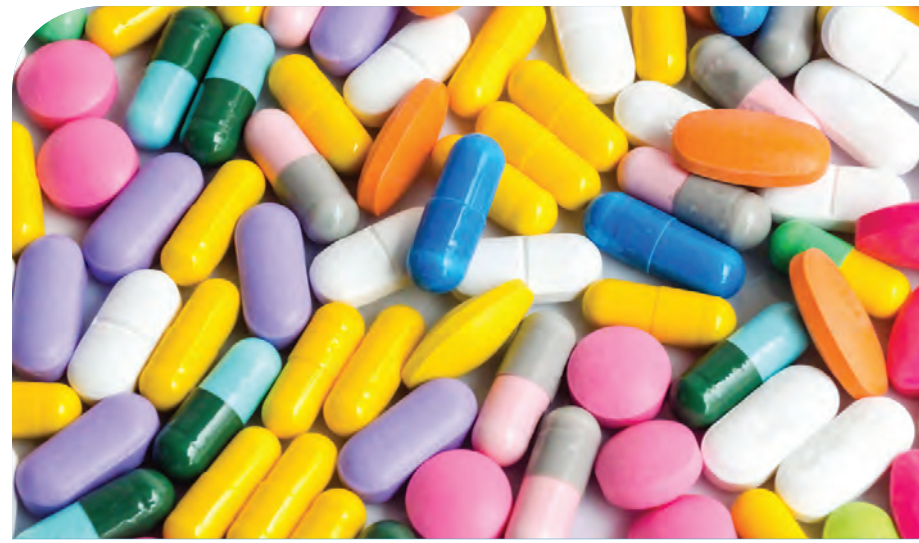
THERAPIES FOR MIGRAINE PREVENTION:

From Famine to Feast

Migraine sufferers are experiencing a relief revolution



Twenty-seven years ago, in 1991, occurred the first revolutionary breakthrough in migraine therapeutics: self-injected Imitrex (sumatriptan) for acute migraine headache of moderate to severe intensity. For millions of migraineurs this "designer drug", the first medication ever synthesized specifically for migraine treatment, has been nothing less than magic. Instead of suffering at home or enduring the harsh neon lights of an ER, those individuals have been empowered to rescue themselves from the misery of an acute migraine attack.

> ... we find ourselves in the midst of a second revolution, this time involving migraine prevention rather than the acute treatment of migraine.

Lagging behind, however, were therapies for migraine prevention. For many years all providers had to offer were a small number of drugs initially developed to treat other medical disorders and often thin on evidence supporting their effectiveness for migraine. As many as 4 million American migraineurs would benefit from prevention therapy, but only a third are receiving such therapy. Clearly we need to do better.

Happily, we find ourselves in the midst of a second revolution, this time involving migraine prevention rather than the acute treatment of migraine. The first distant rumblings came in 1996, with the Federal Drug Administration's (FDA's) approval of Depakote (generic: divalproex sodium) for migraine prophylaxis (prevention). Topamax (topiramate "immediate release") joined the arsenal of migraine prevention therapies in 2004. Six years later onabotulinumtoxinA received FDA approval specifically for the treatment of chronic migraine, and more recently "extended release" formulations of topiramate have emerged to join the IR version of that drug as approved therapies for migraine prevention.

Bursting upon the scene now are the CGRP antagonists, let by Amgen's Aimovig (erenumab) which received FDA approval in May of this year. This is a new class of "designer drugs" synthesized specifically to treat migraine, nearly free of side effects and likely to be highly effective for many of the millions of American migraineurs who require effective migraine prevention treatment.

Your Treatment Options

Many medications are used for the purpose of migraine prevention. Some have little or no scientific evidence to support their use, while others have been tested rigorously in multiple large-scale clinical trials. Along with assessing the evidence that supports their use, it's far better to know a lot about a few of these medications then a little about many.

What will not be discussed here are acupuncture, craniosacral therapy, biofeedback and the various types of devices, surgeries and nerve blocks which have advocated for use in migraine prevention. Attempting to conduct scientifically rigorous clinical trials to study these investigations poses many challenges, and all are associated with the potential for a high placebo response rate.

