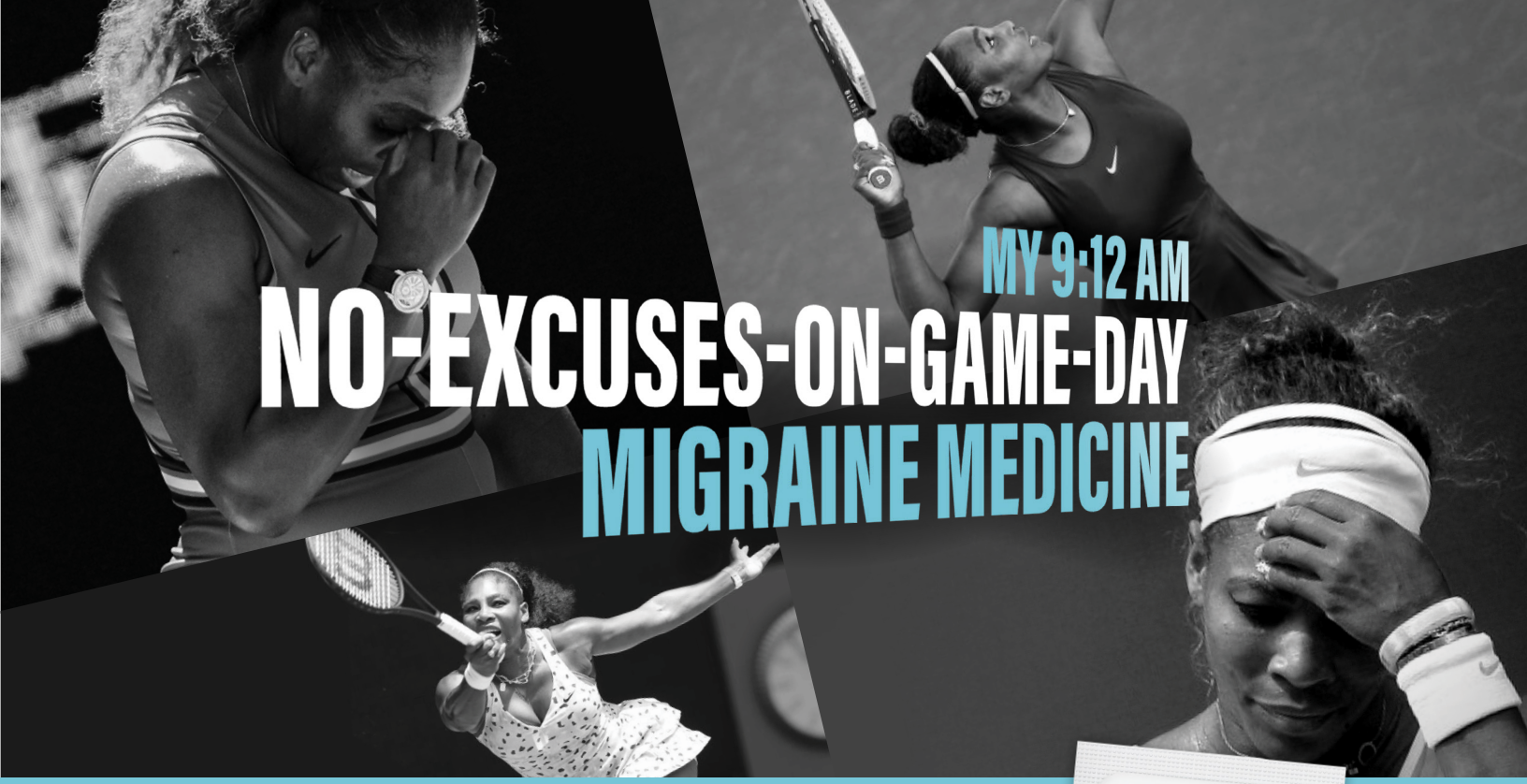
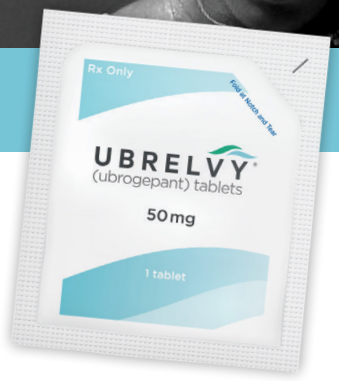


UBRELVY CAN QUICKLY STOP MIGRAINE IN ITS TRACKS.



