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New Horizons in Headache: The 18th Congress of the International Headache Society

Overview

The 18th International Headache Congress (IHC) was held in the beautiful city of Vancouver, British Columbia, Canada, and brought together the global leaders in headache medicine to showcase the newest developments in the advancement of headache science, education and management over 4 days of lectures, networking, peer education and expert panels. IHC 2017 included plenary sessions, an extensive poster display and in-depth scientific presentations showcasing basic and clinical research that promises an exciting future for headache medicine. The theme of the congress, 'New Horizons in Headache', nodded to both the location of the conference and to the event's focus on the new frontier of headache medicine.

In his Welcome Remarks, David Dodick, IHS President and Congress Co-Chair, noted that 'This unprecedented event in headache medicine marks the turning point for a group of diseases that have endured a severe lack of understanding, damaging stigma, historic underfunding for research, and a painfully slow pace of treatment advances'.

Presidential Symposium – New Horizons

Called the most exciting field in neurology, headache medicine is at a major turning point with significant new advancements on the horizon. Addressing four key breakthrough areas in the field, the Presidential Symposium included several insightful presentations: New Horizons in Imaging, Todd Schwedt; New Horizons in Translational Research, Frank Porecca; New Horizons in Genetics, Michel Ferrari; and New Horizons in Novel Treatment Targets, Peter Goadsby.

'Not only is progress being made in acute migraine treatment, but also with new understanding of migraine biomarkers that allow us to develop nuanced treatment options that we have never seen before' said Dr Dodick. 'This is a very exciting time for the field of headache medicine.'

Accomplishments

Since the last IHC in 2015, IHS has made several key developments, reaching critical goals that include sustaining and growing global education, building a global network of researchers, and mentoring and developing future leaders, including the development of a women's leadership programme. In addition, IHS has just surpassed the largest membership base for many years. At the IHC, IHS announced that in 2017 it will launch a full, open access companion journal to *Cephalalgia*, titled *Cephalalgia Reports*. The new journal will include original research papers, review articles, clinical perspectives, case reports, CME articles, technical reports and more.

Awards and Recognitions

The ceremony opened by honouring the accomplished life of Ninan Mathew (1937–2015), founder of the Houston Headache Clinic and former IHS President. Jes Olesen received a special award in recognition of his three-decade leadership of the ICHD (International Classification of Headache Disorders) which provides the basis for advances in the clinical and biological understanding of headache disorders and continues to facilitate the progress in treatment. In addition, Hans-Christoph Diener received the IHS Special

Not only is progress being made in acute migraine treatment, but also with new understanding of migraine biomarkers that allow us to develop nuanced treatment options that we have never seen before

Recognition Award for his outstanding contribution to the formation and advancement of IHS since its foundation.

Global Patient Advocacy Call to Action

To emphasise an imperative focus on patient-centric care, the 2017 congress was preceded by the first ever Global Patient Advocacy Summit, a 1-day intensive meeting connecting leaders in headache medicine with public health organisations, patient advocacy groups and other interdisciplinary allies to establish mutual international patient support goals.

To continue the momentum, a motion to globalise migraine patient advocacy led to the creation of the Global Patient Advocacy Coalition (GPAC). Objectives of the GPAC include country-specific research focused on the formation of a global approach to migraine/headache advocacy, resource allocation to develop local outreach, evaluation of local initiatives, refinement of tactics and a needs assessment.

Co-Chair of GPAC, David Dodick, said 'We have the collective brain trust, commitment, and influence in this room today to change all of that for the hundreds of millions who suffer with disabling headache around the globe by building awareness, raising support, delivering education, and improving access to care.'



Migraine and new treatment options: emerging targets for migraine therapy

Migraine is a pervasive, disabling disease affecting more than 1 billion people around the world with no cure in sight. Researchers continue to pursue further treatments that may ease or alleviate the disease's diverse symptoms, resulting in the dogged search for new mechanisms to target therapeutically. During the IHC, neurologist Cristina Tassorelli and pharmacologist Frank Porreca identified two emerging targets that show potential for the development of future migraine treatments.

Dr Tassorelli, who directs the Headache Science Centre at the C Mondino National Neurological Institute of Pavia in Italy, spoke with optimism about the endocannabinoid system, a group of endogenous cannabinoid receptors located in the brain and throughout the central and peripheral nervous systems that is involved in a variety of physiological processes including appetite, pain sensation, mood, memory, and in mediating the psychoactive effects of cannabis. In her research, Dr Tassorelli investigated the potential

KOR antagonists... could represent a new class of analgesics for the prevention of stress-related pain syndromes including migraine

relationship between endocannabinoids and migraine, using animal models. In studies examining changes in the peripheral nervous system and in central brain areas, such as hypothalamus and brainstem, the peripheral inhibition of fatty acid amide hydrolase proved to reduce migraine pain via both anti-nociceptive and anti-hyperalgesic effects, suggesting it has potential as a possible target for migraine treatment. More testing is needed, but evidence supports the peripheral inhibition of catabolic pathways of endocannabinoid, with the consequent increase in their local availability, as a prospective therapy for migraine pain relief with minimal side effects. 'Migraine is a complex disease, and I personally believe that we need multiple targets to be able to treat it appropriately' Dr Tassorelli said.

Later during the congress, Frank Porreca, Associate Head of the Department of Pharmacology at the University of Arizona College of Medicine, presented on a second emerging target for migraine prophylaxis: kappa opioid receptors (KOR), a member of the opioid neuromodulatory system and central player in the regulation of both reward and mood processes. Symptoms of acute and chronic stress like anxiety, depression and drug-seeking behaviour have proven in the past to be alleviated by KOR antagonists that block the proteins from functioning, leading researchers to extrapolate that the same effect may be helpful in treating stress-related functional pain disorders. Migraine, a disease with sustained, intermittently occurring pain unrelated to any identifiable tissue injury, qualifies as a type of functional pain, with stress as the most commonly reported trigger for migraine attacks.

Finding an alternative treatment for migraine-related pain that doesn't involve triptans would provide significant relief for patients with medication overuse headache, whose repeated use of pain-blocking drugs results in both a latent sensitisation to headache pain and lowered thresholds to triggers, which can only be reversed by abstaining from the medications they rely on to withstand crippling migraine attacks. Dr Porreca presented findings in rat studies wherein KOR antagonists successfully blocked stress-induced allodynia, suggesting this treatment could represent a new class of analgesics for the prevention of stress-related pain syndromes including migraine and other functional pain disorders. He also expressed optimism that achieving this effect therapeutically was within reach. 'We have been studying kappa agonists and now, today, I think making kappa antagonists is an entirely feasible thing to do' Dr Porreca said.

