

2023

Comparing the efficacy of botulinum toxin and CGRP antagonists for chronic migraine prophylaxis

<https://hdl.handle.net/2144/49471>

"Downloaded from OpenBU. Boston University's institutional repository."

BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

**COMPARING THE EFFICACY OF BOTULINUM TOXIN AND CGRP
ANTAGONISTS FOR CHRONIC MIGRAINE PROPHYLAXIS**

by

PHONG LY

B.S., University of Portland, 2015

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2023

Approved by

First Reader

Dan Tzizik, PA-C, M.P.H.
Assistant Professor of General Internal Medicine

Second Reader

John Weinstein, Ph.D., M.S.
Director of Research, Physician Assistant Program
Assistant Professor of Medicine

ACKNOWLEDGMENTS

I would like to thank all those who have helped me complete this thesis, including Professor Dan Tzizik and Dr. John Weinstein for their advice and guidance, and David Flynn for his guidance while searching for resources and information.

**COMPARING THE EFFICACY OF BOTULINUM TOXIN AND CGRP
ANTAGONISTS FOR CHRONIC MIGRAINE PROPHYLAXIS**

PHONG LY

ABSTRACT

Chronic migraines are a neurological disorder, which can be debilitating to patients and result in increased healthcare costs and disability-affected life years. Botox and CGRP antagonists are two drugs used as prophylactic treatments for chronic migraine patients who have failed other medications in the past. However, there are currently no studies that have directly compared the two drugs and existing research indirectly comparing them has had conflicting conclusions regarding efficacy. This double-blind, prospective clinical study aims to determine whether there is a clinically significant difference in efficacy between the two drugs defined as percent reduction in headache days per month. Patients will be recruited and divided into three groups: those who will receive Botox injections, those who will receive Emgality injections, and placebo. The results of this study will be analyzed with ANOVA to determine whether there is a statistically significant difference among the groups, then further analyzed with paired T-tests to determine if one treatment is superior to the other. These results could be used for further research into migraine treatments, as well as to help determine which treatment to trial first in patients with migraines refractory to other medications.

TABLE OF CONTENTS

ACKNOWLEDGMENTS	iv
ABSTRACT.....	v
TABLE OF CONTENTS.....	vi
LIST OF TABLES	viii
LIST OF FIGURES	ix
LIST OF ABBREVIATIONS.....	x
INTRODUCTION	1
Background.....	1
Statement of the Problem.....	2
Hypothesis.....	3
Objectives and specific aims.....	3
REVIEW OF THE LITERATURE	5
Migraine Types and Symptoms	5
Diagnosis of Chronic Migraines	6
Risk Factors	8
Epidemiology and Effect on Patients.....	9
Treatments Overview	11
Botulinum Toxin.....	15
CGRP Monoclonal Antibodies	18

Existing research.....	22
METHODS	27
Study design.....	27
Study population and sampling.....	27
Inclusion criteria	27
Exclusion criteria	28
Treatment	29
Study variables and measures	30
Recruitment.....	31
Data collection	32
Data analysis	33
Timeline and resources	33
Institutional Review Board	34
CONCLUSION.....	35
Discussion.....	35
Summary	35
Clinical and/or public health significance.....	36
LIST OF JOURNAL ABBREVIATIONS.....	38
REFERENCES	39
CURRICULUM VITAE.....	42

LIST OF TABLES

Table	Title	Page
1	Migraine without aura diagnostic criteria according to the International Classification of Headache Disorders (adapted from Weatherall 2015)	6
2	Meta-analyses comparing the efficacy of Botox and CGRP antagonists	20
3	Example of a migraine diary for 1 week	27

LIST OF FIGURES

Figure	Title	Page
1	Standard injection sites for botox (Adapted from FDA label for botox).	15

LIST OF ABBREVIATIONS

CGRP	Calcitonin Gene-Related Peptide
DALY	Disability-Adjusted Life Year
FDA.....	Food and Drug Administration
GBD19	Global Burden of Disease Study of 2019
NSAID	Nonsteroidal Anti-Inflammatory Drug
PREEMPT.....	Phase 3 Research Evaluating Migraine Prophylaxis Therapy
RCT.....	Randomized Control Trial
SNARE	Soluble N-ethylmaleimide-Sensitive Factor Attachment Protein Receptors
WMD	Weighted Mean Differences
YLD	Years Lived with Disability

INTRODUCTION

Background

Chronic migraines, characterized by at least 15 headache days per month, at least eight of which present with additional migraine symptoms, are estimated to affect 1% of the global population. In 2019, migraines of all types ranked 14th worldwide among causes of disability-adjusted life years (DALYs) and were estimated to be responsible for 41.1 million years lived with disability (YLDs), or 4.76% of all YLDs, making them the third leading cause of YLDs. In the United States, this neurological disorder is estimated to affect 12% of the population, most commonly females between the ages of 15-49 years.¹ The pathophysiology of this disorder is complex and not fully understood.

