ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

POSTER perspectives

Scientific Advances in the Management of Migraine: From Knowledge to Practice

Source: American Headache Society Annual Meeting, held June 9-12, 2016 in San Diego, California.

Target Audience
This activity was developed for headache specialists, neurologists, and other health care professionals who have an interest in treating patients with migraine headaches.

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

- Summarize the latest research developments in the prevention and treatment of migraines
- Incorporate evidence-based research into clinical practice

Faculty
Lawrence C. Newman, MD
Professor of Neurology
Icahn School of Medicine at Mount Sinai
Director, Headache Institute
Mount Sinai West
New York, New York

Accreditation and Certification
The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure Statement
It is the policy of the Annenberg Center for Health Sciences to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All faculty and planners participating in sponsored programs are expected to identify and reference off-label product use and disclose any relationship with those supporting the activity or any others with products or services available within the scope of the topic being discussed in the educational presentation.

The Annenberg Center for Health Sciences assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CE/CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by the Annenberg Center for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. The Annenberg Center is committed to providing its learners with high-quality CE/CME activities and related materials that promote improvements or quality in health care and not a specific proprietary business interest of a commercial interest.

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosures has been made:

Lawrence C. Newman, MD

Research Support:	ATI
Consultant:	Alder, Allergan, Amgen, Lilly, Teva

The faculty for this activity has disclosed that there will be discussion about the use of products for non-FDA approved indications.

Additional content planners
The following has no significant relationship to disclose:

Greg Scott, PharmD, RPh (medical writer)

Annenberg Center for Health Sciences
John Bayliss, VP, Business Development, spouse is an employee of Amgen, Inc; all other staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

This activity is supported by educational funding provided by Amgen.

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the material, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was originally released on September 1, 2016 and is eligible for credit through *August 31, 2017*

Our Policy on Privacy
Annenberg Center for Health Sciences respects your privacy. We don't share information you give us, or have the need to share this information in the normal course of providing the services and information you may request. If there should be a need or request to share this information, we will do so only with your explicit permission. See Privacy Statement and other information at http://www.annenberg.net/privacy-policy/

Contact Information
For help or questions about this activity please contact Continuing Education:
ce@annenberg.net
Annenberg Center for Health Sciences
39000 Bob Hope Drive
Dinah Shore Building
Rancho Mirage, CA 92270
Phone 760-773-4500
Fax 760-773-4513
8 AM – 5 PM, Pacific Time, Monday – Friday

ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

POSTER perspectives

A Phase IIb Randomized, Double-Blind, Placebo-Controlled Trial of Ubrogepant for Acute Treatment of a Migraine Attack

Hello. This is Dr. Lawrence Newman, professor of neurology at the Icahn School of Medicine at Mt. Sinai, and director of the Headache Institute at Mt. Sinai West. I will be discussing A Phase IIb Randomized, Double-Blind, Placebo-Controlled Trial of Ubrogepant for Acute Treatment of a Migraine Attack, presented by Dr. Lipton and colleagues at the 58th Annual Scientific Meeting of the American Headache Society, held June 9-12, 2016, in San Diego, California.

In summary, this study supports the efficacy and safety of ubrogepant for the acute treatment of migraine. This study is important because it provides further evidence that calcitonin gene-related peptide receptor antagonists are viable options for the acute treatment of migraine. While many agents are currently utilized for acute treatment of migraine, none are universally effective, and safety and tolerability are often limitations to their use.

The methods of this study are as follows:

Patients with migraine were randomized to treat a single migraine attack with ubrogepant 1 mg, 10 mg, 25 mg, 50 mg, 100 mg, or placebo in a one-to-one ratio. The co-primary endpoints were pain freedom and headache response at 2 hours. Headache response was defined as a reduction in headache severity from severe or moderate at baseline, to mild or none. The first hypothesis tested the dose response trend for 2-hour pain freedom using the logistic regression model. Subsequent hypotheses tested the effects of each dose on the co-primary endpoints using a closed, sequential testing procedure to control for multiplicity.

The key findings of this study were as follows:

640 patients received study medication, 527 received ubrogepant, and 113 received placebo. There was a positive and statistically significant trend across ubrogepant doses as measured by the proportion of participants who achieved 2-hour pain freedom. Ubrogepant 100 mg was significantly superior to placebo for 2-hour pain freedom, but not for the 2-hour headache response end point. The nonsignificant headache response for 2 hours precluded further hypothesis testing. Overall, adverse events were similar between ubrogepant and placebo.