The global impact of migraine: how the Global Burden of Disease Surveys estimate disability burdens

Specialists in the field of global health must contend with profoundly complex and enigmatic medical problems. However, some of the challenges influencing their study are not scientific, but logistical ones. When it comes to global diseases, how can international agencies determine the scope and severity of global health problems across multiple countries and cultures, each with unique medical infrastructures and diverse cultural interpretations of the impacts of disease?

Lars Jacob Stovner, a Professor of Neurology at the Norwegian University of Science and Technology, explained the empathetic process behind these essential calculations. The formula used to assign numerical values to world health crises is called the Global Burden of Disease study, first commissioned in 1990 by the World Bank and performed in partnership with the World Health Organization. Since 2000, the study has undergone annual revisions by the WHO, and starting in 2010 its assembly became a more collaborative process between more than 300 institutions from 50 countries, including the Institute for Health Metrics and Evaluation at the University of Washington, Seattle, Johns Hopkins University, the University of Tokyo, Imperial College London and the Harvard School of Public Health.

Migraine, the third most prevalent and sixth most disabling medical illness in the world, has a Disability Weight of 0.441 out of 1

The Global Burden of Disease study is designed to distinguish the intensity of need for public health intervention from the visibility and prominence of interest groups, ensuring that the most urgently pressing crises get immediate attention, not necessarily the ones with the loudest advocates; to include non-fatal health outcomes along with information on mortality, since significant quality of life issues can be as arresting as deaths; and to quantify health problems into time-based units that can be standardised from country to country.

To shoulder the complex task of standardising the human experience of widely different diseases across diverse cultures, the Global Burden of Disease study first needed to establish units of measurement that accurately reflected the intensity of human suffering. The central unit in this survey is the 'person-year', a unit of 1 year of life lived by an individual, whether affected by an illness or unencumbered by disease. The study assigns equal value to all person-years in all environments and circumstances. Building on that, additional units considered are 'Years of Life Lost' (YLL), the number of years lost due to premature mortality and 'Years Lived with Disability' (YLD), years lived in less than ideal health due to the affecting illness.

While premature mortality has a universally standard effect on quality of life regardless of the affliction that caused it, YLD exists on a spectrum depending on the intensity of the disability. YLD disabilities include conditions such as influenza, which may last for only a few days, or blindness, which can last a lifetime. To account for the varied intensity of YLD affects, the Global Burden of Disease study assigns Disability Weights to each ailment being evaluated.

'Of course it's not the same to live 1 year in a wheelchair as 1 year in a cemetery' Dr Stovner said, 'so there must be some way to adjust for this; we can't just add them'.

Disability Weight is that adjustment. Determining Disability Weight, which is reflected as a value between 0 and 1 assigned to each specific illness being studied, presents significant standardisation challenges. The solution was a broad public survey of more than 30,000 individuals in many countries that presented various conditions and symptoms in paired comparisons. Respondents would be presented two lay descriptions of hypothetical people, each with a randomly-selected condition, and indicate which person is 'healthier'. This placed each individual condition on a value-based spectrum adjusted for cultural diversity, as in the case where some cultures may evaluate loss of sight and loss of hearing differently.

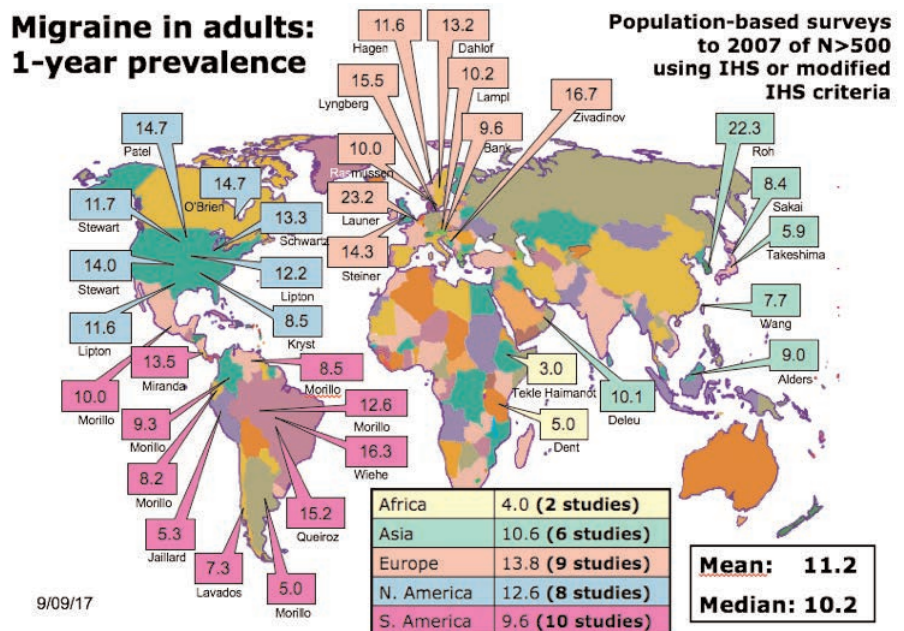
As a point of cross-reference, researchers then conducted a second survey using similarly paired Population Health Equivalence questions focused on disease treatment priorities. Similar hypothetical questions were posed to respondents. For example, imagine two health programmes, one that prevented 1,000 people from getting an illness that caused rapid death, and one that prevented 2,000 people from getting an illness that is not fatal, but causes complete deafness. Which programme would you say produced the greater overall population health benefit? The resulting disease rankings from this line of questioning were cross-referenced with the symptom intensity questions to produce a numerical value between 0 and 1 for each disease.

Thus, a ranking and numerical value is assigned to all illnesses considered in the complex global public health decision-making process, which includes resource allocation and determining the urgency of a necessary response as in the case of the Ebola and Zika health crises. On that scale, tension headaches have a Disability Weight of 0.037, medication overuse headache ranks at 0.223, and migraine, the third most prevalent and sixth most disabling medical illness in the world, has a Disability Weight of 0.441 out of 1.

The idea behind this, in lifting the burden of headache, is that headache is not a luxury disease that should be treated only in the US, Canada and Europe

Establishing a formula to translate migraine prevalence and expression across diverse environments into data allows for the broader study of patterns in global migraine experiences, which has led to some illuminating observations. Timothy Steiner, Director of the Global Campaign against Headache, spoke to the importance of studying worldwide migraine data to better understand this often mystifying disease.

