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Migraineur

For those who strive to live well despite migraine

MIGRAINE AND EVOLUTION:

The Ascent of the Redheaded Female Migraineur?

ANOTHER MIGRAINE REVOLUTION!:

Exciting New Prevention Therapies in Development

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.*

In my editorial for the last issue of this magazine, published shortly after the atrocities of October 7, I expressed my support for the Israeli survivors of those atrocities and my sympathy for the those Palestinians innocent of such behavior and victimized by the barbarians of Hamas, men more intent upon eliminating the state of Israel than serving the needs of the people they at one unfortunate point were elected to lead.

I did not expect any particular response and was not looking for one. Although I appreciated the expressions of gratitude that came from a few friends and colleagues, it seemed to me a given that one should oppose rape, murder, and kidnapping. I consequently was taken off guard by the brief storm of vitriol that came my way – one of the less graphic and accusatory messages was brief and to the point: "You filthy Jew!"...which I found a bit ironic, given that I indicated in the editorial that I had been baptized a Christian and confirmed in the Episcopalian church.

Far more concerning to me has been what I perceive to be an escalating tsunami of misplaced passion, erupting antisemitism and pure stupidity in America and the Western democracies. How in the space of only a few months has this tsunami gathered? *Why* has it gathered?

I have no enthusiasm for converting this healthcare magazine into a political screed or to waste pages chastising misguided college and medical students for their unfathomable behavior, and I will close my editorial simply with this quote from Solzhenitsyn's *Warning to the West:*

Human nature is full of riddles...One of these riddles is: how is it that those who soar unhampered over the peaks of freedom suddenly appear to lose the taste for freedom, lose the will to defend it, and, hopelessly confused and lost, almost begin to crave slavery...societies with access to every kind of information suddenly plunge into moral lethargy, into a kind of mass blindness, a kind of voluntary self-deception.

John F. Rothrock

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Migraineur

VOLUME 21/WINTER 2024

Special Features

In Every Issue

Migraine and Evolution

The Ascent of the Redheaded Female Migraineur?

As regular readers of this magazine will recall, a few years ago the editor and some of his clinical research colleagues began to question the long-prevailing cultural cliché that females with migraine are somehow less "sexual" than females free of migraine. This led them to conduct a study which they assumed would show that no such difference existed, but to the surprise of those investigators the results demonstrated that females with migraine appeared to have a higher level of self-perceived sexuality and more positive sexual function than matched controls free of migraine. The migraine population reported a significantly higher frequency of heterosexual intercourse, more satisfaction with intercourse and, specifically, a higher likelihood of intercourse resulting in orgasm. The married subgroup of the migraine subjects had more offspring than married female non-migraineurs (average number of children 3.1 versus 1.7).

More or less coinciding with this was a publication from another group of investigators indicating that between 1990 and 2019 there had been a 16% increase in the global prevalence of migraine in females.

So what? Perhaps the result recorded by the editor and his colleagues in their investigation of female migraineur sexuality was an "outlier" resulting from selection bias, simply reflecting, say, the relatively affluent, well-educated and geographically-restricted (metropolitan DC area) population studied. Well… maybe, but there was a matched control group. Perhaps the migraine subjects who were migraine patients threw the game by recording answers they felt the investigators would prefer. Well…maybe, but there was a group of migraineurs studied who were *not* migraine patients, and the results were the same in that group. Perhaps this result cannot be generalized to larger and more diverse populations; as only heterosexually self-identifying and sexually active females were included in the study. It could be that inclusion of female migraineurs who are not heterosexually active would have yielded a very different result. Well…maybe, but…so what? This was not intended to be a study of females who were not heterosexually self-identifying or sexually inactive.

Or the result could have been skewed by some other and as-yet unidentified confounder or methodologic defect Maybe. It's certainly true that confounders are common in clinical research, and the potential for confounders may be especially high in clinical research involving issues related to sex and sexuality. Maybe the results of the study mean little, and maybe the apparent increase in global prevalence of migraine in females is simply an artifact of increased public awareness of the disorder.

Maybe, but what if the findings from this these two very different investigations are very much intertwined? What if female migraineurs are in fact more "sexual" and sexually active than female non-migraineurs, and what if the global prevalence of migraine in females is in fact actually increasing? What if the two results are indeed linked? Why would this be?

We have discussed the topic of migraine and natural selection previously in this magazine. Briefly, migraine has been with

us for a long time. Millennia. Writings that date back nearly 4,000 years to the ancient civilizations of Mesopotamia poetically describe what clearly is migraine *(Headache is like the dread windstorm… blowing… flashing… scorching… hostile… [and] no one knows its course)*. How has migraine persisted for so long? Why should a disorder that inflicts so much suffering and cost remain so prevalent in the human species? While natural selection sometimes may require a long period of time to prune a useless branch off the evolutionary shrub, in some cases a species change can occur in no more than a single lifetime. Where are you, natural selection?

Could it be that genetic migraine conveys some evolutionary advantage that was, at least until relatively recent times, useful to human survival? For most of our existence on this planet we lived primarily as hunter-gatherers, dispersed in tribes believed to have numbered no more than 25 individuals. Migraineurs have *sensitive* brains…brains sensitive to changes in the internal environment (eg, fluctuations in sex hormone levels) but also to changes in the *external* environment: weather changes, stress, maybe even - who knows? – impending movements of the buffalo herd or other game. Perhaps every tribe of 25 needed 1 or 2 *sensitive-brained* migraineurs to serve as weather forecasters. Even shamans.

But we largely shifted from a nomadic hunter-gatherer society of small tribes to an agrarian and settled society of far larger groups at the onset of the Neolithic Revolution approximately 12,000 years ago. Without a need for wild game and a weather-savvy shaman, who needs a bunch of "sensitive brain" migraineurs hanging around to bore you with anecdotes about how barometric pressure changes trigger their headaches? 12,000 years! Surely enough time to dust off and use those pruning shears of natural selection.

Or maybe natural selection just doesn't care. If natural selection is focused on procreation and thus preservation of the species, and if there is nothing inherent to migraine that hinders procreation, maybe natural selection has better things to do than be bothered with eliminating migraine.

