HeadWise®

A Voice for People with Migraine and Headache Disorders
From the National Headache Foundation

New Options for Acute Migraine Therapy

Although the drugs have been previously approved, new methods of administration are providing alternatives for the patient trying to manage an acute migraine attack.

A New Tool for Identifying Migraine Triggers and Symptoms

Personalized results for 150 individual migraine sufferers illustrate that virtually every migraineur is different and one treatment may not fit all.

In Memoriam

We remember two giants of headache medicine – Oliver Sacks, MD and Ninan Mathew, MD

The Headache Clinics

Focus on The Headache Center at University of Pittsburgh Medical Center

$6.99

Volume 5, Issue 1 • 2015
www.headaches.org

NATIONAL HEADACHE FOUNDATION™

Get HeadWise® at home

Become a member today!

NATIONAL HEADACHE FOUNDATION™

If you think a headache is just a headache, think again. Millions of Americans suffer from migraines, cluster headaches, and other serious headache disorders. Chances are, headache disorders affect you or someone you love.

Join the cause by becoming a member of the National Headache Foundation, the world's largest voluntary organization for the support of people with migraine and headache disorders. For 45 years, the NHF has assisted millions of individuals and inspired hope through awareness, advocacy, education, and research.

Individual membership:	**$20 per year**
Professional membership:	
Physician (M.D. or D.O.):	**$125 per year**
Allied health:	**$75 per year**

With your membership, you'll receive:

A subscription to HeadWise® magazine

The *NHF News to Know* monthly e-newsletter: Access to a wealth of headache research, support, and information. Plus, your donation will support the NHF and help advance headache advocacy, education, and research.

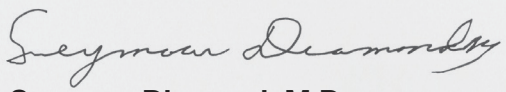
To join, go to www.headaches.org/become-a-member/ or call 1-888-NHF-5552

FROM THE EXECUTIVE CHAIRMAN:

As a physician who participated in the original sumatriptan studies, I am fascinated by the number of new methods of administration for the triptans. In this issue, we feature an article describing a battery-operated, disposable patch system which contains sumatriptan. This method may solve treatment issues for patients who experience nausea and vomiting as part of their acute migraine attack. This transdermal method may facilitate the absorption of sumatriptan into the blood stream at a much quicker rate, and provide faster relief for the migraine sufferer.

In the section, "NHF News," we address the National Headache Foundation's efforts at providing the Certificate of Added Qualification in Headache Medicine (CAQ). The certification process for headache specialists has become more difficult and limited because of the draconian requirements for credentialing. There is also a large group of physicians and allied health practitioners who evaluate and treat patients, and who have no process for gaining recognition or credentialing for their ability and experience in headache medicine. The CAQ may also influence insurance reimbursement.

The NHF has undertaken an extensive project of education and credentialing for headache practitioners. Our goal was to assure the patient seeking treatment for their headaches that their clinician has been adequately education and examined for their headache proficiency. Once they have met these requirements, the candidates will receive their certificate, a plaque recognizing their achievement, and will be identified by the title National Headache Foundation Certified Headache Practitioner – NCHP.



Seymour Diamond, M.D.
Chicago, Illinois

HeadWise®

The National Headache Foundation • www.headaches.org

NATIONAL HEADACHE FOUNDATION™

Mission
To cure headache, and end its pain and suffering.

Vision
A world without headache.

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This publication discusses a broad range of headache information in an effort to inform and educate readers, but is not intended to substitute for the advice of your health care provider. Statements expressed herein are not necessarily those of NHF.

Send Us Your Feedback
Letters, manuscripts, stories, materials or photographs are welcomed but will not be returned. Submission of letters implies the right to edit and publish all or in part. Submissions may be sent to: mfranklin@headaches.org. Please indicate your name, address and phone number.

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Check out additional *HeadWise*® and NHF content at www.headaches.org.

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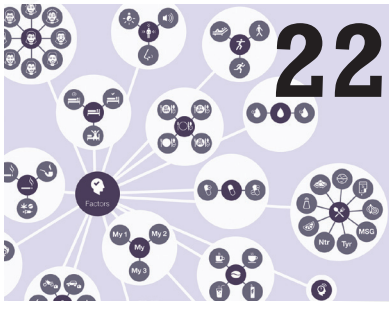

IN EVERY ISSUE

2015 Certificate of Added Qualification in Headache Medicine

The National Headache Foundation is proud to announce the inaugural class of health care practitioners who have successfully passed the exam for the Certificate of Added Qualification in Headache Medicine (CAQ). The CAQ was originally created in 2000 to recognize physicians with an advanced level of experience in headache medicine. In 2005, board certification in headache medicine was established by the United Council for Subspecialties (UCNS), and the CAQ program became dormant.

The Board was aware that many health care providers were not receiving acknowledgment for their work and experience in headache medicine. As a service to those experiencing headache, they determined that the NHF-endorsed CAQ should be reinstated. The goals are to establish the standards for headache practice and assist those with headaches in locating clinicians who could provide optimal headache-related health care. Board member, Timothy Smith, MD, R.Ph., has chaired the CAQ committee for the past 4 years, and with other physician members of the Board has established the requirements to receive the CAQ.

Last fall, those physicians who received CAQ prior to 2007, were asked if they would like to continue their credentialing. Of the original 60 physicians with CAQ, 28 have renewed their CAQ. Those physicians are listed later in this section.

Those eligible for CAQ must be able to evaluate and treat patients independently, and include physicians (MD or DO), advanced practice nurses (NP), physician assistants (PA), dentists, and psychologists. The new requirements for CAQ include a valid license in their discipline, 3-years experience in headache medicine, and successfully passing a 100-question examination. The CAQ is valid for 5 years. To renew CAQ, the clinician must either demonstrate that he or she has received 60 hours of Continuing Medical Education (CM) credits in headache medicine over the previous 5 years, or retake the CAQ exam.

This exam was developed by physician members of the NHF Board as well as thought leaders in headache medicine, including physicians, nurse practitioners, physician assistants, and psychologists. We would like to thank those clinicians who assisted us with development and review of the exam:

José Biller, MD
Jo H. Bonner, MD
Jan Lewis Brandes, MD
Roger K. Cady, MD
Wade Cooper, DO
Kathleen Farmer, PsyD
Alexander Feoktistov, MD, PhD
Frederick G. Freitag, DO
Leah Green, MD
Mark Green, MD
Vincent Martin, MD
Alexander Mauskop, MD
Maureen Moriarty, DNP, ANP-BC
Robert A. Nicholson, PhD
Lori K. Peters, MS, CRNP
Timothy R. Smith, MD, R.Ph (Committee Chair)
Christina Treppendahl, FNP-BC
Ira Turner, MD
Lana Tymouch, PA-C

The next examination will be held from March 7 through 21, 2016. Candidates may take the exam in testing centers throughout the U.S. For clinicians interested in receiving CAQ, please contact the NHF staff at nhf1970@headaches.org or call 1-888-NHF-5552. For patients interested in locating health care providers who have received certification, please view Health Care Practitioner Finder at www.headaches.org or call one of our staff.

Finally, we wish to congratulate the 2015 group of clinicians who have met the requirements for CAQ:

Congratulations

Johnny Michael Jones, PA-C
Anacortes, WA

Heather McCoy, DNP
Scottsdale, AZ

Christina Treppendahl, FNP-BC
Ridgeland, MS

Polly Vaughan, NP, APRN
Wilmington, OH

CAQ renewal

The following physicians have opted to renew their CAQ for the next 5 years:

James Banks, III, MD
Gary Berman, MD
Jan Lewis Brandes, MD
Roger K. Cady, MD
Mary Corbitt, MD
Michael Cronen, DO
Merle L. Diamond, MD
Seymour Diamond, MD
Arthur H. Elkind, MD
Lawrence Fogel, MD
Frederick G. Freitag, DO
Gerald Friedman, MD
R. Michael Gallagher, DO
Andrew Gasecki, MD
Joel Konikow, MD
Stephen Landy, MD
Gary L'Europa, MD
Eliot Lewit, MD
Vincent Martin, MD
Dhanpat Mohnot, MD
Loretta Mueller, DO
Louis Pearlstein, DO
George Rederick, MD
Robert Roeshman, DO
Gary Ruoff, MD
Howard W. Sander, MD
Timothy Smith, MD, R.Ph.
Paul Winner, DO

New Board Member Elected

On September 4, 2015, the NHF Board elected a new member, Emily Kaplan Kandel. Emily Kandel is an interior designer in the New York Metropolitan area. Her design experience ranges from high-end residential to health care interiors. After completing a BFA in design, Emily worked in the facilities department of Citibank Credit Card Services. Subsequently, she worked for M (Group), a high-end interiors firm in NYC. After leaving M (Group), Emily went out on her own, first founding Inverness Design Group with a partner, and for the past 3 years, she has owned Emily Kandel Design.

Emily was raised in New York City, and attended the Brearley School. She has a BA from Bryn Mawr College, and a BFA from The Parsons School of Design.

She and her husband, Paul, who serves on the NHF Honorary Board, live in Scarsdale, New York. Emily, her husband and daughters, Allie and Libby, established the Libby Fund in 2012. The Libby Fund is an affiliate of the National Headache Foundation and supports research into adolescent migraine. HW

"A World Without Headache" Video Contest Winner

In honor of National Migraine and Headache Awareness Month in June, the National Headache Foundation hosted a video contest to increase awareness of the impact of headache and migraine. Entrants were asked to imagine "a world without headache" and capture what that would mean to them in a short video. We want to thank our Board member, Alan Rosenberg, MD, for his generous support of this contest.

Videos were submitted from sufferers all over the country with four being selected for a chance at the grand prize of $1,000. In early July, readers were given the opportunity to view and vote for their favorite video on www.headaches.org. **Voters selected Julie Fleck and her "*My World Without Headache*" video as the winner.** We want to thank everyone who participated in the "World Without Headache" video contest.HW

To watch all of the videos entered in the contest, visit: http://bit.ly/without-headache-vote

MAY
HOLD THE DATE
21
HOLD THE DATE
2015

Plans are underway for the 30th Annual Benefit of the NHF, *The Purple Ball – Rule Your Headache*, will be held on Saturday, May 21, 2016, at the Ritz-Carlton Chicago. The evening will include dinner, dancing, silent auction, raffle, and Wall-of-Wine.

