migraineurmagazine.com

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Migraineur

For those who strive to live well despite migraine

MIGRAINE INTERNATIONAL:

South Africa

TREATMENTS OF THE MONTH:

The Oral Triptans

BOTOX® onabotulinumtoxinA injection

CHRONIC MIGRAINE

BOTOX® for Chronic Migraine?

BOTOX® prevents headaches in adults with Chronic Migraine: 15 or more headache days a month, each lasting 4 hours or more. BOTOX® is not approved for 14 or fewer headache days a month.

BOTOX® prevents, on average, 8 to 9 headache days and migraine/probable migraine days a month (vs 6 to 7 for placebo).

does it work?

what about cost?

Questions about BOTOX®? It's time to ask your doctor.

INDICATION

BOTOX® (onabotulinumtoxinA) is a prescription medicine that is injected into muscles and used 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 and older.

It is not known whether BOTOX is safe and 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. 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 preexisting 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; drooping eyelids; hoarseness or change or loss of voice; trouble saying words clearly; loss of bladder control; trouble breathing; and trouble swallowing.

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.

BOTOX may cause loss of strength or general muscle weakness, vision problems, or dizziness within hours to weeks of receiving BOTOX. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.**

Do not receive BOTOX if you are allergic to any of the ingredients in BOTOX (see Medication Guide for ingredients); had an allergic reaction to any other botulinum toxin product such as Myobloc® (rimabotulinumtoxinB), Dysport® (abobotulinumtoxinA), or Xeomin® (incobotulinumtoxinA); have a skin infection at the planned injection site.

The dose of BOTOX is not the same as, or comparable to, another botulinum toxin product.

Serious and/or immediate allergic reactions have been reported, including itching; rash; red, itchy welts; wheezing; asthma symptoms; dizziness; or feeling faint. Get medical help right away if you experience symptoms; further injection of BOTOX should be discontinued.

in a survey,

97%

of current BOTOX® users say they plan to keep using it!*(n=71)

and

92%

of current BOTOX® users said they wish they'd talked to a doctor and started sooner!*(n=71)

BOTOX® prevents headaches in adults with Chronic Migraine before they even start.

It's about 10 minutes of treatment once every 3 months.†

It's time to talk to your doctor about BOTOX® and ask if samples are available.

By participating in the BOTOX® Savings Program, you acknowledge and agree to the full Terms & Conditions set out at BOTOXSavingsProgram.com/TermsandConditions. Patients enrolled in Medicare, Medicaid, TRICARE, or any other government-reimbursed healthcare program are not eligible. Other restrictions and maximum limits apply.

you may pay

$0

text SAVE to 27747‡

BOTOX® onabotulinumtoxinA injection

CHRONIC MIGRAINE

BOTOXChronicMigraine.com

*2020 BOTOX® Chronic Migraine Patient Market Research BOTOX® Current Users. †BOTOX® injections are given by your doctor. ‡See Privacy & Terms: http://bit.ly/2RvxiWr. Message & data rates may apply. Message frequency may vary. Text HELP for help or STOP to end.

IMPORTANT SAFETY INFORMATION (continued)

Tell your doctor about all your muscle or nerve conditions, such as ALS or Lou Gehrig's disease, myasthenia gravis, or Lambert-Eaton syndrome, as you may be at increased risk of serious side effects, including difficulty swallowing and difficulty breathing from typical doses of BOTOX.

Tell your doctor about all your medical conditions, including if you have or have had bleeding problems; have plans to have surgery; had surgery on your face; have weakness of forehead muscles, trouble raising your eyebrows, drooping eyelids, and any other abnormal facial change; are pregnant or plan to become pregnant (it is not known if BOTOX can harm your unborn baby); are breastfeeding or plan to (it is not known if BOTOX passes into breast milk).

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using BOTOX 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 in the past.**

Tell your doctor if you received any other botulinum toxin product in the last 4 months; have received injections of botulinum toxin such as Myobloc®, Dysport®, or Xeomin® in the past (tell your doctor 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 aspirin-like products or blood thinners.

Other side effects of BOTOX include dry mouth; discomfort or pain at the injection site; tiredness; headache; neck pain; eye problems such as double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes; drooping eyebrows; and upper respiratory tract infection.

For more information, refer to the Medication Guide or talk with your doctor.

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 see accompanying Summary of Information about BOTOX®.

If you are having difficulty paying for your medicine, AbbVie may be able to help. Visit AbbVie.com/myAbbVieAssist to learn more.

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Summary of Information about BOTOX® (onabotulinumtoxinA)

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

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, trouble saying words clearly, loss of bladder control, trouble breathing, and trouble swallowing

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.

BOTOX® may cause loss of strength or general muscle weakness, vision problems, or dizziness within hours to weeks of taking BOTOX®. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.**

BOTOX® dosing units are not the same as, or comparable to, any other botulinum toxin product.

What is BOTOX®?

BOTOX® is prescription medicine a medical professional injects into muscles 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 and older.

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

Who should not receive BOTOX®?

Do not receive BOTOX® if you are: allergic to any of the ingredients in BOTOX® such as botulinum toxin type A and human serum albumin; had an allergic reaction to another botulinum toxin product such as Myobloc® (rimabotulinumtoxinB), Dysport® (abobotulinumtoxinA), or Xeomin® (incobotulinumtoxinA); or have a skin infection at the planned injection site.

What should I tell my doctor before treatment?

Tell your doctor about all your muscle or nerve conditions, such as amyotrophic lateral sclerosis (Lou Gehrig's disease), myasthenia gravis, or Lambert-Eaton syndrome, as you may be at increased risk of serious side effects.

Tell your doctor if you have or have had breathing problems such as asthma or emphysema; swallowing problems; bleeding issues; plan to or have had surgery; have forehead muscle weakness such as trouble raising your eyebrows; drooping eyelids; or any changes to your face.

Tell your doctor if you are pregnant, plan to become pregnant, are breastfeeding or plan to breast feed. It is not known if BOTOX® (onabotulinumtoxinA) can harm your unborn baby or if BOTOX® passes into breast milk.

What Are Common Side Effects?

The most common side effects include neck pain; headache; migraine; slight or partial facial paralysis; drooping eyebrows; eyelid drooping; bronchitis; musculoskeletal stiffness; muscular weakness; pain in 1 or more muscles, ligaments, tendons, or bones; muscle spasms; injection site pain; and high blood pressure. Other side effects have been reported including allergic reactions e.g. itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint.

These are not all of the possible side effects. Call your doctor for medical advice if you experience any side effects after treatment with BOTOX®.

What Should I Tell My Doctor About Medicines and Vitamins I Take?

Using BOTOX® 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® in the past.** Tell your doctor if you have received an injection with another botulinum toxin product in the last 4 months, such as Myobloc®, Dysport®, or Xeomin®. Be sure your doctor knows which product you received.

Tell your doctor about all prescription and over-the-counter medicines, vitamins and herbal supplements you take; recent antibiotic injections; anticholinergics; muscle relaxants; allergy or cold medicine; sleep medicine; aspirin-like products; and blood thinners. **Ask your doctor if you are not sure whether your medicine is listed above.**

To Learn More

If you would like more information, talk to your doctor and/or go to BotoxChronicMigraine.com for full Product Information.

You may report side effects to the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

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Migraineur

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Special Features

In Every Issue

Editor's Note

*Dr. Rothrock is director of neurology advanced practice provider training and professor of neurology at Inova Health and the University of Virginia School of Medicine. He has served as editor of **Migraineur** since the magazine's inception in 2016.*

Vox Calamitas

I was in the process of completing this issue of ***Migraineur*** when I first learned of the horrific events that were occurring in southern Israel. I listened with increasing disbelief to the accounts of civilian citizens dragged from their homes to be murdered, mutilated, raped, and kidnapped. Of children witnessing the murder of their parents and then snatched off by the murderers to serve as hostages or worse…innocent puppets manipulated for political theater.

Celerity Press, the publisher of this magazine, has made a substantial donation to Magen David Adom, Israel's equivalent of the American Red Cross. We offer to those Arab Muslim citizens of Israel our most profound expression of respect and admiration for the compassion and courage you have shown by providing aid and comfort to the Jewish refugees forced to flee from their homes. We grieve for the innocent civilians of Palestine who have suffered so much already, and - as a consequence of the acts of those who purport to lead them - now are suffering yet more.

Each of the individuals who contribute to this magazine has his or her own perspectives and passions, but we are united in our sympathy for the innocent on either side of this tragic conflict. Our thoughts and prayers are with you.