When I took UBRELVY for the first time, I forgot I even had a migraine.
—Serena Williams

One dose of UBRELVY works fast. In clinical studies, many people had pain relief and some even had pain freedom within 2 hours. Unlike older medicines, UBRELVY directly blocks CGRP protein, which is believed to be a cause of migraine.

UBRELVY. The migraine medicine for anytime, anywhere migraine strikes, without worrying if it's too late to take it or where you happen to be.*

*People took UBRELVY within 4 hours of a migraine attack.

Eligible patients may pay as little as $0 a month†

ASK YOUR HEALTHCARE PROVIDER ABOUT UBRELVY.

LEARN MORE AT **UBRELVY.COM**.

What is UBRELVY® (ubrogepant)?
UBRELVY is a prescription medicine used for the acute treatment of migraine attacks with or without aura in adults. UBRELVY is not used to prevent migraine headaches.

IMPORTANT SAFETY INFORMATION

Who should not take UBRELVY (ubrogepant)?
Do not take UBRELVY if you are taking medicines known as strong CYP3A4 inhibitors, such as ketoconazole, clarithromycin, itraconazole.

What should I tell my healthcare provider before taking UBRELVY?
Tell your healthcare provider about all your medical conditions, including if you:
- Have liver problems
- 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?
The most common side effects are nausea (4%) and sleepiness (3%). These are not all of the possible side effects of UBRELVY.

You may report side effects to the FDA at 1-800-FDA-1088.

Please see full Patient Information on the following page.

†Patient out-of-pocket costs may vary. Terms and Conditions apply. This offer is only valid for commercially insured patients. Offer not valid for patients enrolled in Medicare, Medicaid, or other federal or state healthcare programs. Please see full Program Terms, Conditions, and Eligibility Criteria at UBRELVY.com.

UBRELVY® (ubrogepant) tablets

THE ANYTIME, ANYWHERE MIGRAINE MEDICINE

Mono-therapy vs Polytherapy:

