Mechanisms and Clinical Targets of Chronic Migraine: Clinical Perspectives and Advancements
A Town Hall Forum

Offering in-depth analysis and highly interactive audience discussion

Thursday, June 2, 2011

Grand Hyatt Washington
Washington, DC

12:30 PM  Program
2:00 PM  Adjourn

To participate in other CME/CE programs about chronic migraine, please visit PrimaryPerspective.org/migraine

Jointly sponsored by the Annenberg Center for Health Sciences at Eisenhower and CogniMed Inc.
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This CME-certified lunch symposium is not part of the 53rd Annual Scientific Meeting of the American Headache Society®.
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INTENDED AUDIENCE
This activity was developed for neurologists and headache specialists in attendance at the 53rd Annual Scientific Meeting of the American Headache Society®.

STATEMENT OF NEED
Chronic migraine (CM) is a highly disabling neurologic disorder, with heterogeneous characteristics resulting in a range of symptom profiles, burden, and disability, that remains largely underdiagnosed and undertreated. Affecting nearly 2% of the general population, CM is one of the most disabling of the primary headache disorders, imposing considerable economic burden while interfering with social, occupational, and educational functioning; it remains an enormous challenge in neurologic and headache practices.
Treatment of CM has evolved into a multifaceted approach, including lifestyle modification, trigger management, behavioral therapy, pharmacologic therapy, education, support, management of expectations, and close follow-up. Topiramate, divalproex, and onabotulinumtoxinA have been evaluated as prophylactic treatment of CM in randomized, double-blind, placebo-controlled or active comparator-controlled trials. OnabotulinumtoxinA received approval October 15, 2010, from the US Food and Drug Administration for prophylactic treatment of CM.

This educational activity will review the diagnosis, risk factors, economic burden, and optimal treatment of CM. This activity will be highly interactive, with brief presentations and extended discussion sessions between faculty and audience members after each presentation.

**Educational Objectives**

At the conclusion of this activity, participants should be better able to:

- Integrate diagnostic criteria for chronic migraine (CM) into clinical practice to facilitate earlier diagnosis
- Identify changes in brain structure and function associated with CM and examine mechanisms of action for acute and prophylactic therapies
- Assess the increased cost of CM and the burden on medical resources
- Define CM patient populations for whom prophylactic therapy has shown clinical benefit and utilize prophylaxis in this population as needed

**Accreditation and Certification**

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The Annenberg Center for Health Sciences designates this live activity for a maximum of 1.5 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Dawn C. Buse, PhD, is a consultant for Allergan, Inc.; Endo Pharmaceuticals; Iroko Pharmaceuticals; and MAP Pharmaceuticals, Inc.

Peter J. Goadsby, MD, PhD, DSc, FRACP, FRCP, receives research support from Amgen Inc.; Boston Scientific Corporation; GlaxoSmithKline; MAP Pharmaceuticals, Inc.; Merck Sharp & Dohme Limited; and Neuralieve Inc. He is a consultant for Air Products and Chemicals, Inc.; AstraZeneca; Bristol-Myers Squibb Company; NeuroTherapeutics Pharma, Inc.; Pfizer Inc; and Vertex Pharmaceuticals Incorporated, and serves on the speakers bureaus of Almirall, Merck Sharp & Dohme Limited, and Pfizer Inc.

Joel R. Saper, MD, FACP, FAAN, receives research support from Allergan, Inc.; AstraZeneca; Boston Scientific Corporation; Eli Lilly and Company; Forest Laboratories, Inc.; Johnson & Johnson; Medtronic, Inc.; Merck & Co., Inc.; NeurogesX Inc.; Novartis; NuPathe Inc.; Pfizer Inc; St. Jude Children’s Research Hospital, Inc.; and Vanda Pharmaceuticals Inc. He is a consultant for Allergan, Inc.; Autonomic Technologies, Inc.; Gerson Lehrman Group, Inc.; Medtronic, Inc.; St. Jude Children’s Research Hospital, Inc.; and WellPoint, Inc., and serves on the speakers bureau of Merck & Co., Inc., and the advisory board of Bristol-Myers Squibb Company. He is a significant shareholder of POZEN, Inc.