The Oldies (but Goodies?)

Beta-blockers

The beta-blockers initially were designed to treat hypertension (high blood pressure) and various heart conditions. By serendipity they were found to reduce headache frequency in some individuals with migraine, and on the basis of what now would be considered rather sparse scientific evidence two of the beta-blockers, propranolol and timolol, received FDA approval for migraine prevention.

Even in heart-healthy individuals with no hypertension the beta blockers tend to slow the heart rate and lower blood pressure, and these actions may produce side effects that limit their usefulness in treating migraine. Patients can experience lightheadedness, especially with positional change (eg, going from a sitting to standing position) or decreased exercise tolerance. Regarding the latter, a healthy young woman (or man) who enjoys running for exercise may not take kindly to a noticeable drop in pace or mileage… much less an uncharacteristic need to pause for breath after merely climbing a short flight of stairs.

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Tricyclic "antidepressants"

Before the advent of the SSRIs (eg, Prozac), bupropion (eg, Wellbutrin) and the SNRIs (eg, Effexor), the tricyclic antidepressants were the mainstay for drug treatment of depression. With time their use extended to treatment of insomnia, various types of neurologic pain and headache prevention. The most commonly used tricyclic for headache is amitriptyline (trade name Elavil), and a number of studies performed over the years – some scientifically rigorous, some not so rigorous – eventually earned the drug a "gold star" rating for migraine prevention. Because amitriptyline can cause sedation, its molecular cousin, nortriptyline (trade name Pamelor), believed to be less sedating, has become a popular choice for migraine prevention. The evidence supporting nortriptyline for that indication is essentially non-existent.

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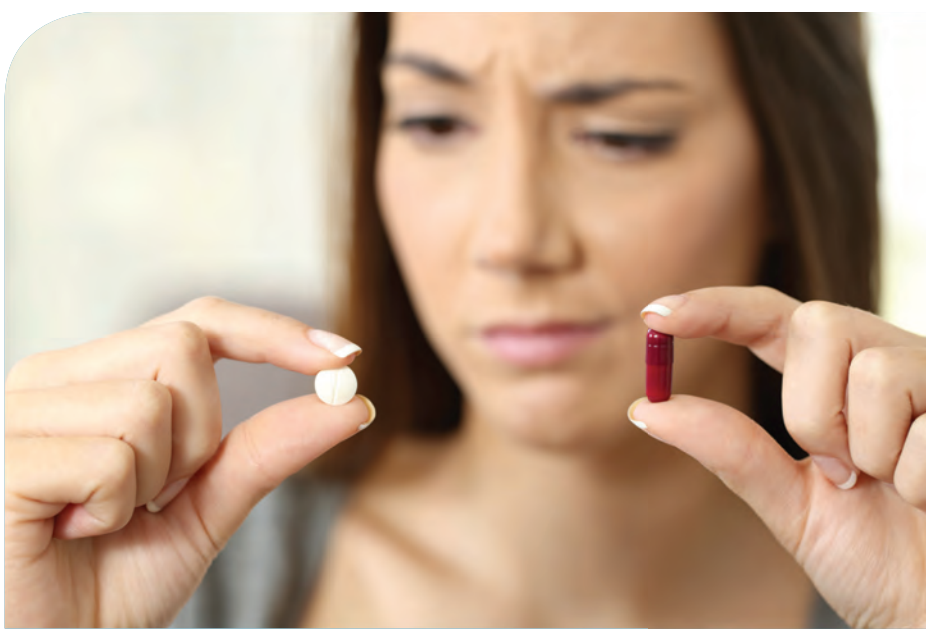
The tricyclics can be tough to take. Even at the low doses usually prescribed in the setting of migraine they can cause daytime sedation, paradoxical insomnia, dry mouth and weight gain.

Others (gabapentin, verapamil, etc)

An inside joke amongst neurologists is that gabapentin, developed for epilepsy, is good for just about everything neurologic except epilepsy. While this is an overstatement, it's true that gabapentin is a rather weak antiepileptic medication and that it may be quite useful for patients with disorders such as painful peripheral neuropathy associated with diabetes. Suffice it to say that its track record in migraine prevention is less than impressive. One study showed that it may be effective for some patients with chronic migraine, but the dose required was rather high at a level that often is poorly tolerated.