For information about the gala, please contact our staff at 1-888-NHF-5552 or info@ headaches.org.

Your Contributions to the National Headache Foundation Help Fund Projects

What's being done to help your headache problem? There is an unprecedented amount of research being undertaken regarding migraine and other headache pain. The National Headache Foundation is involved in this effort with the help of funding from you. Contributions are a key part of the financial support of important headache research. Your gift provides funds for (a) NHF-financed research projects, (b) advocacy with health policy decision makers, and (c) patient-education initiatives. You can help! The National Headache Foundation, the #1 source for headache help, provides these services and many others through the generosity of people like you.

Please select one of the following giving categories:

❒ $250 ❒ $125 ❒ $100 ❒ $75 ❒ Other _____

Name: _____

Address: _____

City: _____

State/Zip: _____

Daytime Phone: _____

Method of Payment:

Check or Money Order payable to National Headache Foundation

❒ Visa ❒ MasterCard ❒ Amex ❒ Discover

Card #: _____ Expiration Date: _____

New Membership | Toll-Free (888) NHF-5552 | www.headaches.org

Individual Membership:

☐ $20.00 to receive ***HeadWise***® plus the monthly e-newsletter, ***NHF News to Know***, when you join the National Headache Foundation

In addition, I'd like to make a tax-deductible contribution in support of **NHF's educational programs** in the amount of: ☐ $10 ☐ $25 ☐ $50 ☐ Other: $_____

_____
Name (Please Print)

_____
Address

_____
City/State/Zip/Country

_____
Preferred Phone # E-mail Address

Payment:

☐ Payment enclosed (check payable to National Headache Foundation)

Charge to my credit card: ☐ Amex ☐ Discover ☐ Mastercard ☐ Visa

_____
Credit Card Number Expiration Date

_____
Cardholder's Signature

_____
Billing Address (If different from mailing address)

_____
City/State/Zip/Country

Please mail this form with your payment to: National Headache Foundation, 820 N. Orleans, Ste. 411, Chicago, IL 60610 or renew online by visting www.headaches.org

Leave a legacy to the National Headache Foundation.

Charitable Giving

There are different ways that individuals can support the mission of the National Headache Foundation through donations. A present donation of money or other items of value is the most frequent manner of support. Provisions for specific bequests or residual bequests in one's will or trust are often utilized. As part of one's estate planning or planned giving, an individual can provide for charitable giving that may minimize gift and estate taxes while providing for (a) the smooth transfer of ownership, (b) the care and support of dependents, and (c) the avoidance of disputes among survivors.

Three commonly used planned giving vehicles are:

1. **Charitable remainder annuity trust.** Assets (generally securities) are transferred to a trust. The trust makes fixed annual payments to the donor or other specified beneficiaries named by the donor. When the trust terminates upon the death of the donor or other specified beneficiaries, the remainder of the assets in the trust pass to the charity. A trust document is required. The donor retains the ability to change the designated charity.

2. **Charitable remainder unitrust.** Assets are transferred to a trust. The donor or other specified beneficiaries named by the donor receive fluctuating payouts from the trust (a percentage of the value of the principal) and, upon the death of the donor or other specified beneficiaries, the remainder of the assets passes to the designated charity. A trust document is required. The donor retains the ability to change designated charity.

3. **Charitable gift annuity.** The donor, under a contract with a charity, transfers cash or securities to the charity. The charity pays the designated beneficiary a fixed income for life. Upon the death of the beneficiary, the remaining balance passes to the charity. No trust document is required and the charity cannot be changed.

NATIONAL HEADACHE FOUNDATION™

Tired of searching the internet for answers?

It's time to learn from those in the know. In every issue of HeadWise®, our experts respond to reader-submitted questions about migraine and headache disorders.

TOLOSA HUNT SYNDROME

I have recently been diagnosed with Tolosa Hunt Syndrome. I am hoping that you may have up to date information on this rare condition. I have just finished taking steroids and am suffering from the many side effects. Can you advise me how to manage this?
– Jan J, Perth, Australia

This is a rare syndrome of pain and paralysis of eye movements, associated with an inflammatory mass behind the eye. A rapid response to steroids, associated with improvement in the scan, is expected. If this is not the case, the evaluation should continue, which may include a biopsy to rule out other masses which could be causing the same symptoms.

There is little experience with agents other than steroids, but some have responded to azathioprine or methotrexate. If the dose of corticosteroids needed to continue to make you comfortable is otherwise unacceptable due to side effects, you should speak to your doctor about the possible use of these other agents. Even when these medications help, the response is not immediate and steroids may need to be continued. You might start this discussion early.

Mark Green, MD
Mt. Sinai Medical Center
New York, NY

VITAMINS AND HEADACHE

Can you please tell me the best type of vitamins and minerals to take for headaches? I have been taking a supplement of A-Z multivitamins and minerals for at least 90 days. What effects should this have on the body and the type of condition it should be in after 90 days use? My diet is very good. I try to incorporate all the five food groups in my meals as well as a 10 minute daily exercise routine. I'm 5.7 in height and wear a size 8 dress in British size. I'm not sure whether my size plays a factor into the headaches I receive. Can you please offer some suggestions as to how to remedy this issue?
–Claudine J, United Kingdom

There are many supplements that are being used for the prevention and treatment of headaches. The ones with the most scientific evidence supporting their efficacy include magnesium, CoQ10, and riboflavin. All three have been specifically tested for the prevention of migraine headaches. Multivitamins usually do not have enough of any of these supplements to help with headaches.

Up to half of patients with an acute migraine and 40% of those with cluster headaches have been found to be deficient in magnesium. The recommended dose of magnesium is 400 mg a day and the types of magnesium that tend to be better absorbed are two of the so called chelated forms - magnesium glycinate and magnesium aspartate. Some patients have poor absorption of magnesium and may need to take 400 mg twice or even three times a day. Magnesium should be taken with food, which reduces the chance of it causing diarrhea. Some patients who do not absorb magnesium taken by mouth require intravenous infusions, which are usually administered monthly.

According to a very large study (1,550 patients; mostly adolescents), 35% of migraine sufferers are deficient in CoQ10. The dose of CoQ10 used in one of the studies is 100 mg, taken three times a day. Since CoQ10 often makes people feel more energetic, some cannot fall asleep if they take it at night. I recommend taking 300 mg once a day, in the morning.

Riboflavin, 400 mg daily was shown to help prevent migraines, although a clear effect occurred after 3 months of taking it. Riboflavin causes urine to turn a bright yellow color, so do not get alarmed.

Alexander Mauskop, MD
New York Headache Center
New York, NY

reader mail

You ask. Our headache experts answer.

Continued from page 11...

ORGASMIC HEADACHE

Please, could you refer me to studies or give me any advice, other than propranolol and naproxen, about orgasm migraines? It's so bad I can't get up for a whole day and it doesn't go away for days. It's ruining my marriage.

Orgasmic or pre-orgasmic headaches are usually short in duration, but severe pain can last as long as 24 hours. It is important to exclude secondary causes of the headache after the first episode, such as subarachnoid hemorrhage or arterial dissection, with appropriate imaging studies. The headache usually occurs on both sides of the head and can start as dull at the beginning of sexual activity and then become intense with orgasm. The first line of treatment is usually the anti-inflammatory, indomethacin, (used for gout), which can be titrated up to higher doses depending on a patient's tolerance to the gastrointestinal side effects (i.e. ulcers, stomach, and esophageal irritation, etc.). This can be used with or without a beta blocker such as propranolol. Other forms of acute treatment such as ergotamines do not have any substantial evidence to support the use in orgasmic headache. Most current clinical studies involve acute and prophylactic treatment for migraine or cluster headache, and there are no current national studies for exertional or orgasmic headaches.

George R. Nissan, DO
Baylor Headache Center
Dallas, TX

For adults with Chronic Migraine, 15 or more headache days a month, each lasting 4 hours or more,

BOTOX® is the first and only preventive treatment proven to reduce headache days every month.

BOTOX® is the only FDA-approved, preventive treatment that is injected by a doctor every 3 months for people with Chronic Migraine. BOTOX® prevents up to 9 headache days a month, versus up to 7 days for placebo. BOTOX® is not approved for adults with migraine who have 14 or fewer headache days a month.

FOR ADULTS WITH
CHRONIC MIGRAINE

BOTOX®
onabotulinumtoxinA injection

Find a headache specialist near you at

BotoxChronicMigraine.com

BOTOX® is a prescription medicine that is injected to prevent headaches in adults with Chronic Migraine who have 15 or more days each month with headache lasting 4 or more hours each day in people 18 years or older. It is not known whether BOTOX® is safe or effective to prevent headaches in patients with migraine who have 14 or fewer headache days each month (episodic migraine).

IMPORTANT SAFETY INFORMATION

BOTOX® may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems any time (hours to weeks) after injection of BOTOX®:

- **Problems swallowing, speaking, or breathing,** due to weakening of associated muscles, can be severe and result in loss of life. You are at the highest risk if these problems are pre-existing before injection. Swallowing problems may last for several months.
- **Spread of toxin effects.** The effect of botulinum toxin may affect areas away from the injection site and cause serious symptoms including: loss of strength and all-over muscle weakness, double vision, blurred vision and drooping eyelids, hoarseness or change or loss of voice (dysphonia), trouble saying words clearly (dysarthria), loss of bladder control, trouble breathing, trouble swallowing. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.**

There has not been a confirmed serious case of spread of toxin effect away from the injection site when BOTOX® has been used at the recommended dose to treat Chronic Migraine.

Please see additional Important Safety Information on adjacent page.

MEDICATION GUIDE
BOTOX® and BOTOX® Cosmetic (Boe-tox) (onabotulinumtoxinA) for Injection

Read the Medication Guide that comes with **BOTOX** or **BOTOX Cosmetic** before you start using it and each time it is given to you. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. You should share this information with your family members and caregivers.

What is the most important information I should know about BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic may cause serious side effects that can be life threatening, including:

- **Problems breathing or swallowing**
- **Spread of toxin effects**

These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX or BOTOX Cosmetic:

1. Problems swallowing, speaking, or breathing. These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX** or **BOTOX Cosmetic**.

- People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with **BOTOX** or **BOTOX Cosmetic**.
- Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX** or **BOTOX Cosmetic** have the highest risk of getting these problems.

