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by D. Woods

SUMMARY

Allergan's Botox migraine data looked positive, but doctors are very skeptical about the results. Still, patients are likely to ask for it, and it will be used at least as a last resort for those willing to pay for it or able to convince their insurance companies to cover it. ♦ **MAP Pharmaceuticals' Levadex**, a self-administered, orally inhaled form of dihydroergotamine, seems to be effective, but doctors still want more data. ♦ **Merck's telcagepant**, a calcitonin gene-related peptide (CGRP) antagonist, works well, but enthusiasm was muted due to some confusion about whether or not the company has put it on hold due to questions about liver toxicity. ♦ **NuPathe's Zelrix**, an iontophoretic transdermal sumatriptan patch, appears to work and is well tolerated by patients particularly those bothered by stomach problems and nausea associated with other treatments.

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INTERNATIONAL HEADACHE CONGRESS(IHC) HOSTED BY THE AMERICAN HEADACHE SOCIETY (AHS)

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There are still no magic bullets for migraine headaches, but several new treatments discussed at the International Headache Congress look promising, and they take a variety of different approaches – an ***injectable*** botulinum toxin, an ***inhaled*** form of dihydroergotamine, an ***oral*** first-in-class calcitonin gene-related peptide (CGRP), and a sumatriptan ***patch***.

GLOBAL HEADACHE PERSPECTIVE

As many as half of the world's population suffers from headaches. Migraine is the No. 19 cause of disability worldwide and No. 12 among women. According to the World Health Organization's (WHO's) Global Burden of Disease project, migraine is a serious problem, and the total burden of tension type headaches is larger than the burden of migraine.

In the U.S., chronic migraine headaches affect an estimated 1.2-3.6 million people, and 112 million bedridden days per year are due to migraine. That translates to 400,000 people spending 24 hours in bed every day.

Headaches affect more than 50 million Europeans, and they lose 180 million days from work or school every year. A recent health economic survey in Europe suggests that migraine is the most expensive neurological disorder to society physically, mentally, and also in euros (~€27.3 billion or US$40 billion). In Europe there were a little more than 40 million anxiety disorders in 2004, and ~40% of these were migraines, with the least cost per patient estimated at €579 (US ~$850).

The direct costs of headaches include medication, consultation, hospital admissions, and diagnostic investigations. Of the total costs of migraine, 80%-90% is due to indirect costs, which include work absence and reduced working efficiency. To put this in perspective, migraine was in the middle in terms of cost in Europe compared to various brain disorders. Migraines also have a big impact on worker productivity. Productivity is just 65% of normal when working with a headache. On average, each migraine patient loses six work days every year due to migraines.

According to Lars Jacob Stovner, PhD, of the Trondheim University Hospital and the Norwegian University of Science and Technology, headache disorders are trivialized and not recognized as a large public health problem by healthcare

1-Year Prevalence of Headaches

Type of headache	Percentage *
General headaches	50%
Migraine	11%
Tension type headache	40%
Chronic headache	3%
Possible medication overuse headache (MOH)	1%

*** Adds to >100% due to overlap.**

providers, healthcare authorities, and politicians. He called headache research funding inadequate, saying that more than half of the world's population lives in countries where no research has been done on headache disorders, including China, Russia, Australia, and most of Africa.

However, several groups are working on initiatives to bring attention to headache epidemiology, including the ***European Journal of Neurology***, Lifting the Burden global campaign, the Eurolight Online project in Europe, and WHO. The Eurolight Online project measures the burden of headache in Europe by following all the relevant headache burden studies. It also has a questionnaire used in many European countries. The project is a consortium of 24 partners – public groups, patient organizations, scientific organizations, hospitals, and headache experts – in 15 European countries and is an active participant in the Lifting the Burden organization, which is supported by WHO. Colette Andree, PhD, of the Centre de Recherche Public (CRP-Sante) in Belgium said that the project aims "to provide solid justification for politicians that headache should be high amongst healthcare priorities in Europe." The Eurolight Online project has a questionnaire for that purpose.

Dr. Andree debuted the first population-based results from Eurolight Online – from the tiny country of Luxembourg, which has only 460,000 inhabitants.

- Nearly three-quarters of men and 87% of women have suffered from headaches in the last 12 months.
- 8% of males and 11% of females probably suffer from migraine.
- Even though everyone in the country has health insurance, most people do not know their headache diagnosis, including chronic daily headache patients.
- Chronic headaches and migraines have a major impact on working days per year, with 20 working days lost per year if combined. Chronic headaches impact 50 household work days per year, and migraine impacts 20 household work days per year. Chronic headaches cause a loss of 20 family days per year, and migraines cause a loss of nine family days every year. Of people whose partners suffer from headaches, 5% cannot go to work themselves. Ten percent of people without headaches missed social activities because of a partner with a headache.
- Fewer than 10% of migraine sufferers use triptans. This is in a country where triptans are paid for, and there are no access problems. Most people with headaches use acetaminophen, aspirin, or NSAIDs. Only 13% of migraine sufferers with headache frequency of 10-14 per month use prophylactic treatment.
- There is a clear relationship between quality of life and headache types. Migraine and probable migraine headaches are similar in quality of life, and chronic daily headaches are significantly different from migraines.
- Frequency of headache is more important than what kind of headache a person has.

ALLERGAN'S BOTOX (ONOBOTULINUMTOXIN-A)

Two Phase III trials of Botox presented at IHC showed that the injectable drug is effective, safe, and well tolerated for the treatment of chronic migraine headaches in adults. However, most doctors interviewed at the meeting were skeptical or negative about the data, saying that past studies showed that Botox does not work for headaches and questioning its use for chronic migraine sufferers. A few doctors said that Botox is effective for ***some*** patients for whom nothing else seems to work. Furthermore, reimbursement continues to be a problem; most insurance companies won't pay for it unless pressed by the doctors, and so use is restricted to patients willing to shell out several hundred dollars a month for the injections.