Maybe. But…what if migraine actually serves to *favor* human procreation? Would not natural selection, in turn, actively *favor* migraine? And if this is occurring, should we not expect to see a gradual increase in the prevalence of migraine…especially in females, as far more than males they serve as the resource most critical to sustained procreation? If female migraineurs have an increased inclination to engage in heterosexual intercourse and this results in their producing relatively more offspring, would not natural selection favor the genetic permutations that predispose to migraine…resulting in a progressive increase in female migraineur prevalence as the decades and centuries pass. Simplistic? Definitely. Difficult to prove? Most certainly. Plausible? I think so.

So where might redheads fit in? As with female migraineurs, female redheads have come in for their fair share of cultural slings, arrows and clichés: *fiery, tempestuous, quick-tempered. Temperamental temptresses. Witches,* even.

As it turns out, female redheads *are* biologically and behaviorally distinct

Are female redheads more likely to have migraine?

from non-redheads, and that distinction is paralleled by differences in how we perceive female redheads. How are they different? Well, for one they are relatively rare. Unlike the gene for, say, black hair

Phillips After 5. "2013-12-07-pa5-redhead". The Phillips Collection. 5 December 2013, https://www.phillipscollection.org/event/2013-12-04-calling-all-redheads.

or brown eyes, the gene for red hair, MC1R, is recessive. This gene controls the production of melanin, the pigment that gives hair, eyes and skin their color. The gene regulates melanocyte activity, and melanocyte cells produce two types of melanin: eumelanin and pheomelanin. Redheads produce mostly pheomelanin. Global redhead prevalence is only 1-2%, with prevalence rates highest in Ireland (at least 10%), Scotland (at least 6%), England (4%) and the United States (2-6%). There are approximately 18 million redheads in the US, and that relatively high prevalence has been attributed primarily to the Great Irish Immigration that took place between 1850 and 1920.

But enough about genetics and prevalence rates: how are redheads biologically and behaviorally different? For one, they have a somewhat paradoxical response to pain. Although their threshold of tolerance to heat and cold is lower than non-redheads, their pain threshold overall appears to be higher. While redheads respond more effectively to opiate and opioid medications and may not require as high a dose of those medications for pain relief than do non-redheads, they are more resistant to anesthesia; it is estimated that they require anesthetic doses 20% higher than those administered to non-redheads so as to have the same clinical effect.

Likely reflecting their geographic ancestry and their fair skin, redheads produce more vitamin D than non-redheads. On the downside, they appear to be more susceptible to skin cancers, including melanomas, and to developing both Parkinson's disease and certain types of gynecologic cancer. Redheads *smell* different than non-redheads, perhaps a consequence of their having a slightly more acidic skin mantle. In 1886 one early physician investigator declared that redheaded women emitted a distinctive and singularly "intoxicating" aroma.

There may be a bit of truth to the previously described cultural characterizations of redheads. Although such variables are not simple to assess objectively, there are data to suggest the redheads are more emotionally reactive than non-redheads. Interestingly, in terms of other societal perceptions, studies have demonstrated that redheads are judged by others to be approximately two years older than their chronologic age when compared with non-redheads. While female redheads often have been characterized as "promiscuous" and "sexually liberated", in one controlled study young males were most likely to solicit attention from blond females and least likely to solicit redheads. In what would seem somewhat incongruent with that result, a 2014 study found adult female redheads to be disproportionately overrepresented in primetime television commercials. Finally, redheads commonly have been said to possess a higher tolerance for alcohol, but the evidence to support that particular trope is thin to none.

More relevant to the issues considered here, investigators have reported that female redheads have a higher libido and engage in more heterosexual intercourse than non-redheads. Whether or not they tend to have more offspring than non-redheads is still not well-established, but in in one epidemiologic survey of redheaded female Czechs and Slovaks the redheads had more offspring than

non-redheads, and at least one other study confirmed that finding in a different ethnic population and also found that redheads began having children at an earlier age.

If female redheads are more "sexual" than non-redheads and possibly more likely to procreate, this naturally leads to a number of questions:

- I*s the prevalence of female redheads increasing, as it appears to be for female migraineurs?* Although some authors have suggested that it is, no clear and convincing data have emerged to confirm their claim.

- *Is there a correlation between redheadedness and migraine prevalence? Put another way, are female redheads more likely to have migraine than female non-redheads?* Again, not clear. What we do know is that the prevalence of redheadedness increases significantly as one moves into and through northern Europe, the ultimate ancestral home of most redheads. We also know that investigators have reported the prevalence of migraine to be 3.5 times higher in women with fair skin and a lower "melanin index"…both highly characteristic of redheads. This increase in migraine prevalence appears to be linked to a relative deficiency of eumelanin, and as already noted redheads are relatively deficient in eumelanin.

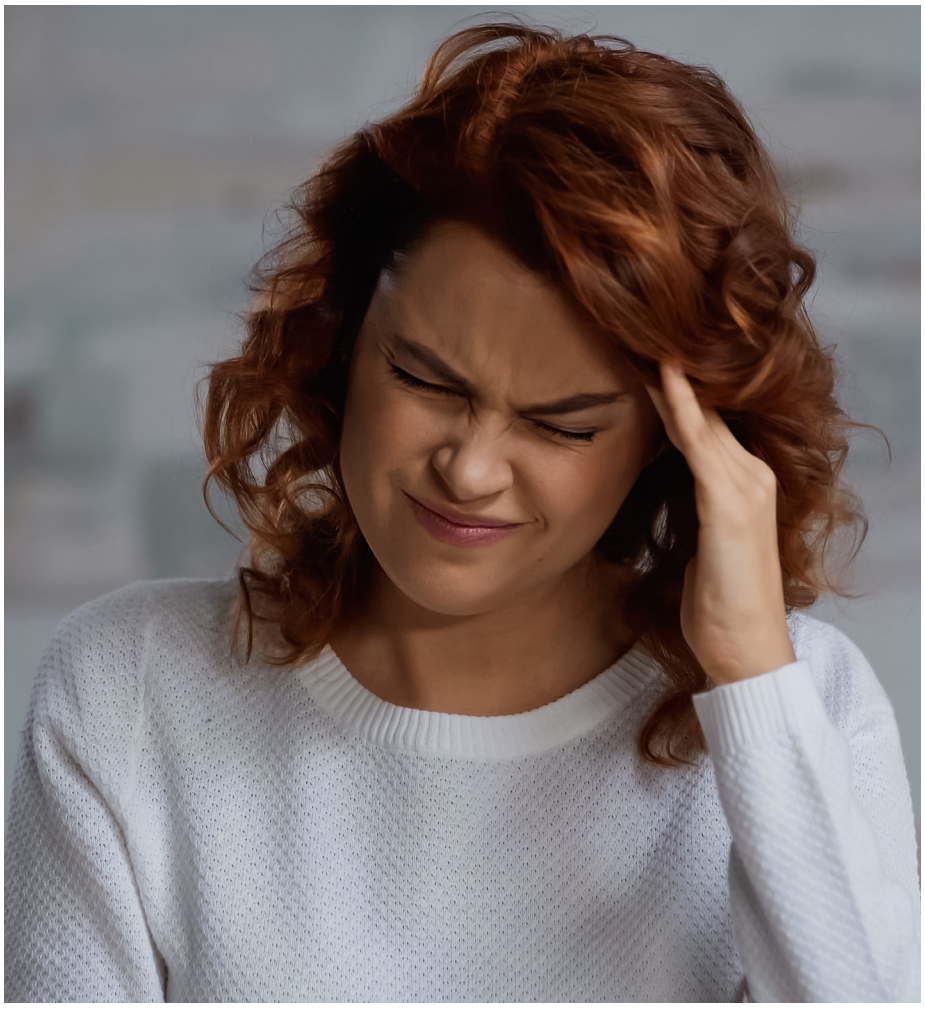
  In our study referred to at the outset of this article we unfortunately did not record hair color, and so from our relatively small population of research subjects with migraine we cannot offer any insight as to whether redheads do or do not have a predilection for migraine.