2. Spread of toxin effects. In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:

- loss of strength and muscle weakness all over the body
- double vision
- blurred vision and drooping eyelids
- hoarseness or change or loss of voice (dysphonia)
- trouble saying words clearly (dysarthria)
- loss of bladder control
- trouble breathing
- trouble swallowing

These symptoms can happen hours, days, to weeks after you receive an injection of **BOTOX** or **BOTOX Cosmetic**.

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving **BOTOX** or **BOTOX Cosmetic**?"

There has not been a confirmed serious case of spread of toxin effect away from the injection site when **BOTOX** has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, or when **BOTOX Cosmetic** has been used at the recommended dose to treat frown lines and/or crow's feet lines.

What are BOTOX and BOTOX Cosmetic?

BOTOX is a prescription medicine that is injected into muscles and used:

- to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat leakage of urine (incontinence) in adults with overactive bladder due to neurologic disease when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- to treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

BOTOX is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

BOTOX Cosmetic is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults for a short period of time (temporary).

BOTOX Cosmetic is a prescription medicine that is injected into the area around the side of the eyes to improve the look of crow's feet lines in adults for a short period of time (temporary).

You may receive treatment for frown lines and crow's feet lines at the same time.

It is not known whether **BOTOX** is safe or effective in people younger than:

- 18 years of age for treatment of urinary incontinence
- 18 years of age for treatment of chronic migraine
- 18 years of age for treatment of spasticity
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm

BOTOX Cosmetic is not recommended for use in children younger than 18 years of age.

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective to prevent headaches in people with migraine who have 14 or fewer headache days each month (episodic migraine).

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective for other types of muscle spasms or for severe sweating anywhere other than your armpits.

Who should not take BOTOX or BOTOX Cosmetic?

Do not take **BOTOX** or **BOTOX Cosmetic** if you:

- are allergic to any of the ingredients in **BOTOX** or **BOTOX Cosmetic**. See the end of this Medication Guide for a list of ingredients in **BOTOX** and **BOTOX Cosmetic**.
- had an allergic reaction to any other botulinum toxin product such as *Myobloc®*, *Dysport®*, or *Xeomin®*
- have a skin infection at the planned injection site
- are being treated for urinary incontinence and have a urinary tract infection (UTI)
- are being treated for urinary incontinence and find that you cannot empty your bladder on your own (only applies to people who are not routinely catheterizing)

What should I tell my doctor before taking BOTOX or BOTOX Cosmetic?

Tell your doctor about all your medical conditions, including if you:

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"
- have allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- have or have had a breathing problem, such as asthma or emphysema
- have or have had swallowing problems
- have or have had bleeding problems
- have plans to have surgery
- had surgery on your face
- have weakness of your forehead muscles, such as trouble raising your eyebrows
- have drooping eyelids
- have any other change in the way your face normally looks
- have symptoms of a urinary tract infection (UTI) and are being treated for urinary incontinence. Symptoms of a urinary tract infection may include pain or burning with urination, frequent urination, or fever.
- have problems emptying your bladder on your own and are being treated for urinary incontinence
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal products. Using **BOTOX** or **BOTOX Cosmetic** with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX or BOTOX Cosmetic in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as *Myobloc*® (rimabotulinumtoxinB), *Dysport*® (abobotulinumtoxinA), or *Xeomin*® (incobotulinumtoxinA) in the past. Be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine
- take anti-platelets (aspirin-like products) and/or anti-coagulants (blood thinners)

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take BOTOX or BOTOX Cosmetic?

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles, skin, or bladder.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.
- **Your doctor will tell you how often you will receive your dose of BOTOX or BOTOX Cosmetic injections.**

What should I avoid while taking BOTOX or BOTOX Cosmetic?

BOTOX and **BOTOX Cosmetic** may cause loss of strength or general muscle weakness, or vision problems within hours to weeks of taking **BOTOX** or **BOTOX Cosmetic. If this happens, do not drive a car, operate machinery, or do other dangerous activities.** See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

What are the possible side effects of BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic can cause serious side effects. See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

Other side effects of BOTOX and BOTOX Cosmetic include:

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- urinary tract infection in people being treated for urinary incontinence
- painful urination in people being treated for urinary incontinence
- inability to empty your bladder on your own and are being treated for urinary incontinence. If you have difficulty fully emptying your bladder after getting **BOTOX**, you may need to use disposable self-catheters to empty your bladder up to a few times each day until your bladder is able to start emptying again.
- allergic reactions. Symptoms of an allergic reaction to **BOTOX** or **BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **BOTOX** and **BOTOX Cosmetic**. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about BOTOX and BOTOX Cosmetic:

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about **BOTOX** and **BOTOX Cosmetic**. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **BOTOX** and **BOTOX Cosmetic** that is written for healthcare professionals.

What are the ingredients in BOTOX and BOTOX Cosmetic?

Active ingredient: botulinum toxin type A

Inactive ingredients: human albumin and sodium chloride

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by: Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, Inc.
2525 Dupont Dr.
Irvine, CA 92612

Revised: 09/2013

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Based on 72284US16
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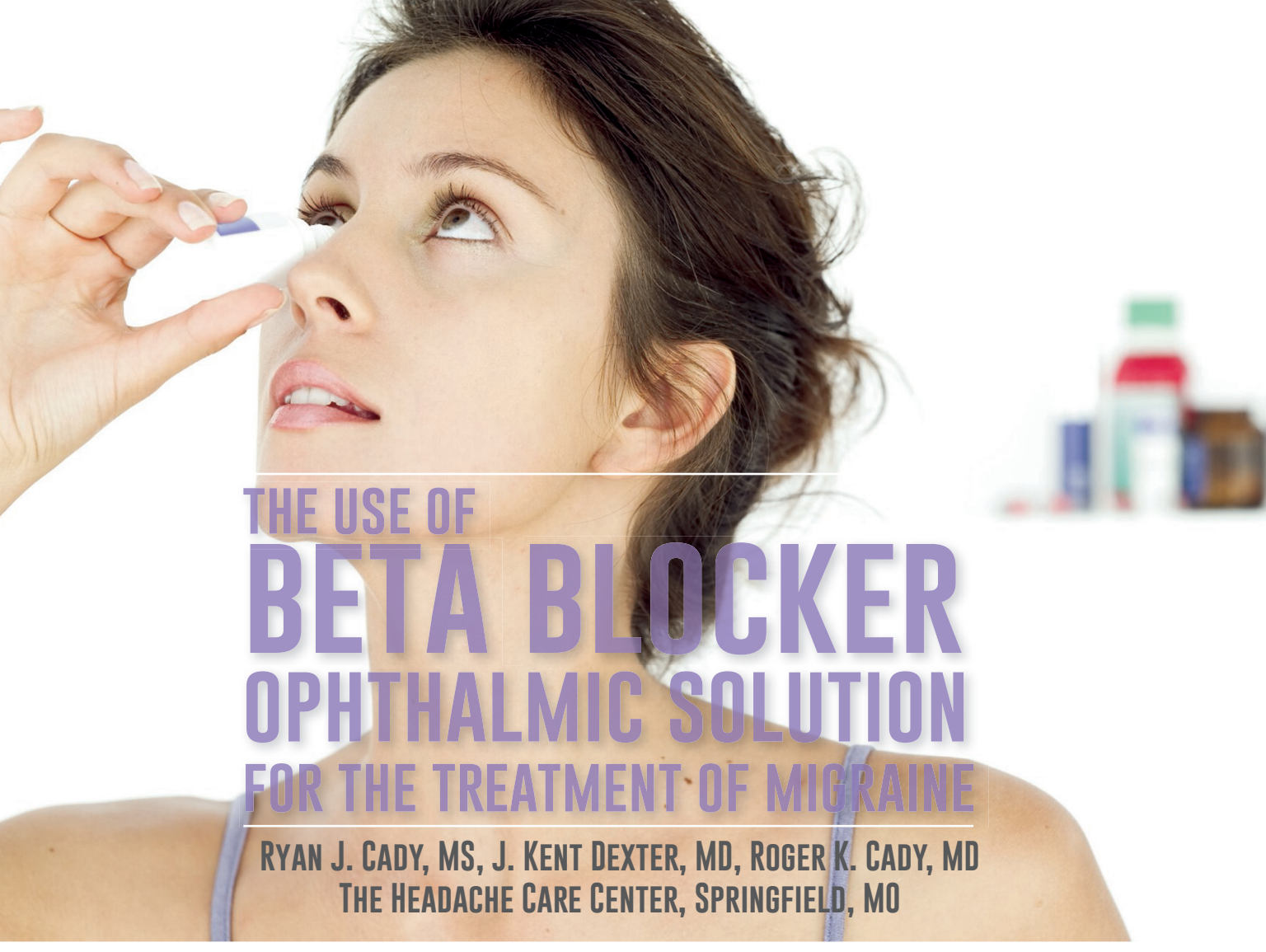


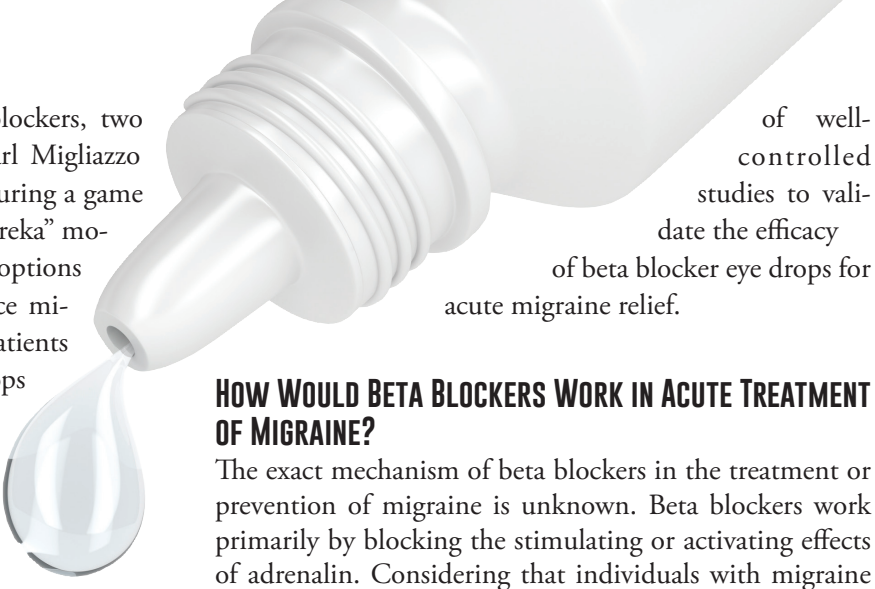
THE USE OF BETA BLOCKER OPHTHALMIC SOLUTION FOR THE TREATMENT OF MIGRAINE

RYAN J. CADY, MS, J. KENT DEXTER, MD, ROGER K. CADY, MD
THE HEADACHE CARE CENTER, SPRINGFIELD, MO

IN THE ANNALS OF MIGRAINE, one of the more fascinating stories is how, in 1966, a physician named Robert Rabkin observed that the drug propranolol could prevent migraine. Dr. Rabkin was actually conducting a study using a beta-blocker (propranolol) to treat heart pain (angina) and fortuitously observed that one of his research subjects had a remarkable reduction in the frequency of his migraine attacks. A decade later, Drs. Seymour Diamond and John Graham presented their experience treating 86 migraine patients with daily propranolol to the Food and Drug Administration (FDA), and demonstrated that propranolol was indeed efficacious and safe for migraine prophylactic therapy. Subsequently, propranolol became the first FDA-approved medication for the prevention of migraine.