There was one oral presentation and nine posters on Botox for headache at the meeting.

PREEMPT trial results

Dr. David Dodick, a neurologist from the Mayo Clinic in Scottsdale AZ, presented the results of two Phase III trials which showed that Botox is effective, safe, and well tolerated for treating adults with chronic migraine headaches. As the principal investigator of the PREEMPT-1 and -2 trials, he said that Botox use resulted in significant improvement vs. placebo across multiple headache symptoms, including:

- reductions in frequency of headache days.
- reduction in episodes and frequency of migraine days and episodes.
- reduction in frequency of moderate/severe headache days.
- reduction in the cumulative number of headache hours on headache days.
- improvement in disability, functioning, vitality, psychological distress, and overall health-related quality of life.

The two 56-week PREEMPT trials were randomized, double-blind, placebo-controlled studies conducted across 122 sites in North America and Europe. The baseline phase was four weeks, during which patients kept electronic diaries, followed

by a 24-week, double-blind phase in which there were two double-blind injections, followed by three injections in the 32-week, open-label phase. The study lasted 56 weeks. Most of the study participants were Caucasian (89.7%) and female (87.6%) and were described as a "highly disabled group of patients."

Based on data from a previous Phase II trial of Botox, the PREEMPT clinical program (PREEMPT-1 and -2) was conducted to evaluate the safety and efficacy of Botox in adults with chronic migraine (CHD-II) – patients with 15 or more headache days per month. PREEMPT-1 was conducted from 2006 to 2008 at 56 North American sites.

Dr. Dodick reported the 24-week, double-blind results, noting that there were no surprises in terms of adverse events. The most common adverse events were neck pain (8.7%) and upper respiratory tract infection (5.3%). In the PREEMPT-2 trial, one treatment-related serious adverse event in a Botox-treated patient resulted in hospitalization.

Interestingly, Dr. Dodick was the first speaker in the late-breaking abstracts session, and he was literally pushed aside by the moderator when he finished his talk, saying that there wasn't enough time for questions. However, every other speaker was allowed questions from the audience. Asked about this after the session, Dr. Dodick appeared dumbfounded, with no idea why he was sent packing off the stage. A colleague asked him how doctors might determine which patients would benefit from Botox, and they both agreed that it is impossible to say right now. His colleague answered his own question, "The only way to know is to try it."

*Asked how long treatments might last in patient*s, Dr. Dodick answered, "We do know that in longer time periods it is sustainable."

PREEMPT *Pooled Analysis*: Efficacy in the 24-Week, Double-Blind Phase

Measurement	Botox	Placebo	p-value
Primary endpoint: Frequency of headache days	- 8.4%	- 6.6%	<0.001
Secondary endpoint #1: Frequency of migraine days	- 8.2%	- 6.2%	<0.001
Secondary endpoint #2: Frequency of moderate/severe headache days	- 7.7%	- 5.8%	<0.001
Total cumulative headache hours on headache days	- 119.7	- 80.5	<0.001
Secondary endpoint #3: Total HIT-6 score	- 4.8	- 2.4	<0.001
Patients with severe (≥60) HIT-6 score	67.6%	78.2%	<0.001
Frequency of headache episodes	- 5.2%	- 4.9%	0.009
Frequency of migraine episodes	- 4.9%	- 4.5%	0.004
Frequency of acute headache medication intake	- 10.1%	- 9.4%	Nss, 0.247
Adverse events			
Any adverse events	62.4%	51.7%	---
Treatment-related adverse events	29.4%	12.7%	---
Serious adverse events	4.8%	2.3%	---
Deaths	0	0	---
Discontinued due to adverse events	3.8%	1.2%	---

Botox posters

Nine posters at the meeting provided additional information on Botox in headache.

1. **Pooled analysis of the two Phase III PREEMPT efficacy/safety trials.** Dr. Dodick referred to this poster during his talk, and most of the information in the poster was in his talk. The additional information gleaned from this poster included:
   - Multiple intramuscular injections of 155-195U of Botox per treatment cycle, administered every 12 weeks, were safe and well tolerated.
   - Most adverse events were mild or moderate in severity, and adverse events were resolved without sequelae.

Asked how long an episode had to last to be called an episode, Dr. Dodick said four hours. However, several questioners tried to get a clear answer on whether a subject might register an episode, then thinking the headache was gone, register it as finished but have the headache come back. They wanted to know if that would be a separate episode. Dr. Dodick's answer was yes – if it lasted four hours. Dr. Dodick was also asked to predict when American Academy of Neurology guidelines might be revised showing that headache days are not a good endpoint, and he said not for at least two years.

2. **Pooled analysis of the 32-week, open-label phase of PREEMPT.** Dr. Sheena Aurora, director of the Swedish Headache Center in Seattle WA, presented the results of the open-label phase of the trials that followed the double-blind phase. In the open-label portion, 688 patients got Botox, and 696 got placebo. She reported that the mean improvement was statistically significant with Botox at all time points, "This type of treatment (over 56 weeks) is safe, and there was improved function…(But) at Week 24 the placebo continued to improve as well as Botox. In the open-label phase, the group initially exposed to Botox continues to do better than the group that was exposed to placebo (before switching to Botox)."

In the open-label phase, one patient had migraine resulting in hospitalization, and there were no deaths.

Dr. Aurora said. "(In the double-blind phase) there was significant improvement in patients with HIT-6 (Headache Impact Test-6)…and there was continued improvement (in the open-label phase)." However, an audience member asked if the placebo group ever caught up with the Botox group, and Dr. Aurora answered, "Not quite…I think that there is evidence in a lot of chronic migraine

trials that the placebo group never catches up. It may be the doses…but if you start earlier, you do better, and that's known in the multiple sclerosis field as well."