Several treatment methods exist for migraines, from non-medication treatments aimed at managing migraine triggers to drugs that either reduce the frequency of migraines or the severity and duration of an ongoing attack. Of the migraine prophylactics available in the United States, onabotulinumtoxinA, or Botox, has been used for over a decade, since its FDA approval in 2010 for chronic migraine patients that have failed at least two other prophylactic drugs. Botox is a neurotoxin derived from *Clostridium botulinum*, which causes flaccid paralysis of affected muscles. It is thought that this may inhibit the release of certain neuropeptides involved in the sensation of pain. It is better tolerated than oral prophylactics, although there are concerns about its safety regarding the possibility of it spreading to other more distant sites.

More recently, studies into the pathophysiology of migraines have prompted the development of newer drugs, called calcitonin gene-related peptide (CGRP) monoclonal antibodies, aimed at targeting CGRP or its receptor. There are currently four CGRP antibodies approved by the FDA. Most of these drugs, including galcanezumab-gnlm (sold under the brand name Emgality), target the CGRP peptide directly, while only one (erenumab-aooe, sold under the brand name Aimovig) targets the CGRP receptor. Like Botox, these drugs have been shown to be effective, well-tolerated, and safe, although there are few long-term studies on safety, as they have only been developed recently.

Statement of the Problem

Both Botox and CGRP antagonists are expensive medications, which, especially in the case of Botox, may take several weeks to months to take effect. It is important that chronic migraine patients quickly find an effective treatment for their attacks since they more commonly describe their pain as moderate to severe in intensity. In addition, they are more likely than non-migraine patients to miss work or apply for disability due to their symptoms.² Botox treatments are spaced three months apart and, in one study, over half of patients did not experience at least 50% improvement in their symptoms until after their second round of injections. Since chronic migraine patients experience a headache attack at least every other day, their condition may still significantly impact their lives while they wait for their next round of treatment.

CGRP antagonist injections, while more frequently administered (every month compared to once per three months), still leave a significant amount of time between treatments and may take several rounds of injections to take effect or to determine treatment failure so the patient can trial another medication.

Additionally, these medications can be costly, especially to uninsured patients. According to some reports, a year of Botox treatments can vary between \$1200 to \$3000³ and Aimovig's list price (excluding insurance) is \$676.46 per month.⁴ Thus, knowing which drug is more efficacious may help patients decide which treatment to trial first if finances are a concern. However, although there are several meta-analyses that indirectly compare the efficacy of Botox and CGRP antagonists, no clinical studies currently exist that compare these drugs to each other directly. This can make it difficult for providers and patients alike to decide which treatment to try first.

Hypothesis

In a clinical direct comparison study, CGRP antagonists will be clinically superior to botulinum toxin for chronic migraine prophylaxis.

Objectives and specific aims

This thesis proposes a clinical study directly comparing botulinum toxin to CGRP antagonists, which aims to:

1. Determine if there is a statistically significant difference in efficacy between botulinum toxin (Botox) and the CGRP antagonist Emgality for chronic migraine prophylaxis.
2. If a statistically significant difference between the two exists, determine if this difference is also clinically significant.

REVIEW OF THE LITERATURE

Migraine Types and Symptoms

Headaches are a group of diseases, which can be divided into primary and secondary types. Secondary headaches occur as a symptom of another condition, such as dehydration, certain infections, or vascular issues, while primary headaches do not have a clear underlying cause and may be associated with pain-related structures in the head. Migraines, a type of headache associated with throbbing unilateral head pain, with or without an aura, fall into this latter category.

There are four stages to a migraine episode, although most patients do not experience all four stages. The first stage is a prodrome, or “pre-headache,” phase, which may last from hours to days. During the prodrome phase, a patient may have trouble concentrating, speaking, or reading and experience irritability, depression, insomnia, nausea, fatigue, photosensitivity, phonophobia or sensitivity to sounds, muscle stiffness, increased urination, or food cravings. These symptoms occur in 10-20% of migraine patients. The second stage is an aura, which is much shorter comparatively, lasting between five and 60 minutes. It is comprised of a group of symptoms that often serve as a warning that a migraine will occur. These symptoms may include vision changes, such as seeing flashes or temporary partial or full vision loss, numbness or tingling of the skin, speech changes, hearing changes such as tinnitus, and changes in smell or taste. Most migraine patients do not experience auras associated with migraines; these types of migraines are termed common migraines. Migraines that occur with an aura are called complicated migraines

and affect about 15-20% of migraine patients. Silent or acephalgic migraines present with an aura but without the subsequent headache.⁵ The third stage is the hallmark headache, which may last from hours to days. These headaches often present as a throbbing, pulsing pain that affects one side of the head but may radiate to the other side. The patient may experience neck pain or stiffness in addition to head pain. Other associated symptoms, such as nausea, vomiting, sensitivity to light or sounds, and worsening pain with movements, may occur. They may also experience diaphoresis, chills, pallor, fatigue, dizziness, blurred vision, or, rarely, fever.⁵ The final stage is called the postdrome and may last one to two days. During the postdromal phase, the main part of the migraine has resolved but residual symptoms persist, which may include inability to concentrate, depression or euphoria, fatigue, and lack of comprehension.