John F. Rothrock

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Stay in the Know

As always, we welcome all interested parties to Migraineur magazine and invite you to become an **electronic subscriber**. It will cost you nothing, and by subscribing you will receive an email notification as soon as a new issue is out and posted on our open-access website as well as access to blogs and special announcements. To subscribe, simply go to our website (migraineurmagazine.com), find "Subscribe", type in your name, email address and zipcode and then hit "Submit".

QULIPTA™ (atogepant) tablets CAN HELP PREVENT MIGRAINE ATTACKS

Migraine attacks? You can't always avoid triggers, like changes in the weather. QULIPTA™ gets right to work to prevent migraine attacks and keeps them away over time.

In a 3-month study, QULIPTA significantly reduced monthly migraine days.

Ask your healthcare provider about QULIPTA.

WHAT IS QULIPTA?

QULIPTA (atogepant) is a prescription medicine used for the preventive treatment of episodic migraine in adults.

IMPORTANT SAFETY INFORMATION

Before taking QULIPTA, tell your healthcare provider about all your medical conditions, including if you:

- Have kidney problems or are on dialysis
- Have liver problems
- Are pregnant or plan to become pregnant. It is not known if QULIPTA will harm your unborn baby
- Are breastfeeding or plan to breastfeed. It is not known if QULIPTA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking QULIPTA

Please see Brief Summary of the full Patient Information on the next page.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. QULIPTA may affect the way other medicines work, and other medicines may affect how QULIPTA works. Your healthcare provider may need to change the dose of QULIPTA when taken with certain other medicines.

The most common side effects of QULIPTA are nausea, constipation, and fatigue. These are not all the possible side effects of QULIPTA.

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.

If you are having difficulty paying for your medicine, AbbVie may be able to help. Visit AbbVie.com/myAbbVieAssist to learn more.

abbvie

QULIPTA™ (atogepant) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

QULIPTA is indicated for the preventive treatment of episodic migraine in adults.

CONTRAINDICATIONS

None.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of QULIPTA is 10 mg, 30 mg, or 60 mg taken orally once daily with or without food.

Dosage Modifications

Dosing modifications for concomitant use of specific drugs and for patients with renal impairment are provided in Table 1.

Table 1: Dosage Modifications for Drug Interactions and for Specific Populations

Dosage Modifications	Recommended Once Daily Dosage
Concomitant Drug *[see Drug Interactions]*	
Strong CYP3A4 Inhibitors	10 mg
Strong and Moderate CYP3A4 Inducers	30 mg or 60 mg
OATP Inhibitors	10 mg or 30 mg
Renal Impairment *[see Use in Specific Populations]*	
Severe Renal Impairment and End-Stage Renal Disease (CLcr <30 mL/min)	10 mg

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of QULIPTA was evaluated in 1958 patients with migraine who received at least one dose of QULIPTA. Of these, 839 patients were exposed to QULIPTA once daily for at least 6 months, and 487 patients were exposed for 12 months.

In the 12-week, placebo-controlled clinical studies (Study 1 and Study 2), 314 patients received at least one dose of QULIPTA 10 mg once daily, 411 patients received at least one dose of QULIPTA 30 mg once daily, 417 patients received at least one dose of QULIPTA 60 mg once daily, and 408 patients received placebo. Approximately 88% were female, 80% were White, 17% were Black, and 12% were of Hispanic or Latino ethnicity. The mean age at study entry was 41 years (range 18 to 74 years).

The most common adverse reactions (incidence at least 4% and greater than placebo) are nausea, constipation, and fatigue.

Table 2 summarizes the adverse reactions that occurred during Study 1 and Study 2.

Table 2: Adverse Reactions Occurring with an Incidence of At Least 2% for QULIPTA and Greater than Placebo in Studies 1 and 2

	Placebo (N= 408) %	QULIPTA 10 mg (N=314) %	QULIPTA 30 mg (N=411) %	QULIPTA 60 mg (N=417) %
Nausea	3	5	6	9
Constipation	1	6	6	6
Fatigue/Somnolence	3	4	4	6
Decreased Appetite	<1	2	1	2

The adverse reactions that most commonly led to discontinuation in Studies 1 and 2 were constipation (0.5%), nausea (0.5%), and fatigue/somnolence (0.5%).

Liver Enzyme Elevations

In Study 1 and Study 2, the rate of transaminase elevations over 3 times the upper limit of normal was similar between patients treated with QULIPTA (1.0%) and those treated with placebo (1.8%). However, there were cases with transaminase elevations over 3 times the upper limit of normal that were temporally associated with QULIPTA treatment; these were asymptomatic, and resolved within 8 weeks of discontinuation. There were no cases of severe liver injury or jaundice.

Decreases in Body Weight

In Studies 1 and 2, the proportion of patients with a weight decrease of at least 7% at any point was 2.8% for placebo, 3.8% for QULIPTA 10 mg, 3.2% for QULIPTA 30 mg, and 4.9% for QULIPTA 60 mg.

DRUG INTERACTIONS

CYP3A4 Inhibitors

Coadministration of QULIPTA with itraconazole, a strong CYP3A4 inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects. The recommended dosage of QULIPTA with concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is 10 mg once daily. No dosage adjustment of QULIPTA is needed with concomitant use of moderate or weak CYP3A4 inhibitors.

CYP3A4 Inducers

Coadministration of QULIPTA with steady state rifampin, a strong CYP3A4 inducer, resulted in a significant decrease in exposure of atogepant in healthy subjects. Concomitant administration of QULIPTA with moderate inducers of CYP3A4 can also result in decreased exposure of atogepant. The recommended dosage of QULIPTA with concomitant use of strong or moderate CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort, efavirenz, etravirine) is 30 mg or 60 mg once daily. No dosage adjustment of QULIPTA is needed with concomitant use of weak CYP3A4 inducers.

OATP Inhibitors

Coadministration of QULIPTA with single dose rifampin, an OATP inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects. The recommended dosage of QULIPTA with concomitant use of OATP inhibitors (e.g., cyclosporine) is 10 mg or 30 mg once daily.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of QULIPTA in pregnant women. In animal studies, oral administration of atogepant during the period of organogenesis (rats and rabbits) or throughout pregnancy and lactation (rats) resulted in adverse developmental effects (decreased fetal and offspring body weight in rats; increased incidence of fetal structural variations in rabbits) at exposures greater than those used clinically *[see* Data*]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The estimated rate of major birth defects (2.2%-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

Animal Data

Oral administration of atogepant (0, 5, 15, 125, or 750 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreases in fetal body weight and in skeletal ossification at the two highest doses tested (125 and 750 mg/kg), which were not associated with maternal toxicity. At the no-effect dose (15 mg/kg/day) for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 4 times that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Oral administration of atogepant (0, 30, 90, or 130 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in an increase in fetal visceral and skeletal variations at the highest dose tested (130 mg/kg/day), which was associated with minimal maternal toxicity. At the no-effect dose (90 mg/kg/day) for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 3 times that in humans at the MRHD.

Oral administration of atogepant (0, 15, 45, or 125 mg/kg/day) to rats throughout gestation and lactation resulted in decreased pup body weight at the highest dose tested (125 mg/kg/day), which persisted into adulthood. At the no-effect dose (45 mg/kg/day) for adverse effects on pre- and postnatal development, plasma exposure (AUC) was approximately 5 times that in humans at the MRHD.

Lactation

There are no data on the presence of atogepant in human milk, the effects of atogepant on the breastfed infant, or the effects of atogepant on milk production. In lactating rats, oral dosing with atogepant resulted in levels of atogepant in milk approximately 2-fold higher than that in maternal plasma. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for QULIPTA and any potential adverse effects on the breastfed infant from QULIPTA or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Population pharmacokinetic modeling suggests no clinically significant pharmacokinetic differences between elderly and younger subjects. Clinical studies of QULIPTA did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

The renal route of elimination plays a minor role in the clearance of atogepant. In patients with severe renal impairment (CLcr 15-29 mL/min), and in patients with end-stage renal disease (ESRD) (CLcr <15 mL/min), the recommended dosage of QULIPTA is 10 mg once daily. For patients with ESRD undergoing intermittent dialysis, QULIPTA should preferably be taken after dialysis. No dose adjustment is recommended for patients with mild or moderate renal impairment.

Hepatic Impairment

No dose adjustment of QULIPTA is recommended for patients with mild or moderate hepatic impairment. Avoid use of QULIPTA in patients with severe hepatic impairment *[see Adverse Reactions]*.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Atogepant was administered orally to mice (0, 5, 20, or 75 mg/kg/day in males; 0, 5, 30, 160 mg/kg/day in females) and rats (0, 10, 20, or 100 mg/kg in males; 0, 25, 65, or 200 mg/kg in females) for up to 2 years. There was no evidence of drug-related tumors in either species. Plasma exposures at the highest doses tested in mice and rats were approximately 8 and 20-35 times, respectively, that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Mutagenicity

Atogepant was negative in in vitro (Ames, chromosomal aberration test in Chinese Hamster Ovary cells) and in vivo (rat bone marrow micronucleus) assays.