In comparing the statistically low prevalence of migraine in China, Taiwan and Japan to the rates in neighbouring Nepal, which has the highest recorded instance of migraine, researchers uncovered an unexpectedly direct correlation between migraine incidence and altitude. 'We weren't really aware of how strong the influence of altitude is, not just to the prevalence, but to the expression of migraine' Dr Steiner said.



The ongoing commitment of IHS to nurture collaboration and data-sharing with headache specialists from across the globe represents a continued investment in advancing the global, longitudinal study of migraine, and together finding the answers hidden within.

'The idea behind this, in lifting the burden of headache, is that headache is not a luxury disease that should be treated only in the United States, Canada and Europe,' said Session Chair Zaza Katsarava, Department Chief of Neurology at Evangelical Hospital in Unna, Germany. 'I think this is very important work that demonstrates how important headache is all over the world.'

These new developments in acute and preventive treatments of migraine and cluster headache reinforce that this is a critical time in neurology, chronic pain and the field of headache

Lifting The Burden

1-year prevalence of migraine in population-based door-to-door studies

India (N=2,329) 25.6%	Georgia (N=1,145) 15.6%
Nepal (N=2,100) 34.7%	Russia (N=2,023) 20.3%
	Lithuania (N=578) 18.8%
Pakistan (N=4,223) 22.9%	
Saudi Arabia (N=2,316) 25.2%	Zambia (N=1,085) 22.9%
Morocco (in analysis)	Ethiopia (N=2,461) 20.4%
	Global mean in 2007:
China (N=5,041) 9.3%	Mean: 11.2
Mongolia (in progress)	Median: 10.2

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TJ Steiner

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new developments in the acute and preventive treatments of migraine and cluster headache

The results of five clinical trials demonstrated new acute therapy and preventive treatment options for both migraine, chronic migraine and cluster headaches.

'These new developments in acute and preventive treatments of migraine and cluster headache reinforce that this is a critical time in neurology, chronic pain and the field of headache' noted David Dodick.

Migraine acute therapy

Comparative effects of three doses of zolmitriptan patch (M207) and placebo on pain and most bothersome symptom for the acute treatment of migraine: the ZOTRIP study

Results of a study showing the comparative effects of three doses of zolmitriptan patch (M207) and placebo show that M207 (ZP-zolmitriptan) 3.8 mg, the largest dose tested, was effective and well tolerated for the acute treatment of migraine. Efficacy was robust across several subgroups of traditionally difficult to treat subjects. The most common adverse events were application site reactions (redness and bruising) and >90% of these were considered mild. The most common neurological adverse event was dizziness, reported in 4.4% on M207 3.8 mg patients (Abstract OC-MC-001). The study was designed to compare three different doses of the ZP-zolmitriptan patch to placebo in the acute treatment of adults with migraine, in search of a treatment option with fewer side effects.

Migraine preventive therapy

Efficacy of erenumab in subjects with episodic migraine with prior preventive treatment failure(s)

The STRIVE trial was a large, multicentre, double-blind, placebo-controlled, phase III study of erenumab 70 mg and 140 mg, a fully human calcitonin gene-related peptide (CGRP) receptor

monoclonal antibody. This study previously demonstrated both doses to be superior to placebo in reducing mean monthly migraine days. In a separate analysis of patients who had failed ≥ 1 or ≥ 2 previous oral preventive migraine medications, erenumab was shown to be superior to placebo in both subgroups. The odds of responding to erenumab increased in those who failed more than two prior preventive medications since the placebo response was attenuated. This analysis suggested that erenumab is effective in those patients who have failed multiple previous preventive medications. In a separate prospective trial in patients who had failed prior preventive medications, these results were confirmed (Abstract OC-MC-002). This study explores new treatment options to satisfy the high unmet need for new preventive migraine treatments, especially for patients who have failed existing migraine therapies.

A single intravenous administration of ALD403 (eptinezumab) reduces use of triptans among patients with chronic migraine

In a study examining the triptan use of chronic migraine patients, patients aged 18–55 received a single intravenous administration of ALD403 (eptinezumab) or a placebo. Results recording triptan use over a 12 week post-administration period demonstrated a rapid decline from baseline after the drug was administered, with high triptan users demonstrating the most significant change. This study explores new methods to treat those living with chronic migraine and medication overuse headache, who are also high triptan users. A single monthly injection of eptinezumab may provide a treatment strategy that enables difficult to treat patients with chronic migraine and triptan overuse headache to reduce their use of acute headache medications and minimise headache-related disability (Abstract OC-MC-004).

Cluster headache and other trigeminal autonomic cephalalgias

Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache

Findings from the randomised, double-blind, sham-controlled ACT2 study of non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache show that the device was superior to placebo in patients with episodic cluster headache, but not for patients with chronic cluster headache (Abstract OC-MC-003). This study explores new treatment options to satisfy the high unmet need for new preventive migraine treatments, especially for patients who have failed existing cluster headache therapies.

Genetics and biomarkers of headache disorder

Genomic variants related to verapamil response in the treatment of migraine

Verapamil is an L-type calcium channel blocker that exerts a prophylactic effect in a subgroup of migraine patients. In a study designed to test the effectiveness of verapamil, while also analysing the DNA of participants to look for patterns between DNA and response to the drug, patients were separated into categories of responsiveness, then genotyped to measure the genetic variations of single nucleotide polymorphisms. In the first study of its kind, functional molecular identifiers relevant to the anti-migraine action of the drug investigated were identified, which may be useful in the prediction of response or non-response to treatment with verapamil (Abstract OC-MC-005). This study investigates a biologically-based rationale for drug selection for migraine, which may lead to more effective prediction of the effectiveness of migraine treatment options on an individual level.

Single-pulse TMS demonstrated significant potential as a non-invasive therapy, providing acute and preventative relief without major safety concerns

Migraine and neuromodulation treatments – review of new data on neuromodulation treatments in primary headache

Migraine is a debilitating disease with no cure, so many sufferers rely on medications to prevent or alleviate their attacks. However, frequent drug intake carries its own risks, including medication overuse headache (MOH), which decreases the effectiveness of treatment and can only be treated by stopping medications. For patients who risk MOH by necessity due to intense, crippling migraines, abstaining from treatment altogether is a paralysing prospect. This conundrum makes advances in the field of neuromodulation particularly exciting for patients and doctors alike.