- *If the global prevalence of migraine in females is increasing, are redheads making a making a significant and disproportionate contribution to that increase?* Probably not. In the study referred to earlier, an increase in migraine prevalence was observed in females even in African countries where native redheads are scarce.

  There are those who believe things happen for a reason and those who believe things…just happen. The former can be divided into those who take a faith-based approach that implies intervention via a power that lies beyond our ability to know and those who believe in science (with the caveat that believing in the scientific method does not by any means ensure ultimate discovery of "the reason").

As for me, while I believe, as Loren Eiseley wrote, that "if there be magic on this planet, it is contained in water", and although I fully acknowledge there may exist much in this life that we are not given to know, I am more inclined to preoccupy myself with science than magic. It is intensely curious to me that the global prevalence of female migraineurs seems to be increasing. I find it intriguing to hypothesize that natural selection may be favoring migraine and, in particular, redheaded female migraineurs. Now all I have to do is prove it.

Disclaimer:
Given that he has been long and happily married to a female redheaded migraineur, the author cannot exclude the possibility that his observations and hypotheses may possess some small measure of bias.



Of Lids, Brows and Botox

Cosmetic considerations when receiving Botox for chronic migraine

Your editor recently spent his Saturday in a DFW airport hotel conference room in the company of a group of cadavers, learning how to avoid and treat cosmetic complications of onabotulinumtoxinA (BotoxA) administered for prevention/suppression of chronic migraine. Not precisely his idea of the perfect way to spend a Saturday but nevertheless productive.

The training session was supervised by Dr. Andy Blumenfeld, an old friend and colleague who is director of the Headache Center of Southern California. It was Dr. Blumenfeld who first Instructed me in the administration of BotoxA for chronic migraine over 20 years ago. I subsequently have treated thousands of patients with BotoxA and have conducted a fair amount of clinical research involving BotoxA and chronic migraine, but even after all these years I still find I can learn something new from Dr. B (see this issues "Migraine Tip of the Month".

BotoxA is a remarkably "clean" therapy for suppressing chronic migraine. Over the 20+ years I have been administering the neurotoxin, about the only side effect I have encountered is ptosis (eyelid droop) which in my population of patients complicates less than 1% of treatments but in clinical trials involving Botox for chronic migraine was reported to occur in as many as 4% of patients receiving Botox. Ptosis can be quite mild and is inevitably transient, reversing as the BotoxA effect wears off over a period of weeks, but it can be distressing for patients nonetheless.

The ptosis most commonly associated with BotoxA therapy is "brow ptosis", occurring when Botox is injected into the frontalis muscle that acts to elevate the eyebrow (see Figure 1). If the frontalis injections are made too low in the forehead or the neurotoxin diffuses down to the lower portions of the muscle even when injected high, the muscle loses its tone and "slumps". This causes asymmetry of the brows and excess tissue overhanging the eye. The brow ptosis may involve only the medial portion of the brow or the entire brow, medial and lateral. Notice in Figure 2 that especially with the complete brow ptosis the left eyebrow clearly sits lower than

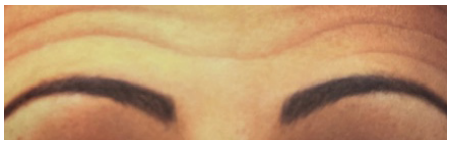


Fig 1 Contraction of the frontalis muscle elevates the eyebrows

the right…especially when the frontalis muscle is voluntarily contracted in the attempt to raise the eyebrows.

To avoid producing brow ptosis your

injector/provider will take pains to inject the frontalis muscle high in the forehead and well away from the eyebrows. He/she also will also take particular care in injecting the corrugator muscles that depress the

Fig. 2 Left brow ptosis, medial and complete

brows when you squint or frown (Figure 3), using a technique that minimizes the chance of BotoxA extending beyond the corrugator and into the lower portion of the frontalis muscle.

"Lid ptosis" is more cosmetically prominent and, happily, far less common. Compare the complete left brow ptosis in Figure 2 with the left lid ptosis in Figure 4. Notice how in lid ptosis the eyebrow elevates normally with contraction of the frontalis muscle while the lid remains "drooped". Although it long has been thought that lid ptosis resulted from diffusion of Botox inferiorly to paralyze the small muscles that elevate the eyelid, those muscles in fact are anatomically protected from downward diffusion of Botox. It now appears that in many cases what is believed to be a Botox-induced lid ptosis may in fact represent pre-existing and clinically mild lid ptosis made more apparent by Botox-induced brow ptosis (see paragraph below for more on this). To assist in differentiating lid and brow ptosis and specifically to determine whether some degree of pre-treatment ptosis may exist, we routinely obtain pre-treatment photographs to have available for comparison if treatment-related ptosis should occur. On those occasions when Botox does produce lid ptosis, there are eyedrops (apraclonidine) available that can serve at least partially to offset the ptosis.