HIT-6 measures disease impact on disability and functioning as a mean change from baseline. HIT-6 is a six-question survey instrument that covers content categories represented in widely used surveys of headache impact, with domains in pain, role functioning, social functioning, energy or fatigue, cognition, and emotional distress. Total HIT-6 scores can range from 36 to 78, with higher scores reflecting greater adverse disease impact on functioning. A score of 49 or below indicates little or no impact, 50-55 some impact, 56-59 substantial impact, and 60 or more represents severe impact. Health-related quality of life was measured with the Migraine-Specific Quality of Life Questionnaire, a 14-item questionnaire that measures how migraines affect and/or limit daily performance over the long term.

Asked by an audience member why Botox was tested in chronic migraine and frequent migraine but not in episodic migraine patients, Dr. Aurora said, "I can only speculate. I think that it may be working more as a modulated peripheral and have effect centrally, whereas in patients with episodic migraine, there is not an ongoing central desensitization."

She reported:

- Repeated treatment with Botox over the 56-week period demonstrated significant improvements from baseline vs. placebo, and the changes were sustained over multiple treatment cycles and consistent across multiple headache symptom measures at the Week 24 primary time point as well as at other time points.
- Statistically significant reductions across multiple headache symptom measures are clinically relevant, which was confirmed by patients treated with Botox experiencing substantially reduced disease burden and improved functioning and quality of life.
- During the open-label phase, when all patients were treated with Botox, there were statistically significant within-group improvements from baseline at all time points for all efficacy variables evaluated.
- No between-group differences were observed in the frequency of acute headache medication intake. However, statistically significant differences in the frequency of triptan acute medication intake favoring the Botox/Botox group vs. placebo/Botox group were observed for all visits in the double-blind phase ($p<0.001$) as well as in Weeks 28, 32, 36, and 52 in the open-label phase.
- By the end of the open-label phase, 48% of patients had achieved a mean HIT-6 score in the less-than-severe (<60) category. At all time points except the Week 56 exit visit, Botox significantly reduced disability and improved functioning, vitality, and psychological distress as measured by the HIT-6 score ($p<0.022$ at each time point).
- When patients were compared based on the double-blind phase treatment for all variables, at many of the open-label visits there were significant between-group differences favoring Botox (Weeks 28-56).
- Botox significantly improved overall health-related quality of life at all visits in the 24-week, double-blind phase for all domains of the Migraine-Specific Qualify of Life Questionnaire (MSQ) ($p<001$). Significant within-group quality of life improvements through Week 56 were also observed at all visits in the open-label period.
- Botox treatment significantly reduced the impact of headache on health-related quality of life as assessed by significant change from baseline through Week 56 in Headache Impact Score (HIS).
- As in the double-blind phase, the most common adverse events with Botox were neck pain (5.8%) and sinusitis (5.1%). Treatment-related adverse events throughout the entire 56-week study were consistent with the known tolerability profile of Botox, and no safety or tolerability issues emerged. One serious adverse event, exacerbation of migraine, was considered to be treatment-related. Over the 56-week study, the overall adverse event rate progressively decreased with subsequent Botox treatments.

3. PREEMPT-1 trial double-blind phase. This was another Swedish Neuroscience Institute (Dr. Aurora) poster. Most of the conclusions mirrored what had already been reported by Dr. Dodick in the pooled PREEMPT trial analysis.

In PREEMPT-1:

- Botox treatment was ***not*** shown to be more effective than placebo on the frequency of headache episodes at Week 24 or at any other post-treatment time point.
- Despite a large within-group decrease from baseline, no significant between-group difference was observed for the primary endpoint.
- In a post hoc analysis of headache episode frequency, there was no significant between-group difference during the first 14 days of the 4-week baseline phase (Nss, $p=0.137$). When the baseline was used, significant between-group differences favoring Botox over placebo were demonstrated for headache episode frequency at Week 4 ($p=0.015$), Week 8 ($p=0.012$), Week 20 ($p=0.05$), and Week 24 (Nss, $p=0.49$).
- A conservative Bonferroni multiple comparison adjustment was applied to compare p-values to a critical level of 0.01, which adjusts the type 1 error rate of 0.05 for all five variables pre-specified as primary or secondary in the study. The reduction in headache days and migraine days favoring Botox remained statistically significant following this adjustment.

24-Week PREEMPT-1 Double-Blind Efficacy Results

Measurement	Botox	Placebo	p-value
Change from baseline in frequency of			
Headache episodes	- 5.1%	- 5.3%	Nss, 0.344
Headache days	- 7.8%	- 6.4%	0.006
Migraine days	- 7.6%	- 6.1%	0.002
Migraine episodes	- 4.8%	- 4.9%	Nss, 0.206
Acute headache medications	- 10.3%	- 10.4%	Nss, 0.795
Number of moderate/severe headache days	- 7.2%	- 5.8%	0.004
Total cumulative headache hours	- 106.7	- 70.4	0.003
Total HIT-6 scores	- 4.7	- 2.4	<0.001
Patients with severe (≥60) HIT-6 score	68.9%	79.9%	0.001
Adverse events			
All adverse events	59.7%	46.7%	---
Treatment-related adverse events	25.3%	11.7%	---
Serious adverse events	5.3%	11.7%	---
Treatment-related serious adverse events	0	0	---
Discontinuation related to adverse events	4.1%	0.9%	---
Death	0	0	---

- Highly statistically significant improvements from baseline favoring Botox were observed for the secondary endpoints frequency of headache days and frequency of migraine days.
- Despite large within-group decreases from baseline in the frequency of migraine episodes and acute head pain medication intake, there was no between-group difference.
- Post hoc analyses found that Botox was highly significantly more effective than placebo in reducing both the cumulative hours of headache on headache days and the frequency of moderate/severe headache days.
- Botox patients reported improved functioning, vitality, and psychological distress, as demonstrated by significant decreases in disability compared to placebo-treated patients, as measured by mean change in total HIT-6 score. Botox treatment significantly improved health-related quality of life compared to placebo treatment, as measured by changes on the three MSQ role function domains: restrictive, preventive, and emotional.