As one of many beta blockers used commonly to prevent migraine, propranolol currently, is probably the mostly widely prescribed medication in the world for prevention of migraine. Beta blockers are used to treat multiple diseases including high blood pressure, heart pain, and irregularities of the heart as well as conditions such as anxiety and certain types of tremors. Beta blockers have been so successful that they are considered one of the most important medical discoveries of the 20th century.

In 1978, a second beta blocker, timolol, also received FDA approval as the first topical beta blocker for the treatment of glaucoma. Although clinical trials demonstrated a very strong benefit from using timolol as a migraine preventive, neither it nor propranolol have demonstrated efficacy as an acute treatment for migraine. However, these previous studies have focused on oral preparations of these drugs and the drug was not absorbed quickly enough to be effective as an acute treatment. Interestingly, since the 1980s, there have been rare case reports of patients with glaucoma being treated with timolol eye drops who experienced migraine relief.



Considering the history of these beta blockers, two ophthalmologists – John Hagen and Carl Migliazzo –recently made a startling observation. During a game of golf, these ophthalmologists had an "eureka" moment while discussing possible treatment options for Dr. Hagen's daughters who experience migraine. They observed that some of their patients treated for glaucoma with timolol eye drops reported that if the timolol eye drops were instilled during a migraine, the headache would be rapidly terminated.

Following their discussion on the use of beta blocker eye drops for the treatment of acute migraine, Drs. Hagen and Migliazzo reported on a series of seven patients who had successfully treated acute attacks of migraine with timolol eye drops, which was published in *The Journal of the Missouri State Medical Association* in 2014. The seven patients in these case reports were all female, ages 38 to 76, who presented with migraine syndromes, with and without aura. Five of the seven patients reported complete pain relief, with one patient reporting complete pain relief within 10 minutes of treatment. The two remaining patients reported pain relief of 8 and 9.5 on a 1 to 10 scale, with 10 representing complete relief. These patients were all instructed to use 1 or 2 drops of their beta blocker eye drops as early as possible during their acute migraine attacks. Patients were advised to blink several times to encourage the eye drop to pass into the lacrimal drainage duct. Interestingly, one patient used timolol drops sublingually and reported receiving pain relief. The eye drops were generally well-tolerated with only one reported side effect of shortness of breath which only occurred if eye drops were used in both eyes. Drs. Hagen and Migliazzo stress all patients underwent a complete medical history and ophthalmic examination prior to the initiation of topical beta blockers. Patients were advised to read the package insert and inform their primary care physicians of their acute use of beta blocker eye drops.

Since the publication of these case reports, Drs. Hagen and Migliazzo have received multiple messages and phone calls from fellow physicians who have reported success with patients using beta blocker eyes drops for migraine relief. Although these represent only a few case reports, they provide additional evidence of the use of topical beta blockers in acute migraine, and the treatment appears to be well-tolerated. The physicians are hopeful to see the development of well-controlled studies to validate the efficacy of beta blocker eye drops for acute migraine relief.

How Would Beta Blockers Work in Acute Treatment of Migraine?

The exact mechanism of beta blockers in the treatment or prevention of migraine is unknown. Beta blockers work primarily by blocking the stimulating or activating effects of adrenalin. Considering that individuals with migraine have inherited a nervous system that is more excitable than those without migraine, it is easy to assume that beta blockers may in some way reduce this inherent excitability. In other words, the beta blockers may make the nervous system less vulnerable to migraine. While this likely explains the migraine prevention benefits, it also may provide a rationale for their use in the acute treatment of migraine headaches.

One can imagine that during a migraine, the threshold for nervous system activation has already been surpassed and hence the process of migraine occurs. Beta blocker eye drops enter the nasal cavity through the lacrimal duct (a small passageway from the eye to the nose that drains tears from the eye) very quickly. Once in the nose, the eye drops are rapidly absorbed into the blood. Conceivably, they could block the activating effects of adrenaline and allow the nervous system to reverse migraine. Beyond the speed of entry into the blood, another major advantage of nasal absorption is that medications do not have to pass through the liver before entering the systemic circulation, thus avoiding their metabolism by the liver and allowing a much smaller dose of medication to be effective. Beta blockers have also been found to reduce the electrical excitability of nerve cells, and this too may be part of their potential mechanism.

When oral preparations of beta blockers are used to prevent migraine, levels build up slowly in the blood. This action works well for prevention but during migraine, these levels would increase too slowly to be effective. Using an eye drop with rapid absorption through the nose circumvents that problem. Also, nerves in the nasal cavity may become activated and potentially, beta blockers could act directly on these nerves. Finally, it is possible that some of the beta blocker eye drop could be absorbed into the brain and exert their beneficial effect in that manner.

Would Beta Blocker Eye drops Be a Breakthrough for the Acute Treatment of Migraine?

Currently, the medications used to treat acute migraine generally are either triptans or nonsteroidal anti-inflammatories (NSAIDs). Triptans act by constricting blood vessels and blocking the release of calcitonin gene-related peptide (CGRP) from the nerves activated during migraine. CGRP cause blood vessels to swell and initiates the cascade of inflammatory events leading to pain. The NSAIDs are believed to work primarily by blocking the synthesis of another inflammatory pathway mediated by prostaglandins. If beta blockers are found to be an effective acute treatment for migraine, their efficacy would likely be due to a novel mechanism(s) and provide a third line of potential treatment success. This finding would undoubtedly represent a major medical advancement for the acute treatment of migraine.

Also, because beta blockers are already used on a daily basis to prevent migraine, it is unlikely that their frequent use to treat acute migraine would be associated with medication-overuse headache. This finding would be welcome news for those individuals with high treatment requirements. The beta blocker eye drops also would likely have a good tolerability profile as the dose of actual medication received would be quite low relative to oral beta blocker therapy. Clearly, the need to obtain good clinical trials is indicated before making claims for their use or safety.

What Are the Risks and Limitations?

Oral beta blocker therapy is not tolerated by everyone. Beta blockers can lower blood pressure and slow the heart rate. These effects have been occasionally noted with beta blocker eye drops as well. Rarely, beta blockers can have an adverse effect on asthma. Finally, for those patients with diabetes who are prone to hypoglycemia (low blood sugar), beta blockers can mask some of the warning symptoms and would have to be used with caution. However, beta blockers, and in particular timolol, have been used for decades on a daily basis for treatment of glaucoma, and are generally well-tolerated even with daily use. It is assumed that as an acute treatment for migraine, the beta blocker eye drops would be used on an intermittent basis which should increase their tolerability. In the future, studies may be conducted on the administration of beta blockers as a nasal spray.

What Are the Next Steps?

As with any new potential treatment, the next step is rigorous clinical studies. However, much of the initial work has probably been accomplished, and can be extrapolated from completed studies of beta blocker in glaucoma patients and in migraine patients using beta blockers for migraine prevention. However, the initial step is to undertake a pilot study to establish a proof of concept that timolol eye drops are indeed effective as acute treatment of migraine. If that conclusion can be established, large clinical trials must be undertaken to further establish efficacy and safety of their use in acute migraine. Efforts are currently underway to conduct a pilot proof of concept study. If the proof of concept is established, then involvement of the FDA will be needed before the beta blocker eye drops could be an approved treatment of acute migraine.

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Recalling My Role in Propranolol Research in Migraine Preventive Therapy

Seymour Diamond, MD
Chicago, IL

As my headache practice grew during the 1970s, I was always keen on identifying new options for migraine prevention. An article on the use of the beta blocker, propranolol, in angina pectoris, was published by Rabkin and his colleagues in 1966, and incidentally reported on a patient who had managed to control his migraine attacks while being treated with propranolol. In 1972, in the journal, *Neurology*, Weber and Reinmuth expanded our knowledge of the topic by describing their work using propranolol for a group of migraine patients. These articles piqued my curiosity and by 1973, I had begun prescribing propranolol for some of my patients, although the drug had not been approved by the Food and Drug Administration (FDA) for migraine prevention.

In my clinical practice, patients treated with propranolol were reporting significant decreases in the frequency and duration of their migraine attacks. Subsequently, I contacted Ayerst Laboratories, the manufacturers of propranolol, and suggested that they undertake clinical studies on propranolol use in migraine, in order to obtain approval by the FDA for that indication. Rudy Widemark, MD, was the physician supervising research at Ayerst, and he visited my office and agreed to initiate these studies. Through our collaboration, Dr. Widemark and I became friends. Later, when Rudy joined the staff at the FDA, he invited me to serve as a headache consultant.

With my colleague, Jose L. Medina, MD, I published the results of a study involving 83 patients who used either propranolol or placebo for migraine prevention. Sixty-two patients completed the study. The article was published in the March, 1976, issue of the journal, *Headache*. Later that year, I traveled to Bethesda, MD, at the invitation of the FDA to appear before a panel of noted neurologists from across the US. At that meeting, I discussed the results of my study as well as that of John Graham, MD, of Faulkner Hospital, Boston.

Despite the small number of patients involved in the two studies, the indication for propranolol use in migraine prevention was approved. However, the panel limited the indication to non-classical migraine (migraine without aura). At first, I wanted to argue the point because there were few patients in the 1976 study who were diagnosed with classical migraine (migraine with aura). Subsequently, I considered my argument carefully because at that time, there was little consensus in the medical community that both types of migraine acted similarly. Also, I did not want to stall the approval process for propranolol.