Even when Botox is administered according to the paradigm proven to be effective for treating chronic migraine and recommended by the FDA, patients can be left with what some call the "Jack Nicholson effect" (I prefer to take a more positive approach and refer to it as the "Nicole Kidman effect"). This occurs because BotoxA partially paralyzes the muscle that elevates the medial portion of the eyebrow but allows the lateral portion to elevate as per normal. This can result in a transient facial appearance that some dislike intensely, some simply ignore and could care less, and a few actually find pleasing. if you fall in the first group, you can request that your provider/injector inject an additional small amount of Botox a bit more laterally in the muscle that elevates the eyebrow, taking care not to inject too low or too much (which can result in brow ptosis). With this result, neither eyebrow will elevate as high as it normally does, but the two brows will elevate symmetrically. A somewhat different technique can be cosmetically effective if there is prominent asymmetry of brow elevation, with one elevating normally and the other lagging behind.

Again, subtle pre-existing brow and lid asymmetries may be accentuated by administration of Botox for chronic migraine. The female photographed pre-Botox in the illustration introducing

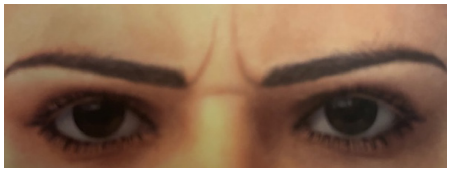


Fig 3 Contraction of corrugator muscles depresses the brows

> **BotoxA is a remarkably "clean" therapy for suppressing chronic migraine**

Fig 4 Left lid ptosis

this article has a naturally arched left eyebrow, and if you look closely you can see that her left upper eyelid comes down over the eye slightly more than its counterpart on the right; administration of Botox potentially may accentuate the asymmetry between the two brows or reduce it, depending upon where and how Botox is administered to the frontalis. If from Botox she should develop a brow ptosis on the left, it may combine with the slight pre-existing ptosis to mimic a lid ptosis.

All this said, BotoxA is a safe, effective and well-tolerated therapy for suppressing chronic migraine. Side effects associated with its use are rare, but to avoid cosmetic side effects in particular it is advisable to receive your treatments from a skilled injector experienced in performing the procedure.

Navigating Perimenopause/ Menopause with Migraines

The Highs and the Lows

Between the ages of 15 and 45 migraine is roughly 3 times more prevalent in females than males. Prior to puberty and following menopause this disparity is less apparent, and it's entirely possible that the genetic predisposition for migraine is just as common in males as in females.

So then what accounts for this the disparity in migraine prevalence during the childbearing years? In a woman's life, migraine tends to emerge or, if already present, worsen at several distinct times: menarche/onset of puberty, menses, the first trimester of pregnancy, the period immediately following childbirth and perimenopause/early menopause. Common to all of these times is an often dramatic fluctuation in the levels of sex hormones and in the level of estrogen in particular. Put another way, women may have no more of a genetic predisposition to migraine than men, but consequent to these hormonal fluctuations they are more likely to clinically express that genetic predisposition.

While for many women menopause may bring with it a dramatic reduction in migraine burden or even cessation of migraine, recall once again that the only "always" in migraine is that nothing about migraine is ever "always". There are women who may experience a significant worsening of migraine with perimenopause/ menopause, and there are even women who first begin to experience migraine after the onset of menopause.

Regardless, in the 20 issues of this magazine published to date we have devoted many pages to migraine and pregnancy and to menstrual migraine, but we have offered readers relatively less information regarding the impact of perimenopause/early menopause on migraine. With the help of our invited contributor who has much experience in this area, Ms. Caroline Stowe, we will begin our attempt to correct this deficiency.

For individuals experiencing migraines, the journey through perimenopause and menopause can present unique challenges. The hormonal fluctuations during this phase of life often influence the frequency, intensity, and patterns of migraine, making these years a significant challenge to navigate even for those already veterans of dealing with these debilitating headaches.

Several renowned figures have spoken candidly about their struggles with

menopause and the challenges posed by migraine during this phase of life. Here are two:

Michelle Obama The former First Lady has shared her experiences with menopause, highlighting its impact on both physical and emotional well-being. She addressed the changes in her body, emphasizing how her migraine episodes became more frequent and intense during menopause.

Gwyneth Paltrow Known for her holistic lifestyle approach, Paltrow has openly discussed her menopausal symptoms. She has emphasized the importance of seeking therapies that will reduce the impact of menopause on one's daily life.

Understanding Perimenopause and Menopause

Perimenopause marks the transitional phase before menopause and is characterized by hormonal fluctuations and irregular menstrual cycles. As estrogen and progesterone levels fluctuate, these changes can trigger migraines in those who are predisposed. Menopause, defined as the cessation of menstrual periods for 12 consecutive months, occurs around the age of 51 on average, but the hormonal changes can begin earlier, during perimenopause. Naomi Watts recently spoke out about her experience with perimenopause and migraine, emphasizing how she felt very alone during that time and how much better she might have felt if perimenopause was a more prominent public topic.

Impact on Migraine

Hormonal fluctuations play a pivotal role in triggering migraine. Estrogen is known to affect neurotransmitters, blood vessels, and pain perception, all which can influence the experience of migraine. During perimenopause and menopause, the erratic hormone levels may lead to increased migraine frequency, increased headache severity or other changes in migraine symptomatology for some.

Positive Aspects of Perimenopause/Menopause for Migraine Sufferers

1. Reduced Frequency Some (but definitely not all) lucky women experience a reduction in migraine frequency or intensity during menopause. This is attributed to the stabilization of hormone levels that occurs post-menopause, providing welcome relief for those migraineurs who have suffered from the disorder for much of their lives.

2. Freedom from Menstrual Migraines Women who regularly have experienced

menstrual migraine often find welcome relief as their periods cease during menopause. For them, the absence of the hormonal fluctuations associated with menstruation removes that unhappy headache week from their monthly calendars.

3. Potential Treatment Options Healthcare providers may suggest hormone replacement therapy (HRT) or other medications to manage menopausal symptoms for qualifying candidates who do not have contraindications for HRT. These treatments can affect migraine positively or negatively, and their use requires careful consideration and subsequent monitoring by your healthcare provider.