Impairment of Fertility

Oral administration of atogepant (0, 5, 20, or 125 mg/kg/day) to male and female rats prior to and during mating and continuing in females to Gestation Day 7 resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (AUC) at the highest dose tested are approximately 15 times that in humans at the MRHD.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions

Inform patients that QULIPTA may interact with certain other drugs, and that dosage modifications of QULIPTA may be recommended when used with some other drugs. Advise patients to report to their healthcare provider the use of any other prescription medications, over-the-counter medications, herbal products, or grapefruit juice *[see Drug Interactions]*.

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Forest Laboratories Ireland Ltd.
Dublin, Ireland

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US-QLP-220043

abbvie

Migraine International

South Africa


"Crossroads" Township

In past issues of this magazine we have explored how the epidemiology and management of migraine may differ in other nations when compared with the United States. Not surprisingly, we often find that a nation's modern political history can exert powerful influences on its healthcare delivery system generally and its management of migraine specifically. We found this to be true in Croatia, a geographic area first recognized as an independent nation as recently as 1991 and still healing from the physical and cultural ravages of a violent ethnic and religious conflict that escalated into an equally violent full-scale regional war. Croatia's old city of Dubrovnik was largely spared by the war's opposing forces, and while there remain on its ancient walls and buildings the pockmarks inflicted by Serbian shellfire, it appears *undisturbed*, as structurally magnificent now as it has been for centuries. In this issue we turn to South Africa, where the influence of that nation's political history has produced a society that is evolving in the wake of profound political change.

Via Ethiopian Air the ***Migraineur*** field team embarked on the long journey from Dulles to Cape Town International Airport. Driving into the city from the north in a rental car, one soon can appreciate the familiar outline of the enduringly iconic Table Mountain. Eventually we arrived at the Table Bay Hotel, with its namesake waters shimmering just beyond, Table Mountain looming behind and a pleasant waterside complex of shops and restaurants just steps away. The hotel was established by Nelson Mandela to provide a source of employment for the disenfranchised. It is a beautiful place, and the service provided us was friendly, polite and competent.

After a few days of enjoying Cape Town we traveled up the northeastern coast towards Port Elizabeth, stopping here and there along the way and overnight in Plattenberg Bay.

Our northern destination was Shamwari, a game preserve of extraordinary beauty and the culmination of a project begun in a 1992 by Adrian Gardiner, a Zambian-born businessman with a vision. Gardiner sought to restore over 60,000 acres of degraded, drought-ravaged and over-farmed land so as to return the native flora and fauna of South Africa to a natural environment that pre-dated our human presence. Cheetahs, hippos, lions, giraffe and warthogs. All roam freely, safe from human predation. A magical place.

But what of migraine and its management in this beautiful country? The legacy of colonialism, *apartheid* and what followed the political ending of *apartheid* are reflected in the country's uneven delivery of healthcare to its citizens. While South Africa's constitution guarantees its citizens access to healthcare through a two-tiered public/private system, the resources of the public component are scant, and both quality and geographic accessibility are low. Although only 18% of the population regularly use private providers, medical expenditures within that sector account for about half of the nation's spending on healthcare. Almost 80% of physicians work within the private sector, leaving only a 5th for the public sector. Only 16% of the total population has private medical insurance coverage because the associated cost is still a barrier for the majority of South Africans.

Robben Island

Samuel Lankford

Compounding the inequities, since the 1970s there has been an exodus of physicians and other health care professionals to other nations, often those with membership in the British Commonwealth. In one survey of physicians trained in South Africa who relocated to Canada, the respondents reported an overwhelming preference for their new homes and practices. Specifically, they preferred working within a socialized health insurance environment that granted wider accessibility over South Africa's imbalanced two-tiered system.

> **South Africa is struggling…**

It is hardly surprising that migraine care in South Africa would be sparse. The primary care services upon which most migraineurs should be able to rely for diagnosis and initial treatment are limited, and specialist treatment costs too much to be widely accessible. Many of the medications used to treat migraine are either not yet available in South Africa or are not funded by either the public or the private healthcare system. One doctor working in South Africa noted that "for the majority of [migraine] patients you can make a very good clinical diagnosis. But the dilemma comes with the level of treatment that you can provide." Another South African physician noted that migraine is not perceived by payors to be a serious condition, and that "the burden and the disability of migraine in South Africa are grossly underestimated and under-recognized …leading us to trail the developed world in terms of treatment and management." For most citizens and physicians in South Africa, then, migraine is a medical afterthought. This is perhaps understandable given the healthcare system's limitations but is nonetheless most unfortunate as regards a disorder which the World Health Organization (WHO) ranks 2nd – above AIDS, malaria, sickle cell anemia - amongst the chronic medical disorders that erode quality of life. And #1 for females.

To neurologists generally falls the responsibility for managing the more complex cases of migraine. Some recent reports estimate that in South Africa, a nation of approximately 60 million, there are as few as 150 adequately trained and clinically skilled neurologists. By way of comparison, one survey reported there are over 3,000 neurologists in greater Los Angeles. The average US neurologist makes about $264,000 annually; while this is lower than many other US specialties, the average South African neurologist makes about $53,000.

We thoroughly enjoyed South Africa and were invariably treated with kindness and civility. South Africa is struggling to produce a just and peaceful society whose system of healthcare delivery is effective and equitable, and on behalf of migraineurs in particular we applaud and endorse that effort.

John F. Rothrock
Benjamin A. Lankford
Photography: Samuel A.Lankford

Editor's note

Our team took the ferry across Table Bay to Robben Island. Alcatrazesque in its proximity to Cape Town, Robben Island served as Nelson Mandela's home for 18 of his 27 years of imprisonment. As I stood before his cell, it seemed to me literally transcendent that this man emerged from his imprisonment sufficiently unembittered that as his nation's first black president he could lead with grace, compassion, dignity and restraint. Revisionist historians will have their way with Mr. Mandela, but having seen some small portion of the path he walked and the country he served, I can only be sorry that those years spent on the island could not have been applied instead to a longer tenure as his nation's chief spokesman. His passing was a great loss for his country. For all of us.

In some ways, choosing to become a physician is the easy way out. With that choice skin color becomes as much of an irrelevance as are age, gender, religion, socioeconomic status, or any other biologic or demographic factor. You – our "they" – are simply…patients. And it is our sworn obligation to treat you all equally and to the best of our abilities. If our prejudices, be they conscious or unconscious, interfere, then we clearly have failed to meet our sworn obligation. And there will be no reward for that lapse.

Out there, beyond the hospitals, emergency, rooms, and clinics…life is not so simple. Together we must find the way to make it so.

JFR

Samuel Lankford

Nelson Mandela's cell block on Robben Island

From the Patient's Perspective

The Migraine Experience

Headache is like the dread windstorm
No one knows its course
No one knows its full time or its bond.

"That no one dies of migraine seems to someone deep in an attack as an ambiguous blessing."

Be it an anonymous Mesopotamian poet carving on clay tablets 4000 years ago or Joan Didion writing in her *White Album*, those who personally experience migraine are often the most adept at describing and explaining the "migraine experience". In this issue, we introduce a new and recurring feature that offers readers the opportunity to examine migraine from the patient's perspective.

Brain Pain

Ilene Haddad

It starts with a blinding sucker punch to my right temple. Now my head is a giant grape in a vise, ready to split open and ooze its juices down my neck. The pressure increases; the nausea erupts from my gut. Time becomes thick with throbbing and worry. I try to escape its grasp, but the struggle makes it worse. Sometimes medicine works—but not today.

I crawl into bed, defeated, yet sleep evades me. The pain is so extreme it hurts to lie down. Then it hurts to sit up. I walk in circles trying to outpace the headache. I lean against the wall with tears about to spill over the shelves of my eyes, willing myself not to cry. Pain multiplies when you cry

Time passes—sometimes hours, occasionally days—but eventually the smog of misery begins to dissipate, and I can see again. I lie back down to recover with my dogs who are oblivious to my condition. Tomorrow I will feel sore from the fierce workout.

Released from my painful prison sentence, I notice a snowy layer of dust blanketing my bedside table. Giddy with relief, I ready myself to start over again. At no point do I think to wipe off the table. Time on either side of a migraine is too valuable to spend housekeeping.