During the next decade, we continued to study the long-term use of propranolol as well as a long-acting form of the drug to ensure patient compliance with a once-daily dose. Propranolol is probably the most widely used drug in migraine prevention. In the accompanying article by the group at the Headache Care Center, the suggested novel approach to acute migraine therapy with a beta blocker ophthalmic solution may provide significant help to migraine patients. And it can easily trace its roots back to an incidental finding in 1966. HW

Suggested reading

Diamond S, Medina JL. Double blind study of propranolol for migraine prophylaxis. *Headache* 1976; 16:24-27.

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Rabkin R, Stables DP, Levin NW, et al. The prophylactic value of propranolol in angina pectoris. *Am J Cardiol* 1966; 18:370-380.

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A New Approach to Acute Migraine Treatment

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National Headache Foundation
Chicago, IL

Serotonin is a neurotransmitter that is involved in the transmission of nerve impulses. It can trigger the release of substances in the blood vessels of the brain that in turn cause the pain of migraine. Serotonin is also key to mood regulation; pain perception; gastrointestinal function, including perception of hunger and satiety; and, other physical functions.

During the 1970s, Patrick P.A. Humphrey and his team of researchers at Glaxo in the United Kingdom attempted to identify the serotonin receptor types responsible for the beneficial effects of serotonin in headache. They identified a serotonin receptor, type 5-HT1B, which is mainly found in cranial blood vessels rather than peripheral blood vessels. Because of this discovery, the scientists were able to design agonists that could stimulate the receptors and trigger constriction of the cranial blood vessels and help terminate an acute migraine attack. In 1988, they utilized a serotonin (5-HT)(1B/1D) agonist called sumatriptan to treat migraine and certain other headaches. The triptans act by binding to serotonin receptors in the brain, which leads to a reversal of blood vessel swelling. Sumatriptan was effective for their patients and it was well-tolerated.

Sumatriptan was approved in the US by the Food and Drug Administration (FDA) and became available by prescription in 1992. Initially, sumatriptan was only administered as a subcutaneous injection. Eventually, other triptans were approved and were available in a variety of forms for administration, including oral, intranasal, and intradermal. In 2013, the FDA approved a single-use, disposable patch system that delivers sumatriptan through the skin. Teva Pharmaceuticals acquired this drug, Zecuity®, in 2014, and it became available by prescription in the US in September, 2015.

Because nausea and/or vomiting are associated symptoms of an acute migraine attack, patients may delay treatment or avoid using drugs that are available as oral preparations. The use of a patch system helps the patient avoid using agents that would be metabolized by the GI tract.

Zecuity® is worn on the upper arm or thigh for about a 4-hour period, during which sumatriptan is delivered through the skin. It is prepared in an iontophoretic transdermal system that uses a mild electrical current through the skin to deliver the drug. The system is single use, battery-operated, and disposable.

In one study of Zecuity®, at 2 hours following application, 18% of patients using this drug reported no headache pain as compared to 9% of patients using a non-medicated patch system. Also, at 2 hours following application of the system, 84% of the patients in the group with active drug reported no nausea as compared to 63% of patients in the second group. Other significant improvements were noted in sensitivity to sound (55% versus 39%), sensitivity to

light (51% versus 36%), and headache pain relief (53% versus 29%). The most common side effects reported by the patients on the active drug were pain, tingling, itching, warmth, discomfort, or a change in the skin color at the application site of Zecuity®.

Vincent Martin, MD, Vice President of the National Headache Foundation noted:

"Zecuity® has a novel drug delivery system that bypasses the stomach and small intestine, and allows absorption of the drug directly into the blood stream through the skin. It is first of its kind!

Generally, sumatriptan produces side effects such as pins and needles of the skin, neck tightness, flushing, and chest pain. One of the advantages of Zecuity® is that these side effects rarely occur. It is a very good medication for those migraine patients who vomit or have severe nausea during their headache attacks."

Patients who should avoid the system include those with: a history of heart problems; history of stroke, transient ischemic attacks (TIAs), or problems with circulation; narrowing of blood vessels in the legs, arms, stomach, or kidney (peripheral vascular disease); uncontrolled high blood pressure; severe liver problems; a diagnosis of hemiplegic or basilar migraine; and, an allergy to sumatriptan. The Zecuity® system should not be used if you have taken another triptan within the last 24 hours. The triptans include sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, and rizatriptan. It should be avoided if, in the past 24 hours, you have taken the combination agent of sumatriptan and naproxen, any ergotamines, or dihydroergotamine (DHE).

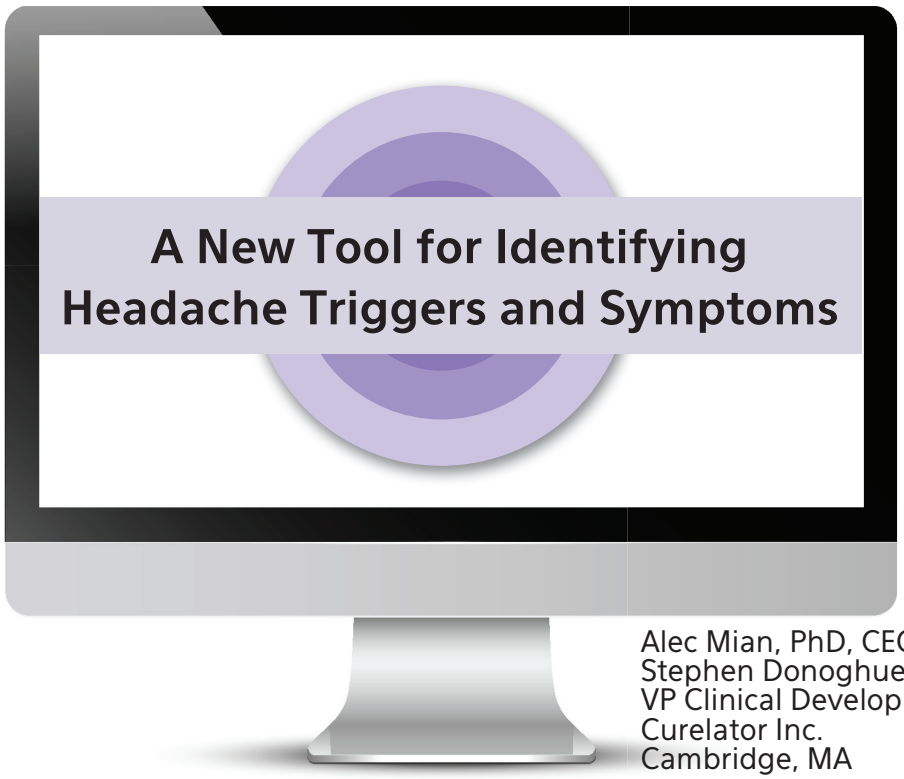
While the Zecuity® system is applied, the patient should not bathe, shower, or swim. Since the drug can cause dizziness, weakness, or drowsiness, patients wearing the system should not drive, use machinery, or any other situation where you need to be alert. Because the system contains metal parts, it would need to be removed before a patient underwent an MRI procedure.

The most common side effects of Zecuity® are pain, tingling, warmth, discomfort, or a change in the skin color at the application site of the system. Patients may note some skin redness after removing the system from the skin. This redness usually disappears after 24 hours. Allergic contact dermatitis is a serious skin reaction which may occur at the application site. As with other sumatriptan preparations, the Zecuity® system may cause serious side effects such as: heart attack or other heart problems; stomach and intestinal problems; changes in color or sensation in the fingers and toes; increases in blood pressure; seizures (in patients without any seizure history); and, problems with blood circulation to the legs and feet.

This drug should not be used if you are also using antidepressants called SSRIs or SNRIs as it may cause the Serotonin Syndrome which is rare but serious. Symptoms of the Serotonin Syndrome include mental changes such as hallucinations, agitation, and coma; rapid heart beat; changes in blood pressure; high body temperature; tight muscles; difficulty walking; or, nausea, vomiting, or diarrhea. Frequent use of the system may lead to Medication Overuse Headaches. Patients should communicate any adverse effects to their health care provider, and also report on the effectiveness of the drug.

The addition of Zecuity® to the armamentarium of migraine therapies is welcome. As noted by Roger Cady, MD, Associate Executive Chairperson of the NHF:

"Zecuity is a unique product that uses a tiny electrical current to drive sumatriptan across the skin and directly into the blood stream. Sumatriptan delivery occurs even in the presence of nausea. Also, Zecuity® is well-tolerated and there is a low incidence of the typical triptan-associated side effects. It will be a useful therapeutic tool for many people seeking better treatment of their migraine." **HW**



Alec Mian, PhD, CEO
Stephen Donoghue, PhD,
VP Clinical Development
Curelator Inc.
Cambridge, MA

Curelator Headache is a transformational digital tool that allows individuals to track and discover the myriad factors that are associated with: a) increasing; b) decreasing; or, c) have no effect on their risk of migraine headaches. The Company collaborated with some of the world's leading migraine neurologists to develop a comprehensive list of migraine triggers and symptoms, which were translated visually into a series of pictorial icons titled, Visual Migraine Language (VML) (Figure 1). VML factors and symptoms must be tracked daily for 45 to 90 days before an individual's maps can be generated, based on the analysis of their data.

An example of an anonymous individual user's results – delivered in the format of three sets of maps: Trigger, Protector, and No Association Maps – are presented in Figure 2. Users also receive a Personal Summary Report to share with their physician. All of this information is designed to help users experiment with behavior modifications, with the goal of reducing the number and severity of their migraine attacks.

Curelator Headache/National Headache Foundation Study: What do migraine triggers & protectors of 150 individuals look like?

In a recent collaboration with the National Headache Foundation (NHF), Curelator Headache recruited migraineurs to test the clinical utility of its digital platform. The NHF with their commitment to furthering clinical understanding of migraine was a perfect partner to recruit migraineurs who were likely to be interested in using such a tool.

The goal was to scientifically determine some of the conditions and factors that may trigger or protect an individual from a migraine headache attack. After 90 days of data were entered, personalized results were generated for 150 individuals, including NHF members across the U.S., as well as some individuals in the United Kingdom. Surprisingly, these results illustrate that virtually every migraineur is different – as shown visually in the interactive Curelator Headache Population Trigger Map.

This discovery has immediate therapeutic implications.