The type of migraine is determined by its duration and associated symptoms. Migraines that occur 14 or fewer days per month are termed episodic migraines, while migraines that occur 15 or more days per month over a span of at least three months are chronic migraines. It is estimated that 3% of patients with episodic migraines progress to chronic migraines each year.⁶ When a single migraine episode lasts over 72 hours, or three days, it is termed status migrainosus.

Diagnosis of Chronic Migraines

The diagnostic criteria for a migraine includes at least five headache attacks that fulfill additional criteria associated with migraines in terms of their duration, pattern, and

associated symptoms and are not better explained by another diagnosis (see Table 1).⁷

Chronic migraines in particular are defined as headaches occurring at least 15 days per month, in which at least eight of these days must present with said migraine features.⁶ As noted earlier, these migraines are accompanied by other additional symptoms not listed as diagnostic criteria.

Table 1. Migraine without aura diagnostic criteria according to the International Classification of Headache Disorders (adapted from Weatherall 2015).⁷

Disorder	Criteria
Migraine	A history of at least five headache attacks that fulfill each of the below criteria.
	Attacks must last 4-72 hours, either untreated or unsuccessfully treated.
	Attacks must occur with at least two of the following characteristics: 1) Unilateral head pain 2) Pulsating in quality 3) Moderate or severe in intensity of pain 4) Aggravated by or causes avoidance of routine physical activity such as walking
	Must experience at least one of the following associated with headache attacks: 1) Nausea and/or vomiting

	2) Photophobia and phonophobia (sensitivity to lights and sounds)
	Headaches cannot be better explained by another diagnosis
Chronic Migraines	At least 15 headache days per month. 1) At least eight of these headaches must meet the diagnostic criteria for migraines listed above per month.

Since migraines are diagnosed based on history and symptoms, instead of physical examination findings or diagnostic tests, practitioners must differentiate between chronic or episodic migraines and other headache disorders, such as cluster headaches, which are shorter in duration, or secondary headaches that occur as a result of another condition. This is accomplished via taking a detailed history of the patient’s medical history, symptoms, and risk factors to determine whether it fits the profile of a migraine or if a different diagnosis better explains their symptoms.

Risk Factors

Factors that may increase a person’s risk of developing chronic migraines in the future are: psychological disorders, such as anxiety or depression; medical conditions, such as other pain disorders, obesity, asthma, or persistent nausea; certain life events, such as significant stressors or trauma to the head or neck; and lifestyle choices, such as smoking or caffeine use or withdrawal.⁶ In addition, there may be a genetic component involved, as up to 80% of migraine patients report having a first degree relative who also has

migraines. A child has a 50% chance of developing migraines if one of their parents has a history of migraines; if both parents have a history of migraines, this risk increases to 75%. In addition, female patients are at higher risk of developing migraines, particularly between the ages of 15 and 55, which coincide with changes in estrogen level due to menses in between puberty and menopause.⁵

Factors that increase one's risk of developing migraines may later become "triggers" for the onset of an attack, such as changes in estrogen level with migraines more commonly occurring near menstrual periods. In addition, factors that may worsen migraines may also trigger them, such as fatigue, loud noises, bright or flashing lights, and exposure to certain smells, such as perfumes or cigarette smoke. Other noted migraine triggers include weather changes, dehydration, changes in sleep pattern, and certain medications.

Epidemiology and Effect on Patients

Globally, headache disorders, comprised of only specific diseases such as migraines and tension-type headaches, ranked 14th among causes of disability-adjusted life years (DALYs) in patients of all ages and genders in the 2019 Global Burden of Disease study (GBD19). This group of disorders ranked 10th in DALYs among females overall and second among females aged 15-49, behind gynecological diseases. Among males of the same age group, they ranked tenth.

In terms of years lived with disability (YLDs), headache disorders were estimated to be responsible for 46.6 million YLDs overall, 5.4% of total YLDs. The vast majority (88.2%) of these YLDs, or 41.1 million, were attributed to migraines, specifically. As ranked causes of YLDs, headache disorders were third overall among all age groups, behind low back pain and depressive disorders, and first among those aged 15-49. There were geographical variations in this data depending on region and income level. Headache disorders as a cause of YLDs were highest in Europe and Central Asia, where they ranked second.¹ One out of twenty (4.5%) Western Europeans meet the criteria for chronic headaches, having headaches at least 15 days per month.⁷ In contrast, headache disorders as a cause of YLDs were the lowest in North America, ranking sixth, with other regions falling in between.¹ Globally, approximately 1% of the population may meet the diagnostic criteria for chronic migraines.⁷ The association between headache disorders and socioeconomic status is less clear. More YLDs were lost to headache disorders in countries classed by the World Bank as lower- or upper-middle income but fewer in low- or high-income countries. Split into specific disorders, migraines were ranked second in overall cause of YLDs, behind low back pain, and contributed to 4.9% of total YLDs. Because migraines most commonly affect younger females, being the number one cause of YLDs in females aged 15-49, they tend to rank higher in YLDs in countries with a lower life expectancy and higher proportion of young adults.¹

In the United States, headaches account for nearly 5% of all general practice consults, 20% of all outpatient neurology consults, and 5% of all medical admissions to hospitals.