   In May of this year, the FDA approved the first non-hormonal drug to ease menopause hot flashes. The new pill, called Veozah (fezolinetant), is from a class of drugs called neurokinin 3 (NK3) receptor antagonists. This is exciting as women who experience migraines are more likely to experience vasomotor symptoms during menopause.

Challenges

1. *Change in Migraine/Change in Treatment*

   What therapies that have "always" worked for your migraine may not work as well during menopause. There are both preventive and abortive treatments appropriate for use in cases of post-menopausal migraine, and the number of monthly headache days you are experiencing, the intensity of your headaches, your associated migraine symptoms and your medical history will influence the management plan you and your healthcare provider develop.

   Regardless, I tell each such patient that there's light at the end of the tunnel. Approximately 70% of patients will experience a decline in their migraine burden as they settle into menopause.

2. *Increased Migraine Frequency*

   For many, perimenopause can be a period of heightened migraine activity due to hormonal fluctuations. This

Hormone replacement therapy (HRT)... can affect migraine positively or negatively

can be frustrating and challenging to manage alongside other menopausal symptoms, and it may be time for a course of prevention therapy to stabilize your migraine and reduce headache burden.

3. *HRT and Migraines*

   Hormone replacement therapy, while helpful for managing menopausal symptoms, can sometimes exacerbate migraine. Finding the right type, dose and preparation of HRT requires consultation with a knowledgable and sympathetic healthcare provider.

4. *Altered Migraine Pattern*

   Some individuals may notice changes in their typical migraine pattern during menopause. This shift may involve different triggers or new symptoms, and amongst the new symptoms many women experience is the first emergence of aura (most commonly visual) or, more often, resurgence of aura after its absence for many years. Benign aura symptoms may be misinterpreted by patients and clinicians as "mini-strokes", a diagnostic wrong turn that can produce much unnecessary anxiety and expense.

   Coping Strategies and Management: Healthy Lifestyle Prioritize regular exercise, balanced nutrition, adequate sleep, stress management, and hydration to help manage migraines during this phase. There is very little more important to brain health than regular exercise.

   Track and Monitor Keeping a migraine diary can help identify triggers and patterns specific to perimenopause/menopause, aiding in the development of management strategies tailored to your specific needs.

   Consult Healthcare Providers Seek guidance from healthcare professionals with experience in managing both migraine and menopause so as to construct a "customized" management plan.

Conclusion

Perimenopause and menopause can significantly impact individuals already dealing with migraine, bringing some relief and others new challenges. Understanding the hormonal shifts that are occurring and how they influence migraine can empower you to seek, find and implement an effective management strategy so as to navigate this transitional phase with more comfort and control.

Resources for learning more:

https://www.fda.gov/consumers/womens-health-topics/menopause

https://americanmigrainefoundation.org/resource-library/migraine-and-menopause-webinar-recap/

https://www.migrainedisorders.org/education/patient-resources/

https://drsusanhutchinson.com/books/

Caroline Stowe

The author, Caroline Stowe, DNP, MSN, FNP-BC, AAHIVS, AQH, MSCP, trained at the College of Charleston, the Johns Hopkins University, and George Mason University. She has been practicing as a family nurse practitioner for over 14 years and has a specific interests in telemedicine, primary headache disorders and sexual/reproductive health, including menopause. Ms. Stowe is a member of the faculty at the George Mason University School of Nursing in the MSN-FNP program and lives in Fairfax, VA with her husband and 2 children.

Shout Out

M&N's Pizza Redux

Some years ago the ***Migraineur*** team established the tradition of giving "shout-outs" to interesting individuals, very special businesses and just plain beautiful natural settings that we have been lucky enough to come upon and wanted to share with our readership.

The recipients of our shout-outs have been a varied lot: a wonderful Croatian artist in Dubrovnik; The Chile Shop in Santa Fe; a surfing neurologist in Encinitas, California; the C&O Canal towpath that runs from Cumberland, Maryland to and through Georgetown… and many more. In this issue we return to a previous "Shout-Out" to celebrate a happy and well-deserved honor recently bestowed.

In the Fall 2022 issue we featured a local favorite, M&N's Pizza, fortuitously located just down the road from the ***Migraineur*** headquarters here in Bethesda, Maryland. Since 2006, 10 years prior to the inception of ***Migraineur***, Manoj and Nazaneen Mehta, the husband and wife who developed M&N's, have been gifting this region with some of the most uniquely delicious pizza and other offerings you could ever hope to bring home to enjoy after a long Friday at work.

We are so pleased to share with the readers the most excellent news that M&N's was listed this year by ***Yelp*** as 82nd amongst America's top 100 tastiest and most popular restaurants!

Congratulations to Manoj and Nazaneen, two of the most pleasant and hardest-working individuals this magazine's editor has ever been fortunate to know.

If you are ever in the metro DC area, do yourself a favor and pick up a couple pies and a gyro or two at M&N's:

4914 Del Ray Ave, Bethesda, MD 20814

(301) 656-6262

www.mandnspizza.com

Migraine Treatment of the Month

A Vyepti "Real World" Update

Epitenzumab (*Vyepti*) was highlighted in this magazine as a "migraine treatment of the month" in the Fall 2022 issue. To summarize, Vyepti is an anti-CGRP monoclonal antibody that, in the manner of a good marriage, binds long and with powerful attraction to the CGRP protein molecule; this binding prevents CGRP from docking with its receptor within the migraine circuitry and consequently "rheostats down" the sensitivity of that circuitry and so reduces headache production. To stretch the analogy even further, Vyepti and the CGRP protein molecule to which it binds so strongly require only a very short engagement before the marriage commences. Because the medication is infused intravenously (every three months), it is 100% "bioavailable" immediately post-infusion. In summary, then, Vyepti is designed to have high selectivity specifically for the CGRP molecule, strong and prolonged binding to that molecule and a rapid onset of that binding process.