FIGURE 1 *Curelator Headache Population Map Displays Trigger & Protector Profiles for 150 Migraineurs*

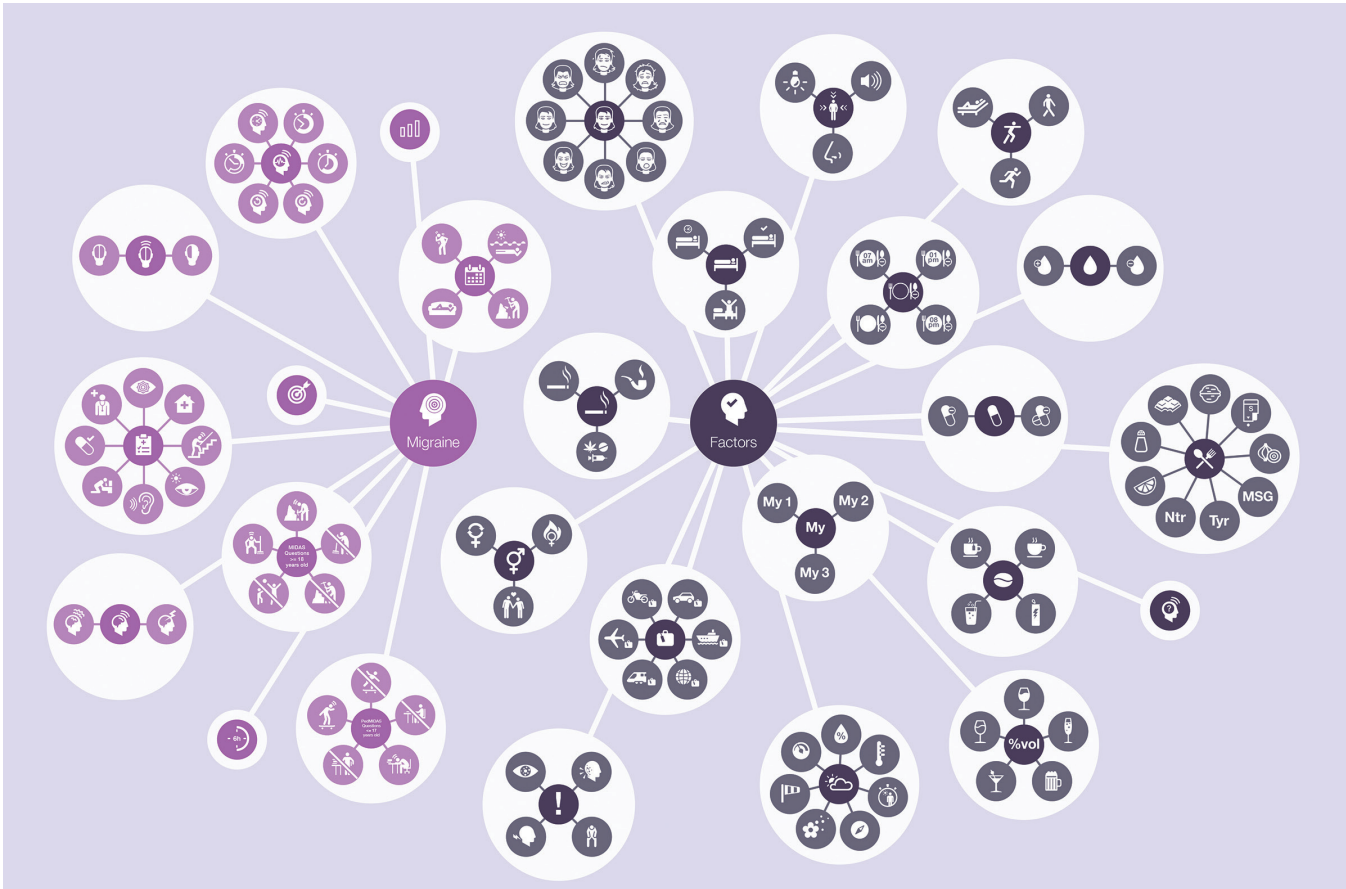


Figure 1 Visual Migraine Language™ (VML) was developed with migraine neurologists and graphically describes the world of factors and symptoms that may influence an individual's risk of attack. This pictorial approach eases data entry and reduces tracking time to 2 to 3 minutes per day. VML factors and symptoms are tracked daily for 45 to 90 days. Surprisingly, these results illustrate that virtually every migraineur is different – as shown visually in the interactive Curelator Headache Population Trigger Map

https://curelator.com/nhf-population-trigger-map/

The foremost is that in migraine (and perhaps other chronic diseases with episodic attacks as well), one treatment may not fit all. Therefore, it may be difficult, if not impossible, to find a common therapy for everyone. This factor would certainly help explain the puzzle and frustration of limited effectiveness of current migraine therapeutics.

Triggers in some migraineurs are protectors in others? Really?

In the study results shown in the NHF Population Trigger Map, Curelator Headache went one step further than simply identifying migraine triggers. It also looked for factors that were associated with decreasing an individual's risk of an attack, so-called "protectors." Doesn't it become a singularly depressing mandate to find all the things in life we need to avoid? Why not look for positive things to embrace as well? But perhaps even more important, protectors revealed yet another level of individuality. Triggers in some people appear to be protectors in others!

By considering the individual associations of various factors, we observed that many appear as triggers in some individuals and protectors in others – potentially a very important discovery because it leads directly to the following question. If certain factors can be triggers in some and protectors in others, could it be possible that some individuals are able to neutralize their triggers or possibly even turn them into protectors?

The best way to answer this question was to interview as

many of the patients in the study as possible to understand the details of each individual's condition. Fortunately, we were able to interview several dozen patients in the study.

The following is what we learned.

Car Travel

In six patients, car travel was protective for their attacks and in seven it served as a trigger. We interviewed several of the patients in whom car travel was a protector and all of these patients indicated that during car travel they were able to enjoy some solitude. In some cases, the car ride offered an opportunity to listen to their favorite music. Conversely, in those in whom car travel was a trigger, they seemed more aware of the traffic or the journey towards a stressful job. In other words, it didn't seem to be the car, but the person's state of mind in the car that was the determining factor.

Wine and Alcohol

Wine and alcohol were less common triggers than expected and much more commonly found as a protector. In several interviews, patients explained that when they drank alcohol it was usually a relaxing occasion – a glass of wine with their spouse or significant other, or a beer with friends. In a contrasting example, in which sparkling wine was a trigger, the patient recognized that she drank sparkling wine at formal occasions such as weddings where the crowds of guests became stressful. Similar to car travel, it was not the factor itself but the occasion associated with the factor that seemed critical.

Tyramine

Fully 18% of the patients in the Curelator Headache/NHF study associated tyramine with their migraine attacks. More unexpected is the finding that in roughly half of these patients, tyramine served as a protector rather than a trigger. Curiously, the appearance of tyramine as both trigger and protector in different individuals may indicate its potential to function in both capacities, depending on the patient.

Stress

The population trigger map reveals that many patients relate an association with stress and their attacks – in our study, 42%. What stands out, however, is that a small percentage of participants – only about 10% – described stress as a protector. How could stress lower the risk of a migraine attack?

We interviewed one of these patients, who also was puzzled that stress was identified as a protector on his map. The first question we asked this patient was, "What did you do when you experienced stress?" The patient advised that he practiced a series of stress management techniques that included deep breathing, meditation, and sitting quietly until he calmed himself. Did this routine reverse the risk of a migraine attack? It seems the answer is, "Yes, very effectively."

Anger

Another participant indicated anger and anxiety as protectors. Upon reflection, he thought it was quite possible that he had developed a series of coping mechanisms that were so effective that they protected him from attacks. "Anger" on the Population Map demonstrated that four patients reported it as a protector while an additional 20 individuals have "anger" as a trigger. It is only through analysis of the individual patient that practical treatments were discovered by the patients themselves.

Earlier we raised the question of whether it might be possible to transform a trigger into a protector. The profiles of more than a few of these interviewees suggest that this had been accomplished. Dr. Paul R. Martin OAM, Professor of Clinical Psychology at Griffith and Monash University in Australia – a leading migraine researcher – shared the following observation with us:

> *"Note that at least with some triggers, deviations in either direction have been suggested to cause headaches. For example, headaches allegedly can be precipitated by too little sleep but also too much sleep, and by stress but also relaxation. Perhaps one of the reasons that eating certain foods has been controversial as a headache trigger is because it is complicated to pin down - whether it is a good or bad thing to eat certain foods depends on circumstances. Eating a certain 'dose' of chocolate is beneficial when blood sugar levels are low, but not when they are high. Certainly, as a clinician, I go down this pathway."*

A different kind of diary approach for managing migraine headaches

There is universal consensus that using electronic diaries is the first step in understanding the episodic nature of migraine and how to improve it. However, simple

FIGURE 2

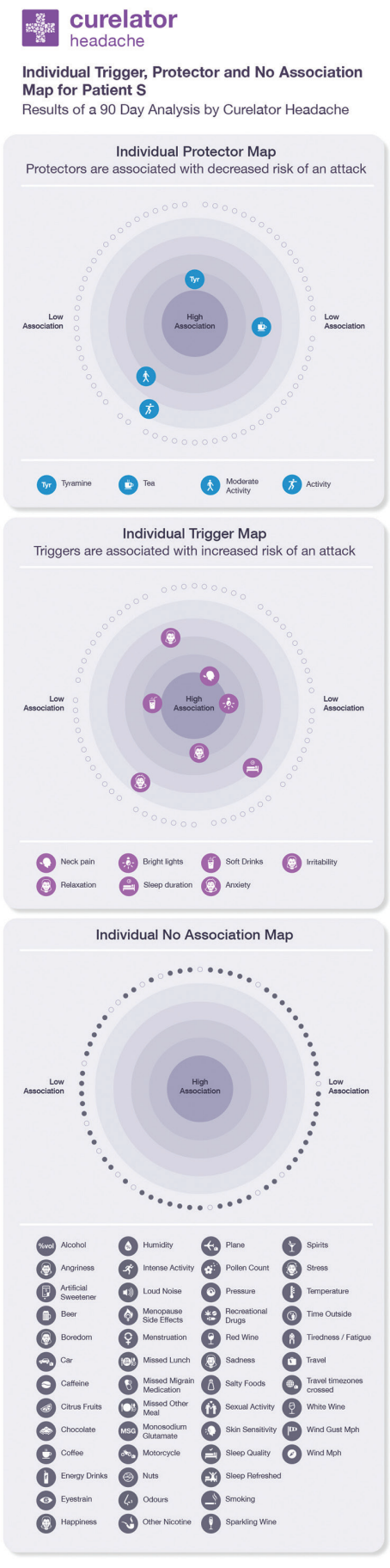


Figure 2 A real-life example of an individual user's Protector, Trigger, and No Association Maps™. Factors found closer to the center of the target indicate a higher degree of association with respect of decreasing (protector) or increasing (trigger) risk of migraine attacks.

automated diaries only accelerate a manual process. They are not able to dismiss suspected triggers that, in fact, are not associated with attacks. Additionally, the ability to identify protectors – factors that are associated with decreasing the risk of an attack -- has not been within reach of conventional diaries.