It is estimated that one in five Americans will be affected by migraines at some point in their life. This equates to 44.5 million US adults with females approximately three times more likely to experience migraines than males.⁸ Since the prevalence of migraines peak during early and middle adulthood, this affects people during their most productive years of life when they are most likely to be furthering their education, working, or starting their careers and families.⁶ In 2016, the economic burden of migraines was estimated to be \$36 billion in the US. This estimate consists of direct costs, including the use of healthcare resources, as well as indirect costs such as lost productivity. Roughly 80% of this lost productivity was attributed to absenteeism. Those with migraines were estimated to have total annual costs (direct and indirect) nearly \$9000 higher per patient than their non-migraine counterparts. In addition, they were twice as likely to use opioids and nearly twice as likely to have a short-term disability claim than matched controls.²

Treatments Overview

The pathophysiology of migraines is not fully understood but has been proposed to involve inappropriate C-fiber nociceptor activation in the dura, which releases calcitonin gene-related peptide (CGRP). This may sensitize nociceptors and activate pain fibers.⁹ Despite a lack of understanding of their cause, there are various treatments for migraines. These treatments are divided into three groups: lifestyle modifications aimed at avoiding and managing migraine triggers; prophylactic medications aimed at preventing migraines from occurring or reducing the frequency of attacks; and acute treatments aimed at

reducing migraine symptoms during or at the onset of a migraine episode. Patients with migraines are managed with a combination of these three treatment types.⁷

Lifestyle modifications aimed at managing migraine triggers can be effective in reducing the frequency of migraine attacks; however, patients with chronic and severe migraines may have difficulty recognizing triggers simply due to their frequency and ubiquity. Common triggers, such as sleep disturbances, bright or flashing lights, certain sounds, dehydration, and stress, may be difficult for patients to avoid. In addition, comorbid conditions, such as depression and other pain conditions, as well as overuse of the medications used to treat them, may exacerbate headaches. When lifestyle modifications are feasible, changes, such as decreasing caffeine consumption, smoking cessation, and maintaining a regular sleep schedule, can be effective in managing the frequency of migraine attacks. Despite this, a sizeable portion of patients require additional prophylactic and/or abortive treatments for their migraines.⁷

Acute treatments aimed at reducing migraine symptoms and their duration after an attack has already begun depend on the severity of the symptoms. For mild or moderate migraines, high doses of over-the-counter medications, such as 1000 mg acetaminophen or clinically equivalent doses of non-steroidal anti-inflammatory drugs (NSAIDs), are considered first-line treatments. The choice of treatment depends on the intensity of the attack and side effect profile; acetaminophen, although less effective than NSAIDs in clinical trials, has a more favorable side effect profile, which did not include a higher risk

of gastric ulcers. Conversely, although caffeine is a known migraine trigger, a combination of acetaminophen, aspirin, and caffeine is considered an effective first-line treatment for migraines.

Most migraines, though, tend to be moderate to severe and triptans, such as sumatriptan, are the first-line treatment for these. All triptans are 5-hydroxytryptamine receptor agonists with a common mechanism of action that differ in their pharmacokinetics and routes of administration. Some patients may prefer long-acting triptans for frequent recurring migraines. However, with all triptans, up to three quarters of patients (42% to 76%) experience headache relief within two hours and up to half (18% to 50%) have complete resolution of pain within that time. Triptans are more cost-prohibitive than over-the-counter medications and most have a side effect profile that includes fatigue, dizziness, chest discomfort, drowsiness, and nausea.

For symptom relief at two hours, combination therapies consisting of a triptan plus another treatment, such as NSAIDs, provided the most relief, while triptans alone fared about equal or slightly worse and over-the-counter medications equal or slightly worse yet. For refractory migraines, dihydroergotamine (a 5-HT receptor agonist) and antiemetics are recommended as second- or third-line treatments but are less effective than the aforementioned medications and have a greater side effect profile due to their lower receptor specificity. In addition, both triptans and dihydroergotamine are contraindicated in pregnant patients; triptans increase the risk of spontaneous abortion

and dihydroergotamine is associated with a four-fold increased risk of prematurity, as well as a increased risk of teratogenic effects found in toxicology studies on rodents.¹⁰ Since most migraine patients are reproductive-age females, a number of whom may be or plan to become pregnant in the future, this limits their treatment options. Triptan use may be considered for pregnant patients with severe symptoms but this is controversial. For all acute treatments, it is recommended that patients take their medication early in an attack before symptoms peak. In patients that experience an aura, evidence suggests that, for best results, patients take their medication at the onset of stage three, when the headache occurs, rather than stage two, when they experience an aura.⁸