4. PREEMPT-2 double-blind phase. PREEMPT-2 was conducted from 2006 to 2008 at 66 global sites (50 in North America and 16 in Europe).

The conclusions in this Mayo Clinic (Dr. Dodick) poster also mirrored the pooled results presented orally and in other posters by Dr. Dodick:

- Botox-treated patients reported improved functioning, vitality, and psychological distress as demonstrated by a significant decrease in disability compared with placebo-treated patients, measured by mean change in total HIT-6 score at Week 24 (Botox patients -4.9, placebo -2.4, p<0.001).
- Botox was significantly more effective than placebo in reducing the frequency of headache days (primary endpoint) in patients with chronic migraine.
- Botox significantly improved multiple headache symptoms over placebo for all secondary endpoints evaluated.
- Botox patients achieved significant improvements vs. placebo-treated patients in functioning, vitality, psychological distress, and overall quality of life.
- Botox represents an effective, safe, and well tolerated treatment for the prophylaxis of headache in adults with chronic migraine.
- Botox-treated patients showed statistically significant improvements vs. placebo-treated patients for the primary endpoint and all secondary efficacy endpoints.
- Most adverse events were mild or moderate in severity and resolved without sequelae. The only individual adverse events occurring at a rate ≥5% were neck pain (9.8%) and muscular weakness (5.2%) in the Botox group. Treatment-related adverse events were consistent with the known tolerability profile of Botox, and no newly emerged safety findings were observed. There was one treatment-related serious adverse event reported for Botox (migraine requiring hospitalization).

5. Health-related quality of life in the PREEMPT program. This Allergan poster looked at pooled data on disease impact on disability and health-related quality of life data from the 24-week, placebo-controlled, double-blind phases of PREEMPT-1 and -2.

The added information from this analysis included:

- A majority of patients were severely impacted by chronic migraine and had reduced health-related quality of life at baseline.
- Treatment of chronic migraine with Botox is associated with reduced headache impact and improved health-related quality of life vs. placebo.
- The magnitude of the improvement in functioning and health-related quality of life was statistically significant and reflected clinically meaningful improvements in functioning and vitality and a decrease in psychological stress associated with treatment with Botox compared to placebo.
- Statistically significant between-group differences were found for all three domains of the MSQ assessed at Week 12 and Week 24. A greater improvement in health-related quality of life was observed in patients treated with Botox than in placebo-treated patients.

6. **PREEMPT chronic migraine subgroup overusing acute headache medications at baseline.** This pooled, pre-specified subgroup analysis compared 445 Botox patients to 459 placebo patients over the 24-week, double-blind, placebo-controlled phase of PREEMPT-1 and -2.

This Allergan poster found:

- Treatment with Botox resulted in highly significant improvements for multiple headache symptom measures for the medication overuse subgroup vs. placebo.
- Botox significantly reduced headache-related disability and improved functioning and overall quality of life for this difficult-to-treat subgroup of patients.
- Botox represents an effective, safe, and well tolerated treatment for the prophylaxis of headache in adults with chronic migraine in this subpopulation of patients.
- There were no new safety findings in the subgroup.

PREEMPT 24-Week Results in Medication Overuse Subgroup

Measurement *(change from baseline)*	Botox (n=445)	Placebo (n=459)	p-value
Frequency of headache days	- 8.2%	- 6.2%	<0.001
Frequency of migraine days	- 8.1%	- 6.0%	<0.001
Total cumulative hours of headache on headache days	- 114.5	- 70.8	<0.001
Frequency of moderate/severe headache days	- 7.7%	- 5.7%	<0.001
Patients with severe (≥60) HIT-6 score	71.0%	81.9%	<0.001
Frequency of headache episodes	- 5.4%	- 5.1%	0.028

7. **Primary pain on the vertex – successful treatment with Botox.** Researchers at Jeonbuk National University, Republic of Korea, concluded from a study of 44 cases that moderate-to-dramatic improvements were seen in 79.5% of primary pain on the vertex (POV) cases after three months of consecutive Botox treatments. Two patients complained about post-injection pain, but the symptoms were resolved in a few days.

8. **Botox treatment in herpetic neuralgia and allodynia – possible pharmacotherapeutic mechanisms of Botox.** Another Jeonbuk National University study concluded that Botox was very effective in the treatment of herpetic neuralgia and allodynia.

9. **Sustained efficacy of Botox on migraine-related disability over 3 treatment cycles in a community-based setting.** A physician in private practice gathered data on 40 patients treated for either chronic migraine or high frequency migraine (8-14 days per month) who underwent three consecutive courses of Botox treatment at three month intervals. The study concluded that there was a sustained reduction in migraine-related disability, headache days, and acute medication use with Botox.

Headache days decreased from a baseline of average 20.7 days per month to 11.6 (treatment 1), 9.9 (treatment 2), and 9.5 (treatment 3) days per month respectively. Monthly acute medication doses decreased from a baseline average of 51.5 to 27.85 (treatment 1), 24.25 (treatment 2), and 21.4 (treatment 3) for the three cycles of treatment.

PREEMPT Results of Botox on Disability

Measurement *(change from baseline)*	Treatment 1	Treatment 2	Treatment 3
Average migraine disability assessment score (MIDAS)	Down 33.6	Down 31.7	Down 38.0
Headache days	Down 9.1	Down 10.8	Down 11.2
Monthly acute medication doses	Down 23.65	Down 27.25	Down 30.1

Physician reaction to Botox headache data

Despite the positive study results, 10 out of 17 doctors asked about using Botox for chronic migraine were skeptical or outright negative about the idea. Only seven were positive in any way about its use. The skeptics cited past studies showing that Botox does not work for migraine and questioned the one indication (chronic migraine) being touted now. Others worried about the cost, saying that reimbursement is a huge hurdle. Some doctors questioned the first Botox study, which failed its primary endpoint, and wondered about the validity of pooled data. The most cynical said that pure greed is responsible for the "ruthless promotion" of Botox in the U.S. However, a few said that there will be some demand from the public, despite the $300 per month cost.