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I worked at my father's clinic the summer I was 14, filing patient charts in the medical records department, back when there were paper files stuffed with pages and pages of physician notes. One afternoon while eating lunch at my desk, the room started to shimmer. I thought perhaps I was suffering from a lack of air and sunlight, but then the shimmer undulated and so did my stomach. Suddenly, my vision exploded like fireworks and collapsed in on itself, forming a nauseating tube of twisted light. I later learned these visual effects were called "auras." I no longer wanted lunch. I wanted my daddy.

I stumbled down the long hall toward his office, passing door after door of other doctors' suites. My peripheral vision was still intact, but the space directly in front of me seemed to swallow itself up, revealing only a vibrating outline. I felt like the Predator in the eponymous movie about an out-of-this-world bounty hunter who enjoys a lively game of death tag. His unfair advantage is an ability to travel from victim to victim, defined only by a slight warping of the space around him.

"Uh-oh," my dad said when I described my symptoms. I wanted to ask if that was an actual medical term, but a wave of nausea

washed away the sarcasm.

"It sounds like you're having a migraine. Do you feel any pain yet?"

I was pondering his use of the word "yet," when I became vaguely aware of a throbbing behind my left eyeball. The throbbing quickly grew to a stabbing feeling then finally organized itself into a bashing-head-against-wall feeling.

My father appeared to be taking this a little more seriously than he usually did my ailments. In our family, unless there was a stake in the heart or a blood tsunami, we were instructed to take some aspirin and lie down. When I was sick with a stomach bug as a child, I pleaded with my parents, "Call a doctor!" to which my father replied, "I am a doctor!"

That day in my dad's office was the beginning of my relationship with pain—one that has lasted more than 40 years.

***

When I get a migraine, time stops, then seems to go in reverse. It stretches beyond imagination. Not only does time slow to a halt—everything else does too. I can't take care of my dogs no matter how much they try to get me to pet or walk them. I can't run errands, and I've missed many events, including half of my 15th birthday party, due to migraines.

I suffered with these headaches occasionally throughout my teens and twenties, but the misery escalated once I reached my thirties. Fifteen years after my first migraine, my parents were no longer who I went to for help though; instead it was my husband, Bill. And these acute headaches affected him almost as much as they did me.

We had been married about five years when my headache pain and frequency began increasing. Bill found me on the bathroom floor one night and panicked; he wanted to call an ambulance. I reassured him that I was just nauseated from my headache, and the cool floor tiles were soothing. When lying on the bathroom floor became something of a hobby for me, Bill stopped worrying about calling 911. But the emergency room still loomed in

my future, waiting.

He once took me to the ER where we waited four hours…only to discover I had an allergy to the medication they were pumping into my veins. I yanked out the IV because I couldn't breathe. The doctor told me this was a normal side effect. Not breathing isn't normal, I thought. So I got dressed, and disappointed we left.

Another time at the ER the doctors deemed me to be a "drug seeker". Not really, I thought. More a relief seeker. But I diligently obtained a written indication from my doctor advising other medical providers that it was appropriate to give me narcotic pain medication in the hospital. Unfortunately, the card rarely worked. Agony and dread that I wouldn't get relief combined with the ER's bright clinical lighting in to intensify the headaches, and so I eventually stopped going to the hospital altogether.

One memorable afternoon in the spring of 2007, a friend was driving me home after lunch when suddenly my mouth couldn't form words. My speech was garbled; I sounded like the caricature of a drunk trying to say something important. And I was trying to say something important: I thought I was having a stroke. Fortunately, we were near my doctor's office, and so my friend exited the highway and sped to a nondescript building mere seconds away. We dashed inside, and after my friend explained what was happening, the receptionist hurried away to inform my doctor.

Dr. Kennedy rushed out to the waiting room to meet us. He gave me the quick once-over, had me try to speak and then led me toward an examination room. I spoke to him, enunciating slowly and nontheless slurring my words, "I'm thcared." To which he replied, "This is so interesting." I wasn't thrilled to be described as "interesting", but even more so I was confused by the doctor's rather causual response to what seemed to me to be a clear emergency.

He brought me into a cold white room where he did a cursory exam and then proclaimed, "I've never seen this type of aura before. You're having a migraine." I sloppily replied, "Buhut mai headth doesthant hurburt."

This was a new one for me too. Auras typically present with visual disturbances and are a signal that migraine pain is fast approaching, but this one affected my speech rather than my vision. Apparently the Thai food I'd eaten for lunch was loaded with MSG, a common migraine trigger. Since then I've learned that my triggers also include caffeine, alcohol, perfume, and raw onions (oddly, cooked ones are okay).

A Brief History of Migraines

Migraine has a long history. Sufferers of note include Napoleon, Darwin, Einstein, Elvis, and Elizabeth Taylor. Generals Robert E. Lee and Ulysses S. Grant also suffered from these excruciating headaches, which might have been the only thing they had in common. Joan of Arc was said to have experienced both migraines and bipolar disorder, which explains a lot.
Like most things medical in the Middle Ages, the treatment for migraine could be worse than the disorder itself. Everything from bloodletting to witchcraft was employed to cure the agony of these headaches. Remedies included applying hot irons and electric eels to the head, boring holes into the skull and cauterizing the muscle of the temples. Then there was the peculiar practice of fastening a dead mole to one's head. No lie-look it up.

Even as late as the 1970s, you couldn't

do much better than an ice pack in a dark room. When I was hit with a migraine in the early 1980s, I would take a handful of pills (which I'm certain were essentially placebos) over the span of several hours. While nearly always unsuccessful, at least taking the medicine gave me something to do between surges of pain. About a decade later a drug was invented that would change my life forever…and eventually land me back in the hospital.

Junkie

Sumatriptan was a game changer. This medication could abort a migraine in as little as 30 minutes, which is why migraineurs often refer to it as a "miracle drug." And for me, it was effective 90 percent of the time. When it first came out under the name Imitrex™, it was administered using a rather large tubular device that resembled a primitive vibrator and automatically jabbed a needle into the thigh. Often the injection gun startled me…which would cause my hand to jerk away from my leg…resulting in $100 worth of medication dribbling out of the needle, wasted.

Scientists, to whom I am forever grateful, later produced it in nasal spray and pill forms. Sumatriptan was truly life-changing. Side effects were minimal, although while researching this essay I learned that an overdose can cause your blood to turn green…which is kind of exotically cool as far as side effects go and probably would make you the queen of St. Patrick's Day. The most insidious side effect of sumatriptan is so-called "rebound" headache…better known as "medication overuse headache." Simply put, if you take pain medication too often, it stops working and – worse – begins to promote headache. Even over-the-counter meds such as Advil and Tylenol—or more questionable ones such as opioids and heroin—have this effect. You must take more and more of the drug to feel results, until eventually you find yourself living in the dark under a blanket.

On a good day I could go grocery shopping or make the bed, but those days were becoming fewer and fewer. My 2 migraines a month became 6, then 10, and kept getting worse until I couldn't be pain-free for more than a couple of days at a time. And the more medicine I took, the more headaches I got. When I hit 20 migraines a month, my neurologist told me I was suffering from "intractable migraine." More simply, that means one endless headache, broken up by mere days–sometimes only hours–of relief.

I spent months more or less unconscious, barely functioning. I lost touch with

friends and couldn't take care of simple things like making dinner or driving to the store. I slept for hours during the day. I stopped going to yoga class. The house was depressing, and so was I. This wasn't just hard on me—it was hard on Bill. Not only did he have to support us both financially since I could hardly work, but he also had to live with me. I set up a home base on the couch and roamed between there and the bedroom for the better part of a year. By then the medication I once worshipped had stopped being effective, and the constant pain led to a deep depression which affected both of us as much as my migraine did.

> **Time on either side of a migraine is too valuable to spend house-keeping.**

The most severe headaches made me feel especially lonely. I needed to be by myself, yet I also craved comfort from Bill. During the worst throes, I emerged from the darkened cave that was once our bedroom, tears streaming down my face. I implored him to bring some relief, which of course he couldn't. The painfully intense light streamed through our kitchen window, forcing me to return to my stuffy cave, shoulders sagging in defeat. Meanwhile, Bill was left to cope with a sense of helpless anxiety.

About nine years in, I felt as if I was checking out of our marriage, and I imagined Bill felt the distance too. We didn't talk as much because there wasn't much to say. Talking about migraines is boring and painful, for more reasons than one. How many times can you use the phrase "ice pick in my eye" before it becomes redundant?

Intimacy was no longer hot and steamy. To the contrary—love-making now entailed a continuous train of ice packs, which never did anything but make me shiver and wish I were dead. Sitting alone in the cold darkness for hours took me so far away. When you're suffering from a severe migraine, you might as well be dead.