The third group of migraine treatments, aimed at preventing or reducing the frequency of attacks, is considered when the frequency or severity of a patient's headaches interferes with their daily life, as is often the case with chronic migraines. For these treatments, the lowest dose is prescribed first to decrease the risk of side effects. The dose is then gradually titrated upwards until an effective therapeutic dose is reached or the maximum dose is reached without significant improvement in migraine frequency and severity. In the latter case, the patient is considered to have failed the medication and another treatment is trialed. Anticonvulsants, such as topiramate, are recommended as first-line preventatives for migraines; however, practitioners may decide to use other medications, such as tricyclic antidepressants or beta blockers, instead due to their similar efficacy and more favorable side effect profile. Other options include calcium channel blockers, especially for patients with auras, and angiotensin blockers. In the case that a patient fails

multiple preventative treatments, treatments such as Botox injections or CGRP antagonists may be considered.⁷

Botulinum Toxin

Botulinum toxin, sold under the brand name Botox, is a protease, which has been used for migraine prophylaxis for over a decade. Multiple types of botulinum toxin exist and are named A through G but the most common in migraine treatment is botulinum toxin A. It is produced by *Clostridium botulinum*, an anaerobic, gram-positive, spore-forming bacterium, which was first isolated as the cause of botulism by Émile van Ermengem in 1897.⁹

Once in the body, the toxin irreversibly binds to cholinergic receptors located in the presynaptic membrane of voluntary motor and autonomic neuromuscular junctions in the peripheral nervous system; it is unable to cross the blood-brain barrier into the central nervous system. After binding, it is endocytosed into these presynaptic cells and cleaves soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) involved in the release of the neurotransmitter acetylcholine from presynaptic nerve terminals. Without these SNARE proteins, vesicles cannot bind to the membrane to release acetylcholine, thus inhibiting muscle contractions and causing muscle relaxation. Currently, no treatment is available to reverse this effect; instead, the body must form new axon terminals unaffected by the toxin, which may take three months.¹¹ For this

reason, botox injections for migraines are given every three months, once the last dose has worn off.

The use of Botox in medicine began in 1977, when Alan Scott used it to treat strabismus. In 1989, it was FDA-approved for the treatment of strabismus, blepharospasm, and hemifacial spasm. Research in its use for tension-type headaches and migraines began in the 1990's, after it was observed that some patients given Botox for cosmetic purposes also experienced a reduction in the severity and intensity of their headaches. In an open-label study in 2000 involving 77 migraine patients, 51% reported complete symptom elimination with a mean response duration of 4.1 ± 2.6 months. Another 38% reported at least 50% reduction in the frequency or severity of their headaches for 2.7 ± 1.2 months¹² but it was not until 2010 that Botox (generic name onabotulinumtoxinA) was first approved in the US for chronic migraine prophylaxis.⁹ Since its approval, it has been indicated for refractory chronic migraines that have failed at least two other prophylactic drugs in two different classes. The medication is available in vacuum-dried form and must be reconstituted by mixing with 0.9% saline. The recommended route of administration is 5 unit, or 0.1 mL, intramuscular injections across 31 sites in seven head and neck muscles (specifically the corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal, and trapezius muscles), for a total of 155 units in 3.1 mL injected per session (see Figure 1).¹³ Some clinicians may opt to inject 40 additional units in sites where patients report the most pain for a total of 195 units. Since the effect of the neurotoxin eventually wears off, these injections must be repeated every three months,

although some patients are able to reduce the frequency of their injections or discontinue them completely.



Figure 1. Standard sites for botox injections (Adapted from FDA label for botox).¹³

The exact mechanism of action is unknown but it has been proposed that the toxin binds to receptors on C-fiber nerve terminals, after which it is endocytosed into nerve cells. It then cleaves synaptosomal-associated protein (SNAP-25), which inhibits the fusion of vesicles with nerve membranes similarly to the mechanism of botulism. A major difference is that, instead of preventing the release of acetylcholine, this prevents the release of neuropeptides, such as calcitonin gene-related peptide (CGRP), involved in the sensation of pain.^{9,14} Eight percent of subjects experience a reduction in migraine frequency or severity within 1 year of starting treatment with only 9.3% losing efficacy in that same timeframe.¹⁵

Botox is tolerated better than oral prophylactic drugs with fewer subjects in randomized trials discontinuing treatment due to adverse reactions compared to topiramate or

amitriptyline.^{9,16} Overall, 14.4% of patients reported an adverse reaction during the first year.¹⁵ The most common adverse reactions were neck pain and headache, each affecting at least 5% of subjects in phase 3 trials during the drug approval process. Other reactions, including worsening migraines, muscular weakness or pain, infection, and eyelid ptosis, have been reported. The FDA warns clinicians and patients that Botox may spread from the initial site of injection into surrounding areas and cause unintended effects, including eye issues and difficulty with breathing or swallowing, although there are no reports of this occurring with Botox used for migraines, specifically. In addition, its safety and efficacy have not been established in pediatric patients or patients with episodic migraines.¹³