So how did Vyepti perform in clinical research trials involving individuals with migraine? The PROMISE-1 and PROMISE–2 studies clearly established Vyepti to be safe, well-tolerated and effective for migraine prevention in research subjects with episodic migraine (PROMISE-1) and chronic migraine (PROMISE-2). In the chronic migraine study more than 60% of the patients randomized to Vyepti had experienced at least a 50% reduction in their migraine burden by 3 months following their initial infusion treatment. Testifying to the rapidity of the medication's action, separation from placebo was observed as early as 1 day following the initial infusion. While research subjects randomized to Vyepti continued to experience an improvement in their migraine over the six months of study, the most striking decline in headache occurred early on, during the first month following the initial infusion. The only adverse reactions that occurred more commonly in the research subjects receiving Vyepti versus those receiving placebo were nasopharyngitis or related to hypersensitivity. In short, Vyepti appeared to be a remarkably "clean" therapy in terms of its side effect profile.

These large-scale phase 3 trials which earned Vyepti its FDA approval for the treatment of episodic and chronic migraine were meticulously conducted by experienced clinical investigators. How does Vyepti hold up when it is used as a treatment for migraine prevention in the "real world"? It is in the "real world" of clinical practice, where the "science" of medicine smacks head-on with the "art" of medicine, that we learn really how much or how little a new addition to the therapeutic arsenal will mean to us, the healthcare providers, and to our patients. If unexpected side effects, hurdles erected by insurance companies more intent on the financial bottom line than their clients' best medical interests or one of the countless other issues that can arise serve to dim the luster of a new treatment when one leaves the rarified atmosphere of clinical research for the day-to-day slog of clinical practice, the pragmatic usefulness of a new treatment can diminish considerably.

The REVIEW study was conducted specifically to determine just how well

Vyepti would hold up as a new treatment for the suppression of chronic migraine. In REVIEW, 94 adult participants with chronic migraine were treated with at least two consecutive Vyepti infusion cycles. These patients all had previously tried and failed prevention therapies intended to reduce their migraine burden, and the great majority (89%) previously had tried one of the subcutaneously self-injected anti-CGRP monoclonal antibodies. In other words, this was a tough group of chronic migraine patients who were hardly treatment-naïve and thus inclined to respond to *any* reasonable treatment intervention. They were not "cherry-picked" so as to make Vyepti look good.

"brain fog" improved in 86%

So what happened? The average number of "good days" per month prior to initiation of treatment with Vyepti was 8, and this increased to 18 after Vyepti was begun. The majority of the participants were over-using either prescription or over-the-counter medication for acute migraine treatment prior to beginning Vyepti. After starting Vyepti nearly 2/3rds of those patients no longer were over-using symptomatic medication.

Perhaps most interesting to the author of this article, prior to beginning Vyepti 80% of the participants reported "brain fog", and following initiation of treatment that symptom improved in 86%. Until he began helping with the clinical development of topiramate (*Topamax*) for migraine prevention in the early 2000s, the author had never heard the term "brain fog" used by patients. Topiramate clearly can produce a variety of cognitive side effects that many patients rapidly came to refer to as "brain fog", and the term literally assumed epidemic proportions with the arrival of Covid. Topiramate and Covid aside, many patients with chronic migraine describe impaired cognition, and typically that impairment resolves in parallel was successful treatment of their chronic migraine. To the authors knowledge, REVIEW represents the first migraine treatment study wherein "brain fog" was included as an outcome variable to be examined, and it is extremely good news to learn that Vyepti may be helpful in dissipating that "fog".

The "real world" verdict? Vyepti is a safe and extremely well-tolerated prevention therapy for high frequency episodic migraine and chronic migraine which substantially reduces migraine burden in a high percentage of patients and often begins to do so quite rapidly after initiation of treatment. It even appears to reduce or eliminate the "brain fog" which may complicate chronic migraine! In his clinical practice the author/editor considers Vyepti to represent a 1st line therapy for suppression of chronic migraine.

Another Migraine Revolution!

Exciting New Prevention Therapies in Development

Within the last 3 decades there have been 3 revolutions in migraine therapeutics. The first occurred in the early 1990s, when injectable Imitrex was introduced in the US and triggered the Triptan Revolution. That seismic event opened the door to our recognizing migraine to be a biologic disorder that was eminently treatable if the right pharmacolgic key could be designed to fit the disorder's biologic lock. It is hard to overestimate the impact made by the triptans on public and professional interest in the biology and treatment of migraine.

In the early 2000s a second and less heralded but nevertheless significant therapeutic revolution occurred with the simultaneous identification of chronic migraine, as a common and important variant of migraine and onabotulinumtoxinA (BotoxA) as an effective therapy for suppression of chronic migraine.

On the heels of the Botox Revolution came the identification of calcitonin gene-related peptide (CGRP) as an important component of the biologic circuitry that generates migraine, and shortly following this discovery came the introduction of the anti-CGRP monoclonal antibodies and gepants for migraine prevention (both episodic and chronic) and acute migraine treatment.

To focus on chronic migraine specifically, despite the disorder's high prevalence and disproportionate share of the adverse impact migraine imposes on the public health, prior to 2010 there existed no evidence-based therapy for its management. Courtesy of the BotoxA and CGRP Revolutions, by 2022 healthcare providers and their patients had available to them for treatment of chronic migraine no less than 6 evidence-based therapies of proven safety, high tolerability and clear effectiveness.

Now we are on the cusp of a fourth revolution in migraine therapeutics. There are about to commence large scale, multi-center studies investigating abobotulinumtoxinA (*Dysport*) as a potential alternative to BotoxA for suppression of chronic migraine; in addition, this neurotoxin is being evaluated for its utility in treating episodic migraine as well (BotoxA is not currently indicated for episodic migraine: ie, migraine with <15 days of headache per month). Pilot studies have indicated that prophylactic polytherapy – combining two evidence-based treatments – and specifically adding erenumab (*Amovig*) or atogepant (*Qulipta*) to BotoxA potentially may be synergistic in suppressing chronic migraine. There is now a large scale, multi-center research study (UNCHAINED) now in progress that is examining the safety, tolerability and effectiveness of adding Qulipta to the treatment regimen of patients already receiving BotoxA.

Yet another component of this fourth revolution in migraine therapeutics may be the most interesting of all. Investigators have identified another protein target within the migraine circuitry that offers an entirely new way of attempting to reduce the activity of that circuit and thus reduce migraine burden. This protein, pituitary adenylate cyclase-activating polypeptide (PACAP) represents a therapeutic target distinct from CGRP. A neutralizing monoclonal antibody directed against PACAP and now being investigated in the migraine population may represent an effective alternative for the ~40% of migraine patients who require prevention therapy and fail to respond to the anti-CGRP drugs. In addition, PCAP may be especially abundant in the hypothalamus of the brain. The hypothalamus is believed by many to be the source of the prodromal symptoms experienced by so many migraineurs and, for some, as or more distressing than the headache of migraine. A therapy that inactivated or blocked PACAP theoretically could reduce or eliminate migraine prodrome, a feature which would make that therapy unique amongst the migraine preventatives.