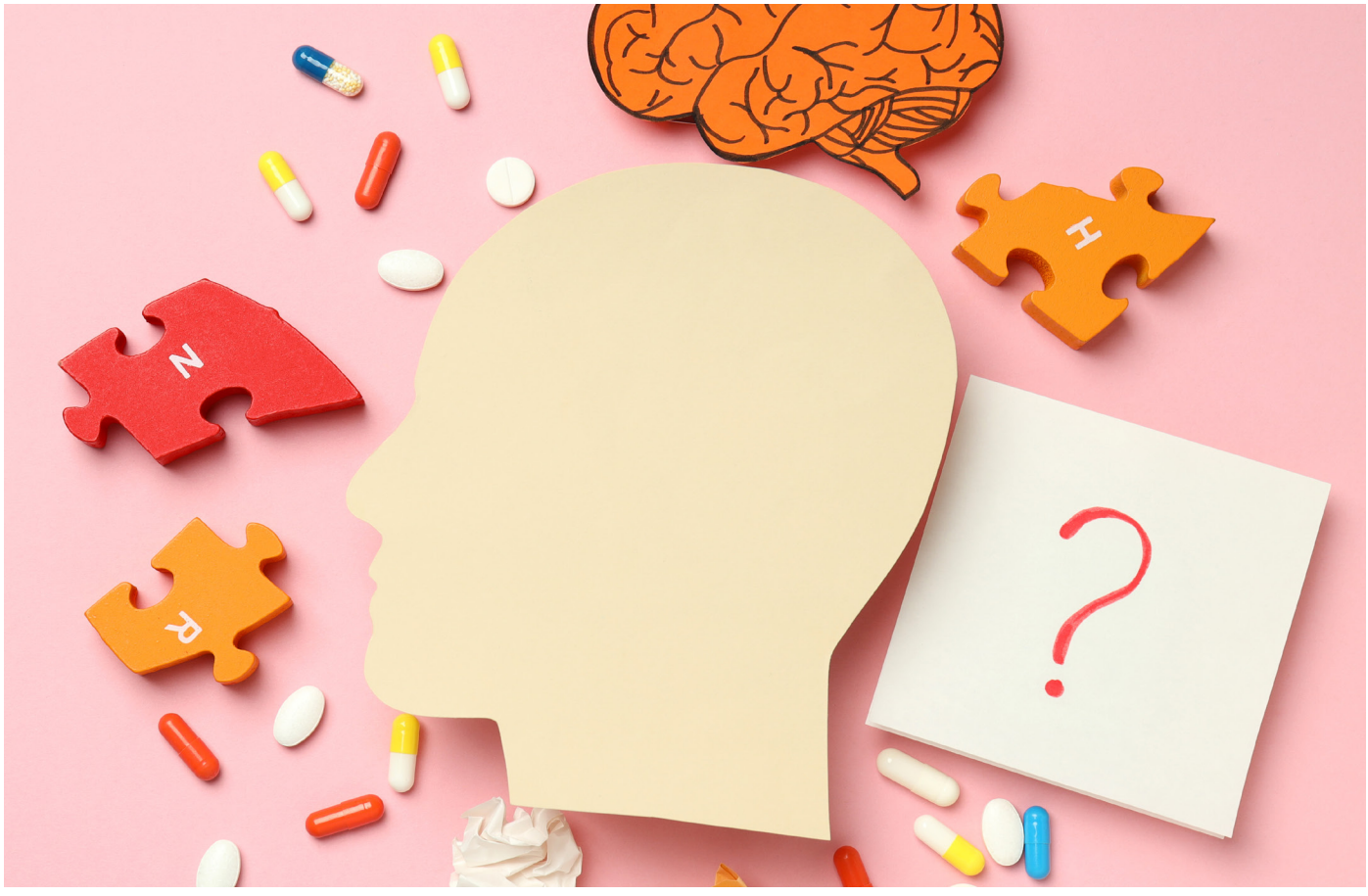
When is Two Better Than One?

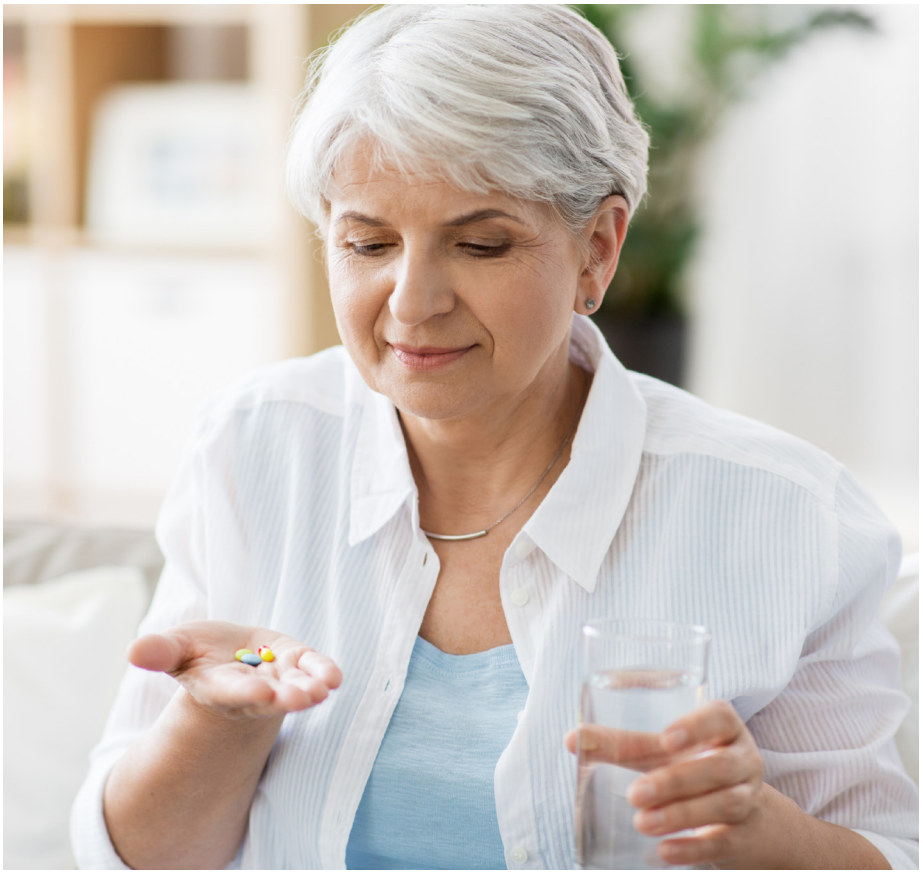
In the last issue of this magazine we focused on the relative attractiveness of the "old" medications for migraine treatment compared to the newer "designer drugs". In the end we offered the observation that "new" is not necessarily better than "old"...but that it's nice to have available to us an increase in the number of therapeutic options.