Here are my thoughts and analysis of this study:

The main point of this phase 2b randomized, double-blind, placebo-controlled trial is that the 100 mg dose of ubrogepant demonstrated statistically significant benefits for 2-hour pain freedom in the treatment of 1 attack of an acute migraine. Adverse events for all the doses were similar to placebo. Pain freedom, in which a subject has attained total pain relief, is actually a more clinically useful end point for our patients than is headache response.

Since the introduction of the triptans nearly 20 years ago, there have been no new acute migraine specific agents that have been developed. There are, however, significant unmet needs for our patients who require acute medications. These include the lack of consistent response, headache recurrence after the initial relief, incomplete response, as well as several contraindications to their use.

Clinicians and their patients are often in desperate need of new treatment options for acute migraine management. The currently available medications are not a panacea. Many patients who were once good candidates for these agents, now have comorbidities that preclude their use, and they are left without any good choices.

Further studies are warranted. This study investigated treatment for 1 attack of migraine only. The utility of ubrogepant over multiple attacks must be evaluated.

ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

POSTER perspectives

Acute Medication Utilization Among Migraine Patients Initiating Prophylaxis

Hello. This is Dr. Lawrence Newman, professor of neurology at the Icahn School of Medicine at Mt. Sinai, and director of the Headache Institute at Mt. Sinai West. I will be discussing Acute Medication Utilization Among Migraine Patients Initiating Prophylaxis, presented by Dr. Bonafede at the 58th Annual Scientific Meeting of the American Headache Society, held June 9–12, 2016, in San Diego, California.

In this large, commercially insured population of migraine patients receiving prophylactic treatment, the use of acute medications was common. Topiramate and beta-blockers were the most commonly utilized as prophylactic medications. A triptan and/or an opioid were the most common medications used for acute treatment.

This study is important because it underscores the unmet need for better medications used to prevent migraine. The Truven Health MarketScan research database was used to identify adults with migraine who initiated prophylactic medications between the years 2006 and 2012. Patients were required to be enrolled at least 12 months before and 24 months following initiation to prophylaxis.

The methods of this study were as follows:

Migraine diagnosis was based on a predefined number of inpatient, emergency department, or outpatient visits due to migraine or prescriptions for a triptan or ergotamine, or topiramate.

The key findings of this study were as follows:

Nearly 150,000 met the study criteria, of which nearly 98,000 had 3 or more years of follow-up after initiating prophylactic medication for migraine. The most common prophylactic medications initiated were topiramate in 28%, beta-blockers in 19%, tricyclics in 15%, other anticonvulsants in 14%, and serotonin-norepinephrine re-uptake inhibitors in 11%. Eighty-four percent of patients used at least 1 acute medication within 1 year of initiating prophylaxis, increasing to 97% over the 5 years of follow- up. Half of the patients used the triptan within 1 year with an average of 101 days' supply in the first year increasing to 419 days over 5 years. Half of the patients used an opioid within 1 year with an average of 84 days' supply in the first year, increasing to 291 days over 5 years. NSAID use was common as well.

Here are my thoughts and analysis of this study:

This was a large scale review of the use of both specific and nonspecific acute medications in patients who were initiating preventive treatment for their migraine. Patients were followed up to 5 years after beginning the preventive medication regimen. In this study, although half the patients were using a migraine specific acute medication—a triptan—a similar percentage used an opioid. Furthermore, those groups demonstrated increased usage pattern despite preventive strategies being employed.

Current guidelines recommend that patients be treated with migraine-specific medications as first line options and that opioid-containing medications be used only as a last resort. In this cohort, half of all patients were using opioids prior to prevention, and the trend was that of increasing usage over the course of the study. This study highlights the more effective, preventive agents to both decrease the frequency and severity of acute attacks. Although this study is limited in that it was conducted only in a commercially insured population, similar need for effective, preventive medications exists in other populations such as Medicare and Medicaid.

Improvement in agents available, will reduce the impact of migraine upon the patient, reduce disability, and hopefully result in more migraine-specific agents being used as first line therapy. It is puzzling to me that despite years of education as to the proper use of acute treatment, nonspecific agents such as opioids—which have the potential to transform migraine from an episodic to a chronic disease—are still used so frequently.

ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

POSTER
perspectives

A Real World Analysis of Outcomes in Migraineurs Receiving Preventive Migraine Treatment

Hello. This is Dr. Lawrence Newman, professor of neurology at the Icahn School of Medicine at Mt. Sinai, and director of the Headache Institute at Mt. Sinai West. I will be discussing A Real World Analysis of Outcomes in Migraineurs Receiving Preventive Migraine Treatment, presented by Dr. Ford and colleagues at the 58th Annual Scientific Meeting of the American Headache Society, held June 9–12, 2016, in San Diego, California.

This real world analysis found that preventive treatment was not associated with significantly greater reduction in the number of headache days per month or difference in headache-related disability compared with no preventive treatment. These results suggest that there's still an unmet need for efficacious preventive therapies for patients who suffer from migraine headaches.

The methods of this study were as follows:

The primary objective of the study was to compare headache days per month and headache-related severity of disability assessed by the MIDAS questionnaire in patients with migraine who receive preventive treatment vs those who did not. Data was taken from the Adelphi Migraine United States Disease Specific Program, a cross-sectional survey of physicians and their patients with migraine in the United States. Patients were required to experience 4 or more headache days per month and be eligible for preventive therapy.

The key findings of the study were as follows:

Three hundred twenty-four patients received preventive therapy and 135 did not. Patients experienced an average of 10 headache days per month. The mean decrease from baseline in the number of headache days per month was 4.1 in the preventive therapy group and 1.5 in the no preventive therapy group. Propensity score matching to control for confounding factors found no significant difference in the number of headache days per month between the 2 groups. The average MIDAS score was 17, indicating moderate disability, with no difference between the groups. However, the lack of MIDAS score at baseline limits the interpretation of this finding.

Here are my thoughts and analysis of this study:

Unlike case reports or small-scale epidemiologic studies, this study looked at patients we are all likely to see or are currently in the process of treating. The patients in the report had high frequency migraine with moderate disability and were candidates for prevention. These results speak to the fact that currently there is a dearth of effective preventive therapies for our patients with migraine.

In this study, the use of preventive medications did not result in a statistically significant change in headache days per month or in reduction in disability. New agents for migraine prevention are desperately needed. There have been no preventive agents developed specifically for migraine in over half a century and it is not surprising that patients continue to suffer and have a high rate of disability. Only when new, effective, preventive agents are developed will unmet needs be properly addressed.

ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

POSTER perspectives

Efficacy and Safety of LY2951742 in a Randomized Double-Blind, Placebo-Controlled, Dose-Ranging Study in Patients with Migraine

Hello. This is Dr. Lawrence Newman, professor of neurology at the Icahn School of Medicine at Mt. Sinai, and director of the Headache Institute at Mt. Sinai West. I will be discussing Efficacy and Safety of LY2951742 in a Randomized Double-Blind, Placebo-Controlled, Dose-Ranging Study in Patients with Migraine, presented by Dr. Oakes and colleagues at the 58th Annual Scientific Meeting of the American Headache Society, held June 9–12, 2016, in San Diego, California.

Monthly subcutaneous injections of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, is safe, well tolerated, and effective, in the prevention of migraine. This study is important because it provides evidence that a monoclonal antibody to calcitonin gene-related peptide is a viable option for the prevention of migraine. While many agents are currently utilized for prophylactic treatment of migraine, none are universally effective, and safety and tolerability are often limitations to their use.

Now, here are comments from Dr. Oakes, the lead author of the study.

In this dose-ranging study, the 2 highest doses of galcanezumab (LY2951742) appear to be efficacious in patients with episodic migraine. The 120 mg dose met the primary objective in achieving a greater reduction in the number of migraine headache days at month 3, compared to placebo, and both the 120 mg and 300 mg doses were significant compared to placebo in the overall change in migraine headache days, from baseline, over 3 months of treatment. Galcanezumab was well tolerated with the majority of patients completing the study.

The methods of this study were as follows:

The primary objective was to assess whether at least 1 dose of LY2951742 was superior to placebo in the prevention of migraine headaches. Superiority was defined as a 95% or greater posterior probability of greater improvement for any LY2951742 dose, compared with placebo, as measured by the mean change from baseline in the number of migraine headache days during the last month of the treatment phase. The study was a randomized, double-blind, placebo-controlled study at 40 centers across the United States. Adults with 4 to 14 headache days, and at least 2 migraine attacks per month, where randomized to LY2951742 at a dose of 5 mg, 50 mg, 120 mg, or 300 mg, or placebo, given subcutaneously, once-monthly, for 3 months.