Dr. Jes Olesen of Denmark, one of the leading headache researchers in the world, said, "The effects are 10% better than placebo, which is significant, but in a study with 1,300 patients, everything almost becomes significant. So p-value is not necessarily an indication of a promising result. I don't think the results are presented in a fair way. There is a difference between statistical significance and clinical significance. It is not clinically significant because it is only 10% compared to the expensive and invasive treatment. The study doesn't evaluate whether patients were blinded or not. And Botox makes it impossible to blind. If patients are not blinded, they tend to favor the active treatment. Also, all the studies of episodic migraine and tension headaches have been negative, and there is no idea here of why it works in chronic migraine. There is no rationale of why the drug should work in chronic migraine. It's a little surprising that it doesn't work in other migraines, then. And finally, when is enough enough? They've been studying the drug for more than 10 years in 20 trials, and sooner or later you have to see something. Here is the first positive experience, and they may, in fact, have had too many trials. So many negatives, and here is the first positive trial."

Other comments by skeptical doctors included:

- *Maryland:* "I don't see the data as impressive; it doesn't look like a clear cut win."
- *Ohio:* "I started out suspicious because of the history. There have been no good studies. Chronic migraine may be different, and its use may be justified."
- *Italy:* "Botox for chronic migraine patients, I think, would be difficult. These are very difficult-to-treat patients, and they often have psychiatric comorbidities and don't ever get better."
- *Colorado:* "I don't have any experience with it, and I am very skeptical. Previous results have shown no benefit. It is a reasonable study, and it looks to have benefit and may give patients relief. Patients are willing to try it, and doctors will be willing to try it."
- *Netherlands #1:* "I'm not convinced that Botox is effective. There have been a lot of studies done, and they are not convincing. Several show only a modest effect, and some of the effects still need observation. I also have a question about the difference between Botox and placebo on open-label. When everyone is on Botox, the difference between Botox and placebo persists. It doesn't make sense. Could it be neuroprotective? That would be amazing, and it needs explanation. There is a lot of pressure from industry, however, and the press will write about it, and the public will ask for it...Botox has failed in other indications but may work in chronic migraine. Plus, the effect is really modest. The effect may be real, but the population size is very small. On average, these patients have headaches 20 days a month, and Botox reduces that by two days."
- *Netherlands #2:* "It is a painful treatment, and it is not user friendly. Still, people will ask for it. If you have a headache every day, you will want to at least try it. There is not much Botox hype in Europe, and it won't get a lot of good press (there)."
- *California:* "I'm highly suspicious. (It is) something that has been studied for years, and now they find an indication in chronic migraine. I get a feeling that it is suspicion. Until it is published and is peer reviewed, I'm going to continue to be very skeptical."
- *Pennsylvania:* "It didn't meet its primary endpoint in the first trial, and I'm not impressed."
- *Oklahoma:* "Can you select the patients who are going to respond? The answer is no. Also, the patient has to plunk down $1,000 in order to participate in the trial. But the insurance companies won't pay for it. I have one patient who got Botox in California, and I was able to convince the insurance company to pay. We've tried everything for other patients…You can get a trial of amitriptyline for $10 and compare it to Botox for $300, and then you have to have Botox every three months. There will be a place for it, but it will be for those with chronic migraine who have tried everything else…Statistical significance is also different from clinical significance. Ten percent of patients responding out of 2,000 may be statistically significant but may not be clinically significant. There may also be a huge placebo effect…I'd say that 20%-30% would be clinically significant, but 10% is not."
- *Virginia:* "I don't use Botox for chronic migraine. Reimbursement is a huge problem."
- "Every patient on Botox knows she is on Botox. The promotion of Botox is only in the U.S. It is driven by money and is unconscionable."

Some doctors were in favor of using Botox for chronic migraine patients, asking why not try it on patients for whom nothing else works?

- *California:* "The data are pretty solid for a hard-to-treat population. For that patient population, that one and a half day difference (between Botox-treated and placebo) is pretty important, and when you look at the hours, there is a 30-hour difference, and that's meaningful for a tortured patient."
- *Pennsylvania:* "Who are the targets? That's the question. We will have to try it on everyone."
- *Texas #1:* "I don't use Botox for chronic migraine, but I do for some neck-generated headaches, cervical trauma, and non-cervical disease. If the headache is one-sided, I tend to think about using it. If the migraine is one-sided, you get better results with Botox. I also have my own method (of injecting Botox), which is not going into the muscle, but under the skin. But fewer than 5% (of patients) will get it. In my practice we try to be selective. Some doctors start earlier, but I'm interested in better success."
- *New York:* "It beats everything we have…I'm going to use Botox whether the FDA approves it or not. I did my own study of patients who came back every three months – a very tough group with high frequency migraines – and there was a sustained reduction in migraine-related disability, headache days, and acute medication use… Cost is the big issue. Most pay out of pocket, but I do have two insurance companies that have paid: Oxford under certain circumstances and Cigna, which will approve only if you appeal…There are no side effects except browtosis. Also, some younger patients with long slim necks have some neck pain, but I avoid injecting in the back of the neck."
- *Texas #2:* "It works in some patients; we don't know which. It's intelligent trial and error. I think that in the future maybe 5% of my patients will get it. It is expensive, and there are some side effects, like no forehead wrinkles, which some patients really don't like. However, it always wears off, which is both a good and a bad side effect."

MAP PHARMACEUTICALS' LEVADEX

There was some buzz over this self-administered, novel, orally inhaled form of DHE **(**dihydroergotamine**)** in development as a 1.0 mg nominal dose (approximately 0.5 mg systemic equivalent dose), with T_{max} and AUC similar to an intravenous infusion but with markedly lower C_{max}. Doctors said that the device looks extremely promising for treating a broad spectrum of migraine and for patients resistant to other therapies, but doctors still want more data.