On the surface, verapamil, a "calcium channel blocker" presumed to oppose blood vessel constriction and used to treat hypertension, would be an attractive choice as a therapy for migraine prevention. About the only side effects the drug may cause are lightheadedness and constipation. Although verapamil often is prescribed for migraine prevention, it should be considered at best a third line agent for that condition. Verapamil and the other calcium channel blockers just don't seem to help very many migraine patients… especially when subjected to careful analysis in the setting of a clinical trial.



The Sort of New

Divalproex sodium (trade name Depakote)

Divalproex sodium initially was developed to treat epilepsy, a medical disorder reflecting brain hypersensitivity. Because migraine also results from brain hypersensitivity and divalproex reduces that hypersensitivity, it should come as no surprise that the drug proved to be effective for migraine prevention. https://www.migraineurmagazine.com/migraineur/migraine-101-what-is-migraine

Divalproex sodium was carefully evaluated for prevention of episodic migraine in large-scale headache prevention studies of unprecedented rigor and received FDA approval for migraine prophylaxis in 1996. Since then it has been demonstrated to have potential effectiveness in a few clinical trials involving patients with chronic migraine https://www.migraineurmagazine.com/migraineur/winter/managing-your-migraine, but the evidence base for its use in chronic migraine remains quite limited.

Limiting the popularity and use of divalproex sodium has been its side effect profile and potential for causing harm to a developing fetus in female migraineurs who are pregnant and take the drug. Even the once per day/extended release formulation of divalproex sodium may cause weight gain and hair loss. In regards to the latter, the hair follicle self itself -the cell within the scalp that grows the hair - remains healthy, but the hair shaft becomes fragile and may snap off. With discontinuation of the drug the patient's hair grows back, and any drug-related weight gain reverses. As for the pregnancy issue, divalproex sodium is absolutely contraindicated if the patient is pregnant or at risk of becoming pregnant. Taken during the first trimester of pregnancy, it may cause severe nervous system defects in the developing fetus.

All that said, the extended release formulation of divalproex sodium (trade name Depakote ER) can serve as an easily tolerated and highly effective medication for prevention of episodic migraine in many male migraineurs and in female migraineurs when there is no risk of pregnancy.

Topiramate (trade names Topamax, Trokendi XR, Qdexy XR)

As with divalproex sodium, topiramate initially was developed for the treatment of epilepsy but subsequently found to be effective for migraine.

> The drug's most common side effect is tingling...

The drug's most common side effect is tingling, occurring in about one third of patients, involving virtually any part of the body. The tingling is typically intermittent, most prominent early in treatment and of no clinical significance. The drug may cause a change in taste; in particular, carbonated beverages may taste "flat". In contrast to divalproex sodium, topiramate tends to promote weight *loss*.

The drug's most treatment-limiting side effects involve impaired concentration, impaired memory and impaired verbal fluency (word-finding difficulties); these cognitive and language side effects tend to be dose-related, but some patients experience "brain fog" and speech hesitancy even at low doses. The cognitive and language side effects appear to occur most commonly with the "immediate release" (IR) formulation of the drug (eg, Topamax) and especially when that drug/formulation is taken at a dose higher than what is recommended by the FDA (100 mg total daily). Taking the IR formulation once daily (eg, at bedtime) leads to a dramatic fluctuation in blood levels of topiramate, and there is no evidence to suggest that doing so will reduce the likelihood or intensity of side effects. For migraine prevention, the IR formulation is meant to be taken twice daily at a target dose of 50 mg twice daily.

Preliminary evidence suggests that a once daily "extended release" formulation of topiramate (Trokendi XR) is less likely to cause impaired thinking and language than is the IR formulation and that Trokendi XR is possibly more effective in suppressing chronic migraine than topiramate IR. Those findings await confirmation via a larger and more scientifically rigorous investigation.