Why in 2022 do we find ourselves with an abundance of evidence-based *mono*-therapies for migraine prevention and acute migraine treatment but so very little in the way of evidence-based *poly*-therapies for such use? If migraine prevention drug X is helping to reduce a patient's migraine burden, could adding in prevention drug Y eliminate that burden altogether? Now receiving more attention is this question of whether combining two or more different medications (polytherapy) might in some circumstances provide an advantage over use of a single medication (monotherapy).

Why are there so few data available regarding the safety, tolerability and effectiveness of polytherapy? Much of the answer lies in the manner in which new medications for migraine are identified and developed. Not surprisingly, drug development in migraine therapeutics is almost entirely funded by the pharmaceutical industry, and the development process is a costly one. To gain FDA approval of a promising experimental medication for general clinical use requires years of time and millions of dollars. Along with pre-clinical studies involving lab animals and preliminary pharmacokinetic and safety studies involving healthy human volunteers, the company owning the drug in question must conduct *phase* 3 clinical trials that typically involve a randomized, double-blind, placebo-controlled and large-scale/multicenter study using a protocol deemed acceptable by the FDA, and the study's results receive careful scrutiny by the FDA prior to drug approval.

Post-approval/"post-marketing" *phase*





4 studies conducted after a migraine drug is approved for general clinical use typically are intended to evaluate issues not addressed in the phase 3 trials process, and on occasion a phase 4 trial may evaluate the new drug's safety, tolerability and effectiveness relative to another existing treatment (an *active comparator trial*), but large-scale and scientifically rigorous active comparator trials are few and far between, are not commonly found in the peer-reviewed medical literature and often do not convey the impact on clinical practice associated with phase 3 trials. Clinical neuroscientists interested in carefully evaluating the relative merits of, say, sumatriptan (*Imitrex*) versus rimegepant (*Nurtec*) may find it difficult to secure funding for that research. Pharmaceutical companies, for-profit corporations with an obligation to their employees and stockholders, have little incentive to underwrite an expensive phase 4 clinical research trial when the results might well show their drug is no better or, God forbid, inferior to a competitor's drug.

Thanks largely to the untiring efforts of certain highly motivated child neurologists/clinical neuroscientists sub-specializing in headache, the NIH did fund a large scale, multi-center study, CHAMP, evaluating the safety, tolerability and effectiveness of topiramate versus amitriptyline versus placebo as preventive therapy for migraine in the pediatric and adolescent migraine population (ages 8-17). That study demonstrated no clear difference between the two drugs; neither drug was more effective than placebo, and both active drugs caused more side effects than placebo. Disappointing.