It is - yet again - an exciting time to be involved in migraine research. Stay tuned for more.

Migraine Myth of the Month

Migraine Always Improves During Pregnancy

As with all matters migraine, the problematic word in the title of this month's myth is "*Always*". It can never be emphasized enough: the only thing "always" about migraine is that no aspect of migraine is ever "always".

The female preponderance of migraine between the ages of 15 and 45 is widely believed to reflect the impact of the monthly fluctuations in sex hormones – especially estrogen – that occur in cycling females. Prior to puberty and following the age when menopause tends to occur, the inequity in migraine prevalence between the two genders flattens out considerably. If migraine is indeed typically, if not always, genetic in origin, it is quite possible that the genetic prevalence of migraine is more or less equal in males and females but that the clinical expression of migraine will be greater in females during their childbearing years consequent to the excitatory effect of fluctuating sex hormone levels upon migraine's biologic circuitry.

There are certain times during a female's life when migraine tends to either arise or, if already present, worsen: menarche (the onset of puberty), menses, first trimester pregnancy, the immediate post-partum period and the perimenopausal years. Common to all are the associated changes in sex hormone levels, and it would seem to follow that the stabilization of sex hormone levels that occurs with pregnancy would be paralleled by a progressive reduction in migraine.

While it is *generally* true that the clinical expression of migraine declines as pregnancy advances and even may be absent altogether during pregnancy, this is far from invariable. A significant minority of migraineurs report no change in their migraine burden with pregnancy. At least 1 in 20 female migraineurs experiences worsening of her migraine during pregnancy, and for some this may persist throughout the full term. Some of the most miserably ill patients that the author has encountered in his clinical practice have been pregnant females literally sick with migraine every day for months on end. Some females may experience their first-ever migraine headaches while pregnant, and some may experience migrainous aura, with or without associated headache, for the first time.

How does one treat a pregnant female's migraine effectively without potentially causing harm to the fetus? What therapies are known to be "safe" for use during pregnancy? Good questions. Surveying the medical literature to find well-designed prospective studies evaluating the safety of a given migraine therapy in pregnancy is about as futile as searching for a cool freshwater lake in the Sahara. This issues Doctor on Call summarizes the path typically traveled before a new migraine medication comes to be regarded as "acceptable" for use in pregnancy, a consideration of acceptable therapeutic options, and a bit about onabotulinumtoxinA (BotoxA) in particular.

A last word. In no circumstance does a history of migraine guarantee that every headache a migraineur experiences is a consequence of migraine, and that applies in particular to pregnant migraineurs. For example, pre-eclampsia, a potentially quite serious multisystem disorder, can arise unexpectedly in the last half of pregnancy and often begins with persistent headache. While it remains unclear whether migraine may be associated with an increased risk of developing pre-eclampsia, it is a certainty that pregnant migraineurs can develop the disorder. If you are a pregnant migraineur and you experience a significant change in the character or frequency of your headaches – and especially if that change is accompanied by symptoms unusual for you such as visual blurring or focal numbness/weakness, *seek medical attention* so as to exclude pre-eclampsia and other serious headache-producing conditions that may complicate pregnancy.

Migraine Tip of the Month

Avoiding "Botox failure"

For reasons often not obvious or perhaps not even identifiable, a patient's migraine prevention therapy that has proven to be beneficial in keeping the migraine burden low for many months or even years rather abruptly can lose its effectiveness.

While this unhappy phenomenon rarely was observed in long-term clinical trials involving onabotulinumtoxin A (BotoxA) administered for suppression of chronic migraine and seldom has been experienced by patients treated in the author's clinical practice, the potential for this particular type of "Botox failure" does exist. Again, this is entirely different from an absolute failure to respond to BotoxA; more than a third of chronic migraine patients will report no improvement in their headache burden consequent to treatment with BotoxA. These are instead chronic migraine patients who have been doing quite well on BotoxA therapy for a year or more and then – for no obvious reason – experience relapse to chronic migraine despite continued treatment. Why might this be?

A goodly number of patients simultaneously receive Botox from different providers for different purposes, and in the population treated with BotoxA for suppression of chronic migraine by far the most common other purpose involves cosmetic therapy. Often the treatments are scheduled weeks apart from one another, and this can pose a problem.

The body's immune system is always on the alert for the intrusion of foreign proteins ("antigens"), and some medications are composed of proteins. If a "protein medication" is detected, the system may respond by producing "neutralizing antibodies" that inactivate the perceived invader. The Botox protein rarely evokes this neutralizing antibody response, but when it does this may affect the biological activity of the neurotoxin and negatively impact clinical response.

There is evidence to suggest that receiving multiple treatments with Botox on a schedule that permits only weeks – rather than months - to pass between treatments may increase the likelihood of a patient developing neutralizing antibodies that potentially may reduce or eliminate its therapeutic effect. If you simultaneously receive BotoxA from different providers for different clinical indications, care should be taken to consider the timing of treatments.

If you are receiving Botox both for cosmetic purposes and for suppression of chronic migraine, work with your providers to ensure that the two treatments are performed within no more than a few days of one another rather than weeks apart. While as much as 360 units of BotoxA may be administered safely within a given 12 week period, administering 155 units for chronic migraine and then after a period of a few weeks administering 40 units for cosmetic purposes may increase the chance of your developing neutralizing antibodies.

As in much of life, timing is everything.

Doctor on Call

Migraine therapy during pregnancy

Olivia, a 31-year-old environmental scientist who lives in Kensington, Maryland, writes:

Dear Doctor,

I just returned from seeing my neurologist, and I'm both confused and very alarmed. For the past two years she has been treating me for chronic migraine. After prescribing me multiple oral drugs that did nothing to help and often caused side effects that were worse than my headaches, she started administering Botox every three months. With Botox I was doing great! Rarely having headaches, and able to treat them easily when I did.