Topiramate possesses a respectable evidence base for use in treating chronic

Options for Migraine Prevention

Oldies	The Sort of New	The Brand New	Soon to Come?
Beta Blockers	Depakote (Divalproex Sodium)	Aimovig (Erenumab)	More Mabs & 'Pants*
Tricyclic Antidepressants	Topamax (Topiramate IR)		TMS**
Nerve Blocks	Topiramate XR		
Others (Gabapentin, Verapamil)	OnabotulinumtoxinA (Botox)		
Devices	Others (Memantine, Candesartan)		
	More Devices (eg, Cephaly)		
	"Migraine Surgery"		

*subcutaneously, intravenously and orally administered
**transcranial magnetic stimulation

migraine as well as episodic migraine. At least in regards to the IR formulation, however, tolerability issues may render it less clinically effective than serial BotoxA injection therapy.

Because it may cause cleft lip or (less often) cleft palate in a developing fetus, topiramate is contraindicated in females who are pregnant or at significant risk for pregnancy.egnant or at significant risk for pregnancy.

BotoxA represented a tremendous step forward...

OnabotulinumtoxinA (BotoxA)

BotoxA represented a tremendous step forward in the treatment of chronic migraine https://www.migraineurmagazine.com/migraineur/winter/managing-your-migraine . Until the recent release of Aimovig, it was the only therapy with a specific FDA indication for the suppression of chronic migraine, and it clearly deserved that indication.

About 50% of chronic migraine patients receiving serial BotoxA injection therapy experience a 50% or greater reduction in headache days per month. The treatment is extremely well tolerated, and in the hands of an experienced injector the toxin can be administered quickly and with minimal discomfort. For those who are responders, the therapy has been a godsend.

One of the few downsides: to achieve maximum effectiveness, the toxin should be administered at intervals not exceeding 12 weeks, and, for better or worse, this stipulation has the effect of "tethering" the patient to the injector.

Others (memantine, candesartan, tizanidine, Cephaly device, transcranial magnetic stimulation)

This group of "others" ranges from a medication developed to slow memory loss in patients with Alzheimer's (memantine) to a medication developed to treat high blood pressure (candesartan). What they generally have in common is limited evidence of their effectiveness for the prevention of episodic migraine and no real evidence to support their use in suppressing chronic migraine. Certain of the "others" offer little hope of benefit and a high likelihood of side effects; tizanidine, for example, has little evidence to support its use in migraine prevention and is notorious for causing daytime sedation. In short, these are therapies one should consider only when the better-established therapies have failed.

Perhaps the most promising of the "others" is transcranial magnetic stimulation (TMS), already FDA-approved for the treatment of acute migraine, for anxiety and for depression. TMS is currently under investigation for its safety and effectiveness in the prevention of migraine.

Brand Spanking New

...the CGRP antagonists were developed to 'fit' migraine.

The Glutamate Antagonists

Now arrives on the scene a new class of medications for migraine prevention unprecedented in their specificity. Unlike drugs like amitriptyline, divalproex sodium and topiramate which initially were intended to treat other disorders and have multiple potential mechanisms of action, the CGRP antagonists were developed to "fit" one particular spot within the migraine circuitry and, put simply, to cause a "short" in that circuitry which blocks the conduction of head pain signal. Happily, this high specificity is paralleled by excellent tolerability.

Two links to this article describes the glutamate antagonists in more detail, offer what is meant to be a balanced assessment of the pros and cons of Aimovig (the first of the class to be released for general use) and summarize what we currently know, don't know and hope to learn regarding this exciting new addition to the arsenal of therapies for migraine prevention https://www.migraineurmagazine.com/migraineur/great-expectations-mabs and https://www.migraineurmagazine.com/migraineur/glutamate-antagonists

Summary

This is an exciting time for migraine therapeutics. Over the next 18 months we will witness the emergence of multiple new glutamate antagonists intended for both prevention of migraine and acute migraine treatment. Along with this, we will learn how to better use this new class of medications and also gain access to other new therapies with entirely different mechanisms of action (egs, transcranial magnetic stimulation (TMS) and lasmiditan).

To all you migraineurs out there: keep up with research involving migraine therapeutics and the new therapies this research produces. Your answer may be waiting for you!