, if we could identify who would respond to the different preventive treatments, either based on underlying disease biology or on other response predictors, we could minimise the trial and error that patients go through to get effective migraine prevention. Genetic, biochemical and imaging biomarkers could potentially, in combination with detailed characterisation of clinical features, lead to a more accurate subtyping and the possibility to predict an individual's response to a treatment.

Third, because some patients do not respond to the anti-CGRP treatments, new therapies addressing other components of the disease biology of migraine are urgently needed.

FURTHER DEVELOPMENT OF EPTINEZUMAB

Two large randomised, placebo-controlled trials have been undertaken to further study migraine prevention with eptinezumab.

The RELIEF study (NCT04152083) aims to inform about potential early effects of initiating migraine prevention with eptinezumab infusion during a migraine attack. Patients enrolled in the study received either eptinezumab (100 mg) or placebo by a 30-minute IV infusion within 1 to 6 hours of migraine-attack onset and were followed at the study site the first 4 hours and remotely until week 4. Positive headline results from the RELIEF study was recently announced on lundbeck.com. Lundbeck plans to share the full set of results at upcoming scientific meetings and in peer-reviewed journal articles.

The DELIVER study (NCT04418765) aims to evaluate the efficacy of eptinezumab for the prevention of migraine in patients with 2 to 4 unsuccessful prior preventive treatments. Enrolled patients will follow a 12-week dosing schedule with either eptinezumab (100 or 300 mg) or placebo by IV infusion for 24 weeks. Patients completing the 24-week double-blind period may be eligible to enter an open-label extension study where all patients will receive eptinezumab.

In addition to these studies in migraine prevention, eptinezumab is also being considered for development within cluster headache. This is another primary headache disorder with a high impact on functioning that can take over patients' lives in episodes of weeks to months or continuously without periods of remission.

TARGETING MIGRAINE DISEASE BIOLOGIES

The pathophysiology of migraine is complex and incompletely understood. CGRP is central to current models of migraine pathophysiology and acts in part by promoting meningeal vasodilation, and in part by promoting neurogenic inflammation and altered nociception, ultimately leading to the sensation of pain and headache[15]. Although the trigeminal nerve and its CGRP-releasing ganglion fibers are believed to be an important contributor to the development and maintenance of migraine attacks, other factors could also be potential entry points for alleviating migraine either alone or in combination with blocking of CGRP signaling. One of these factors is the neuropeptide PACAP[16] (**Fig. 2**).

Systemic administration of PACAP can trigger migraine-like attacks in susceptible individuals, and elevated concentrations of PACAP have been reported in patients with migraine during attacks. PACAP receptors are expressed in the CNS and in peripheral structures associated with headache biology, including vagal efferent, middle meningeal arteries, trigeminal ganglia, dorsal root ganglia, trigeminal nucleus caudalis and sphenopalatine ganglia. Collectively, this suggests that PACAP signalling mechanisms are involved in mediating distinct cranial autonomic symptoms, associated with headache and migraine pathophysiology.

Furthermore, and much like CGRP, PACAP is implicated in vasodilation through the sensory nerves that innervate the cranial vasculature. PACAP is also implicated in dural inflammation, peripheral sensitisation, and central pain sensitisation and transmission[17]. Dural mast cell degranulation has been proposed as a putative mechanism for headache pain and migraine[18]. Mast cells release PACAP, which has also been demonstrated to be a significant mediator of mast cell degranulation. PACAP-mediated inflammatory processes within deeper brain structures may also be involved in mediating these dural changes, which again may lead to trigeminovascular activation that could further drive disease pathogenesis[19].

Therefore, PACAP signaling blockade is a promising therapeutic option for migraine prevention. Lundbeck's anti-PACAP monoclonal antibody has, because it binds to the ligand, the potential to broadly prevent PACAP signalling through all its confirmed receptors and is in early-phase clinical development (NCT04197349).

Finally, modulation of the endocannabinoid system (**Fig. 2**), which is an area of interest to Lundbeck in several diseases, might hold promise for the development of future therapies. The endocannabinoid system has been shown to be involved in processing of nociceptive signals in the trigeminovascular system[20]. Targeting multiple levels in the same pathway by stimulating the endocannabinoid system in both the primary nociceptive afferents and at the central level in the presence of CGRP or PACAP blockade might lead to more effective prevention of headache and migraine.

OUR COMMITMENT TO PEOPLE LIVING WITH MIGRAINE

For more than 70 years, Lundbeck has been at the forefront of neuroscience research, advancing our understanding of the biology of the central nervous system and bringing innovative therapies to millions of people living with brain disease worldwide. We are committed to understanding what is most important to people living with migraine and determined to help them achieve the outcomes that matter most to them. Focused on transforming migraine treatment and prevention, we are resolute in our pursuit of therapies that support a future where migraine no longer controls people's lives.

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