

JMCM

JOURNAL of
MANAGED CARE MEDICINE

GBI Reports

Supplement

**Acute and Prophylactic
Treatment of Chronic
Headache Disorders**

Supported by an educational grant from Allergan Inc.

JMCM

JOURNAL OF MANAGED CARE MEDICINE

4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060
(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF

J. Ronald Hunt, MD

PUBLISHER

Jack F. Klose

CME MANAGEMENT

Katie Eads
Ann Patrick

JOURNAL MANAGEMENT

Douglas Murphy
Communications Inc.
8730 Stony Point Parkway, Suite 250
Richmond, VA 23235
(804) 272-9100
fax (804) 272-1694

MANAGING EDITOR

Virginia Sowers
virginia.sowers@douglasmurphy.com

ART DIRECTOR

David Balch

DESIGN ASSOCIATE

Paul Lacy

The Journal of Managed Care Medicine is published by Association Services Inc. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: 8730 Stony Point Parkway, Suite 250, Richmond, VA 23235; Tel (804) 272-9100; Fax (804) 272-1694. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage or retrieval system, without written consent from the publisher. The publisher does not guarantee, either expressly or by implication, the factual accuracy of the material and descriptions herein, nor does the publisher guarantee the accuracy of any views or opinions offered by the authors of said material or descriptions.

JOURNAL of MANAGED CARE MEDICINE

GBI Reports

Supplement

The Official Journal of the
NATIONAL ASSOCIATION OF MANAGED CARE PHYSICIANS
AMERICAN ASSOCIATION OF INTEGRATED HEALTHCARE DELIVERY SYSTEMS
AMERICAN COLLEGE OF MANAGED CARE MEDICINE
AMERICAN ASSOCIATION OF MANAGED CARE NURSES

ACUTE AND PROPHYLACTIC TREATMENT OF CHRONIC HEADACHE DISORDERS

This special edition of the *Journal of Managed Care Medicine* was developed from the proceedings of the 2005 NAMCP Fall Managed Care Forum session on managing chronic headaches.

Target Audience

This is intended for medical directors, neurologists, and practicing physicians involved in the treatment of headaches.

Needs Assessment

Headache is a common disabling disorder that is costly for patients, the healthcare system, and employers, and presents a management challenge for physicians. Patients with chronic daily headache (CDH) require both acute (abortive) treatment and prophylactic treatment. Although not yet FDA-approved for the indication, botulinum toxin A (BoNTA) is one agent that can be used to decrease the frequency of headaches, avoid compliance issues found with oral medications, and decrease the costly use of acute treatments such as triptans.

Learning Objectives

- Upon completing this activity, participants should be able to:
- Discuss the economic impact of CDH on the healthcare system
 - Describe the value of preventive treatment for CDH
 - Review clinical data on prophylactic medications
 - Discuss how one managed care plan implemented a medical policy for the treatment of CDH

Accreditation and Designation

The National Association of Managed Care Physicians (NAMCP) is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. NAMCP designates this activity for a maximum of 1 *AMA PRA Category 1 Credit*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

To receive CME credits, read the entire monograph and answer the post-test questions. An answer sheet is available online at www.namcp.org/seemedia/migraine/post-test.htm.

The release date of this activity is March 15, 2006. This activity is valid through Dec. 31, 2006.

Acute and Prophylactic Treatment of Chronic Headache Disorders

HEADACHES LEAD TO significant burden in terms of treatment costs, patient disability, and impaired quality of life.¹ Chronic headaches are vastly undiagnosed and untreated.² Approximately 12 percent of the U.S. population experiences migraines.³ About 4 percent of the U.S. adult population has chronic daily headache (CDH).⁴ Only about 3.6 million migraine sufferers seek medical attention.³ Even when migraine sufferers seek treatment, it is unlikely that they will be put on a preventive medication, the ideal approach for migraine.^{5,6} Additionally, chronic headache sufferers tend to be high utilizers of medical services.²

Classifying Headache

It is important to distinguish between primary headache, where there is no underlying illness or other cause, and secondary headache, where a specific cause is

identifiable (see Exhibit 1).⁷ If a person has a stable pattern of headache, even if disabling, he or she most likely has a primary headache disorder. Atypical features or recent changes in headache pattern increase the possibility that a headache is secondary to some other medical condition.⁶ Head injury, use of medication, hormonal changes, or exposure to various harmful substances may cause headaches.

Evaluation of headaches begins by distinguishing between primary and secondary headaches. Once secondary origins of headache have been ruled out, it is next helpful to divide primary headaches into episodic and chronic headache disorders. Various chronic primary and secondary headache disorders are listed in Exhibit 2, with secondary causes of CDH listed in Exhibit 3.⁶

The term *chronic*, as defined by the International Headache Society (IHS), applies to those conditions involving attacks occurring more frequently than 15 days per month for more than six months.⁸ Chronic headaches that last more than four hours on any given day are termed chronic daily headache, and, as noted, about four percent of the U.S. adult population suffers from CDH.⁴ The majority has chronic forms of either migraine or tension-type headache. With inadequately

treated CDH, the patient is never completely without symptoms and may develop depression, anxiety disorders, and/or sleep disturbances (see Exhibit 4).⁹

Episodic headache can transform into CDH. Case control and cohort analyses have identified risk factors for conversion from the episodic variety to the chronic variety.¹⁰ Some risk factors are readily modifiable; others are not. Modifiable risk factors include attack frequency, obesity, and medication overuse. Possibly modifiable factors include altering response to stressful life events and treating sleep apnea or other sleep disturbances. Nonmodifiable risk factors include genetic predisposition for migraine, female gender, low education level, low socioeconomic status, and a history of head injury. Modifying risk factors may prevent CDH development, or may increase the remission rate of CDH, reverting the condition to episodic headache.

Medications That Can Lead to Headache

Although effective for treating headaches, analgesics, ergotamine tartrate, and the triptans (sumatriptan, frovatriptan, eletriptan, rizatriptan, naratriptan, and zolmitriptan) can all cause rebound headaches if used to

Faculty

Andrew Blumenfeld, MD
Director, The Headache Center of Southern California
Staff neurologist, Kaiser Permanente
Partner, The Neurology Center
San Diego, Calif.