CGRP Monoclonal Antibodies

Although Botox is a well-studied migraine prophylactic, newer drugs continue to be researched and developed. More recently, the FDA has approved several monoclonal antibodies targeting CGRP. There are two forms of CGRP, α CGRP and β CGRP, which have similar activity. Unlike the century-long history of research into botulinum toxin, CGRP was discovered only 35 years ago as a neuropeptide that plays a role in the modulation of pain. Newer research supports the idea that CGRP also plays a significant role in the pathophysiology of migraines through the trigeminovascular system, where this peptide is abundant in the neurons of the trigeminal ganglia. Its release from peripheral nerve terminals initiates a cascade that sensitizes the trigeminal nerves, enhancing pain in the face and head.¹⁷ It is also present in the meninges, where it acts as a

potent vasodilator that stimulates the release of neuron-sensitizing agents from mast cells, increasing vasodilation in the dura and contributing to neurogenic inflammation. This may create a feedback loop resulting in nociceptor sensitization and, thus, cause headache. Clinical studies have found that CGRP levels are elevated in the plasma, saliva, and tears of patients during spontaneous migraine attacks and that CGRP is both necessary and sufficient to induce migraines in some migraine patients. In non-migraine patients, infusion of CGRP can induce a mild headache. However, the pathophysiology of migraines is complex and these results were not found in all studies.¹⁸ Therefore, more research is needed to determine which other processes may be in play.

Along with ongoing research into the role of CGRP in migraines, there has been research into developing drugs that target this peptide or its receptor. As of 2022, there are currently four drugs in the class of CGRP antagonists: Aimovig (generic name erenumab-aooe), Ajoovy (fremanezumab), Emgality (galcanezumab-gnlm), and Vyepti (eptinezumab-jjmr). The first of these drugs, Aimovig, was approved in May of 2018 with the rest following soon after; the newest CGRP inhibitor, Vyepti, was approved in February of 2020. All are monoclonal antibodies with Aimovig targeting the CGRP receptor to antagonize its function, while the others target the CGRP peptide and prevent its binding to the CGRP receptor.¹⁹ The route of administration for all four is monthly subcutaneous self-injection by the patient through a single-dose prefilled autoinjector. For Aimovig, this is given as a single dose of 70 mg with a maximum dose of 140 mg.²⁰ For Emgality, the first month's dose is given as two 120 mg injections for a total of 240

mg; each subsequent monthly dose is 120 mg.²¹ The injections may be given in the abdomen, thigh, or upper arm with Emgality also having the option of buttock injections.^{20,21}

In a three-month trial submitted to the FDA for drug approval, 84% of chronic migraine subjects given 70 mg of Aimovig once per month experienced a reduction in migraine days per month with nearly 40% reporting a reduction of at least 50% in the number of migraine days. In subjects given 140 mg doses, this reduction increased to 79%.²⁰ In a similar trial with patients given Emgality for three months, 84% reported a reduction in migraine days per month with 28% experiencing a 50% or greater reduction in their number of migraine days.²¹ Although this suggests that Aimovig may be more effective than Emgality, some other studies have reported no differences in efficacy amongst CGRP antagonists, regardless of their mechanism of action.¹⁸ These results are similar to findings amongst botox patients; in one study, 38% of subjects reported a 50% or greater response to treatment within 2.7 months (SD 1.2).¹²

An advantage of CGRP antagonists over Botox is that their increased frequency of injections may result in patients experiencing benefits sooner; Botox may take several sessions, each three months apart, for the same effect. Like Botox, CGRP antagonists are well-tolerated with 95% of subjects in Aimovig drug trials able to complete the trials. The most common adverse reaction found with Aimovig and Emgality in phase 3 trials was injection site reaction; about one in twenty (6%) of subjects given Aimovig

experienced an injection site reaction, such as pain, erythema, or pruritus, compared to 3% given placebo. These reactions were more common in subjects given Emgality; nearly one in five (18%) experienced an injection site reaction compared to 13% given placebo. Less commonly, subjects taking Aimovig also reported constipation, cramps, and muscle spasms.

One concern with monoclonal antibodies is the possibility of immunogenicity, or the body developing neutralizing antibodies against them with repeated use, potentially causing unwanted reactions and the loss of efficacy over time. *In vitro* biological assays performed to detect antibodies in subjects taking Aimovig and Emgality found that the incidence of antibody development was 6.2% (out of a cohort of 778 subjects) and 4.8% (out of a cohort of 688 subjects), respectively. For Aimovig, 4.17% of subjects positive for anti-erenumab-aooe antibodies had *in-vitro* neutralizing ability; for Emgality, this was 97% after six months. However, in a 12-month long open-label study, the percentage of subjects with anti-galcanezumab-gnlm antibodies dropped to 12.5%, with most still testing positive for neutralizing antibodies. These studies did not find that antibody development affected the pharmacokinetics, safety, or efficacy of either drug. However, the available data is still very limited and definitive conclusions cannot be drawn without further research.^{20,21}