The Curelator Headache/NHF study demonstrates that a different kind of diary approach can enable a technology that identifies both triggers and protectors and also dismisses non-relevant factors. This approach, when applied on an individual basis, reveals an extraordinary difference between individuals, and can help us untangle the complex interaction between triggers and protectors that governs attacks.

What's next?

Since some factors can be triggers in some individuals and protectors in others, the Curelator Headache/NHF study shows the importance of daily tracking and measuring possible triggers, protectors, prescription therapies, and even alternative therapies on an individual basis. The next phase of the Curelator Headache/NHF study will be to expand the study to a larger population in collaboration with headache specialists who will receive referral coupons that allow their patients to enter the study cost-free. Participants must obtain a referral coupon through their physician and be willing to be interviewed about their experience after receiving their results.

In parallel, Curelator Headache and the NHF are planning to initiate a similar study with a pediatric population. The pediatric study will focus on factors more relevant to children and adolescents. Additional information, including how to register, may be found on the Curelator Headache website (www.curelator.com). Migraineurs who are interested in the product for their own use, can purchase it on the Curelator Headache website. HW

When the **storm of** Strike

ZECUITY delivers medicine over a 4-hour period **through the skin** and into the bloodstream

In a clinical study, at **2 hours** following application, significantly more patients using ZECUITY vs a non-medicated patch reported, respectively

- No headache pain **(18% vs 9%)**
- No nausea **(84% vs 63%)**
- No sensitivity to sound **(55% vs 39%)**
- No sensitivity to light **(51% vs 36%)**
- Headache pain relief **(53% vs 29%)**

Our **Migraine Support Solutions**[SM] program provides assistance with ZECUITY and a special offer that could save you money on your prescriptions

ZECUITY is a prescription medicine used for the acute treatment of migraine headaches with or without aura in adults. ZECUITY comes in an iontophoretic transdermal system (TDS) to deliver the medicine sumatriptan through your skin.

ZECUITY is used for people who have been told by a healthcare provider that they have migraine headaches. ZECUITY is not used to prevent or decrease the number of migraine headaches you have.

IMPORTANT SAFETY INFORMATION

ZECUITY can cause serious side effects, including heart attack and other heart problems, which may lead to death. Stop using ZECUITY and get emergency medical help right away if you have symptoms of a heart attack. ZECUITY is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. Do not use ZECUITY if you have:

- heart problems or a history of heart problems; had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation; narrowing of blood vessels to your legs, arms, stomach, or kidney

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with

ZECUITY®

(sumatriptan iontophoretic transdermal system)

The **first** and only **patch** system designed to provide **relief from migraine**

- uncontrolled high blood pressure
- hemiplegic migraines or basilar migraines; taken any triptan, ergot, or ergot-type medicines in the last 24 hours. Ask your doctor if you are not sure.
- severe liver problems; or an allergy to sumatriptan, the medicine in ZECUITY, or any of the components in ZECUITY.

ZECUITY may cause other serious side effects including:

- injury during a Magnetic Resonance Imaging (MRI). ZECUITY contains metal parts and must be removed before an MRI.
- allergic contact dermatitis—a serious skin reaction where ZECUITY is applied.
- changes in color or sensation in your fingers and toes
- stomach and intestinal problems
- problems with blood circulation to your legs and feet
- medication overuse headaches
- serotonin syndrome—a rare but serious problem that can happen in people using ZECUITY, especially when used with anti-depressant medicines called SSRIs or SNRIs.
- increases in blood pressure
- serious allergic reactions. Get medical help right away if you have any of these symptoms: swelling of your face, lips, mouth, or tongue; trouble breathing; wheezing; severe itching; skin rash, redness, or swelling; dizziness or fainting; fast heartbeat or pounding in your chest; or sweating.
- seizures.

The most common side effects of ZECUITY include pain, tingling, itching, warmth, discomfort or a change in the skin color at the application site of ZECUITY.

Ask your doctor if ZECUITY may be right for you.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please read the Important Information for ZECUITY on the next page.

Ask your doctor or visit **zecuity.com** for more information.

zecuity®
(sumatriptan iontophoretic transdermal system)
6.5 mg / 4 hours

Drs. Seymour Diamond, Oliver Sacks, Arthur Elkind, 1991

Oliver Sacks, MD

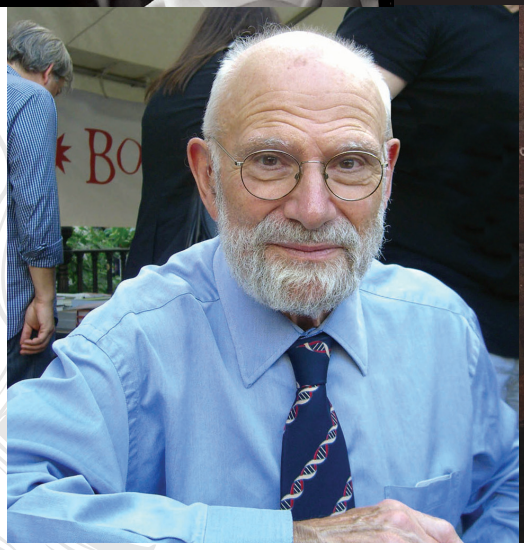
July 9, 1933 to August 30, 2015

Dr. Oliver Sacks, the noted neurologist and prolific writer, was also keenly interested in headache medicine. He was born into a family of physicians in London and like many children of his age, was sent to a rural area of England when World War II erupted. His book, *Uncle Tungsten*, described his experiences at the boarding school but also his fascination with chemistry. He received his medical degree from Queen's College, Oxford, and interned in San Francisco during the early 1960s. In 1965, Dr. Sacks moved to New York to begin a fellowship at the Albert Einstein College of Medicine in the Bronx. His affiliation with that institution ended in 2007, when he began a teaching position at Columbia. In 2012, he became a professor of neurology at the New York University School of Medicine.

In 1971, Dr. Sacks published his book, *Migraine*. His book, *Awakenings*, was published in 1973, and adapted in 1990 for the cinema, in an Academy Award-nominated film of the same name, and starred Robin Williams as the physician and Robert DeNiro as one of his patients with a rare form of encephalitis – *encephalitis lethargica*. On April 27, 1991, Doctor Sacks received the Professional Support Award from the National Headache Foundation at its fifth annual fundraiser in New York City.

In an Op-Ed piece in the *New York Times* in February of this year, Dr. Sacks announced that he had recently been diagnosed with terminal cancer, and was expected to live only a few more months. He continued to write and only a couple of weeks before his death, he submitted an essay, "Sabbath," which appeared in *New York Times*.

Dr. Sacks was a close personal friend of National Headache Foundation Board member, Mark Green, MD and his wife, Leah Green, MD. We are pleased to present Dr. Mark Green's moving tribute to Dr. Sacks. **HW**



source photo by Luigi Novi 9.13.09

Oliver Sacks, undated

Dr. Oliver Sacks, noted physician and author of *Migraine*, published January, 1971, died on August 30, 2015. With his passing, a rich source of clinical description presented in a wonderfully accessible prose is lost to the reading public. His genius lay in his ability to blend clinical narratives with neuroscience in a way that touched and informed his readers. His descriptions brought to life total patients -- how they thought and saw the world as well as their often-elegant accommodations to disability. Dr. Sacks was always interested in the individual behind the medical condition.

During the late 1970s, I was the Director of the Montefiore Headache Unit of the Albert Einstein College of Medicine. Oliver was one of many part-time physicians seeing patients. He would sometimes get lost in the excitement of discovery. He spent countless hours with these patients, but often forgot to prescribe a treatment for their headaches. The patients notified me that they loved all of the attention to the detail of their conditions, were extremely fond of him, and felt greatly understood, but "could he please give me a pill?"

Whatever subject caught his interest, and there were many including the Stereoscopic and Fern Societies of New York, his approach was to learn everything about the topic. Oliver never lost his youthful ability to wander unconstrained by adult limits on viewing the world. On visiting the frog exhibit at the American Museum of Natural History, he wondered aloud "have you ever thought what it would actually feel like to be a frog?" I thought "not really," perhaps I have been missing an opportunity to explore the world around me.

For migraine patients, he validated their condition and invited them to share their experiences with the world. This was often better than a pill. The last time we spoke, Oliver mentioned that despite his illness, he had three more books in him. I am saddened they will not be written.

Mark W. Green, MD
The Center for Headache and Pain Medicine
The Mount Sinai Hospital
New York, NY

Ninan T. Mathew, MD

May 21, 1937 to July 27, 2015

A distinguished member of the headache medicine community, Dr. Ninan Mathew passed away at his home in Houston on July 27. Dr. Mathew was born into a Mar Thoma Syrian Christian family in Kerala, South India. He received his medical degree at Trivandrum Medical College, Kerala, and did post-graduate training in neurology at Christian Medical College, Vellore, India. He moved to the US during the summer of 1970 to complete a fellowship in cerebrovascular disease at Baylor College of Medicine in Houston.

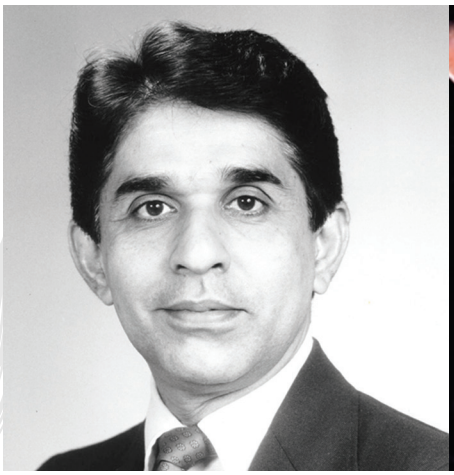
At Baylor, Dr. Mathew was involved in research into measuring cerebral blood flow in migraine patients and thus remained in headache medicine for the remainder of his career. In 1976, he founded the Houston Headache Clinic which was the first headache specialty center in Texas. Later, in 1984, he founded the Dallas Headache Clinic. A few days prior to his death, he was still seeing patients at the Houston Headache Institute.