Neuromodulation is the alteration of nerve activity through the delivery of a targeted stimulus—electrical, thermal, magnetic or chemical—directly to the site responsible for a patient's pain. For both the preventive and acute treatment of migraine, devices are available in both invasive and non-invasive forms.

Matthew Robbins of the Albert Einstein College of Medicine, USA, and Delphine Magis of the University Department of Neurology at CHR Liège in Belgium each overviewed the results of recent studies into two promising arenas of migraine treatment via neuromodulation: central and peripheral. Each survey summarised progress in the ongoing effort to close the wide gap in preventive treatment options for patients with migraine who have limited options to reduce the frequency and intensity of their attacks.

'We know that new therapies are needed because chronic migraine is very common, very burdensome, and persists' Dr Robbins said. 'Chronic cluster headache, and the chronic forms of other headaches, are also terribly devastating, and cluster headache itself has a lifetime prevalence of 1 in 1,000, which is quite high, equal to a disease like multiple sclerosis, which receives way more attention.'

Dr Robbins overviewed new data on the safety and efficacy of several types of central neuromodulation, which targets the central nervous system, i.e. the brain and spinal cord, to strategically stimulate nerves to manipulate their behaviour. He surveyed new research into several subtypes of transcranial magnetic stimulation (TMS), which affect nerve activity via magnetic pulses, transcranial direct current stimulation (tDCS), which uses electrical currents, and several additional novel stimulation techniques. Both electrical and magnetic stimulation strategies have proven to be effective therapies for neurological conditions including depression and schizophrenia in the past, and new experiments tested their potential to treat migraine as well.

Tests of multiple neuromodulation techniques for specific subgroups of migraine patients, including pregnant women, patients with migraine with aura, show that single-pulse TMS (sTMS) demonstrated significant potential as a non-invasive therapy, providing acute and preventative relief without major safety concerns. Conversely, studies involving repetitive TMS (rTMS), tDCS and cervical cord stimulation provided less evidence to support their effectiveness for headache prevention. Hypothalamic deep brain stimulation, a technique being studied for the treatment of chronic cluster headache, short-lasting unilateral neuralgiform headache (SUNCT) and other trigeminal autonomic cephalalgias (TACs), didn't prove to have broad therapeutic reach, but might have potential for long-term improvement in patients with the most severe and chronic forms of migraine who haven't responded to other treatments.

Empowering patients to identify and recognise their premonitory symptoms can be an essential tool in managing and forestalling their pain, and variations in a patient's premonitory symptoms can provide valuable insights into the changing nature of their disease

Similarly, Dr Magis provided a survey of recent developing therapies that stimulate the peripheral nervous system, targeting nerves outside the brain and spinal cord that communicate with the central nervous system. 'If I had to explain this to a patient, I would say it will activate the descending pain pathway' Dr Magis said of peripheral nervous system stimulation.

New treatment strategies in her overview included invasive strategies like sphenopalatine ganglion stimulation, achieved with devices like Pulsante™, which is implanted in the gums to treat chronic cluster headache, and occipital nerve stimulation, achieved with a device implanted at the base of the skull that targets cluster headache and chronic migraine. Non-invasive peripheral nervous system treatments included external trigeminal nerve stimulators, like Cefaly®, which sticks an electrode to the patient's forehead to deliver electrical pulses for episodic migraine, and external vagus nerve stimulators like gammaCore®, which patients press to their neck to treat cluster headaches. New, novel devices whose recent evaluations Dr Magis also touched on were Nerivio, a stick-on arm patch for remote electrical stimulation, and a caloric vestibular stimulation device used to identify nerve damage in the ear. Dr Magis challenged the efficacy of caloric vestibular stimulation citing research results that found 'the sham stimulation was as effective as the true stimulation'.

Dr Magis' survey of peripheral neuromodulation treatments summarised the potential of each treatment approach broadly by category. Sphenopalatine ganglion stimulation, like the Pulsante™ implant, proved useful for both acute and preventive treatment of cluster headaches. Invasive occipital nerve stimulation showed encouraging results for chronic cluster headache treatment, as did non-invasive vagus nerve stimulation like the gammaCore® device, but Dr Magis noted that both need additional randomised controlled trials before conclusions can be drawn about the effectiveness of either strategy. As an acute migraine treatment, external trigeminal nerve stimulation therapies like Cefaly® require more testing, as do the emerging therapies whose overall efficacy is inconclusive at this stage.

The slow pace of innovation in medical treatment is a necessity to ensure therapies are safe, effective and fully understood before they're administered to patients. But migraine and headache researchers, despite being vastly outnumbered, with one specialist for every 65,000 individuals living with migraine in the USA, are unrelenting in their pursuit of new treatments to provide relief to the more than 1 billion sufferers living with migraine and headache around the world.

The premonitory phase of migraine: what is the brain trying to tell us during the prodromal stage of migraine?

Migraine attacks are crippling when they hit, and for patients who rely on acute treatments to curb their symptoms before they worsen, early detection can be the difference between successfully preventing a full-blown attack or reacting too late for medication to be effective. Empowering patients to identify and recognise their premonitory symptoms can be an essential tool in managing and forestalling their pain, and variations in a patient's premonitory symptoms can provide valuable insights into the changing nature of their disease. Peter Goadsby, Professor of Neurology at King's College London, UK, presented insights into the root causes of common premonitory symptoms and what clues they may provide to patients and clinicians.

'What we need to start to understand is the more complete nature of the [migraine] attack, because every aspect of the attack has some element of disability, and if it has an element of disability it behoves us to understand that' Dr Goadsby said to preface his presentation.

Premonitory symptoms can appear anywhere between 2 and 48 hours before a migraine attack, preceding aura for patients whose migraine includes aura, and preceding head pain in migraine patients who do not have aura. The most commonly reported premonitory symptoms are

The long-term goal would be to understand the relationships between premonitory symptoms and corresponding brain activity precisely, so that the most effective treatment method for each migraine attack could be determined based on which symptoms are appearing in the prodrome phase

tiredness, yawning, concentration impairment, neck stiffness, mood change, increased urination and food cravings, typically for sweets like chocolate. Recent studies of these symptoms have uncovered specific neurological activities that correspond to these feelings, shifting conventional theories that they were triggers or early symptoms of a migraine attack, to the new understanding that they are symptomatic of a distinct pre-migraine prodrome phase.