Another concern is safety of the drugs. Since CGRP antagonists are newer, there is little understanding of the long-term effects of blocking CGRP. Because the current drugs

available achieve their effect through a systemic route, entering the bloodstream through a subcutaneous injection before reaching their intended target, there are concerns about these drugs inhibiting the vasodilatory effect of CGRP in the case of hypercoagulable disorders or acute conditions, such as stroke. However, in an ongoing five year open-label treatment phase, 383 patients enrolled for a median of 3.2 (range 1.3-3.4) years experienced no increase in cardiovascular events since starting Aimovig. The most common adverse events were viral upper respiratory infections, sinusitis, influenza, and back pain with a rate of serious adverse events of 4.2 per 100 patient-years, adjusted for exposure.²²

Existing research

Since the first CGRP antibody, Aimovig, was approved for migraine prophylaxis in 2018, several studies have compared the efficacy of CGRP antagonists with that of Botox. All current studies comparing CGRP antagonists to Botox have been meta-analyses and indirect treatment comparisons which take studies comparing either drug to a placebo and using that as a basis for comparison to each other. There are no published head-to-head trials directly comparing these two drugs to each other. In addition, of the meta-analyses comparing the efficacy of these two drug types, there seems to be no consensus on which is more effective. Of the four meta-analyses found via Pubmed and Google Scholar, two support that Botox is more effective in preventing migraines than CGRP antagonists, while the other two support the opposite conclusion, that CGRP antagonists are more effective.

Table 2. Meta-analyses comparing the efficacy of Botox vs CGRP antagonists.

Article Title and Year of Publication	Author(s)	Number and type of studies included in meta-analysis	CGRP antagonist(s) included	Total Number of Patients	Conclusion
Botulinum Toxin in the Treatment of Headache (2020) ⁹	Becker WJ.	3 trials (PREEMPT trials for Botox, Phase 2 trials for Aimovig, and Phase 3 trials for Emgality)	Aimovig, Emgality	3164 (1384 in Botox trials, 667 in Aimovig trials, and 1113 in Emgality trials)	Botox > CGRP . Botox reduced headache hours per month by 39 vs 19 for Aimovig and 22 for Emgality vs Placebo
Calcitonin Gene-Related Peptide Monoclonal Antibody Versus Botulinum Toxin for the Preventive Treatment of Chronic Migraine: Evidence From Indirect	Lu J, Zhang Q, Guo X, et al.	10 indirect treatment comparison studies	Aimovig, Ajovy, Emgality, Vyepiti (eptinezumab)	6325	CGRP > Botox in regards to efficacy as determined by change in frequency of acute analgesic intake (WMD = -1.31, 95% CI = -3.394 to 0.774, p = 0.02113)

Treatment Comparison (2021) ²³					
CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: A systematic review and meta-analysis (2021) ²⁴	Frank F, Ulmer H, Sidoroff V, Broessner G.	32 randomized control trials (RCTs)	Aimovig, Ajovy, Emgality, Vyepiti	17,763 (13,304 in CGRP trials, 1989 in topiramate trials, and 2470 in Botox trials)	CGRP > Botox in regard to 50% response rate (CGRP effect size 2.32 vs 1.30 for Botox)
Corrected: Comparing the Efficacy, Safety, and Superiority of Calcitonin Gene-Related Peptide Monoclonal Antibodies and Botox in Preventing and Treating	Siddiqui M, Shah PV, Balani P, Lopez AR, Nobleza CMN, Khan S.	29 articles (13 review articles, 2 narratives, 3 animal studies, 3 human clinical trials, 4 RCTs, and 5 observational studies)	Aimovig, Ajovy, Emgality	1917	Botox > CGRP (82.8% of Botox trial pts reported a response vs 62.3% of Emgality trial pts)

Migraines (2021) ³					
----------------------------------	--	--	--	--	--

One reason for this discrepancy may be the different methods of determining which is more efficacious. For instance, the Becker study relied solely on phase 2 and 3 research evaluating migraine prophylaxis therapy (PREEMPT) trials, while the others included additional clinical studies completed after the drugs were FDA-approved²⁴. Frank et al. calculated a combined effect size based on the articles included but, as with all current studies comparing the two types of drugs, these were calculated using clinical trials and studies that compared the drugs to either different drugs or to placebos instead of directly to each other. In addition, because CGRP antagonists are newer than Botox, meta-analyses such as Becker that include PREEMPT, Phase 2, and Phase 3 trials may include subjects who were resistant to treatment with Botox.⁹ Furthermore, since for insurance approval for Botox, it is generally required that the patient has failed two other migraine prophylactics in two different classes, these patients may be more likely to be resistant to migraine prophylactics in general, which may affect their results on CGRP antagonists.

It is difficult to compare the meta-analyses to each other due to significant differences in which studies were included in each meta-analysis, the number of total patients, and how these studies defined efficacy. Becker defined efficacy as reduction in headache hours per month, while Lu et al. defined it as reduction in frequency of analgesic use for migraines.^{9,23} Frank et al. defined efficacy as 50% response rate, while Siddiqui et al.

defined it as patient-reported response.^{3,24} The total number of patients in each meta-analysis varied widely from 1917 in Siddiqui et al. to 17,763 in Frank et al. In addition, each meta-analysis included different types of studies from randomized control trials to review articles. Thus, the quality of each meta-analysis varies.