I Was a Botox Guinea Pig.

It took a while before I sought and received the help I required. My neurologist had reached the limits of her ability to treat me. It was time for in-patient care, which was how I wound up in a Houston hospital under the supervision of a mad genius Bill and I referred to as "Dr. Evil".

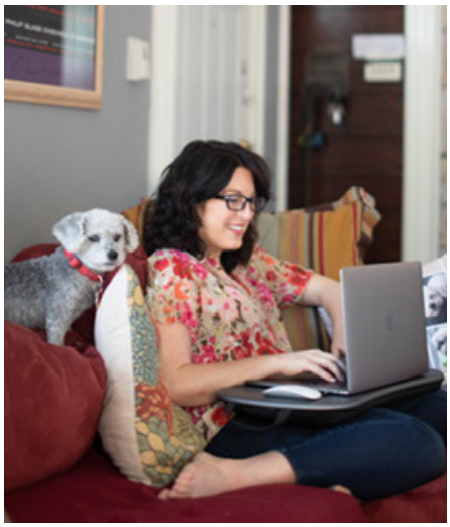
I was hospitalized for a week, during which time I received a load of drugs along with biofeedback, diet restrictions, and the latest magic cure of the day: Botox (this was before it was approved by the FDA, so the cost of the injections was exorbitant, and there was no guarantee they would work).

Bill sat patiently by my bedside in Houston for 7 days of treatments…7 days which succeeded in ending a years-long struggle with daily migraine. It broke a cycle of drug dependence and released me from the dead weight hopelessness of chronic pain. I cannot explain how life-changing it was, andI'll be forever thankful to "Dr. Evil."

I wish I could say my migraine journey ended there, but when the barometer drops or my hormones get rowdy, I still suffer from the headaches. Which is why every three months I go to my neurologist's office for a Botox treatment. The relief provided from the injections is worth every bit of the (very) temporary discomfort. Plus, not long after the procedure, I feel like I've been bobbing for apples in a vat of Novocaine, which is pretty nifty. My neurologist says at my age the migraines might get a little worse before they get better, but they will hopefully get better.

Pain and medications for pain have played monumental roles in my life. I've suffered with migraine throughout every stage of life since adolescence, so my gratitude for medicine that helps is enormous. And it's a good thing we've come this far-I've got no time for so much misery, and I really don't want to strap a dead mole to my head.

The final chapter of this saga is still being written. New medications have emerged since I wrote this piece, and they are truly game-changers. I have had no headaches for the past 2 months.



Award-winning essayist and migraineur, Ilene Haddad is a graphic designer, cartoonist and writer. Her work has appeared in The New York Times, Austin's NPR station, Next Avenue, The Erma Bombeck Writers' Workshop, and other publications. She is an active member of the Writers' League of Texas and was presented with the Women in Communications' Creative Initiative Award for founding BlogathonATX, a central Texas blogging conference. Ilene lives in Austin with her extremely patient husband and an eccentric dog named Harry.

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What should I tell my healthcare provider before taking UBRELVY?
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- Have kidney problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Your healthcare provider can tell you if it is safe to take UBRELVY with other medicines.

What are the most common side effects of UBRELVY?
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Myth of the Month Revisited

Female migraineurs are hyposexual

In the Summer 2023 issue we presented data from research recently conducted by this editor and his colleagues that appeared to contradict the proposition that females with migraine are deficient in libido. In that article I also described my experience of having presented these data in precisely the same manner to two different audiences – one predominantly American at a national headache meeting in Austin, Texas, and the other predominantly European at an international neurology meeting in Budapest two weeks later. The same presentation was received very differently: with a palpable lack of enthusiasm - and even some hostility - by the predominantly American audience and quite positively by the predominantly European audience.

I found that contrast a bit difficult to fathom but definitely interesting, and this revisiting of the last issue's "Myth" is intended to address the American response in particular. More important is the opportunity to explain how the results from research can give rise to new hypotheses that may involve issues of far greater significance than that which generated the original hypothesis.

As I indicated, even mid-presentation in Austin I could sense that all was not going well. This was far from my first rodeo; after a few decades of presenting to audiences of your peers in groups ranging from a handful to a few thousand, you get to know when you're in the groove. Or not. The question and answer session that immediately followed my presentation was brief and uncomfortably strained. A few old friends in the audience tossed me a couple of slow pitch/easy hit questions, the moderator asked if there was anything else, and there was only silence. That was it.

I shrugged it off, returned to my room, changed from coat and tie to T-shirt and shorts and went kayaking with my wife. A few days after I'd returned home I received a call from one of the chairs who had organized the scientific meeting in Austin. Seemed like a nice young guy. Perhaps a bit embarrassed. He advised me that a number of those attending my presentation had found my remarks offensive and asked how I would feel about having my more offending slides and remarks edited from the recorded archives of the meeting. I told him I would feel just fine.

So what specifically might the offended have found offending? Let's see…

Before launching into a description of our research, I introduced the topic by remarking that it had been a somewhat daunting prospect to undertake an exploration of female sexuality during a time when there exists so much controversy and sensitivity regarding the topics of gender, sex, sexual orientation, and sexuality. As an example, I noted the response made by a now-sitting Supreme Court justice to a question posed to her during her confirmation hearing (Q: can you

provide a definition for the word "woman"? A: "I'm not a biologist.").

As to that question (*what is a woman?*), I noted that a computer-assisted analysis of 3.5 million books published between 1900–2008 found the adjectives most commonly used to describe women were "beautiful' and "sexy", while men were most commonly described as "righteous", "rational" or "brave".

I noted that as of February 2014 Facebook offered 58 gender options for user purposes, (including "two-spirit").

Finally, I mentioned that in my Other Life I'm a writer, and when engaged in creative writing and stuck for a well-turned phrase or pithy epigram, I often have looked to to Oscar Wilde. Of women, Wilde wrote: "Men can be analyzed, but women…merely adored." Maybe it was this Oscar Wilde quote that put off the female members of the audience, but c'mon. Is it really offending to be adored? Are you less of a person, less of a female, less of, say, a female physician scientist if you are adored?"

And…give me a break: if I didn't think females and their sexuality were susceptible to analysis, would I have bothered to undertake this particular research?

Or maybe it was the nature of the research itself. Or the researcher. Perhaps this audience found it offensive that a (gracefully) aging white male should be so … (so *what*? intrusive? misogynistic? just generally inappropriate?) as to presume to investigate such complex and highly subjective issues as female sexual desire, performance, and satisfaction.

Enough. That I offended is clear. That I consciously sought to be offensive is…a myth. What I sought was clarity regarding an unsettled issue. Thanks largely to cultural inertia it has become widely accepted as a given that female migraineurs are hyposexual. Our research clearly suggests that this may be quite off the mark. At least in our study population and in what is to my knowledge the largest study of its kind to date, it is the converse that is true: heterosexually, self-identifying and sexually active females with migraine have a higher level of self-perceived sexuality, more positive sexual function, more intercourse and more sexual satisfaction than matched controls free of migraine.

Could this possibly explain why migraine - known to be present in human society for thousands of years - has escaped the merciless scythe of evolution? avoided natural selection pruning it from the shrub of the human genome? The primary purpose of natural selection is propagation of the species. If migraine does convey an increase in female libido and, with this, increased heterosexual activity favoring an increase in progeny, migraine conceivably may be advantageous to the human species. If true, is it possible that over the centuries to come we will witness a progressive increase in the proportion of migraineurs within the general population? In other words, natural selection favoring migraine?

And… presto! Thus one hypothesis (female migraineurs are no less "sexual" than female non-migraineurs) gives rise to a much more far-reaching hypothesis. Albeit an hypothesis that likely will require a multi-generational prospective study to prove.

Migraine Myth of the Month

Never use an oral and injectable triptan on the same day

How this particular myth ever gained traction is something of a mystery, but a persistent myth it is.

As has been pointed out multiple times in previous issues of this magazine, migraine headache comes in all flavors, and because the intensity of migraine headache pain varies so greatly from episode the episode, and even within the same episode, it typically makes sense for the migraineur to have available several different tiers of therapy…with each tier intended for a different level of headache intensity.

As is pointed out in this issue's "Migraine Treatment of the Month", injectable sumatriptan remains the most effective self-administered medication for acute migraine headache of moderate to severe intensity…the most effective "rescue" therapy and the therapy most likely to help you avoid that dreaded trip to the ER. A migraine headache that is already severe or is rapidly escalating towards becoming severe requires a therapy with speed, and a medication's rapidity of therapeutic action is linked to its Tmax. Injectable sumatriptan has a Tmax far faster than that of any orally administrated medication.