Among the posters at the International Headache Conference concerning Levadex were:

1. **Levadex efficacy in treating resistant migraine including migraine with allodynia, morning migraine, disabling migraine, and migraine treated late in its cycle.** This Cleveland Clinic poster examined data from a 792-patient, Phase III trial of Levadex, showing that it is well tolerated and effective in treating a broad spectrum of migraine, including acute migraine, people who are resistant against therapies such as triptans, migraine with moderate and severe pain, migraine with nausea and vomiting, and migraine with and without aura. Levadex had rapid and sustained efficacy in treating migraine, with pain relief at 10 minutes and time to pain relief of 30 minutes.

Results included:

- Pain relief, phonophobia-free, and photophobia-free were all significantly better with Levadex than placebo ($p<0.0001$). There were also more nausea-free patients ($p=0.02$).
- Post hoc analyses showed that Levadex was effective compared to placebo in treating migraine:
  - In patients with or without allodynia that occurs in the early morning.
  - At any time during the attack, regardless of how long patients waited to treat the attack.
  - In severely disabled and non-disabled patients as defined by an HIT-6 score.
  - That is severe as well as moderate intensity of baseline pain.
  - Severe, providing pain relief at 10 minutes.

Levadex Efficacy in Treating Migraine

Measurement	Levadex	Placebo
Sustained pain relief from 2-24 hours	44%	20%
Sustained pain relief from 2-48 hours	36%	17%
Sustained pain free from 2-24 hours	23%	7%
Sustained pain free from 2-48 hours	18%	6%
Adverse events		
Medication aftertaste	6%	2%
Nausea	5%	2%
Chest discomfort	1%	0
Chest pain	0	0
Decreases in lung function	0	0

  - With and without nausea, vomiting, and aura.

2. **Efficacy of Levadex in treating a broad spectrum of acute migraine attacks, including patients using triptans and patients not using triptans.** This Palm Beach Headache Center/MAP Pharmaceuticals poster concluded that Levadex has the potential to be effective in a broad spectrum of migraine.

Post hoc analyses evaluating the efficacy of Levadex in 811 patients in treating a broad spectrum of migraine showed that Levadex:

- Was effective in treating a broad spectrum of migraine attacks.
- Was effective in treating migraine attacks with severe and moderate intensity of baseline pain.
- Led to statistically significant pain relief in 10 minutes in patients with severe intensity of pain.
- Was effective in treating migraine with and without nausea, with and without vomiting, with and without aura.
- Was effective in treating migraine in patients currently using triptans and those not using triptans.

In the severe population, the pain relief response for Levadex was statistically significant compared to placebo at all time points starting at 10 minutes.

Levadex Efficacy in Treating Migraine

Measurement	Levadex	Placebo	p-value
Pain relief at 60 minutes	61%	37%	<0.001
Moderate migraine patients who had pain relief at 2 hours	70%	42%	<0.0001
Nausea			
2-hour pain relief ***with*** nausea	52%	35%	<0.0001
2-hour pain relief ***without*** nausea	70%	33%	<0.0001
2-hour pain free relief ***with*** nausea	28%	10%	<0.0001
2-hour pain free relief ***without*** nausea	31%	9%	<0.0001
Vomiting			
2-hour pain relief ***with*** vomiting	19.5%	41%	<0.05
2-hour pain relief ***without*** vomiting	37%	60%	<0.0001
2-hour pain free ***with*** vomiting	26%	3%	<0.01
2-hour pain free ***without*** vomiting	29%	10%	<0.0001
Aura			
2-hour pain relief ***with*** aura	54%	32%	0.0002
2-hour pain relief ***without*** aura	60%	37%	<0.0001
2-hour pain free ***with*** aura	28%	5%	<0.0001
2-hour pain free ***without*** aura	30%	11%	<0.0001
Triptans			
2-hour pain relief ***with*** triptan	58%	32%	<0.0001
2-hour pain relief ***without*** triptan	60%	38%	<0.0001
2-hour pain free ***with*** triptan	26%	8%	<0.0001
2-hour pain free ***without*** triptan	30%	10%	<0.0001

3. **Efficacy evaluation of Levadex in treating resistant migraine, including migraine with allodynia, migraine treated late in its cycle, morning migraine, and disabling migraine.** This study showed that Levadex has potential to be effective in a broad spectrum of migraine, including resistant migraine subtypes.

Levadex was effective vs. placebo:

- In treating migraine in patients with or without allodynia (all measures p=0.0003 or better).
- Vs. placebo (all measures p<0.0001) if less than four hours to treatment, two-hour pain relief (p<0.05 if treated after four hours) in treating a migraine at any time during the course of the migraine attack.
- In treating morning migraine (all measures p<0.05).
- In treating an acute migraine attack in severely disabled patients (HIT-6 ≥60) and non-disabled (HIT-6 <60), all measures p<0.01.
- Equally effective in treating acute migraine in disabled and non-disabled patients.

4. **Migraine with allodynia.** Patients who have cutaneous allodynia at the time of treatment often do not respond fully to triptans, as these drugs do not reverse central sensitization. This study found that Levadex was effective compared to placebo in migraine patients with or without allodynia. There was no statistically significant difference in efficacy between Levadex-treated migraines irrespective of the presence of allodynia. Results were similar when the presence of allodynia was defined as answering "yes" to one question instead of two. For migraine treated late in its cycle, Levadex was effective regardless of how long patients waited to treat the migraines.

In patients with a disabling migraine (HIT-6 score ≥60), Levadex was effective vs. placebo. It was equally effective in disabled and non-disabled patients. There was no statistically significant difference in efficacy between Levadex-treated migraine irrespective of the level of migraine disability.