Kenneth L. Schaecher, MD
Medical Director for Utilization Management,
Intermountain Health Care
Salt Lake City, Utah

Disclosure of Faculty Relationships and Discussions of Off-Label Uses

Andrew Blumenfeld, MD, serves on the speakers bureau for Allergan Inc.

Kenneth Schaecher, MD, served as moderator at the advisory board meeting held to help determine the content of his presentation but has no other financial relationships that create a conflict of interest.

The faculty members use name brands in this monograph.

excess.¹¹⁻¹⁵ Ergotamine tartrate and analgesic rebound are more firmly established in the literature than is rebound caused by triptans. It is unclear, in part owing to their long duration of effect, whether dihydroergotamine or naratriptan cause rebound.⁶ Decongestants and caffeine also lead to rebound headaches.

The transformation or progression from episodic to daily headache can occur when any of these medications, even at low dosages, are taken regularly more than two to three times per week.⁶

It does not appear to be the total dose but rather the frequency of usage that leads to the development of rebound headache. Combination products containing caffeine and butalbital may be especially likely to generate “analgesic rebound,” whereas medications with a longer duration of action (i.e., a longer half-life) may be less likely to do so.⁶

Abrupt discontinuation of medications in patients with rebound headache usually results in profound escalation of headache intensity (withdrawal headache),

which explains why patients experience great difficulty discontinuing medication on their own and why perpetuation of this process occurs so readily. Even after total discontinuation and termination of the rebound event, “normalization” of the headache process and responsiveness to standard medications may take weeks or even months.⁶ Clinicians should be careful to screen CDH patients for medication overuse and also counsel patients about the risks of analgesic overuse and rebound headache.⁶

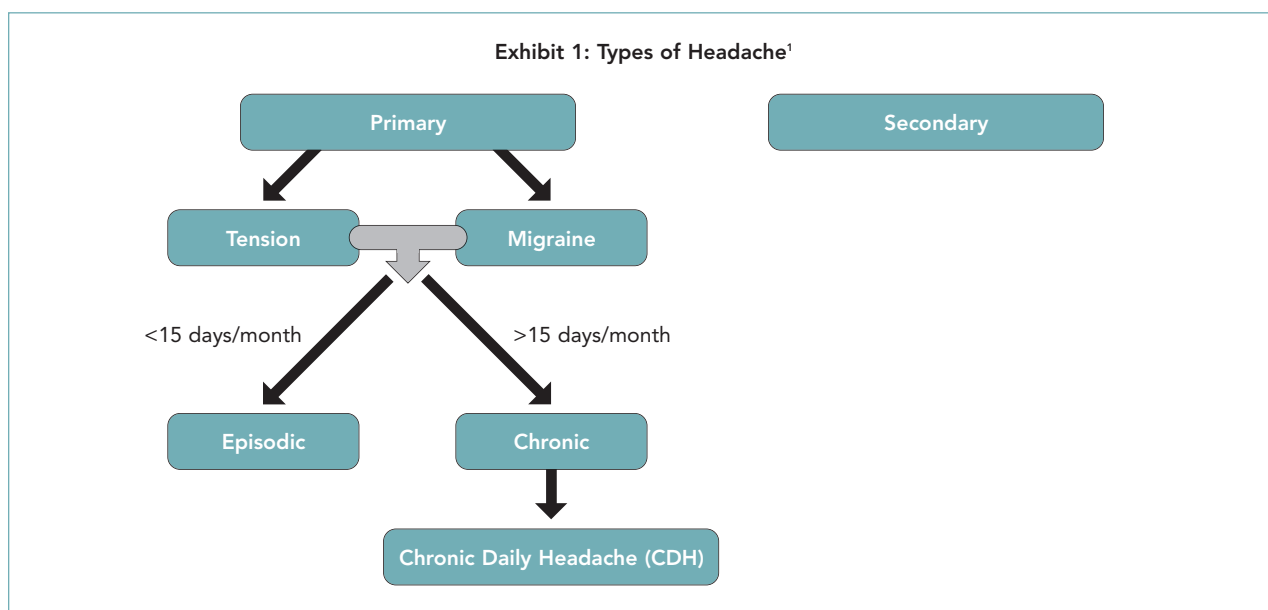


Exhibit 2: Primary Types of CDH⁶

- Chronic tension-type headache
- Chronic migraine (formerly known as transformed migraine with or without analgesic rebound)
- New daily persistent headache
- Chronic cluster headache
- Hemicrania continua
- Chronic paroxysmal hemicrania
- Hypnic headache
- Idiopathic stabbing headache
- SUNCT (short-lasting, unilateral neuralgiform headaches with conjunctival injection and tearing)
- Cranial neuralgias (e.g., trigeminal neuralgia)

Note: All diagnoses may be confounded by medication overuse.

Exhibit 3: Secondary Types of CDH⁶

- Post-traumatic (may mimic any primary headache)
- Cervicogenic (especially C2, C3 upper root entrapment)
- Temporomandibular joint syndrome
- Sinus disease
- Arteriovenous malformation
- Arteritis (including giant cell arteritis)
- Subdural hematoma
- Vascular dissection
- Neoplasm
- Infections
- Intracranial hypertension
- Intracranial hypotension

Note: All diagnoses may be confounded by medication overuse.

Treatment of CDH

Treating patients with CDH can be challenging, particularly if the headaches are complicated by medication overuse. Often, patients do not realize that excessive or frequent self-treatment may actually worsen their condition. Continued overuse of immediate-relief medications, particularly in headache-prone patients, may result in refractoriness to treatment (prophylactic medications may not work), perpetuation of the headaches, and a transformation from a pattern of intermittent headache to one of CDH. A two-month period is required after cessation of medication overuse to establish a diagnosis of chronic migraine with certainty.⁶

For patients with chronic migraine, antimigraine agents such as the triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), and dihydroergotamine can be effective for acutely terminating an attack, provided that the patient has not previously overused any symptomatic medication. Acute treatment of chronic tension-type headache (CTTH) can be effectively managed with analgesics.⁶

Patients with frequent headaches should be treated primarily with preventive medications to reduce the frequency, severity, and duration

of the headaches.^{6,16} Prophylaxis can reduce the use of acute headache pain medications, headache-related visits to physician offices, and emergency room visits. Currently, there is no professional consensus on appropriate prophylaxis in CDH, nor are there FDA-approved agents specifically for prophylaxis of CDH. The evidence of efficacy in CDH with FDA-approved episodic headache preventive agents is quite limited. An obvious need exists for effective, long-term, and well-tolerated prophylactic treatment regimens for CDH.