As is also pointed out in that article, injectable sumatriptan is not typically an appropriate therapy for use early in a migraine episode, when the headache still may be of mild to moderate intensity. In that setting Tmax is of less importance, oral medication is usually the treatment of choice, and an oral triptan is considered to be a first-line treatment.

Along with Tmax, one of the relevant pharmacokinetic variables discussed in the "Treatment of the Month" article is half-life. Injectable sumatriptan's *half-life* is only 1 to 2 hours, and it will have largely passed from the body within only a few hours.

Let's say you awaken in the morning with a migraine headache that already is fully developed and severe in intensity. *You need speed.* Knowing this, you reach for your sumatriptan auto-injector rather than your bottle of triptan tablets. Within 20 minutes the headache is much better, its intensity reduced to the point that you are able to move on with your day. As noon approaches, however, you can feel the headache beginning to return. It is still only mild in intensity, but you can feel it slowly building. What do you do?

Reach for your oral triptan. If you want to maximize its effectiveness, take it with a prescription dose of naproxen sodium and knock it down with a caffeinated beverage. Follow this with vigorous oral hydration using non-caffeinated beverages throughout the afternoon.

If you administered injectable sumatriptan earlier in the day, does that mean you must stick with oral sumatriptan to treat that early recurrent headache? No. A study conducted by your editor and his colleagues and published in the journal ***Headache*** clearly demonstrated that use of injectable sumatriptan and the patient's preferred oral triptan within the same day is safe and associated with a high degree of patient satisfaction (Rothrock J, Morey V. "Mixing triptans": patient satisfaction. Headache 2011; 51:135-140). If rizatriptan (*Maxalt*) is your oral "triptan of choice", then by all means use rizatriptan to treat an early recurrence of headache following use of injectable sumatriptan. If a headache of mild to moderate intensity fails to respond to, say, rizatriptan plus ibuprofen taken together and is building to become severe, then administer injectable sumatriptan for "rescue".

One caveat: allow 2 hours to go by between use of one triptan before taking another. This is more a matter of allowing enough time to pass so as to assess response to treatment than it is a safety issue. In fact, for those migraineurs who consistently experience early recurrent headache following subcutaneous administration of sumatriptan, there are headache specialists who recommend taking an oral triptan *simultaneous with* the injection. The logic: as the injectable sumatriptan is descending from its maximum blood level to exit the body, the oral triptan is coming on board to take its place. Such treatment is "off-label" but nevertheless makes a great deal of sense. M

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Nurtec ODT may cause serious side effects including allergic reactions, including trouble breathing and rash. This can happen days after you take Nurtec ODT. Call your HCP or get emergency help right away if you have swelling of the face, mouth, tongue, or throat or trouble breathing. This occurred in less than 1% of patients treated with Nurtec ODT.

The most common side effects of Nurtec ODT were nausea (2.7%) and stomach pain/indigestion (2.4%). These are not the only possible side effects of Nurtec ODT. Tell your HCP if you have any side effects.

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Nurtec ODT orally disintegrating tablets is a prescription medicine that is used to treat migraine in adults. It is for the acute treatment of migraine attacks with or without aura and the preventive treatment of episodic migraine. It is not known if Nurtec ODT is safe and effective in children.

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Before you take NURTEC ODT, tell your healthcare provider about all of your medical conditions, including if you:

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- are pregnant or plan to become pregnant. It is not known if NURTEC ODT will harm your unborn baby. There is a pregnancy exposure registry for women who take NURTEC ODT during pregnancy. The study is named MONITOR (Migraine Observational NURTEC Pregnancy Registry). A registry is a study. The purpose of this registry is to collect information about your health and the health of your baby. Your healthcare provider can help you enroll in this registry. You may also enroll yourself or get more information about the registry by calling 1-877-366-0324, emailing nurtecpregnancyregistry@ppd.com, or by visiting nurtecpregnancyregistry.com.
- are breastfeeding or plan to breastfeed. Very small amounts of NURTEC ODT pass into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you take NURTEC ODT.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take NURTEC ODT?

- Take NURTEC ODT exactly how your healthcare provider tells you to.
- For the acute treatment of migraine attacks when they occur, NURTEC ODT can be taken 1 time each day as needed. You should not take more than 1 tablet in 24 hours.
  - It is not known if it is safe to take more than 18 doses of NURTEC ODT in 30 days.
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What are the possible side effects of NURTEC ODT?

NURTEC ODT may cause serious side effects including:

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  - Swelling of the face, mouth, tongue, or throat
  - Trouble breathing

The most common side effect of NURTEC ODT in acute treatment of migraine attacks with or without aura is:

- nausea

The most common side effects of NURTEC ODT in preventive treatment of episodic migraine are:

- nausea
- stomach pain
- indigestion

These are not the only possible side effects of NURTEC ODT. Call your doctor for medical advice about side effects.

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This information is not comprehensive. To learn more, talk to your healthcare provider and visit nurtec.com to obtain the full Prescribing Information. You can also call Pfizer Inc. at 1-833-4NURTEC for more information.

July 2023. PP-NNT-USA-0342.

Pfizer

Migraine Treatment of the Month

The Oral Triptans

In this issue's "Migraine Treatment of the Month" and in an effort which is long overdue, we turn our attention to the oral triptans.

This class of medications has played a critical role in the history of how migraine therapeutics has evolved over the past three decades. While in recent years a great deal of attention rightfully has been directed towards the anti-CGRP medications and the new therapeutic options they represent, both within the US and internationally the oral triptans continue to occupy an important place in our current arsenal of weapons for treating acute migraine.

It is in part because of their historical and therapeutic importance that we have devoted more content than usual to this "Treatment of the Month" section, but we did so also because the triptans provide insight into the greater issue of how drug development "works" in our country. The purpose here is neither to glorify nor vilify our current system of drug development or the pharmaceutical industry itself, but rather to help our readers understand how new therapies travel the spectrum from their beginnings as an abstract concept through the painstaking process of "bench to bedside" research to the final endpoint of widespread clinical availability and use.

Is that process flawed? Yes. Has it produced near-miraculous new treatments that have yielded an improved quality of life? Definitely. Can we do better? We can, and we will.

The Oral Triptans

One can argue that for the United States the ongoing revolution in migraine therapeutics began with the introduction of injectable sumatriptan (*Imitrex*) in 1992. While dihydroergotamine (DHE) can make a legitimate claim to having been the first "designer drug" for migraine (ie, a therapy specifically developed for migraine treatment and not naturally occurring in the environment nor synthesized for another medical purpose and subsequently found to be effective for migraine as well), it was injectable sumatriptan that really got the therapeutic ball rolling for migraine.

Even after three decades plus, injectable sumatriptan remains the most effective self-administered therapy for rescue from moderate to severe migraine headache. It is for many millions of migraineurs literally "an ER in my pocket", empowering them to safely, effectively, and efficiently subdue migraine episodes that otherwise would compel them to suffer in silent misery at home or seek urgent/emergent medical attention. Ironically, analysis of studies examining therapies administered for acute migraine headache in the ER place injectable sumatriptan at or near the top of the list – a list otherwise comprised of medications requiring intravenous or intramuscular administration - in terms of effectiveness. Despite this, injectable sumatriptan

remains woefully under-prescribed.

Why? Why should such an effective therapy not be employed more frequently to assist in reducing the enormous public health burden imposed by migraine? Why should we continue to spend thousands of dollars managing a migraine patient who presents to an ER for an acute headache when a self-administered generic medication could have circumvented the ER visit altogether?

Part of the answer lies in the persistent misperception that the triptans are potentially quite unsafe, and no small part of that misperception in perpetuated by healthcare providers. Contributing to and dovetailing with that misperception is the tendency for the triptans to produce side effects such as chest pressure or neck "squeezing" that typically are benign and transient but understandably may be considered by the uninformed to indicate impending heart attack or an anaphylactic reaction. While the the familiar array of triptan side effects may occur with any triptan or triptan formulation (oral, injectable, inhaled) and tend to be more prominent if administration is delayed until the migraine attack has become more advanced, the side effects are most common and more prominent with injectable sumatriptan.

Why? To answer that requires a quick digression to considering a few important aspects of "pharmacokinetics"... a term which relates to how a given drug is handled by the body.

Two particularly relevant aspects of pharmacokinetics as related to the triptans are "Tmax" and "C max". *Tmax* refers to the amount of time required for a drug to reach its maximal concentration in the blood following its administration. *Cmax* refers to the highest blood concentration achieved by that drug.

"an orally administered triptan has the Tmax of your neighbor's Prius.