Several of these symptoms, particularly mood change, tiredness, stiffness and concentration impairment, also frequently appear in the post-attack 'post-drome' phase. To confirm their relationship with the premonitory phase, new research has sought to isolate these symptoms by various methods including longitudinal observation of patients to study their premonitory experiences independently, administering medications during the premonitory and migraine phases to suppress certain symptoms so others can be examined, and inducing premonitory symptoms in patients not experiencing a migraine attack by manipulating the specific neurological functions known to correlate to premonitory symptoms.

Building on insights into the brain function accompanying yawning and tiredness in prodrome, which research suggests relates to dopamine levels, led neurologists to experiment with apomorphine with and without domperidone. In migraine patients administered apomorphine without domperidone, subjects experienced more nausea, sweating, vomiting and dizziness, always preceded by yawning and drowsiness. In apomorphine with domperidone tests, all symptoms were reduced, with yawning and drowsiness unaffected.

As headache specialists continue to discover neurological processes that correspond to premonitory symptoms, doctors will be better able to diagnose the specific causes of individual attacks, and treat those causes specifically. The long-term goal would be to understand the relationships between premonitory symptoms and corresponding brain activity precisely, so that the most effective treatment method for each migraine attack could be determined based on which symptoms are appearing in the prodrome phase.

'It's an incredibly exciting way to link the neurobiology of the brain to that clinical problem that we are most interested in: these primary headache disorders, and in particular, migraine' Dr Goadsby said.

Who is vulnerable to migraine? The role of genetics and epigenetics

Migraine is a painful, disabling disease, and the severity of its symptoms can be compounded by the unpredictability of its onset. New data presented by a panel of experts at the IHC seeks to identify some of the contributing factors that may help determine a person's likelihood of experiencing migraine attacks.

Gisela Terwindt, a neurologist at Leiden University Medical Center, The Netherlands, and also a biologist, and Franziska Denk of King's College in London, UK, explored the role of genetics and epigenetics, respectively, in determining an individual's vulnerability to migraine.

Genetic predisposition to migraine has been long established due to its observable hereditary link: a child who has one parent with migraine has a 50% chance of inheriting it, and if both parents have migraine, the chances rise to 75%. Broad genetic factors like gender directly affect a patient's migraine threshold: the tipping point when a migraine attack is either deflected, or when the symptoms take hold. Having a low baseline, intrinsic

By studying how multiple small, adverse environmental effects on epigenetic 'memory' shape the long-term sensitisation of the nervous system, leading to chronic pain, doctors can map out pathways to combat these adverse effects

threshold to migraine makes the influence of external factors known to exacerbate migraine—like sleep deprivation, caffeine or loud noises—more likely to tip the scales and trigger an attack.

However, there is no one gene that causes the disease. Dr Terwindt's research advances the prediction model for migraine vulnerability, examining genetic factors that increase not only the likelihood of developing the disease, but also factors that can help predict the intensity of migraine attacks, and their frequency. Dr Terwindt explained that although there is no one 'migraine gene', doctors can look for a selection of multiple genetic factors, called genetic risk variants, and examine how they overlap to determine a person's susceptibility to migraine.

Multiple risk variants appearing together may increase the risk for migraine. For example, the likelihood of finding a mutation in the CACNA1A, ATP1A2 or SCN1A genes, all known to be associated with a rare type of migraine with aura called hemiplegic migraine, is increased in patients who also experience epilepsy, patients who had migraine onset at a young age, or who have relatives also affected by the disease. While these commonalities don't explicitly prove that any specific gene causes migraine, the trend suggests that genome-wide association studies can help to identify causal pathways for migraine. Patients with multiple risk factors are more likely to experience migraine, and taking an inventory of how many factors affect a patient can help paint a more complete portrait of their disease.

In a companion presentation at the congress, Franziska Denk also explored risk factors for migraine onset or progression, but from the perspective of epigenetics. Epigenetics looks at the influence external factors can have on gene expression, from diet, to environment, to stress levels to age. 'It's clear that some of us are more vulnerable to develop migraine, and to develop a chronic migraine condition, than others' Dr Denk said.

The promise of epigenetics, according to Dr Denk, is that by studying how multiple small, adverse environmental effects on epigenetic 'memory' shape the long-term sensitisation of the nervous system, leading to chronic pain, doctors can map out pathways to combat these adverse effects, which could pave the way for treatments that target and reverse these effects.

'What is happening in your body when you experience chronic stress that makes it likely you will develop a more chronic migraine condition?' she asked at the beginning of her presentation. While Dr Denk qualified that her research, which mostly consisted of animal models of pain, provides only tentative, early evidence for the involvement of epigenetics in patients' migraine experiences, she asserted that these early findings emphasise a need for further, innovative studies of these factors.

Medical comorbidities of migraine: results from the Chronic Migraine Epidemiology and Outcomes (CaMEO) study

Richard Lipton, Director of the Montefiore Headache Center, New York, USA, presented insights from his research into commonly-occurring comorbidities in migraine patients.

'Migraine is a multi-faceted disease that often presents with a variety of comorbidities' Dr Lipton said. 'Many of the comorbidities are more common in chronic migraine than in episodic migraine, and understanding why that's true, I think, is something that's worthwhile.'

Dr Lipton's Chronic Migraine Epidemiology and Outcomes (CaMEO) Study was designed to characterise the course of disease, to define its societal, familial, and economic burden, and to characterise comorbidities in people with migraine. Examining a systematically recruited sample of people with either episodic or chronic migraine, subjects were asked to complete surveys every 3 months for 15 months in 2012 and 2013 reporting any appearance of 64 symptoms (e.g. dizziness) and conditions (e.g. asthma). Responses relating to 31 respiratory, cardiovascular,

I view this work on comorbidity as one of many early steps in the effort to develop a biologically-based and not just a symptom-based classification of migraine

gastrointestinal, sleep-related and other symptoms and conditions were isolated and analysed relative to their frequency of occurrence in respondents with chronic migraine versus episodic migraine.

The data demonstrated significantly higher comorbidities in patients with chronic migraine than in patients with episodic migraine, with allodynia, anxiety, moderate to severe depression and a higher MIDAS (migraine disability assessment) score proving to be particularly associated with a chronic migraine diagnosis. Significantly more respondents with chronic migraine versus episodic migraine reported having specific medical symptoms or conditions in general as well, and each of the 31 conditions and symptoms studied appeared more frequently in respondents with chronic migraine than in those with episodic migraine. Dr Lipton postulated that these manifestations could be a product of direct or reverse causality, as well as overlapping genetic or environmental risk factors. He also offered that some reported symptoms may be manifestations of migraine.