Without professional consensus, choices for treatment of CDH are best made based on a patient's concomitant or comorbid conditions and the best available evidence. Current FDA-approved therapies for episodic headaches are rarely effective in reducing frequency of headaches more than 50 percent and have significant systemic adverse effects. Medications should generally be started at a low dose, followed by gradual increases in dose until efficacy is achieved, side effects become intolerable, or the ceiling dose is reached. Nonpharmacologic therapies such as biofeedback, stress management, and cognitive behavioral therapy should also be considered.

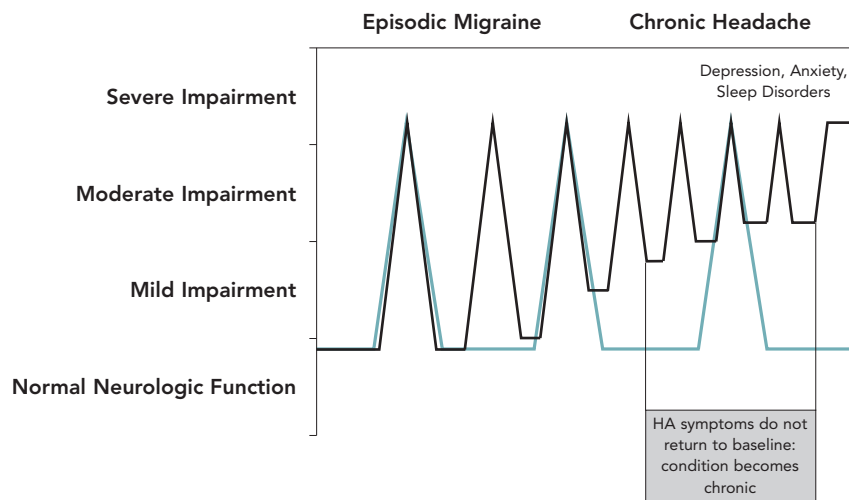
Monotherapy is the preferred prophylactic approach; combination therapy should be reserved for physicians specializing in the treatment of headache.⁶

Common Applications of Currently Used Preventive Therapies

Many drugs are used as preventive therapy for disabling primary headache. The majority are either experimental, off-label, or do not work consistently across all patients. Most are not FDA-approved for the treatment of headache. Exhibit 5 lists a number of commonly used preventive therapies for both migraine and tension-type headaches.¹⁵ Efficacy for most of these therapies is unproven for the treatment of CDH.

Only a few double-blind placebo-controlled trials of medications have addressed the highly debilitated CDH population. This population is commonly seen as refractory and often excluded from clinical trials. Only topiramate (Topamax[®]), tizanidine (Zanaflex[®]), gabapentin (Neurontin[®]), fluoxetine (Prozac[®]) and botulinum toxin type A (Botox[®]) have been systematically studied and reported in a CDH population. The number of patients

Exhibit 4: Episodic vs. Chronic Headache



per trial for the oral medications varies from 28 to 95 patients. In general, oral agents, with the exception of fluoxetine, modestly increase headache-free days.¹⁷⁻²⁰ Fluoxetine appears to be effective in episodic migraine but not CDH.²⁰

Adverse events are common with currently available oral preventive medications. Antiepileptic agents, such as gabapentin and topiramate, can cause gastrointestinal distress, sedation, lethargy, dizziness, and paresthesias.¹⁶ In recent studies of topiramate to prevent episodic migraine, the patient withdrawal rate due to adverse events was greater than 20 percent at the effective doses.^{21,22} Tricyclic antidepressants are known to cause sedation, weight gain, dry mouth, constipation, dizziness, mental confusion, palpitations, blurred vision, and urinary

retention. Calcium channel blockers can cause constipation, peripheral edema, and weight gain, while the use of beta-blockers is associated with drowsiness, fatigue, lethargy, sleep disorders, and depression.¹⁶

The experience of intolerable adverse events may limit patients' adherence to their headache medication regimens. In a recent survey of migraine patients, two out of three sufferers (67 percent) reported that they had delayed or avoided taking a current prescription migraine medication because of concerns about adverse effects.²³ The result of delaying or avoiding the use of prescription medication was more intense pain in 60 percent of respondents.²³

Botulinum toxin (BoNTA) injection has been studied in approximately 1,500 patients with CDH.²⁴⁻³³ These studies are

summarized in Exhibit 6. The mechanism of action of BoNTA in CDH prophylaxis is uncertain, but it appears to block peripheral pain signaling and may eliminate tension in head and neck muscles.³⁴ BoNTA is believed to inhibit the release of neurotransmitters from nociceptive nerve terminals, thereby reducing peripheral and central sensitization. When BoNTA is used for headache, multiple sites across the brow, forehead, temple, back of the neck, and shoulders are injected.

Overall, BoNTA used as a prophylactic agent produces significant, clinically meaningful improvements in

- headache frequency
- headache-free days
- headache days
- mean usual headache severity
- days and use of acute headache medication.²⁴⁻³⁵

Exhibit 5: Acute and Preventive Headache Medications¹⁵

Abortive (Acute)	Episodic Migraine	ETTH	CDH (CM/CTTH)	FDA-Approved
Analgesics (aspirin, narcotics)	X	X	X	X (episodic)
NSAIDs	X	X		
Sympathomimetics (Midrin [®])	X			X (episodic)
Dopamine Antagonists	X			
Triptans	X		X	X (episodic)
Ergot derivatives (ergotamine, dihydroergotamine)	X			X (episodic)
Prophylactic				
Beta-blockers	X			X (episodic)
Antidepressants/SSRIs	X		X (SSRIs)	
Calcium Channel Blockers	X			
Anticonvulsants (Topamax [®] , Depakote [®])	X		X	X (episodic)
NSAIDs	X			
Tizanadine (Zanaflex [®])			X	
Gabapentin (Neurontin [®])			X	
Muscle Relaxants	X	X	X	

ETTH (episodic tension-type headache) CM (chronic migraine)
 CDH (chronic daily headache) CTTH (chronic tension-type headache)