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This program will contain discussion of investigational therapies. Individual clinical judgments should be used in all patient care decisions.

The American Headache Society® does not endorse products discussed in this activity.

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RICHARD B. LIPTON, MD

Richard B. Lipton, MD, is Professor and Vice Chair of Neurology, Professor of Epidemiology and Population Health, and Director of the Montefiore Headache Center at Albert Einstein College of Medicine, in Bronx, New York. He is also the Lotti and Bernard Benson Faculty Scholar at Albert Einstein College of Medicine.

Dr Lipton earned a medical degree at the University of Chicago Pritzker School of Medicine, in Illinois. He completed a neurology residency and clinical neurophysiology fellowship at Albert Einstein College of Medicine and a fellowship in neuroepidemiology at Columbia University, in New York, New York.

His research interests include headache epidemiology and clinical trials, cognitive aging and dementia, and outcomes research.

Dr Lipton is Associate Editor of Cephalalgia and serves on the editorial boards of Neurology and several other journals. He has published 11 books and more than 400 original articles and reviews.

Dr Lipton is Past President of the American Headache Society (AHS). He is a 3-time recipient of the AHS H. G. Wolff Research Award and received the Medical Book Award from the British Medical Association in 1998 for Headache in Clinical Practice.
Minimizing Migraine Chronification: Early Diagnosis and Recognition

Richard B. Lipton, MD

Chronic migraine (CM) is the most disabling of the 4 types of primary chronic daily headache (CDH) of long duration, a syndrome defined by primary headaches 15 or more days per month for at least 3 months with attacks that last 4 hours or more per day on average.

Diagnosis of CDH requires a systematic approach that includes these steps: (1) exclude a secondary headache disorder, (2) identify a primary headache syndrome based on duration and frequency (eg, long-duration episodic or chronic, short-duration episodic or chronic), and (3) with a headache duration of at least 4 hours, use symptomatology to determine the specific headache disorder(s) (CM, chronic tension-type headache, new daily persistent headache, hemicrania continua).

CM is considered a complication of migraine in the appendix to the second edition of the International Classification of Headache Disorders (ICHD-II) and defined by the following features: (a) 15 or more headache days/month over the past 3 months and (b) at least 8 headache days meet criteria for migraine without aura or respond to migraine-specific treatment.

CM often develops from episodic migraine (EM) after a period of increasing headache frequency. This process, chronification, occurs in approximately 2% to 3% of EM sufferers in the general population annually. Chronification is associated with a number of risk factors, some of which cannot be modified, including age and race, and some that are potentially modifiable or avoidable, including obesity, snoring, head injury, stressful life events, depression, and overuse of opioids or barbiturates.

Further studies are needed to determine the possible benefits of risk factor modification in preventing chronification and potential predictors of remission of CM to EM. Furthermore, it is critical to understand the role of medication overuse as it applies to the current definition of CM and its appropriate treatment. The need for clinical vigilance that is highly sensitive yet specific to the diagnosis of CM and when to initiate treatment to help mitigate the risk of chronification will be discussed.
Peter J. Goadsby, MD, PhD, DSc, FRACP, FRCP

Peter J. Goadsby, MD, PhD, DSc, FRACP, FRCP, is Professor of Neurology at the University of California, San Francisco, and a consultant neurologist to the Hospital for Sick Children, in London.

Dr Goadsby received medical degrees and doctorates from the University of New South Wales, in Sydney, Australia, and completed a medical internship and residency at Prince Henry/Prince of Wales Hospital, in Sydney.

Dr Goadsby’s major research interests are in the neural control of cerebral circulation and the basic mechanisms of head pain both in experimental settings and in the clinical context of headache. He specializes in the diagnosis and treatment of headache disorders, including migraines, cluster headache, and other forms of chronic daily headache.

He serves on the editorial boards of numerous journals and served as Editor of *Cephalalgia* from 2000 to 2008. He is also an ad hoc reviewer for *Brain, Headache, Lancet, Neurology, New England Journal of Medicine,* and *Pain,* among many others, and has written more than 1000 abstracts, articles, reviews, chapters, and books.