Ultimately, Dr Lipton said he hopes this research will lay the groundwork to develop diagnoses that are informed by the appearance of specific migraine comorbidities and, in turn, guide treatment choices to offer sufferers optimal solutions for relief. 'I view this work on comorbidity as one of many early steps in the effort to develop a biologically-based and not just a symptom-based classification of migraine' Dr Lipton said. 'The goal is to get past a world in which we have a list of effective treatments and we choose them based on side effects and in a quasi-random fashion.'

Anecdotally, the CaMEO Study also observed that respondents with chronic migraine were more likely to be female, white, with a higher body mass index and in a lower income bracket than respondents with episodic migraine.

Summary of scientific highlights IHC 2017

Nathan Gaw, Julia Hebestreit, Dennis Kies and Anker Stubberud

The International Headache Society awarded 30 travel grants to junior physicians and researchers from all over the world to attend IHC 2017. Three of these were tasked with preparing a summary of the IHC scientific highlights.

Novel clinical research

The 18th Congress of the International Headache Society was held in Vancouver from 7–10 September 2017 under the aphorism 'New Horizons in Headache'. We were certainly shown that new horizons are emerging in every aspect of headache research, including clinical headache research, new treatment targets, genetic insights and imaging.

In his talk about the clinical highlights of the conference, David Dodick emphasised the great importance of the emerging calcitonin gene-related peptide (CGRP) antibodies and antagonists in the treatment of headache disorders, as they offer us the opportunity to better understand the neurobiology of diseases. Several companies presented auspicious data on efficacy and safety of CGRP receptor antagonists and antibodies, underlining the promise of these emerging new treatment options (EP-01-013, EP-01-014, EP-01-016, EP-01-017, PO-01-072, PO-01-085, PO-01-087).

Whereas several studies established the efficacy of erenumab in migraine preventive treatment, effectiveness in acute treatment of patients with chronic migraine and aura was also demonstrated (EP-01-014, EP-01-015, EP-01-016). Early onset efficacy in a phase II clinical trial was reported by Uwe Reuter (Germany), while Peter Goadsby presented some interesting results establishing the efficacy of erenumab in patients who previously failed prior prophylactic

The CGRP antibodies and antagonists... might revolutionise treatment by being the first migraine-specific preventive drugs

KOR blockade in the right central nucleus of the amygdala prevented stress induced cephalic and extracephalic allodynia

treatments (OC-MC-002). These results suggest erenumab to be particularly useful in this subgroup of patients. Furthermore erenumab displayed a reduction of the impact of episodic migraine on functional outcomes in the STRIVE trial, a phase III, randomised, double-blind study (EP-02-035, PO-02-103). Interestingly a study on the effect of fremanezumab on trigeminovascular neurons found this humanised monoclonal CGRP antibody acting at the dural receptor site and proposed that a peripheral site drives the initiation and maintenance of the headache phase of migraine (EP-02-052). Moreover a study indicates that fremanezumab potentially prevents migraine progression to chronic forms (PO-01-080) and decreases migraine symptoms such as nausea, photo- and phonophobia (PO-01-082). In their PROMISE-1 trial, a phase III study, Baker and colleagues (PO-01-085) reported a reduction of monthly migraine days in frequent episodic migraineurs after intravenous eptinezumab treatment over 12 weeks with a responder rate of 50–75%. Eptinezumab also displayed an acute effect at a dose of 300 mg and 100 mg. In another study single intravenous administration of eptinezumab reduced the use of triptans among patients with chronic migraine (OC-MC-004). Reviewing all these promising results from monoclonal antibodies conducted in mainly healthy populations, it might also be important to test them in at-risk patient populations. This aspect was addressed by Christophe Depre from Amgen in his talk where he presented results of a double-blind placebo-controlled study demonstrating that CGRP receptor inhibition by erenumab did not aggravate myocardial ischaemia. Especially with regard to the CGRP antibodies and antagonists, this is a very exciting time in migraine research since most of them are about to be added to the therapeutic armamentarium within the next few years and might revolutionise treatment by being the first migraine-specific preventive drugs.

With nausea being one of the most bothersome migraine symptoms (Munjal et al. IHC2017), oral administration of acute medication is sometimes not feasible. Richard Lipton presented results from a web-based population study in over 15,000 patients describing their symptoms and emphasising the need for fast-acting, non-oral formulae. That need is met by the zolmitriptan patch presented by Zosano, which reaches peak plasma concentration very quickly compared with the oral formula. Promius Pharma presented DFN-02, a nasal sumatriptan spray (10 mg) with an added permeation enhancer, which leads to a quick absorption and efficacy in less than 30 minutes in 44% of patients. Results on the efficacy of lasmiditan (PO-02-180) suggest that this 5-HT_{1F} receptor agonist for the acute treatment of migraine might be available soon. 31% of patients had a pain-free response after 2 hours at a dose of 100 mg; a dose of 200 mg raised the number of responders to 38% (SPARTAN).

Novel treatment targets

One of the other new horizons in headache research are new emerging treatment targets. During the Presidential Symposium, Frank Porreca (USA) gave an overview of new potential treatment targets for migraine, both pharmacological and non-pharmacological, giving us an idea of what might be available as treatments in the future.

The kappa opioid receptor (KOR) is emerging as a potential migraine treatment target. Dr Porreca gave a talk during the 'Emerging targets for migraine treatment' session, explaining how sumatriptan priming is shown to lead to lowered stress-induced trigger thresholds for eliciting migraine attacks in rats. Dr Porreca's research group used an injury-free rat model with features of migraine and medication overuse headache (MOH) to test the use of KOR antagonist to reduce this stress-induced pain. They showed that KOR blockade in the right central nucleus of the amygdala prevented stress induced cephalic and extracephalic allodynia.¹ KOR antagonists may be used to counter this stress-induced mechanism, and thus serve as a potential treatment target. This was also investigated in a study by Nation et al. (EP-02-042) where KOR signalling in the central nucleus of the amygdala was shown to promote a loss of diffuse noxious inhibitory control in MOH rat models.

A PAC-1 antibody inhibits stimulus-evoked neuronal activity in the trigeminal complex, and may serve as a potential preventive treatment target for migraine

Vagus nerve stimulation induces rapid onset of analgesia in healthy subjects and warrants further research for use in acute and preventive treatment of primary headaches

Pituitary adenylate cyclase (PAC)-activating polypeptide 38 and its receptor PAC-1 have also been hypothesised as a potential treatment target. In a study by Hoffmann et al. the use of PAC-1 receptors in an in vivo rat model were investigated (OC-BA-004). They concluded that a PAC-1 antibody inhibits stimulus-evoked neuronal activity in the trigeminal complex, and may serve as a potential preventive treatment target for migraine.

