The New "Designer Drugs" for Migraine

Upsides and Downsides

Acute headache: triptan, gepant or ditan? or just three aspirin and a cup of coffee?

Prevention therapy needed: intravenous anti-CGRP monoclonal antibody? or just a humble old (and less expensive) generic beta blocker like propranolol?
Is newer better, or just…newer?

While 2022 arrived bearing a host of concerns and uncertainties that any sane person would prefer to have evaporated in the year preceding, there is one indisputable and welcome fact for the 12% of our population actively afflicted by migraine: in the past 3 years the list of evidence-based therapies for migraine treatment has continued to expand dramatically.

Until the arrival of sumatriptan (Imitrex) 30 years ago, all of the medications used for acute migraine treatment or migraine prevention initially had been developed for treating other disorders (depression, high blood pressure, epilepsy, etc.) and subsequently were found to be helpful for migraine as well. The triptans, however, were synthesized specifically to "fit" what was felt at the time to be the biologic circuitry that generated migraine. The success of injectable Imitrex fueled the development of multiple triptans that could be taken orally, as nasal sprays, and as an inhalant for treatment of acute migraine headache.

Yet more important, the clinical and commercial success of the triptans produced an unprecedented enthusiasm for understanding migraine, diagnosing migraine and developing other "designer" therapies for subduing migraine. The triptans ignited A Migraine Revolution! which has persisted up to the present.

May 2018 brought to the US market the first designer drug for migraine prevention: erenumab (Aimovig). Whereas the triptans target serotonin receptors within the migraine circuitry, Aimovig and its cousins target a different protein molecule, calcitonin gene-related peptide (CGRP) or its receptor. There are now 6 anti-CGRP medications that possess an FDA indication for migraine prevention, and all are in wide use.

Is erenumab (Aimovig) "better" than, say, topiramate (Topamax)? Topamax is an oral medication that was developed to treat epilepsy but subsequently, in 2004, also FDA-approved for migraine prevention, and it continues to be prescribed frequently for migraine. In the absence of head-to-head active comparator studies where one therapy is prospectively evaluated against the other, it obviously can be difficult to say with confidence which therapy is "better". Well-designed and conducted active comparator trials are relatively rare… and for good reason. The vast majority of research in migraine therapeutics is funded by the pharmaceutical industry, and what drug company in its right mind would want to spend millions of dollars conducting a study that potentially could demonstrate its spanking new (and expensive) therapy is really no better than the old (cheaper) stuff?

And yet, from time to time such studies are conducted. One interesting "real world" study, FORWARD, whose primary results were published in 2019, showed that for suppression of chronic migraine Topamax appeared to be just as effective as onabotulinumtoxinA (BotoxA) but that the side effects associated with Topamax were so common and so bothersome that relatively few patients could tolerate the drug. When tolerability and effectiveness

were combined, BotoxA was clearly the more effective of the two therapies.

In a more recent study, HER-MES, involving patients with both episodic and chronic migraine, investigators evaluated the effectiveness and tolerability of Topamax vs Amivig. As in FORWARD, patients randomized to receive Topamax had a difficult time tolerating the drug; almost 40% discontinued Topamax therapy due to adverse events (4 times the rate of Aimovig discontinuation). In addition, patients randomized to Aimovig were more likely to achieve a meaningful reduction in migraine burden compared to those taking Topamax.

So, there is pretty solid evidence that a) for chronic migraine BotoxA is more likely to be an effective prevention treatment intervention than is Topamax, and b) that Aimovig outperforms Topamax for both episodic and chronic migraine. And that's about it.

How do the other new prevention therapies stack up against one another? How about the other 2 subcutaneously injected anti-CGRP monoclonal antibodies (mabs) and epitenzumab (Vyepti), the intravenously administered mab? Or the newest arrival for migraine prevention: atogepant (Qulipta), an anti-CGRP "gepant"? Or rimigepant (Nurtec), the hybrid oral disintegrating tablet indicated for both acute migraine treatment and migraine prevention? Moving to the new therapies for acute migraine, how do Nurtec, ubrogepant (Ubrelvy), lasmiditan (Reyvow) and intranasal DHE (Trudhesa) perform relative to one another?

Who knows? The most that can be said is that all of these therapies were safe, generally well-tolerated and more effective than placebo medication in large-scale clinical trials. To know whether one is significantly better than its rivals - or better than the older (and cheaper) therapies - will require careful direct comparisons, and those comparisons have not been done.

Again, the welcome news: if you are a migraineur who desires to reduce your

headache burden and choose to seek assistance from a healthcare provider for acute headache treatment and, if needed, for migraine prevention, there now exist many more options than were available just 3 years ago. Even if we don't know which is the best, generally speaking or for you in particular, how could this be anything but good?

Well, for one thing these new options are expensive, and due to that expense most insurers are in no hurry to allow you access to them. Thus they create hurdles. For example, to obtain authorization for prevention treatment with an anti-CGRP monoclonal antibody your insurer may require you already to have tried and failed treatment with no less than 3 "old" prevention medications of 3 different types according to their presumed mechanisms of action.

Complicating matters, virtually all of the new "designer drugs" require prior authorization (PA) by one's insurer, and the burden of obtaining PAs falls squarely upon the healthcare provider. The time devoted to that task by your healthcare provider, is financially uncompensated, and for providers who see a large volume of headache patients and wish to utilize these new therapeutic options it often is necessary to hire additional staff whose work involves solely the PA and appeals process.

So, yes, there's a downside to the newcomers, but there's also plenty of upside. If you've failed to respond well to the triptans for acute headache treatment, whether due to their ineffectiveness or to annoying side effects, you may find Nurtec, Reyvow, Trudhesa or Ubrelvy a most welcome addition to your therapeutic arsenal. If you require prevention therapy for migraine and have had no luck with amitriptyline, propranolol, divalproex sodium, topiramate or others of the older older medications that are taken daily and often cause side effects, the ease, high tolerability and potential effectiveness of a mab subcutaneously self-administered once-monthly should prove appealing.

It's nice to have options.

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

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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†

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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.

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