Exhibit 6: Studies of BoNTA in CDH

Reference	Study Design	CDH Sub-Type/N	Dose*/Location	Outcomes Measure/Results (+) = Positive Outcomes (-) = Negative or NS		Comments
				Primary	Secondary/ Adverse Events	
Schulte-Mattler, et al. ²⁵	DB, RCT, PBO Duration: 12 weeks (single injection)	CTTH (Co-existing migraine excluded) n=112	500 mouse U (Dysport) Multiple pericranial muscles	(-) Headache curve (symptoms from diary over 12 weeks)	(-) HA days (-) Acute medication days (-) Duration of sleep (-) Beck Depression Inventory score	Negative study, but it lacked statistical power to identify clinically significant effect; 7 patients had transient weakness of eyelids, neck, or both; authors suggest dosage was excessive
Padberg, et al. ²⁶	DB, RCT, PBO Duration: 12 weeks (single injection)	CTTH n=40	100 U Muscles with increased tension	(-) Intensity (VAS scale) (-) Mean # HA days (-) Headache hours/day (-) Analgesics/day		Negative study, authors questioned benefit of injecting tender muscles in CTTH, single injection
Schmitt, et al. ²⁷	DB, RCT, PBO Duration: 8 weeks (1 injection)	CTTH n=60	20 U Frontal and temporal muscles	(+) Pain intensity	(-) HA-free days (-) Acute meds No AEs	Primarily negative study but short duration, very low dose, and limited injection sites
Relja, et al. ²⁸	DB, RCT, PBO	CTTH n=16 (DB) n=30 (open- label extension)	100 U Pericranial muscles	(+) Pericranial tenderness	(+) Severity, (+) HA-free days No AEs	Cumulative efficacy effect in open-label extension.
Mathew, et al. ²⁹	DB, RCT, PBO Screened out placebo responders during 30- day screening period Duration: 11 months (2 injections)	CM +/- CTTH n=355	105-260 U Frontal and temporal muscles	(-) HA-free days (Placebo nonrespon- der group, 6.7 days [BTX] vs. 5.2 [PBO])	(+) HA days vs. PBO (+) % pts > 50% ↓ HA frequency (responder rate) (+) Frequency change of HA from baseline/mo AE: 4/173 d/c	79% placebo nonresponders, 21% placebo responders; overall BTX resulted in 7 more headache-free days compared to baseline; only 2 injections; assessment was at 180 days; may not have been long enough out
Dodick, et al. ³⁰	Subgroup analysis of Mathew et al.	CM +/- CTTH n=228 (not taking other prophylactic medications)	105-260 U Frontal and temporal muscles	(+) HA frequency (+) HA days (+) HA severity	Subgroup analyses (+) % pts ≥30% ↓ HA Freq (+) % pts ≥50% ↓ HA Freq (+) Days of Acute Meds	Authors concluded BTX effective and well-tolerated in migraine patients with CDH who are not using other prophylactic medications
Silberstein, et al. ³¹	DB, RCT, PBO Duration: 9 months (3 injections)	CM +/- CTTH n=702	75, 150, or 225 U	(-) HA-free days (NS at day 180 for all doses in placebo nonresponders)	(+) % pts ≥50% ↓ HA Freq Pooled (+) HA Freq (+) Acute HA med use Transient, mild-mod AE (27/702 d/c)	150 U and 225 U were better than placebo at decreasing headache frequency, High rate of placebo response
Ondo ³²	DB, RCT, PBO Duration: 12 weeks double- blind, 12-week open-label (2 injections)	CTTH, CM n=60	200 U	(+) HA free days	33 ± 23 (P) vs. 24 ± 16 (BTX) days without headache (NS) (+) Global impressions, (+) Abortive meds Mild AEs (NS)	Efficacy of BTX appeared to be cumulative with subsequent injections

*All studies used botulinum toxin A. Dysport product used in Schulte-Mattler study is not approved for use in the U.S. CDH, chronic daily headache; DB, double-blind; RCT, randomized controlled trial; PBO, placebo controlled; CTTH, chronic tension-type headache; CM, chronic migraine; BTX, botulinum toxin A; HA, headache; NS, non significant

A single treatment, consisting of carefully placed low-dose injections, has an effective duration that may exceed four months. In clinical practice, BoNTA is injected every three months, and more than one treatment cycle is usually required to get an optimal effect. The adverse effects with BoNTA injection appear to be minimal and resulted in a low percentage of study dropouts. The most commonly reported adverse effects with this agent are pain, tenderness, and bruising at the site of injection.³⁶ Weakness of neck muscles and eyelids has been reported when higher than usual doses of BoNTA are used.²⁵ Although BoNTA is not yet FDA-approved for the treatment of CDH, multiple studies show that some patients stand to benefit from treatment. Potential candidates for BoNTA treatment are cited in Exhibit 7.³⁵ BoNTA should be reserved for specialists who have experience in the exact placement of injections based on the pattern of headache pain.^{37,38}

Outpatient treatment is best conducted in a setting with experienced practitioners who can take a multidisciplinary approach to the medical issues.⁶ A few studies assessing the effectiveness of headache clinics have found them valuable in reducing headache

frequency and intensity, improving quality of life, reducing overall healthcare utilization, and decreasing work absenteeism.^{38,39} Data from one such study conducted at Kaiser Permanente are provided in Exhibit 8.⁴⁰ For CDH patients who fail to respond to outpatient treatment, or whose conditions are too complicated for outpatient detoxification and treatment, inpatient treatment may be considered.⁶

Managed Care Issues With CDH

Headache is among the most common complaints reported by patients visiting the emergency department, accounting for almost 3 million visits in 2000 and representing an annual cost ranging from \$600 million to nearly \$2 billion.⁴¹ Migraine headache occurrences result in estimated annual costs totaling \$13 billion to \$17 billion in the United States.⁴²

The main cost drivers for direct clinical care are medications, emergency room visits, hospitalization, physician services (primary care and specialty), laboratory and diagnostic services, and management of treatment side effects. Indirect costs result from lost productivity in the workplace. In a retrospective chart review of patients who visited an urgent care or emergency department facility for headache over a six-month period, 54 of 518

patients (10.4 percent) made 502 of 1,004 visits (50 percent).⁴³ Among these repeaters, 79.6 percent of all visits during the preceding year were headache-related.⁴³ Similarly, headache was the primary diagnosis in more than 50,000 hospital discharges in 1996, for which costs totaled \$278 million. Migraine accounted for two-thirds of these headache-related discharges and costs.⁴⁴ Headache is also a leading reason for visiting a neurologist, with migraine diagnosed in a large number of these cases. Specialized care may add to the treatment costs associated with migraine, but expert management is still cost-effective if it leads to better outcomes than would be achieved by nonspecialists.