Some interesting insights into the use of green light therapy, a potential migraine prophylaxis, were also reported. Poster EP-01-001 outlined a study that recruited over 900 patients to evaluate colour-dependent light sensitivity during migraine attacks, and found that green lights reduces discomfort. Furthermore, green light therapy in rats was shown to elicit an anti-nociceptive effect persisting for several days following therapy.² The authors hypothesise that green LED therapy may represent a novel, non-pharmacologic approach for pain management.

In addition, nerve stimulation is emerging as a treatment option. A non-invasive vagal nerve stimulation device was featured by Cristina Tassorelli (Italy). This was investigated in a cross-over sham-controlled study (PO-01-029). The study demonstrated that vagus nerve stimulation induces rapid onset of analgesia in healthy subjects and warrants further research for use in acute and preventive treatment of primary headaches. Similarly, the randomised double-blind sham-controlled ACT1 and ACT2 studies showed that non-invasive vagal nerve stimulation was effective in the acute treatment of cluster headache (OC-MC-003, EP-02-005). On the other hand, greater occipital nerve blocks were also evaluated with regard to effectiveness and tolerability for preventive cluster headache treatment (PO-02-017, PO-02-019).

Novel genetic insights

A third new horizon in headache research is the role of genetics in migraines. In the Presidential Symposium, Michel Ferrari (Netherlands) gave an overview and highlighted several new developments of this incipient field.

Some studies found new insights of genetic factors that play a role in cluster headache (PO-02-050, OC-TR-003, PO-02-040). A study conducted by Fourier et al. found that the clock gene CRY 1 expression levels are significantly higher in cluster headache patients compared to controls (OC-TR-003). CRY 1, being one of the key regulators of the circadian clock, may trigger periodically reoccurring cluster headache attacks. However, more research needs to be performed to determine the exact role of CRY 1. Ran and colleagues (PO-02-050) found that the migraine SNP rs1835740 was associated with increased risk for cluster headache in Sweden. When considering patients who suffer from cluster headache and migraine the association of rs1835740 becomes even higher, suggesting that this genetic variant may be a biomarker for severe headache in general.

The functions of genetic markers in cortical spreading depression (CSD) were also further elucidated (EP-02-045, EP-02-046, EP-02-047, EP-02-050, PO-02-144, OC-TR-004). Unekawa (EP-02-047) and Auffenberg (EP-02-050) conducted studies that suggest that patients with familial hemiplegic migraine types 2 or 3 (FHM2 or FHM3) may exhibit high susceptibility to CSD. Additionally, Loonen et al (OC-TR-004) demonstrated that optogenetic CSD induction has significant advantages over current CSD models and that CSD propagation rates were elevated in familial hemiplegic migraine type 1 (FHM1) mice when compared with wild-type. Ma (EP-02-046) found that the P2X7 receptor not only mediates cortex susceptibility to CSD, but also contributes to inducing inflammatory factor TNF- α post CSD.

Novel innovations in imaging

The final new horizon covered in IHC 2017 was imaging. During the Presidential Symposium, Todd Schwedt (USA) discussed several advances of imaging in migraine as well as the view for the future. Topics covered in this discussion included discovering new MRI biomarkers to predict

Combining structural and functional MRI, it was shown that a significantly higher migraine classification accuracy can be achieved than by using a structural or functional MRI alone

migraine outcomes,³ finding new migraine subtypes using MRI data,⁴ more advanced radiomics,⁵ and dynamic functional connectivity.⁶

A study conducted by Schulte and colleagues (EP-01-002) found that chronic migraine is mediated by the hypothalamus. When chronic migraineurs were compared with healthy controls, the anterior right hypothalamus was found to be significantly more activated. Additionally, it was found that the posterior region of the hypothalamus is more strongly activated during headaches.

Lai (EP-01-025) also found white matter microstructural changes related to patients with MOH. When MOH patients were compared with controls, it was found in the parietal white matter (PWM) that the fractional anisotropy value was significantly lower ($p = 0.002$) and the mean and radial diffusivity values were significantly higher ($p = 0.001$). Thus, it was concluded that microstructural PWM damage is a characteristic of MOH.

Another study (OC-TR-001) developed a clinical decision support system that combines multiple MRI imaging modalities for migraine classification using a novel constrained particle swarm optimiser. Combining structural and functional MRI, it was shown that a significantly higher classification accuracy can be achieved than by using a structural or functional MRI alone ($p < 0.01$).

Chiang and colleagues (EP-01-029) found that patients with more frequent post-traumatic headache (PTH) had less cortical thickness in the right superior frontal region. From cortical thickness measures calculated from T1-weighted images obtained on a Siemens 3 Tesla scanner, it was found that patients with persistent PTH had significantly less cortical thickness than healthy controls in the left rostral middle frontal and bilateral precentral, superior frontal and caudal middle frontal areas ($p < 0.01$). This suggests that brain integrity of patients with PTH may be modulated by headache frequency.

Lastly, Kies (OC-IM-002) investigated whether resting-state functional connectivity (rs-fc) measures in chronic migraine patients can be used to predict a favourable outcome after treatment. It was found that chronic migraineurs who responded to treatment (by reverting to episodic) demonstrated a significantly higher rs-fc in the lateral visual network when compared to non-responders.

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Presentation references

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Oral presentations

- OC-BA-004 Nociceptive trigeminal neurotransmission is inhibited by a PAC-1 receptor antibody in an in vivo model relevant to migraine
Jan Hoffmann
- OC-IM-002 Resting-state functional connectivity in the visual network: a possible predictor for treatment response in chronic migraine
Dennis A Kies
- OC-MC-001 Comparative effects of 3 doses of zomig patch (M207) and placebo on pain and most bothersome symptom for the acute treatment of migraine: the Zotrip study
David Kudrow
- OC-MC-002 Efficacy of erenumab in subjects with episodic migraine with prior preventive treatment failure(s)
Peter J Goadsby
- OC-MC-003 Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: findings from the randomized, double-blind, sham-controlled ACT2 study
Peter J Goadsby
- OC-MC-004 A single intravenous administration of ALD403 (eptinezumab) reduces use of triptans among patients with chronic migraine
David Dodick
- OC-MC-005 Genomic variants related to verapamil response in the treatment of migraine
Fred Cutrer
- OC-TR-001 A clinical decision support system using multi-modality imaging data for migraine classification
Nathan Gaw
- OC-TR-003 The clock gene CRY1 is associated with cluster headache in Sweden
Carmen Fourier
- OC-TR-004 Functional characteristics of non-invasively optogenetically induced csd in fhm1 mutant mice
Inge C M Loonen