Valeant Pharmaceuticals sells a DHE nasal spray (D.H.E. 45), but a MAP official claimed that MAP's inhaled DHE, using its proprietary Tempo device, has a faster onset of action.

Doctors were generally enthusiastic about Levadex, although some said they'd like to see more data. They said that Levadex appears to be fast-acting with a spike, which can result in nausea and vomiting for some patients. One doctor said that his patients said that the medication went down their throats and that it tasted like burning rubber. Dr. Stephen Silberstein, who made an oral presentation on Levadex data, said that none of his patients complained about the taste.

Physician comments about Levadex included:

- *Colorado:* "People don't want to use an IV because of side effects, so an inhaler looks promising."

Levadex and Allodynia

Measurement	Levadex	Placebo	p-value
2-hour pain relief ***with*** allodynia	57%	34%	<0.0001
2-hour pain relief ***without*** allodynia	60%	35%	<0.0001
Sustained 2-hour pain relief ***with*** allodynia	44%	20%	<0.0001
Sustained 2-hour pain relief ***without*** allodynia	42%	20%	<0.0001
2-hour pain free ***with*** allodynia	30%	8%	<0.0001
2-hour pain free ***without*** allodynia	27%	12%	0.0002
Sustained 2-24 hour pain free ***with*** allodynia	23%	4%	<0.0001
Sustained 2-24 hour pain free ***without*** allodynia	21%	8%	0.0003
Efficacy of Levadex in treating migraine pain within one hour of start of headache			
2-hour pain relief	66%	41%	<0.0001
2-hour pain free	38%	13%	<0.0001
Sustained 2-hour pain relief	53%	27%	<0.0001
Sustained 2-hour pain free	30%	9%	<0.0001
Efficacy of Levadex in treating migraine pain within 1-4 hours of start of headache			
2-hour pain relief	60%	34%	<0.0001
2-hour pain free	28%	10%	<0.0001
2-24 hour sustained pain relief	45%	15%	<0.0001
2-24 hour sustained pain free	23%	5%	<0.0001
Efficacy of Levadex in treating migraine pain within 4-8 hours of start of headache			
2-hour pain relief	53%	30%	<0.0001
2-hour pain free	22%	8%	<0.0001
2-24 hour sustained pain relief	32%	24%	<0.0001
2-24 hour sustained pain free	18%	5%	<0.0001
Efficacy of Levadex in treating migraine pain after 8 hours of start of headache			
2-hour pain relief	53%	30%	<0.0001
2-hour pain free	22%	8%	<0.0001
2-24 hour sustained pain relief	32%	24%	<0.0001
2-24 hour sustained pain free	18%	9%	<0.0001
Efficacy of Levadex in treating morning migraine			
2-hour pain relief	40%	23%	<0.05
2-hour pain free	21%	4%	<0.05
2-24 hour sustained pain relief	29%	10%	<0.01
2-24 hour sustained pain free	13%	1%	<0.01
Efficacy of Levadex in treating migraine during the rest of the day			
2-hour pain relief	62%	37%	<0.0001
2-hour pain free	30%	11%	<0.0001
2-24 hour sustained pain relief	48%	21%	<0.0001
2-24 hour sustained pain free	25%	7%	<0.0001
Efficacy of Levadex in treating migraine in patients with HIT-6 scores <60			
2-hour pain relief	68%	37%	<0.01
2-hour pain free	28%	10%	<0.01
2-24 hour sustained pain relief	42%	20%	<0.01
2-24 hour sustained pain free	21%	7%	<0.01

- *Netherlands:* "The data are very limited. Also, Levadex is not available in Europe."
- *Texas:* "We participated in the trials, but the only person we enrolled dropped out. I follow the data, and I think that it's an effective method of delivery. There is far less nausea. It's quite a nice advance."
- *California:* "It is effective but very unpleasant when swallowed. There is a bad taste of burning rubber, but it works. It would be a substitute for injection. But the taste is a huge barrier and hard to fix."
- *American Headache Society past president:* "The results are very promising. It's probably not a drug of primary choice for all migraine patients, but patients with a lot of nausea and vomiting who can't tolerate the alternatives can take it. Another indication might be the cluster headache. It is a very interesting advance."
- *Virginia:* "It's an intriguing potential pathway."
- *New York:* "No one complained about the taste. It seems to work and is much better tolerated than other forms. It is a smooth delivery system with no spikes, which cause nausea."
- *Oklahoma:* "I think that it will work for about 60%-70% of patients."
- *Ohio:* "There aren't enough data for me, but it looks good, and it is a delivery mechanism that possibly will be used."
- *Italy:* "The inhaler is a great idea, and patients will love it, especially those who cannot tolerate pills."

MERCK'S TELCAGEPANT (MK-0974), A CGRP RECEPTOR ANTAGONIST

Calcitonin gene-related peptide (CGRP) is a potent vasodilator involved in migraine. The CGRP receptor antagonist olcegepant is effective in migraine but can only be administered intravenously. Telcagepant is an oral CGRP receptor antagonist.

A Merck investigator was very enthusiastic about it, saying that it was used for acute attacks with no problems and very few side effects, "The efficacy is repeated on the same order as triptans." Asked why Merck had the application on hold, he said, "Merck (has said) that in one safety study patients got high doses as a prophylactic, and a small number had aberrations in their liver parameters. This is not how they want to use the drug. They wanted to do a study where everything was wrong to see what would happen. The application is on hold until they fully analyze the data. We do need drugs for acute indications. It works extremely well."

Another investigator said that the application "is not on hold because of liver problems. It is safe and effective. It is safe for acute use, and the indication will be for acute use seven to eight times per month." Asked about any relationship to Merck's drug MK-3207, another CGRP receptor antagonist which Merck killed before Phase II/III trials could begin due to liver problems, he said, "MK-3207 is a different chemical compound from MK-0974. It is totally different. It didn't work, and it's dead."