Employees who suffer from chronic pain cost employers more than \$60 billion annually, with headache being the most frequent pain-related complaint among workers.⁴⁵ Focusing specifically on migraine, one study found the annual cost to employers exceeded \$14.5 billion, of which \$7.9 billion was due to absenteeism, \$5.4 billion to diminished productivity, and \$1.2 billion to medical costs.⁴⁶

Of the total annual cost associated with migraine and its treatment, roughly one-tenth (\$1.5 billion) goes to medication, with triptans accounting for the majority of this

Exhibit 7: Candidate Patient Criteria for BoNTA Therapy for Headache³⁵

- Disabling primary headache
- Failure to respond adequately to conventional treatments
- Unacceptable side effects from existing treatment
- Contraindication for standard preventive treatments
- Special populations or situations (elderly, those at risk for side effects, airplane pilots)
- Misuse/abuse/overuse of medications
- Coexistent jaw, head, or neck muscle spasm
- Preference for this treatment

Exhibit 8: Economic Benefits of Headache Management Program in an HMO³⁹

- Analysis of 184 patients who completed HMP
- 2003 published costs for medications and visits calculated 6 and 12 months pre- and post-HMP
- PCP and ER visits decreased 35%: \$44 and \$12 per patient over 6 months
> Neurology visits increased by \$7 per patient
- Triptans increased (8%), offset by decreased narcotics (15%)
- Overall costs declined by \$41 per patient per 6 months

HMP (headache management program)
PCP (primary care provider)
ER (emergency room)

total (\$1.18 billion).⁴⁷ Although costly, triptans are highly effective abortive therapy. When properly used, triptans' clinical effectiveness justifies their cost.⁴⁸⁻⁵¹ However, overall treatment costs can be needlessly elevated due to misuse of medication. Over-treatment represents waste and a risk factor for increased toxicity, and under-treatment can result in additional visits to the physician's office, clinic, or emergency department to deal with persistent symptoms.

Prophylaxis in headache disorders is aimed at preventing acute attacks and also at preventing conversion from an episodic condition to a costly, disabling, long-term chronic condition. Consequently, utilization of clinical resources and associated costs would be expected to decrease. A retrospective analysis of a large claims database found that the addition of a prophylactic agent to overall migraine management resulted in meaningful reductions in the use of other medications, visits to physicians' offices and emergency departments, and the need for costly diagnostic scans.⁵¹ A cost-effectiveness analysis using data from three double-blind, placebo-controlled clinical trials of prophylaxis

focused on the cost-per-headache prevented and the number of headaches prevented monthly. The cost-per-migraine prevented was \$138 with gabapentin, \$115 with topiramate, and \$48 with divalproex.⁵² Thus, divalproex became cost-effective with prevention of 10 migraines per month, whereas gabapentin and topiramate were cost effective only when the frequency of migraines prevented was considerably higher. This analysis demonstrates that the antiepileptic drugs are cost-effective prophylaxis only for those patients who have frequent migraines. Additionally, the cost-per-migraine prevented is an important determinant of the actual number of headaches per month that must be prevented in order for an agent to be cost effective.

The cost-equivalent number is the monthly number of headaches at which the cost of acute management, including, but not limited to, abortive medications, would surpass the monthly cost of prophylaxis. If this number was lower than the actual number of headaches that typically occur in one month, a preventive agent would be considered cost effective.⁵³ Compared

with the antiepileptics, the beta-blocker propranolol offers effective prophylaxis at low cost.⁵⁴ Unfortunately, beta-blocker prophylaxis has not been studied in CDH.

To evaluate the impact of preventive treatment of migraine with BoNTA on the amount of acute headache medications used, data from four studies of BoNTA treatment for migraine were pooled for an aggregate analysis. All studies were at least 12 weeks in duration. For each study, the quantities of headache medications used following BoNTA treatment were compared with pretreatment baseline amounts and expressed as a percentage change. The results of this pooled meta-analysis indicated a 58 percent (range: 38 to 75 percent) reduction in acute headache medication use in the 8- to 12-week period following injection of BoNTA (see Exhibit 9).⁵⁵ Furthermore, BoNTA was recently shown to significantly reduce acute medication use in CDH patients not taking concurrent prophylactic medications.³⁰

A small open-label trial of BoNTA was conducted in five patients with migraine that was unresponsive to conventional antimigraine medications.⁵⁶ After one year of injections at

Exhibit 9: Pharmacoeconomic Evaluations—BoNTA vs. Acute Medication Use⁵⁵

Study	n	Study Type	Patients	Medication Use Measure	% Change
Barrientos	15	RDBPC	2-8 migraine attacks/month for at least 1 year	Headache treatments used/month	-73
Silberstein	42	RDBPC	2-8 moderate-to-severe migraines/month	Days requiring use of acute migraine medication	-38
Mathew	60	Retro	Chronic migraine	Triptan use, tablets/month	-75
Blumenfeld	50	Open-label	Headache patients identified as high triptan users	Triptan costs for 6-month periods before and after initial BoNTA treatment	-48
TOTAL	167			Average Change:	-58

three-month intervals, the use of other migraine medications had decreased from pretreatment levels, as measured by the change in annual costs for other medications. Before BoNTA treatment, the cost of other medication treatment ranged from \$1,002 to \$3,524. After treatment, the cost of other medication ranged from \$0 to \$1,285.⁵⁶ When the cost of the botulinum treatment itself was included, the total change in annual medication cost ranged from an increase of \$648 to a decrease of \$2,717.⁵⁶

Policy Development

Because of significant costs and a lack of specific FDA indications, managed care plans have had to develop policies on the use of agents for CDH.⁵⁷ These policies seek to achieve optimal clinical outcomes while maintaining cost effectiveness and minimizing medical-legal risk

for the plan and providers. Any policy on medication use has to be evidence-based, relying on whatever authoritative information is available at a given time.⁵⁷

Intermountain Healthcare Health Plans' Experience

In seeking to develop a policy on treatment of chronic headaches with BoNT, Intermountain Healthcare, (IHC) Health Plans examined issues related to migraine headaches within its population (unpublished data). The organization identified several quality issues. Within its population, numerous headache patients were taking two to four triptans per day and not receiving prophylactic therapy. Additionally, patients were receiving large quantities of narcotic analgesics (e.g., 124 Oxycontin 80 mg tablets every 10 days) with subsequent addiction issues arising. Furthermore, migraine patients

were developing CDH due to the inappropriate use of triptans, NSAIDs, and nonuse of preventive medications.