Dr Goadsby is a fellow in the Royal Astralasian College of Physicians and the Royal College of Physicians. Among his many honors, he is a 5-time recipient of the H.G. Wolff, MD, Award from the American Association for the Study of Headache, most recently in 2009.
Chronic Migraine: Mechanisms and Targets for Therapy

Peter J. Goadsby, MD, PhD, DSc, FRACP, FRCP

As our understanding of migraine evolved from a vascular disorder to a brain disorder, approaches to treatment and therapeutic targets for drug development have dramatically changed. Physiologic changes associated with chronic migraine (CM) are now recognized as manifestations of altered neurobiology, including changes in excitability and central sensitization of nociceptive pathways, which may offer new targets for therapy.

Although the pathogenesis of migraine pain has not been fully elucidated, the innervation of the dura mater and large intracranial vessels by trigeminal afferents and reflex connections with the cranial parasympathetic outflow are likely to play a role. Various mechanisms have been implicated in the progression of migraine, including both exogenous factors (eg, medication overuse, and trauma) and endogenous factors.

It seems clear that brain changes occur in CM that are pivotal to expression of the disorder. Morphologic and structural changes, including reduced cortical gray matter of the pain-processing areas of the brain, have been reported in some forms of the disorder. Changes in the periaqueductal gray matter causing trigeminovascular nociception dysmodulation may also be a critical factor in the pathophysiology of CM. As the trigeminocervical complex is recognized to play a pivotal role in nociceptive signaling in migraine, it is increasingly being accepted as a target for putative antimigraine agents.

Opioid overuse in some migraine patients is clearly a problem in terms of management and resolution of their disability. A clearer understanding of the pathophysiology of CM may lead to improved treatment of these patients. The primary classes of migraine-specific drugs, including ergot alkaloid derivatives and triptans, each seems to have the propensity to be troublesome in particular patients when used frequently.

The targets of CM therapy and the proposed mechanisms of action of acute and prophylactic migraine treatments will be discussed.
DAWN C. BUSE, PHD

Dawn C. Buse, PhD, is a licensed psychologist and Director of Behavioral Medicine for the Montefiore Headache Center, in New York, New York. She is also Assistant Professor in the Department of Neurology of Albert Einstein College of Medicine of Yeshiva University and Assistant Professor in the Clinical Health Psychology Doctoral Program of Ferkauf Graduate School of Psychology of Yeshiva University, also in New York.

After earning a master’s degree and a doctorate in psychology from the University of Utah, in Salt Lake City, Dr Buse completed an internship in medical psychology in the Boston VA Medical System and Harvard Medical School and 3 years of postdoctoral fellowships in adult and pediatric headache and pain management at Spaulding Rehabilitation Hospital, Massachusetts General Hospital, Children’s Hospital, Boston, and Harvard Medical School.

Dr Buse conducts research on headache and pain and is involved in the American Migraine Prevalence and Prevention (AMPP) study, a large, longitudinal US population-based study of severe headache. She is co-investigator on another National Headache Foundation study, Familial Risk of Transformed Migraine, and is also investigating migraine attack prediction using an electronic diary.

She has published widely and lectured nationally on the challenges of managing migraine in women, the burden of migraine, and managing migraine and cardiovascular risk and serves as a consultant and reviewer for several journals, including *Neurology, Headache,* and *Cephalalgia.*

Dr Buse also provides clinical care, including assessment, cognitive behavioral therapy, and biofeedback to patients suffering with headache and other forms of pain. She is a member of the American Headache Society’s Electronic Media Committee, serves on the “Occupational Burden of Headache” and “Outcome Measures for Headache” working groups of the World Health Organization “Lifting the Burden” campaign, and co-chairs the AMPP Investigator Initiated Grant Program. She received the National Headache Foundation’s Partners in Excellence Award in 2009.
Chronic migraine (CM) has been demonstrated to be a disabling and burdensome condition. The majority of studies suggest that the population prevalence of CM ranges from 1.3% to 2.4%, although it is one of the most common disorders seen in headache specialty practices.