Episodic migraine

A Merck scientist presented a poster looking at a double-blind, active-controlled study which found that:

- Telcagepant 300 mg capsules/280 mg tablets were generally well tolerated in the long-term, intermittent treatment of acute migraine, when administered to treat up to eight migraine attacks per month.
- Telcagepant 300 mg capsules/280 mg tablets were associated with fewer triptan-related adverse events than rizatriptan 10 mg.
- The transient elevation in transaminases following telcagepant in a small number of patients is under further investigation.

Triptan-Related Adverse Events Within 14 days Post-Dose with Telcagepant

Measurement	Telcagepant (n=641)	Rizatriptan (n=313)	Treatment difference
Primary endpoint: ≥1 triptan-related adverse event	32% (p<0.001)	35%	- 6.2%
Secondary endpoints			
Asthenia	14%	16%	- 2.9%
Chest discomfort	6%	7%	- 1.3%
Chest pain	1%	4%	- 1.1%
Dysesthesia	0	1%	- 0.3%
Paresthesia	13%	12%	- 1.8%
Paresthesia oral	3%	1%	0.1%
Adverse events			
≥1 adverse event	58.7%	63.9%	- 5.2%
≥1 drug-related adverse event	30.7%	46.3%	- 15.6%
≥1 serious adverse event	1.9%	1.9%	0
≥1 drug-related serious adverse event	0.2%	0.3%	- 0.2%
Discontinued due to adverse events	3.0%	3.5%	- 0.6%
Died	0	0	---
Dry mouth	9.7%	13.7%	---
Somnolence	9.2%	16.6%	---
Nausea	9.0%	6.4%	---
Dizziness	8.9%	10.2%	---
Fatigue	4.8%	10.2%	---
Nasopharyngitis	3.4%	3.2%	---
Vomiting	3.3%	3.2%	---
Abdominal pain upper	3.1%	2.2%	---
Diarrhea	2.8%	4.2%	---
Upper respiratory tract infection	2.7%	5.1%	---
Asthenia	2.2%	5.1%	---

Laboratory adverse events were infrequent for both telcagepant (1.9%) and rizatriptan (1.5%). Three patients on telcagepant experienced >3x elevation in hepatic transaminases without any concomitant elevation in total bilirubin. One patient had a co-occurring musculoskeletal injury. One event occurred two months after the last dosing. One event occurred in a patient who continued to treat with telcagepant without further transaminase elevations. All events were clinically asymptomatic, transient, and temporally unrelated to dosing with study medication.

Patients' Attacks with Telcagepant

Measurement	Telcagepant	Rizatriptan	Odds ratio
Pain free at 2 hours			
All patients	38.9%	47.5%	0.59
Non-triptan users	37.6%	41.9%	0.73
Triptan users	40.0%	51.9%	0.49
2-24 hour sustained pain free			
All patients	34.3%	37.7%	0.80
Non-triptan users	34.1%	37.2%	0.79
Triptan users	34.5%	38.0%	0.80

NuPathe's Zelrix (iontophoretic transdermal sumatriptan patch)

Zelrix is an iontophoretic transdermal patch that delivers sumatriptan for the treatment of acute migraine. A few doctors mentioned the Zelrix patch as a promising migraine delivery system. A New York neurologist said that it "is an alternative device that bypasses the guts, and it's pretty easy to work. The only problem we found was some skin irritation."

A randomized, double-blind, placebo-controlled, 530-patient, U.S. Phase III trial showed that:

- Zelrix provided statistically significant improvement vs. placebo for rapid, consistent, sustained relief of acute migraine headache.
- Within one hour following patch activation, a significantly higher proportion of patients who received Zelrix experienced headache pain relief and were nausea-free.
- Within two hours following patch activation, a significantly higher proportion of patients who received Zelrix also were headache photophobia-free, pain-free, and phonophobia-free.
- A significantly higher proportion of Zelrix patients reported sustained pain relief 24 hours after patch activation, was migraine-free two hours after patch activation, and required no rescue medication.
- The incidence of triptan-related adverse events was low. The most common adverse events were related to the application site and were typical of those previously reported with transdermal products.
- Zelrix may offer significant clinical utility for migraine patients by treating all symptoms of migraine with rapid, consistent, and sustained efficacy in a formulation that overcomes the treatment limitations associated with oral, nasal, and subcutaneous delivery of sumatriptan that often lead to delayed or non-treatment of migraine effects.

Treatment emergent adverse events were reported by 51% of patients who received Zelrix and 45 of patients who received placebo. Most adverse events were application site reactions that resolved within two days. The incidence of triptan-specific adverse events typically associated with sumatriptan plasma levels 50 ng/mL or more was very low in the Zelrix group (2%). Two percent of patients discontinued because of adverse events in both treatment groups.

♦

Zelrix Phase III Efficacy and Safety

Hours after patch activation	Zelrix	Placebo
Headache pain-free patients following patch activation		
2 hours	19%	9%
4 hours	48%	21%
6 hours	58%	38%
12 hours	68%	58%
Patients reporting headache pain relief following patch activation		
1 hour	71%	58%
2 hours	84%	63%
4 hours	93%	76%
6 hours	95%	82%
12 hours	97%	90%
Nausea-free patients following patch activation		
2 hours	52%	28%
4 hours	79%	53%
6 hours	81%	61%
12 hours	88%	78%
Most common adverse events		
Application site pain	23%	15%
Application site paresthesia	12%	19%
Application site pruritis	8%	7%
Application site reaction	7%	6%

Zelrix Efficacy

Measurement	1 hour post-dose	2 hours post-dose	3 hours post-dose	4 hours post-dose	6 hours post-dose	12 hours post-dose
Headache pain-free	---	X	X	X	X	X
Headache pain relief	X	X	X	X	X	X
Nausea-free	X	X	X	X	X	X
Photophobia-free	---	X	X	X	X	X
Phonophobia-free	---	X	X	X	X	X