IHC has 475,000 members. For those members diagnosed with headache, triptans were costing \$560.50 per member with headache per year. The plan spent \$2.9 million in 2003 and \$2.1 million in 2004 on triptans. In 2003, topiramate was costing \$703.57 per member per year. Total spending on topiramate was \$1.02 million in 2003, and \$1.2 million in 2004. Total spending on antiepileptic medications was \$5.1 million in 2003, although not all spending was for headaches. That figure rose to \$5.64 million in 2004 primarily because of additional use of antiepileptic medications for diagnoses such as chronic headache. These spending figures do not take into account narcotics or

Exhibit 10: Medical Policy Development—BoNT for Medical Conditions, IHC Health Plan Experience

The Result

IHC Health Plans covers BoNT injections for migraine headache and cervicogenic headaches when *all* the following conditions are met

1. The member has a history of persistent, recurring, and debilitating headaches.
2. A neurologist has thoroughly evaluated the member and has established a diagnosis of migraine or cervicogenic headaches.

3. Adequate trials of *acute* treatment with at least THREE different therapy classes were either not effective or not tolerated.
4. Adequate trials of *prophylactic* therapy from at least FOUR different therapy classes were either not effective or not tolerated.

*Authorization duration is limited to two series of injections over a 24-week period. Clinical documentation of response necessary for continued authorization.

Exhibit 11: BoNT Budgetary Model

Model assumptions:

- Health plan population of 1 million
- Prophylaxis will be given to chronic migraine patients
- 12% of the population has migraine
- 40% of migraine patients seek treatment
- 25% of patients who seek treatment have chronic migraine (at least 15 episodes per month)
- 2% of patients (240) with chronic migraine will receive botulinum toxin as prophylaxis
- BoNT would be given at a standard interval of 3 months, or 4 treatments per year

- Cost of each BoNT treatment = \$521.25
- BoNT treatment will reduce overall use of triptans by 65%
- ➔ Yearly cost of BoNT for 240 patients = $521.25 \times 4 \times 240 = \$500,400$
- ➔ One-year savings from 65% reduction of triptan use = \$576,760
- ➔ Net annual savings = $576,760 - 500,400 = \$76,360$

Estimated savings associated with migraine prophylaxis using BoNT per member per month = \$76,360 divided by 12 million member months = \$0.006 per member per month

other prophylactic medication use. The health plan had other cost issues related to emergency room (ER) visits. It found that 1,256 members spent more than \$0.5 million in 2003 in ERs and urgent care related to headache. Forty-nine members were hospitalized with headache as their primary diagnosis at a cost of \$118,000. Office visits by 5,288 members for headaches accounted for \$732,889 in costs in 2003.

IHC began looking for potential solutions to the costly treatment of headache. One possibility was the controlled use of BoNT. Advocating use of this treatment in migraine was somewhat of an issue for the plan because headache is an off-label indication. Use of BoNT in this circumstance may result in unintentional coverage for cosmetic indications. The available efficacy evidence across all headache types collectively to date has been mixed. Managed care policymakers have been cautious about approval of coverage for this treatment,⁵⁷ and no general consensus has emerged for the use of botulinum toxin across various plans.

To address various concerns about the use of BoNT for headaches, IHC created a policy that allows a trial of this therapy only in high healthcare utilizers, as evidenced by medication and medical services usage. The policy also limits the number of injections to ensure that the treatment is effective before it is allowed to continue. Patients must demon-

strate failure on a large number of prophylactic agents to qualify for BoNT through prior authorization. Additionally, the policy requires a specialist to be involved (see Exhibit 10).

In a post-implementation analysis of the new policy, IHC found that 10 patients received BoNT injections for migraine or chronic headaches in 2004, and 13 in the first six months of 2005. Medical costs for patients receiving injections decreased by approximately 25 percent from 2004 to 2005. Emergency room utilization by patients receiving BoNT decreased 63 percent, and hospitalizations decreased 50 percent. The policy on botulinum toxin use in headache appears to be accomplishing the IHC's goals until such time of FDA approval or consensus guidelines are developed.

Budgetary Model

One example of a budgetary model of the use of BoNTA in chronic migraine patients was recently published.⁴² This model focused on the use of BoNTA for prophylaxis in chronic migraine patients enrolled in a commercial managed care plan. The goal was to assess the impact of a decision to allow the use of botulinum toxin, in terms of cost effectiveness for the plan as a whole.⁴² The model is summarized in Exhibit 11. Based on this model, the use of BoNTA would result in a small cost savings. A decrease in emergency department visits and hospitalization as a result

of effective migraine prophylaxis, while not counted in this model, would be expected to augment these savings.⁴²

Conclusion

Headache is a common disabling disorder that is costly for patients, the healthcare system, and employers, and also presents a management challenge for physicians. Patients with CDH often require an aggressive and comprehensive treatment approach that includes a combination of acute and preventive medications, as well as nondrug therapies. Ultimately, the best approach to CDH is to make a clear diagnosis early and to institute treatment early, before disability becomes manifest and the situation is complicated by medication overuse and psychiatric issues. Early referral of the patient to a practitioner skilled in the diagnosis and treatment of headache is essential. There is little evidence that agents currently approved for treatment of headaches are effective in CDH. Evidence of BoNTA's effectiveness is stronger in the CDH population than in other headache populations. In contrast to available systemic agents, BoNTA, given as low-dose local injections (usually at three-month intervals), avoids compliance problems and is generally well tolerated. It is reasonable to expect improved headache management to yield meaningful cost savings despite increased expenditures for antimigraine medications. **JMCM**

Headache Facts

- More than 45 million Americans have chronic, recurring headaches. This is more than the 33 million sufferers of asthma, diabetes, and coronary heart disease combined.
- Twenty-eight million Americans suffer from migraines annually. One in four households includes at least one migraine sufferer.
- Seventy percent of all migraine sufferers are women.
- Businesses lose \$50 billion per year due to absenteeism and medical expenses caused by headache.
- Migraine sufferers collectively lose more than 157 million workdays each year.