Both clinic- and population-based studies have demonstrated that CM, in comparison with episodic migraine (EM), results in greater migraine-related disability, reduced health-related quality of life, increased healthcare resource utilization and related costs, and higher rates of medical and psychiatric comorbidities, including depression and anxiety. According to a cross-sectional analysis of data from the American Migraine Prevalence and Prevention (AMPP) study, when compared with respondents with EM, respondents with CM were significantly less likely to be employed full-time and almost twice as likely to be occupationally disabled. Those with CM were approximately twice as likely to have anxiety or depression and 2.5 times more likely to also have other chronic pain conditions. In addition, they were at higher risk for respiratory and cardiovascular disorders, 40% more likely to have heart disease and angina, and 70% more likely to have a history of stroke.

These findings highlight the paramount importance of accurate diagnosis, an appropriate treatment plan consisting of a combination of effective pharmacologic and nonpharmacologic strategies, and a patient-centered, multidisciplinary approach to the treatment and management of CM to improve patient outcomes. The tremendous individual and societal burden of CM and how outcomes research may help elucidate and shape future management paradigms will be discussed.
JOEL R. SAPER, MD, FACP, FAAN

Joel R. Saper, MD, FACP, FAAN, is Founder and Director of the Michigan Headache & Neurological Institute, in Ann Arbor, and Clinical Professor of Medicine (Neurology) at Michigan State University, in East Lansing. He is also Director of the Head Pain Treatment Unit of Chelsea Community Hospital, in Michigan.

A board-certified neurologist and certified in pain medicine and headache medicine, Dr Saper is an invited lecturer before universities, medical centers, government and business groups, and lay audiences around the world. He is featured in major television programs and newspapers as an authority in headache and pain and their personal, social, and economic impact. Dr Saper is the author of 8 books and more than 200 medical articles and textbook chapters.

Dr Saper is Past President of the American Association for the Study of Headache, Past Chairman of the American Council for Headache Education, and an educator in the American Academy of Neurology, the American Academy of Pain Medicine, the American Headache Society, and the American Pain Society. He has been cited repeatedly in Best Doctors in America and The Best in Medicine.
Chronic migraine (CM) is the most common of type of chronic headache and frequently associated with medication overuse, serious comorbidity, and disability. Identifying factors that possibly promote the progression of this disorder from episodic migraine (EM) to daily or almost daily headache may optimize treatment approaches, including both pharmacotherapeutic and nonpharmacologic interventions.

Advances in understanding have led to improved diagnosis, CM prophylaxis, and treatment paradigms for EM and intractable CM. For each patient, clinicians must determine whether medication overuse is present and treat accordingly; assessment and management must include carefully weighing when to administer pharmacotherapy, when to utilize interventional and behavioral approaches, and when to impose comprehensive inpatient evaluation and infusion treatment. A comprehensive approach should include appropriate management of behavioral, personality, motivational, and compliance factors, as well as a thorough evaluation of modifiable risk factors, including obesity, stressors, and sleep disturbances. Clinicians should recognize that frequent use of opioids is potentially pro-nociceptive, promoting headache progression and behavioral and physiologic dependency.

While the need to effectively and aggressively control pain is a mainstay of clinical care, treatment of CM remains complex. The dramatic evolution of headache care will be reviewed, including an examination of how current treatment paradigms and inpatient programs have affected the continuity of care to comprehensively and optimally target factors that may provoke CM, helping to close the gaps in the treatment algorithm using an individualized, patient-centered approach.
Suggested Reading


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Presentations

Minimizing Migraine Chronification: Early Diagnosis and Recognition
Richard B. Lipton, MD

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Treatments for Chronic Migraine
Joel R. Saper, MD, FACP, FAAN

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Activity

As a result of this activity, I am better able to:

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Identify changes in brain structure and function associated with CM and examine mechanisms of action for acute and prophylactic therapies

Assess the increased cost of CM and the burden on medical resources

Define CM patient populations for whom prophylactic therapy has shown clinical benefit and utilize prophylaxis in this population as needed

The activity:

Met my expectations

Was relevant to my clinical practice

Was presented without commercial bias

Logistics were well-organized

Environment was conducive to learning

After participating in this activity, I will change my clinical practice by:

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I hereby certify that I have spent _____ hour(s) in this educational activity.

Signature __________________________________________ Date _______________

Thank you.