Allergan (now AbbVie) funded and supervised the FORWARD study, a comparison of onabotulinumtoxinA (BotoxA) versus the immediate release (IR) formulation of topiramate for the prevention/suppression of chronic migraine (CM). The study demonstrated topiramate to be at least as effective as BotoxA in reducing headache burden but much less well tolerated. When those two endpoints - effectiveness and tolerability – were blended, BotoxA clearly emerged as the more desirable therapy of the two. In a more recent trial (HER-MES) sponsored by Amgen (owners of erenumab/*Aimovig*) investigating Aimovig versus topiramate IR for prevention of both episodic and chronic migraine, Aimovig proved to be the much more tolerable treatment of the two and more effective than topiramate IR as well. Given the results from CHAMP, FORWARD and HER-MES, it's not easy to explain why topiramate IR continues to be prescribed so frequently for migraine prevention.

But that's still dealing with the effectiveness of one monotherapy vs another; none of these trials addressed the issue of monotherapy versus polytherapy. There are a number of much smaller and otherwise less scientifically rigorous studies published in the peer-reviewed medical literature which have suggested that the combination of two prevention drugs for migraine may be superior to one alone. More recently and arguably more relevant to the current management of migraine are the so-called "add-on" trials, wherein patients receiving a given medication for migraine prevention and experiencing a partial positive therapeutic response to the therapy are

It's not easy to explain why topiramate IR continues to be prescribed so frequently for migraine prevention.

prescribed a second prevention medication. At least two studies whose results were published in the peer-reviewed medical literature indicated that the addition of Aimovig to the migraine prevention regimen of CM patients who already were receiving serial BotoxA injection therapy appeared to be safe and to yield a further reduction in headache burden.

In a recent single-center study whose results will be presented at the upcoming Migraine Trust meeting in London investigators found that the addition of Qulipta to patients experiencing a partial positive response to serial Botox injection therapy similarly appeared to experience a further reduction in headache burden.

If medications for acute migraine treatment are considered, there is even less evidence available to settle the monotherapy versus polytherapy question. From relatively small case series it appears that the addition of a nonsteroidal anti-inflammatory drug (NSAID: egs, ibuprofen, naproxen sodium) to an oral triptan (egs, sumatriptan/*Imitrex*, rizatriptan/*Maxalt*) is more effective in treating acute migraine headache then either of the drugs, NSAID or triptan, taken alone. A compound drug containing an efficiently absorbed formulation of oral sumatriptan along with a dose of naproxen sodium and initially marketed as *Treximet* offers the benefit of such polytherapy in a single tablet, but this compound has not been proven to be superior to both of its components taken independently but simultaneously (put another way, we don't really know if taking the compound is any more effective or better tolerated than taking generic oral sumatriptan and two or three doses of over-the-counter *Aleve*).

Will an NSAID similarly enhance the effectiveness of newer medications for acute migraine treatment such as ubrogepant (*Ubrelvy*) , *Nurtec* or lasmiditan (*Reyvow*)? At this point, we just don't know.

> **Migraine polytherapy presently is in large part terra incognita.**

To summarize, migraine polytherapy presently is in large part *terra incognita*. If you and your healthcare provider are considering polytherapy for migraine prevention, acute migraine treatment or both, and if the safety and effectiveness of the polytherapy under consideration have not been well-established, there are several general issues to be considered:

- Is there the potential for any adverse interaction between the two drugs?
- Are you taking any other medication, either for migraine or another medical condition, which might have the potential to interact adversely to the new medication being added to its "partner" medication?
- Does simultaneous use of the two drugs make sense? Put another way, is it likely that these two drugs will complement one another by virtue of attacking migraine from different directions because each possesses a different mechanism of action?

If the answers to these questions are no/no/yes, respectively, and you are not satisfied with your current degree of migraine control, then polytherapy may be a path worth taking.