The key findings of the study were as follows:

The key findings of this study were that there were 273 patients randomized to LY2951742 and 137 to placebo. LY2951742 at a dose of 120 mg met the primary objective and was found to be superior to placebo in the last month of treatment. Significantly greater improvement than placebo in the number of migraine headache days was observed with LY2951742 at doses of 50 mg and 300 mg during month 1 and at a dose of 300 mg during month 2. The overall change from baseline over 3 months, in the number of migraine headache days, was significant for LY2951742 at doses of 120 mg and 300 mg.

Treatment emergent adverse events with LY2951742 with an incidence of 5% or greater, and greater than with placebo, were injection-site pain, upper respiratory tract infection, nasopharyngitis, dysmenorrhea, and nausea.

Here are my thoughts and analysis of this study:

This large-scale, double-blind, placebo-controlled, dose-ranging study found that monthly subcutaneous injections of the CGRP monoclonal antibody could reduce the number of migraine headache days when compared to placebo. This study also showed that in a dose of 120 mg, the primary objective was met. That is, LY2951742 was more effective than placebo in preventing migraine headache. All doses of this novel agent appeared to be well tolerated.

Recent studies have demonstrated a large, unmet need with the current agents available for migraine prevention. The currently available agents often do not diminish migraine frequency, are associated with poor patient adherence, or are associated with significant side effects that limit their utility. Preliminary evidence suggests that LY2951742 may decrease migraine frequency and is well tolerated. Additionally, the once-monthly dosing regimen could result in increased patient adherence. More data is needed to see if these trends continue with prolonged administration, and if treatment-emergent adverse events develop with long-term use.

ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

POSTER
perspectives

Unmet Need in Migraine Prophylaxis Treatment in the United States of America. Data From Clinical Practice

Hello. This is Dr. Lawrence Newman, professor of neurology at the Icahn School of Medicine at Mt. Sinai, and director of the Headache Institute at Mt. Sinai West. I will be discussing Unmet Need in Migraine Prophylaxis Treatment in the United States of America. Data From Clinical Practice, presented by Dr. Mutebi and colleagues at the 58th Annual Scientific Meeting of the American Headache Society, held June 9–12, 2016, in San Diego, California.

Nearly half of persons who use prophylactic medication for migraine in the United States have failed the migraine prophylaxis treatment regimen in the past. Failure is generally due to both lack of effectiveness and poor tolerability. This study underscores the substantial, unmet need for more effective and/or more tolerable medications for migraine prophylaxis.

The methods in this study were as follows:

Data were drawn from the 2014 Adelphi Migraine Disease Specific Program, a cross-sectional survey of physicians and their patients with migraine in the United States. Descriptive analyses were utilized to characterize patient use of prophylactic medication for migraine and physician-reported and patient-reported reasons for failure. Physicians were used as the clustering unit, and multi-variable regression was utilized to explore factors associated with patient use of prophylactic medication for migraine.

The key findings of this study were as follows:

Eight hundred eighteen patients utilized migraine prophylaxis, of which 390 or 48% had failed prophylactic medication in the past; 31% were on their second prophylaxis, 11% on their third, and 5% on their fourth or more.

Physician report for reasons patients failed prophylactic medication in this survey were:

Lack of effectiveness only, in 26%, poor tolerability only, in 22%, both lack of effectiveness and poor tolerability in 34%.

Patient report for reasons for failed prophylactic medication were:

Lack of effectiveness only, in 29%, poor tolerability only, in 31%, and both lack of effectiveness and poor tolerability in 33%.

Here are my thoughts and analysis of this study:

The study gives us real world insight into the unmet needs related to our current migraine preventive agents from both the patient and physician points of view. This study highlights the frustration felt by the provider in having limited choices to reduce migraine frequency and by the patient in whom these agents often don't provide substantial benefit and/or induce intolerable side effects. Unmet needs related to migraine prophylaxis will continue to be a significant problem until newer, more effective and better tolerated agents are developed and become available to our patients.

Will the new CGRP monoclonal antibodies in development solve all of these issues? Probably not, but they will increase the options that are currently available, which would go a long way in significantly addressing many of these unmet needs.