Consequent to its subcutaneous administration, injectable sumatriptan has the Tmax of a rocket-ship. In contrast, the Tmax of an orally administered triptan has the Tmax of your neighbor's Prius. Along with this, the rocket-ship delivery of injectable sumatriptan is matched by a much higher Cmax than is achieved by the oral triptans. Combine these two factors, and you have a much higher drug level achieved much more rapidly. Upside for injectable sumatriptan: higher likelihood of headache relief + faster relief. Downside: higher likelihood of side effects

Like an especially prolific hen stimulated to drop egg after egg, the advent of injectable sumatriptan rapidly led the pharmaceutical industry to develop a succession of oral triptans that would possess a mechanism of action similar to injectable sumatriptan but, obviously, require no needle and also produce less frequent and less prominent side effects.

Thus we currently have available in the US 5 "fast onset" oral triptans: sumatriptan, zolmitriptan (*Zomig*), rizatriptan (*Maxalt*), almotriptan (*Axert*) and eletriptan (*Relpax*);

2 "slow onset" oral triptans: naratriptan (*Amerge*), and frovatriptan (*Frova*); and a compound tablet containing a combination of a more rapidly absorbed formulation of oral sumatriptan, and, with it, naproxen sodium (initially marketed as *Treximet*).

Which may lead one to question...

- Are these oral triptans effective?

  Yes. In well-designed and well conducted clinical trials involving patients with acute migraine of moderate to severe intensity, each was more effective than placebo in terms of statistical significance.

- Are any as effective as injectable sumatriptan for the treatment of acute migraine of moderate to severe intensity?

  No. And hardly surprising, given injectable sumatriptan's much faster Tmax and higher Cmax...not to mention its ability to exert a therapeutic effect even in the presence of migraine-associated nausea and vomiting, gastroparesis (ie, delayed stomach emptying) or both.

- Are side effects less frequent and less prominent with the oral triptans than with injectable sumatriptan?

  Yes. Again, the faster, T-max and higher C max of injectable sumatriptan carries with the advantage of greater therapeutic effectiveness but also the burden of more frequent and prominent side effects.

- Are the oral triptans more effective when given early, when the migraine headache is of mild to moderate intensity rather than moderate to severe?

  Yes. For a variety of reasons, the effectiveness of all the oral triptans - and, for that matter, probably all other classes of oral agents used to treat acute migraine headache - will be greater when they are administered early rather than late.

- If injectable sumatriptan is more effective than the oral triptans for moderate to severe acute migraine and the oral triptans are more likely to work if taken early, shouldn't injectable sumatriptan also be administered earlier in the migraine episode...even at the onset of headache?

  No. When a migraine headache has become moderate to severe in intensity, speed (i.e., Tmax) matters. When the migraine headache is beginning to develop and the pain is still at the level of mild to moderate, speed is less important; orally administered medication – including oral triptans –may be quite effective at that point. As effective as injectable sumatriptan? Unclear, but there is some limited evidence to suggest that administration of injectable sumatriptan too early in a migraine episode may be less likely to be effective than administration when the

headache is more severe… the converse of what occurs with the oral triptans.

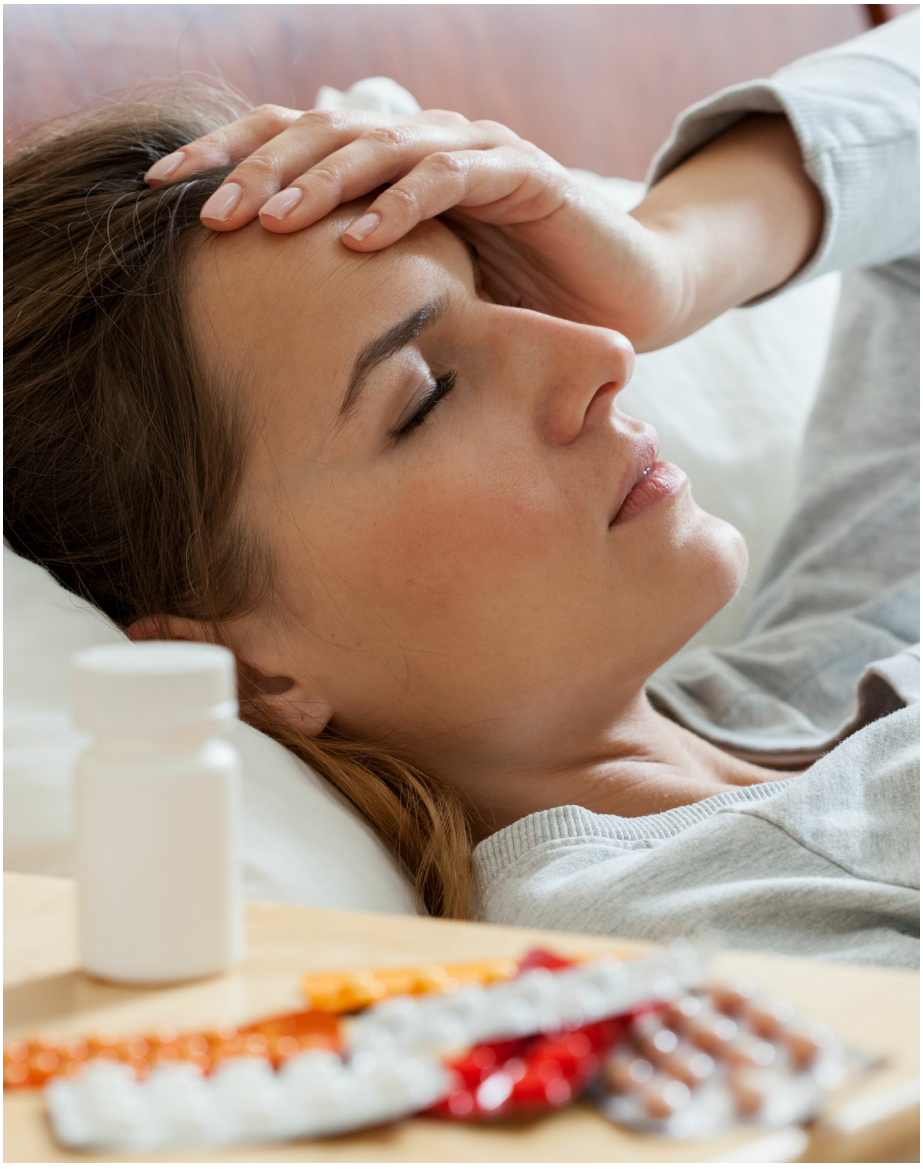
- What is the advantage of the "slow-onset" triptans?

  These triptans (naratriptan and frovatriptan) have a slower Tmax and longer "half-lives"* than their fast-onset molecular cousins (*half-life=the time taken for ½ of the a given drug to be cleared from the body; generally it takes about 4 half-lives for a drug to be cleared entirely). Although it's possible to take make too much of Tmax, Cmax and half-life when it comes to clinical relevance, it does appear that with their longer Tmax times naratriptan and frovatriptan are somewhat less likely to be effective in relieving headache than the fast-onset triptans within the first 2 hours following administration. They also are less likely to cause the typical triptan side effects, and with their longer half-lives (4-6 hours for naratriptan and 26 hours for frovatriptan), the 2 slower-onset but longer-present triptans may be associated with a lower likelihood of early recurrence of headache than their fast-onset brethren.

All this said, there are unquestionably many individual migraineurs who find that a fast-onset oral triptan will consistently relieve their moderate to severe headaches and will do so just as well as injectable sumatriptan and with less frequent/less prominent side effects. Other migraineurs will report that their moderate to severe headaches respond quite well and rapidly to either of the 2 "slow-onset" options. Not to overbeat this paradoxical drum, but this all goes to underscore yet again that the only "always" about migraine is that nothing is ever "always".

Some additional clinical pearls

- A decent amount of evidence exists to indicate that combining an oral nonsteroidal anti-inflammatory drug (NSAID) with an oral triptan is more effective than an oral triptan alone (the NSAIDs with the strongest evidence base in this regard are naproxen sodium and ibuprofen).
- All of the fast-onset oral triptans have relatively short half-lives in the body, and injectable sumatriptan has a particularly short half-life (it is essentially gone from the body within a few hours). When migraine patients report that a triptan is causing "rebound" headache, with the implication that the drug is producing a second and often more severe headache, what most often they actually are experiencing is this: administration of the triptan significantly reduces or even eliminates the headache, but the biologic circuitry generating the headache has remained active and simply reignites when the triptan has passed from the body. Anticipate this, and especially so if the triptan you administered has not entirely eliminated the initial headache. Be ready for the headache to re-emerge and treat it appropriately when it does.
- There is no "best" oral triptan. Head-to-head comparator trials are few, and extensive clinical experience clearly indicates that often for a given patient "not all triptans are created equal". Failure to respond to one oral triptan does not reliably predict failure to respond to another. On the other hand, if you have tried 3 oral triptans and have had no luck, it may be that your particular migraine circuitry is such that the triptan mechanism of action is not suited to your needs. Time to



switch to another class of medications. The same can be said of those who do find that the triptans provide headache relief but that the price paid in terms of side effects is too high. Time to try another class.

