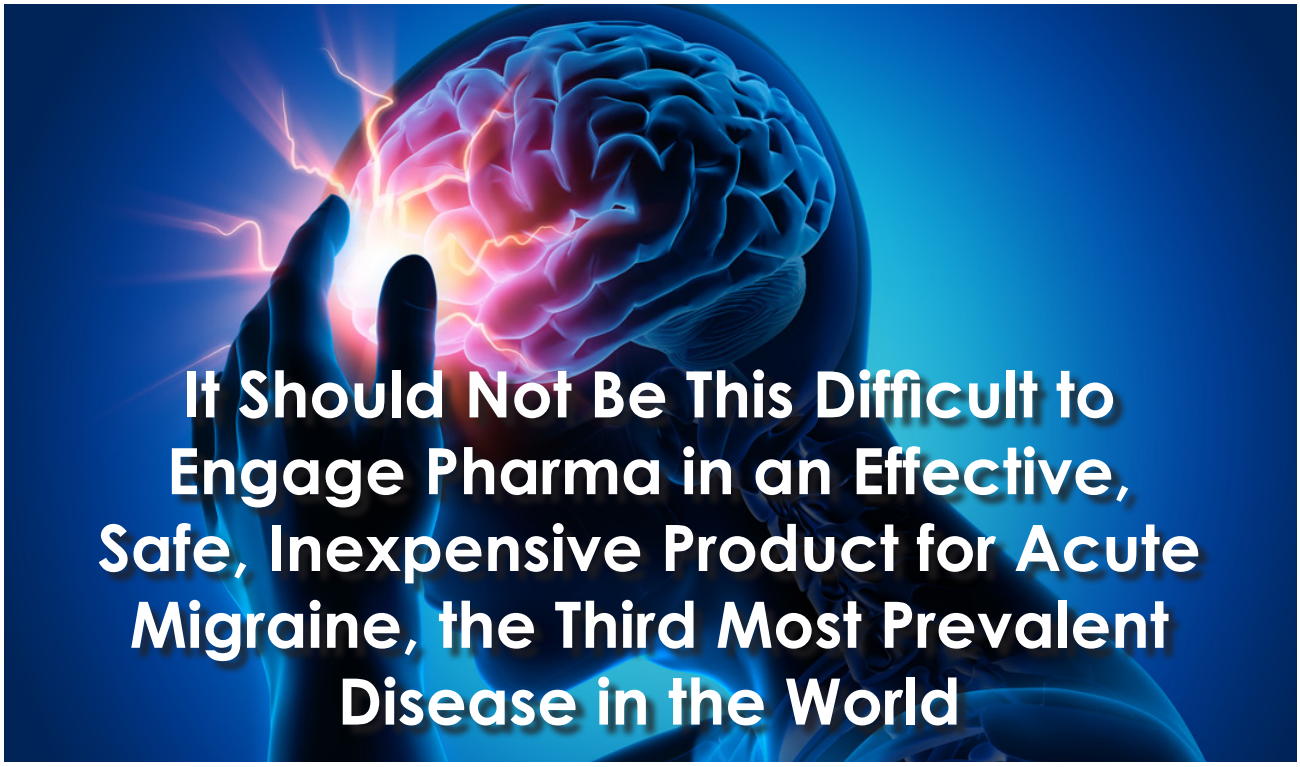


It Should Not Be This Difficult to Engage Pharma in an Effective, Safe, Inexpensive Product for Acute Migraine, the Third Most Prevalent Disease in the World

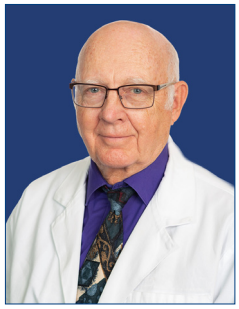
by John C. Hagan III, MD

A *JAMA Ophthalmology* study published in 2020 confirmed research first published in 2014 by *Missouri Medicine* on innovative acute migraine treatment.

Long time readers of *Missouri Medicine* hopefully recall that in 2014 Carl V. Migliazzo, MD, and I reported the largest series of case reports in the world's literature of acute migraines treated successfully with beta blocker eye drops (timolol maleate 0.5% solution).[1]

Our author-masked manuscript had been favorably peer-reviewed by two migraine headache experts. An accompanying editorial explained how this novel acute migraine therapy came about.[2] Three editorials also appeared in that July/August 2014 issue by neurologists,[3] headache specialists,[4] and a neuro-ophthalmologist.[5] They all enthusiastically endorsed the underlying pharmacological mechanism (rapid absorption) and urged further placebo-controlled studies with larger groups of migraineurs.

Dr. Migliazzo and I began contacting pharma: large, small, domestic, and foreign in an effort to find researchers to proceed with placebo-controlled studies. As ophthalmologists, we do not have the migraine volume to do these ourselves. Over the past seven years, we have contacted virtually every major and many minor pharmaceutical companies with a product line in migraine treatment and neurosciences. As of February 2022, the response from pharma has been almost uniform:



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1. The mechanism of applying timolol eye drop solutions topical to the eye, sublingual, or nasally to achieve rapid therapeutic blood levels is likely effective but difficult to patent.
2. Why would (insert company name) want to develop a less costly product for acute migraine that competes with our existing more expensive product line?
3. As a company, we don't see enough profit in this product with or without intellectual property to fund it.