Anyway, suddenly and recently I found myself pregnant. My husband and I weren't really trying to have another baby, but we weren't really trying not to either. After I tested positive for pregnancy, I decided to skip my next Botox treatment, and within just two weeks of skipping that treatment I started having headaches all the time. I'm spending most of my time in bed or sitting in my bathroom trying not to vomit, and my head is throbbing so painfully I can barely think.

When I saw my neurologist today, she told me that the therapeutic effect of Botox had worn off and that I should be treated again as soon as possible. I thought she was kidding! Inject a neurologic toxin into me while I'm carrying a baby? No way!

Am I overreacting? Or is she crazy off-base?

— Pregnant with migraine in Maryland

The Doctor's Reply:

Dear Olivia,

You are not overreacting. You are behaving like a good mom and watching out for the safety of your child. And your neurologist is not "crazy off-base". She is attempting to reduce your migraine burden without exposing your baby to a known risk.

The path a given migraine therapy must travel to become regarded as "acceptable" for use – usually off-label use – during pregnancy is typically long and convoluted.

For example, as recently as 5 years ago, the author's suggestion to obstetricians that continued use of onabotulinumtoxinA (BotoxA) for chronic migraine patients whose migraine had persisted into pregnancy and had worsened off BotoxA routinely was met by expressions of horror. In contrast, many obstetricians now accept such management as quite acceptable and refer their chronic migraine patients who are attempting to conceive or are newly pregnant to the author specifically for BotoxA therapy.

Why? Has there been conducted a well-designed prospective clinical research study that specifically assessed the risk to the pregnancy and fetus potentially conveyed by sequential BotoxA injection therapy for suppression of chronic migraine during pregnancy? No, there has not. The path to the neurotoxin's acceptance for use during pregnancy has followed a familiar path, and one integral part of that path typically involves time. What might seem unthinkable when a new therapy emerges becomes less so as time passes and there is more and more experience with that therapy. BotoxA has been used for decades to treat various medical disorders, and 14 years have passed since Botox received FDA approval for the treatment of chronic migraine.

In parallel with time are pregnancy registries. Such registries typically are sponsored and maintained by the drug's

manufacturer, and they depend upon healthcare providers and their patients to report proactively clinical outcomes when there has been exposure to that drug during pregnancy, regardless of whether the exposure was intended or unintended. As such, pregnancy registries are susceptible to selection bias. Given that they depend on provider or patient inclination and initiative, they are not equivalent in scientific rigor to a carefully conducted prospective study that evaluates all pregnant females exposed to the drug. Even so, it is at least somewhat reassuring when there have been many thousands of such exposures reported and no signal indicating potential harm to the pregnancy or fetus has emerged. So has it been for Botox. And on the acute migraine treatment side, so has it been for sumatriptan, a medication available for use in the US since 1992.

Also helping to propel a therapy down the path to acceptance are published case reports and case series, the former involving single patients or small groups of patients and the latter assessing a larger group of patients. Especially compelling in the circumstance of female migraineurs exposed to Botox during pregnancy are 7 reported cases of pregnant females who suffered actual botulism poisoning during their second or third trimester and whose infants demonstrated no evidence of birth defects or clinical botulism; in one case wherein the mother had severe muscle paralysis, fetal movements were the only visible movements in her body. In one large case series of pregnant females treated with Botox that was published in the journal ***Neurology*** in May 2023 and involved over 900 pregnancy outcomes, the prevalence of fetal defect was 2.6%. For the general population that prevalence varies between 3 and 6%.

Finally, and particularly relevant in the case of BotoxA, there is basic pharmacology. The Botox molecule is large, and as was the case in the botulism suffered by the 7 pregnant females mentioned above, the molecule does not pass from mother to fetus in the placental circulation even when the mother's blood contains concentrations of the neurotoxin far in excess of what is administered to treat chronic migraine.

BotoxA aside, there are a number of therapies for migraine prevention and acute migraine treatment that can be considered "acceptable" for use during attempted conception and pregnancy. In some cases there appears to be near-zero potential for harm to the fetus, and this group would include acetaminophen, devices such as Nerivio, occipital nerve blocks, and "supplements" such as riboflavin and magnesium.

In a thankfully small handful of therapies that have a strong evidence base for use in migraine and are FDA-indicated for such use, the risk to a developing fetus is so unacceptably great that their use is *absolutely contraindicated* if one is at risk of becoming pregnant or pregnant. The most important example is divalproex sodium (Depakote) a medication indicated for migraine prevention, epilepsy and treatment of bipolar disorder. Especially during the first trimester of pregnancy, exposure to Depakote may cause horrific problems with the development of the fetus's brain and nervous system. Because women so often may not know they are pregnant during the first critical weeks of fetal development, no female at risk for pregnancy should take Depakote. Another widely used drug to be avoided if one is at risk for pregnancy is topiramate (Topamax), linked to a risk of cleft lip or palate.

In between these two extremes are a multitude of migraine treatments for which we have no clear evidence of risk to the pregnancy or fetus but also no definitive evidence of "no risk. For some, either because of their relative newness on the clinical scene, a theoretical risk associated with the drug's mechanism of action or both, these are medications better avoided unless the clinical circumstances to support their use are compelling. For others the risk would appear to be minimal at most, and BotoxA falls squarely within this group.

Your concern is both understandable and commendable, but your doctor's recommendation that you resume BotoxA is reasonable and clinically appropriate.

From the Patient's Perspective

The editorial office was fortunate to receive the poem that follows from a particularly articulate and insightful migraineur and scientist, Dr. Ena Bromley. We hope you like it as much as we have.

Pain

Slowly, as a leopard stalking its prey,
You appear in the dark of night,
Pounce onto your enemy,
and with evil intent drain its life away.

The beauty fades,
In a dark mist that fills the brain.
You rob the soul,
Of joy intended.

As the wind howls and gusts,
You come back.
Again and again.
You know no end.

Your journey is a winding path,
Your road is a cliff without guardrails,
There is no mercy, no relief.

Yet here it ends.
For you, pain is a narcissistic thief.
Mercy will steal your sword,
And grace will crush your feet.

Resolve will kill the leopard stalking in the night.
Joy will take your dark cloud and shine its light through it.
Kindness will calm your howling wind into a soft breeze.

You pain, have underestimated strength.
In your pride you overestimated your power.

There is a Love greater than your destruction.
There is a Mountain higher than your dwelling place.
There is a Beauty that will kill the evil beast.

Ena Bromley, PhD

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