- Clinicians often hear from migraine patients that a given oral triptan which was reliably effective for months or even years now is letting them down. The biomolecular basis for the development of this apparent triptan "tolerance" is unknown, but it occurs far too commonly to be dismissed as hearsay. In such situations simply switching to another triptan may be effective. If not, time to try a new class of medication.

Editor's note

The pharmaceutical companies are not dumb, and contrary to what many would have you believe, they are not inherently malevolent. The scientists and physician scientists who work for those companies typically are bright and talented individuals. While there are unquestionably a few bad apples – and some very few (thankfully) very bad apples, amongst the vast orchard – most are dedicated to raising the standard of medical care and thus improving quality of life for their fellow citizens.

The pharmaceutical companies who employ them share that dedication. They also are businesses operating in a capitalist economy, and they consequently are dedicated to making a profit. They'd better be, or they will crumble into dust to be blown away by the winds of competition.

It became clear very quickly to the pharmaceutical industry that injectable sumatriptan's emergence held tremendous implications for drug development in the area of migraine, a disorder, afflicting many millions of Americans. Think of it: upwards of 40 million potential patients/customers…a HUGE market. What medical market could be larger? Obesity? Insomnia? Alzheimer's? Maybe. But in the early '90s, break-thru therapies for obesity and insomnia had yet to emerge (still true for insomnia…and for Alzheimer's, promising but still tentative).

Given that many of those 40 million migraineur Americans would prefer a pill over an injection (especially a self-injection), the race was on to develop an oral equivalent to this revolutionary treatment. And so began the Triptan Wars.

Do we really need 7 oral triptans (8 if you include the sumatriptan/naproxen sodium compound)? Doubtful. But one might as well ask do we really "need" the inevitable next "latest and yet greater" iteration of the iPhone? You be the judge. Yes, you… the physician's patient/insurer's client/economy's consumer.

The economics of capitalism and the biology of natural selection have a lot in common: there may be an excess of entropy involved in the process, but eventually the more utilitarian option will dominate over those found to be inferior.

Doctor on Call

Why don't the treatments work for me?

Melissa, a 32-year-old accountant who lives and works in Charlotte, North Carolina, writes:

I've been having migraine headaches since junior high school, but almost immediately after I delivered my second child my headaches increased dramatically. Over the next 6 months they just kept coming, and eventually I was having headaches practically every day. At least once a week I have a headache that is so severe and makes me so sensitive to light that I can't leave my totally dark bedroom.

My doctor told me that I have chronic migraine, and he referred me to a neurologist to start getting Botox injections. That was OK with me, as my best friend and her sister both had a headaches like mine and are now almost headache-free since they started Botox.

But now, after 9 months and 4 sets of Botox injections, my headaches are if anything, worse. And none of the medicines for acute migraine headache that seem to work for everyone else – sumatriptan, Nurtec, Ubrelvy – don't help at all. I take handfuls of Excedrin just to do something, but that doesn't really help either.

What is wrong with me? Is my diagnosis wrong?

Feeling like a loser in Charlotte

PS
I just had a MRI scan of my brain. To my surprise, it's completely normal. A relief… I guess.

The Doctor's Reply:

Dear Melissa,

That your chronic migraine has failed to respond to the therapies you have tried so far hardly means you are a "loser". Of those who have chronic migraine, a healthy percentage will experience a significant reduction in migraine burden thanks to Botox…but many will not. The same goes for all therapies currently indicated for migraine prevention or acute migraine treatment.

Why is this? There are a myriad of reasons why patients experience a variable response to the evidence-based medications available for acute migraine treatment, but in responding to your letter we'll stick to chronic migraine prevention medications only.

In the case of the oral medications for migraine prevention – and especially the older medications – treatment failure at times may be a consequence of inadequate dose or an inadequate duration of therapy. While certain of the newer oral medications – most notably, atogepant (*Qulipta*) – may begin to exert a positive therapeutic effect as early as one week after treatment is started, with the older oral medications it may take 4 to 6 weeks or longer to know whether or not the medication is going to be effective.

Aside from this, many patients may find the older oral medications difficult to tolerate because of side effects.

There are 7 therapies that possess a strong evidence base for use in suppressing chronic migraine: topiramate (Topamax), onabotulinumtoxin A (*BotoxA*), Qulipta, erenumab (*Aimovig*), fremanezumab (*Ajovy*) galcanezumab (*Emgality*), and epitenzumab (*Vyepti*). Topiramate can be a difficult medication to take consequent to its side effect profile, and typically healthcare providers start the drug at a low dose and then sequentially increase the dose at intervals to reach the recommended regimen of 50 milligrams taken twice-daily. As the likelihood of side effects increases in parallel to dose, that dosing regimen can be difficult to achieve. And, as with the older oral medications that possess less of an evidence base for treating chronic migraine, it also may take some time for topiramate to exert a positive therapeutic

effect even at the recommended dose. Dosing issues are not really a problem with the others. There is only one approved dose of Botox A for suppression of chronic migraine: 155 international units. Of the 4 injectable medications, 2 (*Aimovig* and *Vyepti*) are available in 2 dosages; the other 2 (*Emgality* and *Ajovy*) have only a single recommended dose. Qulipta is available in 3 doses (10, 30 or 60 milligrams taken once-daily, but no topiramate-like dose escalation regimen is required. While patient compliance is always an issue with prevention therapy for migraine, that issue is minimized when the patient is coming in for Botox injections every 12 weeks, self-injecting an anti-CGRP monoclonal antibody once monthly or receiving intravenous infusions of Vyepti every three months.

Even so, there are patients who do not respond positively to *any* of these therapies, and while some portion of that group may respond to a combination of these medications (prophylactic polytherapy), there still remain many who simply do not improve.

We have come a long way in our understanding of migraine's biology… all the way from a simple vascular theory that focused almost exclusively on blood vessels of the head expanding and contracting to a complex circuit that runs from the cortex of the brain through the brain's subcortical regions, the brainstem, the spinal cord, and, finally, a cranial nerve that terminates on blood vessels located within the lining of the brain. Like all nervous system circuits, that complex circuit runs on electrochemical transmission, and two of the big chemicals involved in the transmission of head pain signal are **serotonin** and **calcitonin gene related peptide** (**CGRP**). Our evolving understanding of serotonin's role in the migraine circuitry led to the development of the triptans, and for the past decade attention has turned to blocking or disabling CGRP.

So why do these highly targeted "designer drugs" not work for every migraineur? For one very important thing, a wide variety of genetic permutations may yield the common endpoint of chronic migraine, and it seems quite likely that those genetic permutations also yield subtle and not so subtle differences in the make-up of the individual migraineur's circuitry. While your friend and her sister obviously have circuitry that is Botox responsive, your genes and your migraine circuitry may be quite different from theirs…even though you experience the very same clinical symptoms as they do. You simply may not be a "Botox person".

While your problem may be solved by switching to another type of migraine prevention therapy with a different mechanism of action, it is also quite possible that those who spend their careers investigating the circuitry of migraine not yet identified the biologic variation that is responsible for your chronic migraine. For example, those investigators have identified another chemical (a protein/neuropeptide), with the tongue-twisting name of pituitary adenylate cyclase-activating polypeptide (PCAP) which isdistinct from serotonin or CGRP and may prove to be an excellent target for patients who have failed to respond to our existing therapies.

I will close by sharing one of the of the great paradoxes of migraine. In assessing the chronic medical disorders that adversely affect quality of life - disorders, such as malaria, AIDS, sickle cell, anemia - the World Health Organization ranks migraine ***number one*** for females. And yet despite the high prevalence of this disorder, and its tremendously negative impact on the public health, there are relatively few medical providers who possess the experience, expertise and inclination to effectively manage patients with migraine…and *especially* chronic migraine.

That said, it appears to be time for you to seek out a healthcare provider who has particular expertise in managing "difficult to treat" chronic migraine. One way to do so: go to: **Find A Doctor/** ***American Migraine Foundation*.**

And, again,…failure to respond to Botox does not make you a "loser".


Your special
moments
should never
be ruined
by migraine.
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your back,
no matter where
the trail leads you.
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