An acknowledged leader in headache medicine, Dr. Mathew served as President of the American Headache Society (AHS), the International Headache Society, and was chairman and one of the founders of the Headache Section of the American Academy of Neurology. In 1976, he was the recipient of the Harold G. Wolff Award and in 1994, the John R. Graham Distinguished Clinician Award of the AHS. Dr. Mathew received three Lifetime Achievement Awards – Texas Neurological Society (2012); Headache Cooperative of New England (2013); and, the American Headache Society (2014).

His contributions to the medical literature were many and significant. He was the editor of the 1984 text, *Cluster Headache*, and with Randolph Evans, MD, wrote two editions of *Handbook of Headache*.

In addition to his professional activities, Dr. Mathew served as president of the India Cultural Center in Houston, and with his wife, was a founding patron of the Hobby Center for the Performing Arts and the Asian Galleries of the Museum of Fine Arts, in Houston.

The National Headache Foundation wishes to express our condolences to his wife, Sushila; his three children – Rita Morico, Sanjay Mathew, MD, and Vijay Mathew; and, his six grandchildren. He will be missed by the headache community and his patients. **HW**



Ninan Mathew, MD

Dr. Ninan Mathew, Mrs. Sushila Mathew, Mrs. Elaine Diamond, 1996

My personal interactions with Ninan Mathew, MD, started during the 1970s. As a young researcher and clinician interested in headache, Ninan attended an annual meeting of the American Association for the Study of Headache (now American Headache Society). When attending his second meeting, he approached both Donald Dalessio, MD (then Editor of the journal, *Headache*), and myself as I was then Executive Secretary of the Association. Ninan was interested in increasing his activity with headache medicine in general, and with the Association.

I supported Ninan in his endeavors as he became an officer and champion of expanding the Association. In 1984, when he edited the volume, *Cluster Headache*, I was honored when Ninan invited me to not only contribute a chapter but to write the Foreword.

During those years, Ninan and his wife, Sushila, became friends of my wife, Elaine, and I. We enjoyed meeting them at both social and professional events. We can remember when he and Sushila graciously welcomed us to their beautiful home in Houston, and afforded us the opportunity to meet their three children. Also, I was always happy to see the Mathews at the National Headache Foundation benefits in New York City.

Ninan was an outstanding colleague and to all who met him, a distinguished gentleman. His passing is a great loss to his patients and to the world of headache medicine in general.

Seymour Diamond, MD
Chicago, IL

THE HEADACHE CLINICS

featuring:

The Headache Center
University of Pittsburgh Medical Center
Pittsburgh, PA

The Headache Center was established in 1992 at Allegheny General Hospital in Pittsburgh, PA, by Robert Kaniecki, MD, and was moved to the University of Pittsburgh in 2000. The following is based on an interview with Doctor Robert Kaniecki. In addition to serving as Founder and Director of The Headache Center at University of Pittsburgh Medical Center (UPMC), he is an Assistant Professor in the Department of Neurology at the University of Pittsburgh.

Doctor Kaniecki received a B.S. from the University of Notre Dame, and his M.D. from Washington University School of Medicine in St. Louis, MO. He completed an internship in Internal Medicine and Neurology residency at Barnes Hospital in St. Louis, where he served as Chief Resident in Neurology. Doctor Kaniecki is Board Certified by the American Board of Psychiatry and Neurology in Neurology, and has received subspecialty certification in Headache Medicine from the United Council for Neurologic Subspecialties. In 1999, Dr. Kaniecki was awarded the National Headache Foundation Lectureship and in 2006, he was the recipient of the National Headache Foundation Provider of the Year, for which he was nominated by several of his patients.

During his neurology residency in the early 1990s, he was introduced to headache medicine at a time when the science and therapeutics of headache were advancing significantly. As Dr. Kaniecki related, in 1993 the release of sumatriptan (Imitrex®) demonstrated:

"The scientific excitement and expanding treatment opportunities were developing in a field of medicine that showed great need for compassionate, dedicated specialists. I learned that there were few, if any, areas of medical practice that were more rewarding – where patients would routinely thank you, hug you, for 'giving their lives back.'"

The other health care providers at the Headache Center include Laurie Knepper, MD; Josif Stakic, MD; Barbara Vogler, MD; Clair Yanta, MD; and, Kimberly McGonigle, MPA, PA-C. Adjunct staff include Barb Wintermantel, Practice Manager, and Kris McClone, Office Manager.

Laurie Knepper, MD; Kimberly McGonigle, MPA, PA-C; Robert Kaniecki, MD; Barbara Vogler, MD; Josif Stakic, MD; Claire Yanta, MD

Doctor Laurie Knepper is a graduate of the University of Pittsburgh School of Medicine. She completed an internship in Internal Medicine at Allegheny General Hospital in Pittsburgh, and a residency in Neurology at the University of Iowa Hospitals and Clinics in Iowa City, IA. At the University of Pittsburgh, she completed a fellowship in Cerebrovascular Disease. Doctor Knepper is Board Certified by the American Board of Psychiatry and Neurology in Neurology, and has received subspecialty certification in Headache Medicine and Vascular Neurology from the United Council for Neurologic Subspecialties. Prior to joining the UPMC Headache Center's staff, Dr. Knepper practiced neurology in Massachusetts.

A native of Bosnia-Herzegovina, Doctor Josif Stakic graduated from the University of Cincinnati College of Medicine. Currently, he is pursuing an MS degree in Medical Education at the Institute for Clinical Research Education at the University of Pittsburgh. Dr. Stakic completed an internship in Medicine and residency in Neurology at the University of Pittsburgh, and served as a Headache Fellow at the UPMC Headache Center under Dr. Kaniecki. He is Board Certified by the American Board of Psychiatry and Neurology in Neurology, and has received subspecialty certification in Headache Medicine from the United Council for Neurologic Subspecialties.

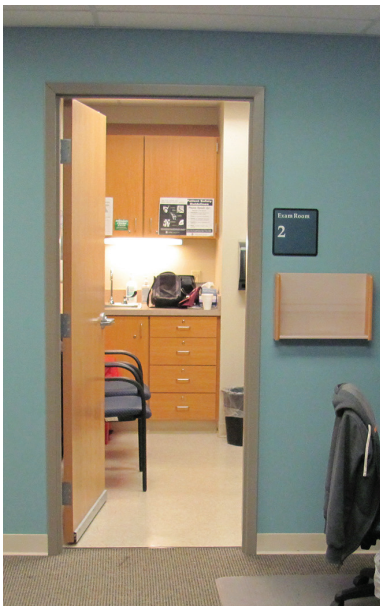
Doctor Barbara Vogler received her MD from the University of Florida School of Medicine in Gainesville, FL. At Yale University Medical Center in New Haven, CT, she completed an Internal Medicine internship, and a residency in neurology. She served as a Headache Medicine fellow at Thomas Jefferson Headache Center, Philadelphia, PA. Dr. Vogler is Board Certified by the American Board of Psychiatry and Neurology in Neurology, and has received subspecialty certification in Headache Medicine from the United Council for Neurologic Subspecialties.

Doctor Claire Yanta recently completed a fellowship in Headache Medicine at the UPMC Headache Center. She received her MD from the University of Chicago Pritzker School of Medicine, and completed an Internal Medicine internship and Neurology residency at the University of Pittsburgh. She is Board Certified by the American Board of Psychiatry and Neurology in Neurology.

Kimberly McGonigle received a Masters of Physician Assistant from Duquesne University in Pittsburgh, and served as a PA at a busy primary care office at UPMC. She has served the UPMC Headache Center since 2000. As the Physician Assistant, she evaluates new and established patients for long-term management of their headaches. Ms. McGonigle manages the care of pregnant and post-partum headache patients, educates patients on their headache condition, pharmacologic treatment, and lifestyle measures necessary for successful outcome.

The UPMC Headache Center does not specialize in any particular headache type/diagnosis. The typical patient at

Sharon Fiorillo, Barb Wintermantel (Practice Manager), Judy McKenna, Kris McClone (Office Manager), Maggie Varhola



Sheila Devey

the Center is an individual who experiences episodic (< 15 days per month) or chronic (> 15 days per month) migraine. The next most common diagnosis is post-traumatic headaches, due in part to the close working relationship with the UPMC Concussion Center. Adults as well as children are evaluated at the Center. A referral from another health care provider is not required.

At the first appointment at the UPMC Headache Center, patients will undergo a comprehensive history and physical examination from one of the Center's physicians. Thorough analysis is conducted on headache details and prior treatment responses, and a review is undertaken on previous scans, testing, and treatments. With their health care provider, the patient will discuss headache type/diagnosis, physiological basis to the headaches, and treatment program tailored to the individual needs of the patient.

During a typical day at the Center, about 60 to 80 patients will be evaluated. Although biofeedback and other alternative therapies are not provided at the Center, off-site access to specialists is available. If the patient requires inpatient therapy, they will be admitted to UPMC Presbyterian Hospital. Dr. Kaniecki advised that the Center continues to grow each year and he anticipates that the Center will continue that path in the future.

At the Center, there is an emphasis on the patient-clinician relationship and the importance of both parties doing their parts in reducing headache frequency and intensity. They find that optimal reduction in disability and improvement in function results from the joint venture. The clinician designs the program and educates the patient. The patient commits to comply with both the natural/lifestyle measures and the medication approaches.

Dr. Kaniecki offered the following general advice for the patient experiencing headache: "*Patience – many treatment programs take months to realize benefits.*" He noted that he enjoys working in Headache Medicine because "*each week, each day, we can make a difference.*" HW

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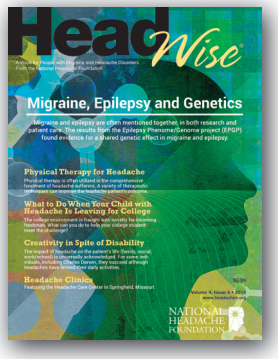

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THE PURPLE BALL

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Celebrate with NHF as we continue to encourage sufferers to rule their headaches through education, advocacy, awareness, and research.

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