Source: National Headache Foundation Fact Sheet, www.headache.org

References

- Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55:754-762.
- Lipton RB, Scher AI, Steiner TJ, Bigal ME, Kolodner K, Liberman JN, Stewart WF. Patterns of health care utilization for migraine in England and in the United States. *Neurology*. 2003;60:441-448.
- Lipton RB, Stewart WF, Scher AI. Epidemiology and economic impact of migraine. *Curr Med Res Opin*. 2001;17(Suppl 1):4-12.
- Scher AI, Stewart WF, Liberman J, Lipton RB. Prevalence of frequent headache in a population sample. *Headache*. 1998;38:497-506.
- Saper JR, Dodick D, Gladstone JP. Management of chronic daily headache: challenges in clinical practice. *Headache*. 2005;45(suppl 1):S74-S85.
- Mathew N, Ward T. Treatment of primary headache: chronic daily headache. In: Standards of care for headache diagnosis and treatment. Chicago (IL): National Headache Foundation; 2004. p. 73-80.
- Silberstein SD, Lipton RB, Slivinski M. Classification of daily and near-daily headaches: field trial of revised HIS criteria. *Neurology*. 1996;47:871-875.
- Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2nd edition. *Cephalgia*. 2004;24(suppl 1):1-150.
- Mathew NT, Stubits E, Nigam MP. Transformation of episodic migraine into daily headache: analysis of factors. *Headache*. 1982;22:66-68.
- Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain*. 2003;106:81-89.
- Saper JR, Jones J. Ergotamine tartrate dependency: features and possible mechanisms. *Clin Neuropharmacol*. 1986;9:244-256.
- Mathew NT, Kurman R, Perez F. Drug induced refractory headache—clinical features and management. *Headache*. 1990;30:634-638.
- Meyler WJ. Side effects of ergotamine. *Cephalgia*. 1996;16:5-10.
- Gobel H, Stolze H, Heinze A, Dworschak M. Easy therapeutical management of sumatriptan-induced daily headache. *Neurology*. 1996;47:297-298.
- Silberstein SD, Lipton RB, Goadsby PJ. Headache in Clinical Practice. Oxford, England: Isis Medical Media. 1998:61-100.
- Silberstein SD, Goadsby PJ. Migraine: preventive treatment. *Cephalgia*. 2002;22:491-512.
- Silvestrini M, Bartolini M, Coccia M, Baruffaldi R, Taffi R, Provinciali L. Topiramate in the treatment of chronic migraine. *Cephalgia*. 2003;23:820-824.
- Saper JR, Lake AE 3rd, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache*. 2002;42:470-482.
- Spira PJ, Beran RG; Australian Gabapentin Chronic Daily Headache Group. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology*. 2003;61:1753-1759.
- Saper JR, Silberstein SD, Lake AE 3rd, Winters ME. Double-blind trial of fluoxetine: chronic daily headache and migraine. *Headache*. 1994;34:497-502.
- Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J, Neto W, Schwabe S, Jacobs D; MIGR-002 Study Group. Topiramate for migraine prevention: a randomized controlled trial. *JAMA*. 2004;29:965-973.
- Silberstein SD, Neto W, Schmitt J, Jacobs D; MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol*. 2004;61:490-495.
- Gallagher RM, Kunkel R. Migraine medication attributes important for patient compliance: concerns about side effects may delay treatment. *Headache*. 2003;43:36-43.
- Dodick D, Blumenfeld A, Silberstein SD. Botulinum neurotoxin for the treatment of migraine and other primary headache disorders. *Clin Dermatol*. 2004;22:76-81.
- Schulte-Mattler WJ, Krack P; BoNTTH Study Group. Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. *Pain*. 2004;109:110-114.
- Padberg M, de Bruijn SF, de Haan RJ, Tavy DL. Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. *Cephalgia*. 2004;24:675-680.
- Schmitt WJ, Slowey E, Fravi N, Weber S, Burgunder JM. Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. *Headache*. 2001;41:658-664.
- Relja M, Telarovic S. Botulinum toxin in tension-type headache. *J Neurol*. 2004;251(suppl 1):I12-I14.
- Mathew NT, Frisberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C; BOTOX CDH Study Group. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Headache*. 2005;45:293-307.
- Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD; BOTOX CDH Study Group. Botulinum toxin type A for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. *Headache*. 2005;45:315-332.
- Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC; BoNTA-039 Study Group. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc*. 2005;80:1126-1137.
- Ondo WG, Vuong KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. *Cephalgia*. 2004;24:60-65.
- Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A. Botulinum toxin A in the prophylactic treatment of migraine—a randomized, double-blind, placebo-controlled study. *Cephalgia*. 2004;24:838-843.
- Ashkenazi A, Silberstein SD. Botulinum toxin and other new approaches to migraine therapy. *Annu Rev Med*. 2004;55:505-518.
- Blumenfeld A. Botulinum toxin type A as an effective prophylactic treatment in primary headache disorders. *Headache*. 2003;43:853-860.
- Botulinum toxin A (Botox®) package insert. Irvine, CA: Allergan, Inc. October 2004.
- Blumenfeld A. Clinical approaches to migraine prophylaxis. *Am J Manag Care*. 2005;11:S55-S61.
- Blumenfeld AM, Dodick DW, Silberstein SD. Botulinum neurotoxin for the treatment of migraine and other primary headache disorders. *Dermatol Clin*. 2004;22:167-175.
- Zeeberg P, Olesen J, Jensen R. Efficacy of multidisciplinary treatment in a tertiary referral headache center. *Cephalgia*. 2005;25:1159-1167.
- Blumenfeld A, Tischio M. Center of excellence for headache care: group model at Kaiser Permanente. *Headache*. 2003;43:431-440.
- McCaig LF, Burt CW. National Hospital Ambulatory Medical Care Survey: 2001 emergency department summary. *Adv Data*. 2003;335:1-29.
- Goldberg L. The cost of migraine and its treatment. *Am J Manag Care*. 2005;11:S62-S67.
- Maizels M. Health resource utilization of the emergency department headache “repeater.” *Headache*. 2002;42:747-753.
- Hospital Inpatient Statistics, 1996, Vol 2004. Agency for Healthcare Research and Quality, Healthcare Cost and Utilization Project; Rockville, Md.
- Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA*. 2003;290:2443-2454.
- Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. *Arch Intern Med*. 1999;159:813-818.
- 2002 Pharmacy Benchmarks. Trends in Pharmacy Benefit Management for Commercial Plans; Sacramento, Calif.; Pharmacy Care Network. 2002.
- Caro JJ, Getsios D. Pharmacoeconomic evidence and considerations for triptan treatment of migraine. *Expert Opin Pharmacother*. 2002;3:237-248.
- Halpern MT, Lipton RB, Cady RK, Kwong WJ, Marlo KO, Batenhorst AS. Costs and outcomes of early versus delayed migraine treatment with sumatriptan. *Headache*. 2002;42:984-999.
- Sculpher M, Millson D, Meddis D, Poole L. Cost-effectiveness analysis of stratified versus stepped care strategies for acute treatment of migraine: the Disability in Strategies for Care (DISC) study. *Pharmacoeconomics*. 2002;20:91-100.
- Silberstein SD, Winner PK, Chmiel JJ. Migraine prevention medication reduces resource utilization. *Headache*. 2003;43:171-178.
- Adelman JU, Adelman LC, Von Seggern R. Cost-effectiveness of antiepileptic drugs in migraine prophylaxis. *Headache*. 2002;42:978-983.
- Adelman JU, Von Seggern R. Cost considerations in headache treatment. Part 1: prophylactic migraine treatment. *Headache*. 1995;35:479-487.
- Adelman JU, Brod A, Von Seggern RL, Mannix LK, Rapoport AM. Migraine prevention medications: a reappraisal. *Cephalgia*. 1998;18:605-611.
- Schim J. Effect of preventive treatment with botulinum toxin type A on acute headache medication usage in migraine patients. *Curr Med Res Opin*. 2004;20(1):49-53.
- Blumenfeld AM. Impact of botulinum toxin type-A treatment on medication costs and usage in difficult-to-treat chronic headache. *Headache Quarterly*. 2001;12:241.
- Owens. Migraine in the Managed Care Environment. *Am J Manag Care*. 2005;11:S68-S71.