Poster presentations

- EP-01-001 Ambient light color variably influences migraine pain intensity and discomfort in the ictal and interictal phase
Kiyoshi Niwa
- EP-01-002 Chronic migraine is mediated by the hypothalamus
Laura Schulte

- EP-01-013 Efficacy of erenumab for the treatment of patients with chronic migraine in presence of medication overuse
Stewart J Tepper
- EP-01-014 Efficacy of erenumab for the treatment of patients with chronic migraine and aura
Messoud Ashina
- EP-01-015 Early onset of efficacy in a phase 2 clinical trial of erenumab in patients with chronic migraine
Uwe Reuter
- EP-01-016 Chronic migraine treatment with erenumab: responder rates
Jan L Brandes
- EP-01-017 Fremanezumab (formerly TEV-48125) reduces headache pain within the first week of beginning treatment in the phase 2 episodic migraine study
Ernesto Aycardi
- EP-01-025 White matter microstructural changes associated with medication overuse in patients with migraine
Tzu-Hsien Lai
- EP-01-029 Cortical thickness in patients with persistent post-traumatic headache
Chia-Chun Chiang
- EP-02-005 Non-invasive vagus nerve stimulation for acute treatment of episodic and chronic cluster headache: pooled analysis of data from two randomised, double-blind, sham-controlled clinical trials
Ilse F de Coo
- EP-02-035 Reducing the impact of migraine on functioning: results from the STRIVE trial: a phase 3, randomized, double-blind study of erenumab in subjects with episodic migraine
Richard B Lipton
- EP-02-042 Endogenous signaling at kappa opioid receptors (KORs) in the central nucleus of the amygdala promotes a loss of diffuse noxious inhibitory controls (DNIC) in a rat model of medication overuse headache
Kelsey M Nation
- EP-02-045 Inhibitory effects of the histone deacetylase inhibitor, Vorinostat, on early life stress-induced increases in CSD susceptibility and anxiety-like behavior in male rats
Stuart Collins
- EP-02-046 P2X7 receptor regulates CSD and CSD-induced TNF- α induction
Dongqing Ma
- EP-02-047 Enhanced susceptibility to cortical spreading depression and different degree in two-types of Na⁺,K⁺-ATPase α 2 subunit-deficient mice as a model of familial hemiplegic migraine 2
Miyuki Unekawa

- EP-02-050 A novel mouse model for familial hemiplegic migraine type 3 reveals increased susceptibility for cortical spreading depression
Eva Aufferberg
- EP-02-052 Selective inhibition of trigeminovascular neurons by fremanezumab
Agustin Melo-Carrillo
- PO-01-029 Peripheral vagal nerve stimulation modulates the nociceptive withdrawal reflex in healthy subjects: a cross-over placebo-controlled study
Roberto De Icco
- PO-01-072 Sustained reduction in days using acute medications with fremanezumab (TEV-48125)
Rashmi Halker
- PO-01-080 Treatment-induced improvement in migraine classification in the fremanezumab HFEM study
Robert Noble
- PO-01-082 Fremanezumab (formerly TEV-48125) decreases migraine symptoms such as nausea, vomiting, photophobia and phonophobia and reduces the need for acute medications in the first week of treatment in the HFEM study
Ernesto Aycardi
- PO-01-085 Rational design of a monoclonal antibody inhibiting calcitonin gene-related peptide, ALD403 (eptinezumab), to provide early onset, high efficacy, extended duration of action, and desired safety for the prevention of migraine
Brian Baker
- PO-01-087 Effect of anti-CGRP receptor antibody AA58 on CGRP receptor internalization and trafficking
Cen Xu
- PO-02-017 RNA-sequencing of trigeminal ganglia and dorsal root ganglia gives insight in transcriptomic differences between the trigeminal and spinal system
Lisette J A Kogelman
- PO-02-019 S100B protein, a marker of trigemino-vascular system glial activation, is not increased in chronic migraine
Julio Pascual
- PO-02-040 Noonan syndrome associated with migraine and cluster headache
Veselina Grozeva
- PO-02-050 Involvement of the migraine SNP rs1835740 in cluster headache
Caroline Ran
- PO-02-103 Reducing impaired days: results from the STRIVE trial, a phase 3, randomized, double-blind study of erenumab for episodic migraine
Richard B Lipton

- PO-02-144 Cortical spreading depression alters expression of inflammatory gene transcript in the dura: (a) sex effects (b) effects of pretreatment with onabotulinumtoxinA
Agustin Melo-Carrillo
- PO-02-180 Phase 3 study (SPARTAN) of lasmiditan compared to placebo for acute treatment of migraine
Linda A Wietecha

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Calendar of events

Date	Event	Country	Contact/information
2018			
10 January	3rd Annual International Headache Symposium in Israel	Tel Aviv, Israel	www.ihsi2018.com
22–25 March	12th World Congress on Controversies in Neurology (CONy)	Warsaw, Poland	www.comtecmed.com/cony/2018
21–28 April	American Academy of Neurology 70th Annual Meeting	Los Angeles, USA	www.aan.com/conferences/annual-meeting/
9–12 May	9th World Congress of the World Institute of Pain	Dublin, Ireland	www.wip2018.kenes.com
16–18 May	4th European Stroke Organisation Congress	Gothenburg, Sweden	www.esoconference.com/2018/Pages/default.aspx
28 June–1 July	American Headache Society 60th Annual Scientific Meeting	San Francisco, USA	www.americanheadachesociety.org/events/60th-annual-scientific-meeting/
6–9 September	17th Biennial Migraine Trust International Symposium	London, UK	www.mtis2018.org
12–16 September	17th World Congress on Pain	Boston, USA	www.iasp-pain.org/Meetings/?navItemNumber=505
28–30 September	12th European Headache Federation (EHF) Congress	Florence, Italy	www.duerrecongressi.com/eventi-2018/
15–18 November	2018 Scottsdale Headache Symposium	Scottsdale, USA	www.americanheadachesociety.org/events/2018-scottsdale-headache-symposium/
2019			
5–8 September	19th Congress of the International Headache Society (IHC)	Dublin, Ireland	www.ihc2019.com

If you would like IHS to include your meeting on the IHS website and newsletter please contact **Carol Taylor** with the details



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