In 2018, researchers in ophthalmology and neurology at the University of Missouri-Kansas City School of Medicine reported[6] in *JAMA Neurology* the first placebo-controlled study using timolol eye drops instilled in normal eyes for acute migraine treatment. Sean Gratton, MD, and Matthew Cossack, MD, lead authors of this study, wrote in *Missouri Medicine* the same year another plea for larger studies and termed this a promising acute migraine treatment.[7] A first-person anecdotal long-term therapeutic success of timolol eye drops for acute migraine appeared in *Missouri Medicine* by Carolyn Csongradi, MS, a former chemistry and neurosciences faculty member at Santa Clara University.[8] Also in that issue, Dr. Migliazzo and I updated our clinical experience[9] using timolol eye drops for acute migraine which goes back over 20 years and includes scores of successfully treated, long-term patients, as well as over 60 anecdotal successes reported to us by other physicians or patients.

In 2020 a study, with dreadful flaws in my opinion and with which I had withdrawn as a collaborator, was published as a supplement to the *Kansas Journal of Medicine*.[10] This study purported to show that timolol eye drops were not helpful for acute migraine. I submitted a letter to the editor listing the numerous problems with the study and its erroneous conclusions. My critique was published[11] without the University of Kansas authors commenting or contesting any of my assertions and critiques.

Regarding route of administration of timolol eye drops, our patients have successfully used both topical installation onto normal eyes or sublingual. Given the convenience and ultra-fast absorption, a nasal spray would be the preferred method of delivery. Working with compounding pharmacists, I developed a compounded nasal spray of 0.25% timolol.[12] My request was for 0.5% timolol, but the compounding pharmacists did not agree to using the higher concentration. A small number of unreported patients tried the 0.25% nasal spray, found it more convenient to use but not as effective as the topical or sublingual 0.5% timolol. Timolol, at least 0.5% concentration, applied to the nasal mucosa would be the ideal way to test and develop for acute migraine use.

While 2020 was for the most part a bummer, it turned out to be a banner year for our research. *JAMA Ophthalmology*[13] published a large (N=50) randomized, masked, placebo-controlled, cross-over study of more than 600 acute migraine attacks that found timolol to be effective in meaningful pain reduction compared to placebo. Whimsically titled "Put a Drop of Timolol Into Each Eye and Call Me in the Morning," an enthusiastic invited commentary[14] by noted neuro-ophthalmologist Bradley J. Katz, MD, PhD, accompanied this study.

After this seminal 2020 *JAMA Ophthalmology* study was published, I contacted the India-based academic authors reviewing our research and proffered the best delivery mechanism would be the nasal route. Hopefully these researchers will be able to attract industry or academic funding for the larger studies necessary to bring an approved timolol beta blocker solution product to migraine sufferers for acute attacks.

During the past six years, I have located two researchers that own intellectual property that might be utilized by pharma to develop a patent-protected, safe, effective, profitable but reasonably priced product that has the potential to be a new and welcome paradigm in the treatment of acute migraine. Migraine in its many manifestations is the leading cause of disability among neurological diseases. Companies or academic departments wishing to do research on a patented product can contact me for details.

Disclosure

When we had our "Eureka Moment" in 2013, I was certain that a Nobel Prize in Medicine and many millions of dollars in royalties would follow. That pipe dream has long ago dissipated. I have no financial interests in any drug or instrument product at this time. I do not accept monetary emoluments from pharma.

Second Disclosure and First Digression

Nothing in this long journey has given me any admiration for pharma, COVID vaccines withstanding. I almost get a migraine at the widespread price gouging of pharma, e.g., seeing generic steroid eye drops that not long ago sold for $4 now going for $80, or reading how a drug company hiked a $40 bottle of pig ACTH to over

SCAN CODES

Beta Blocker Eye Drops For Acute Migraines Original 2014 Research and Report

Beta Blocker Eye Drops For Acute Migraines 2018 Follow-Up Research and Report

Or visit www.msma.org/Missouri-Medicine-Library

$40,000 (https://khn.org/news/mallinckrodt-orphan-drug-acthar-turned-cash-cow-as-drugmaker-raised-price-to-40000-per-vial-emails-show/), and to note the enormous amount of money that is showered by pharma over physician 'opinion makers' for shilling their products. Interested in knowing if your favorite 'opinion leader' is one of more than 700 physicians that have been paid more than one million dollars by pharma? Find out at: https://projects.propublica.org/docdollars/.

And some of the products pharma does choose to develop through FDA approval are risible. What are some of these mind-blowing products pharma chose to develop? How about an electrode to shock the lining of the nose to produce tearing for a dry eye? You would think the Geneva Conventions would outlaw such a device. Or bring to market a century old medication (pilocarpine) to possibly forestall presbyopia reading glasses or bifocals for a few years. Or develop that infamous pig ACTH into an eye medication for uveitis or keratitis for the same bargain price of $40,000 a vial. Gag! Or in a single year to distribute $40 million in salary bonuses to drug representatives to entice physicians to use pain opioids described by the company as 'non-addicting." I'm red-lining near apoplectic so here I shall stop. Thanks for staying with me this far.

Feel free to contact me for questions about beta blocker solutions for acute migraine. It shouldn't be this difficult! Email me at drjhagan3@gmail.com.

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