INSTRUCTIONS

1. Read the monograph first, followed by the questions below. When you're ready to complete the test, log on to www.namcp.org/seemedia/migraine/post-test.htm, and click on "Treatment of Chronic Headache Disorders." Select the option for post-test and evaluation.
2. Next, read the questions and mark your answers. All questions and answers are based on the information in this monograph. Each question has only one correct answer.
3. After completing test, press the "submit" button. Alternatively, you may print the answer sheet/evaluation form (or use the one in this supplement) and fax to 804-747-5316, or mail to NAMCP CME Office, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.
4. You should receive your CME certificate within one month of completion. If you do not receive it, please call 804-527-1905 and ask for Ann Patrick or Katie Eads.

QUESTIONS

1. There is an obvious need for effective, long-term, and well-tolerated prophylactic treatment regimens for migraine and chronic headache.
 - a. True
 - b. False
2. Modifiable risk factors for chronic daily headache are
 - a. Frequency of attack
 - b. Obesity
 - c. Medication over-use
 - d. Low education
 - e. Stressful life events
 - f. Snoring, sleep apnea, sleep disturbances
 - g. A, B, C, E, F
 - h. All of the above
3. Benefits of adding an effective prophylactic medication to the treatment of migraine include:
 - a. Reduction in use of headache pain medications
 - b. Reduction in headache-related physician office visits
 - c. Reduction in emergency department visits
 - d. All of the above
4. Many drugs are used for preventive therapy for the disabling primary headache. The majority are either experimental, off-label, or do not work consistently across all patients and most are FDA-approved for the treatment of headache.
 - a. True
 - b. False
5. Only five compounds have been systematically studied and reported in a chronic daily headache population for preventive therapy.
 - a. True
 - b. False
6. Chronic Daily Headache (CDH) is defined as having more than 15 episodes per month
 - a. True
 - b. False
7. Under-diagnosis of conditions like migraine leads to inadequate or inappropriate treatment, with subsequent increased cost of care.
 - a. True
 - b. False
8. Based on clinical trials, BoNTA (BOTOX) has the best evidence for reducing headache frequency and severity, and may reduce acute med use in the CDH population.
 - a. True
 - b. False
9. A Headache Management Program is a multidisciplinary team approach to headache management.
 - a. True
 - b. False
10. Main cost drivers to MCOs for direct clinical care of headaches include
 - a. Medications
 - b. Emergency department visits
 - c. Physician services
 - d. Laboratory and diagnostic services
 - e. Management of side effects
 - f. All of the above
11. Annual cost to employers in direct and indirect costs exceeds
 - a. \$15.3 billion
 - b. \$5.4 billion
 - c. \$14.5 billion
 - d. \$1.2 billion
12. IHC's medical policy for the treatment of migraine with BOTOX must include the specialist physician.
 - a. True
 - b. False
13. IHC's medical policy has seen a reduction in medical costs, ER utilization and hospitalization since its implementation.
 - a. True
 - b. False

ANSWER SHEET

There is only one correct answer per question.
Circle your answer clearly.

1. a b

2. a b c d e f g h

3. a b c d

4. a b

5. a b

6. a b

7. a b

8. a b

9. a b

10. a b c d e f

11. a b c d

12. a b

13. a b

EVALUATION

Please rate this activity on the following scale:

4 Excellent 3 Good 2 Fair 1 Poor

Activity met my expectations 4 3 2 1

Activity was free of bias 4 3 2 1

Activity content was understandable 4 3 2 1

Method of learning was beneficial 4 3 2 1

I will change my practice patterns to (check all that apply):

- Review the clinical trials in an attempt to establish a medical policy
- Review the current costs of treatment and decide what my next step in migraine treatment should be
- My practice patterns will not change
- Look to neurologists for their input on the need for a medical policy

Name: _____

Mailing Address: _____

City: _____

State: _____ ZIP: _____

Phone: _____

Fax: _____

E-mail: _____

Send my certificate by:

- U.S. Mail
- E-mail