Overall, existing research that indirectly compares Botox and CGRP antagonists has not reached a consensus on which is more efficacious. Often, studies differ in their length of treatment and definition of efficacy, which adds to the difficulty of comparing the two drugs. There does not yet exist a single direct clinical trial comparing the two drugs to each other.

METHODS

Study design

To achieve study objectives, researchers will conduct a prospective, double-blind clinical trial to quantify and compare the efficacy of CGRP antagonists to Botox injections for chronic migraine prophylaxis. Since there are multiple FDA-approved CGRP antagonists available, the study will use Emgality.

Study population and sampling

The study population will consist of migraine patients in Boston and surrounding cities within a 1-hour drive of Boston. The sample size was calculated using three groups, taking into account that statistical analysis will be performed using ANOVA, then paired t-tests. The input parameters were an effect size of 0.25, which indicates moderate effect size. Alpha error was set to 0.05 and power to 0.80. In total, there will be 159 patients divided into three groups: 53 patients in the placebo (control) group, 53 in the group who will receive Botox injections, and 53 in the group who will receive Emgality.

Inclusion criteria

Patients must be at least 18 years old at the time of recruitment. Patients must be diagnosed with chronic migraines (15+ migraine days per month with at least eight having migraine features) by a healthcare provider and have trialed and failed at least two FDA-approved medications for migraine prophylaxis in the past. Patients must reside in

or near Boston because this study will require them to travel to Boston once per month for checkups.

Exclusion criteria

Patients with a contraindication to either or both drugs, such as pregnancy, will be excluded. Patients with atypical migraines or other headache disorders such as cluster headaches will be excluded.

The study will exclude those who have trialed Botox and/or CGRP antagonists in the past, including Botox for reasons other than migraines. Patients with a known allergic reaction to either drug will be excluded. This study will require that patients discontinue their current migraine prophylactic, so patients who are unwilling to do so will be excluded. Patients will be able to continue their current migraine abortive medication during this study.

Patients with any concurrent chronic pain syndrome will be excluded, as will patients who are currently taking pain medications for reasons other than migraines. If a patient is currently on a medication that is also used for migraine prophylaxis, even if the medication is being used for a different diagnosis, they will be excluded. Examples include taking propranolol for essential tremors or amitriptyline for depression.

Treatment

This will be a double-blind study pending IRB **approval**. Patients will receive Botox injections once every three months, Emgality via syringe to self-inject every month, or placebo. Those receiving Botox injections will receive 155 units of Botox injected into 31 sites per standard protocol once every three months by a medical provider who is certified to administer Botox. These will be administered on months 1, 4, 7, and 10 of the study. Botox will be reconstituted with 0.9% normal saline at a ratio of 1 unit/0.02 mg 0.9% normal saline; 0.1 mg of the mixture will be injected into each site. Those receiving Emgality will be provided a syringe once per month to self-administer in front of a medical provider for directly-observed therapy. The first dose will be a 240 mg bolus given as two syringes, each with 120 mg of Emgality. During the first dose, patients will be provided education on how to self-administer this medication. Each subsequent dose will be 120 mg in a single syringe.

Group A (placebo) will receive both Botox and Emgality placebos. For month 1, they will receive 31 injections of 0.9% normal saline as Botox placebo. Each injection will contain 0.1 mg of saline for a total of 3.1 mg injected. They will also receive 240 mg of 0.9% normal saline in a syringe as Emgality placebo to self-administer in the presence of a medical provider. Subsequently, they will receive 120 mg of 0.9% normal saline in a syringe to self-administer once per month in the presence of a medical provider and be administered 31 saline injections per above on months 4, 7, and 10.

Group B (Botox) will receive Botox injections per above on months 1, 4, 7, and 10 of the study. In addition, they will receive Emgality placebo in the same manner as Group A.

Group C (CGRP antagonist/Emgality) will receive Emgality self-injections once per month, beginning with a 240 mg bolus for month 1 and 120 mg doses starting month 2. They will also receive Botox placebo injections every 3 months in the same manner as Group A.

Study variables and measures

Demographic information will be collected using a survey each patient will complete. The information obtained will include sex, age, race, and ethnicity. The survey will also ask about the number of migraines per month the patient experiences, if the patient has migraines with aura, and which medications they are currently using as a migraine abortive. Patients will be stratified by these variables.

Independent variables will be whether the patient is receiving placebo (Group A), Botox (Group B), or Emgality (Group C). Dependent variables will be change in frequency of headaches, defined as the percentage decrease in headache days per month from baseline. Change in number of headache days will be the primary outcome measured in this study. Other variables that will be measured are: change in headache severity, defined as percentage decrease from baseline on a scale of 0-10; change in length of headaches,

defined as percentage decrease in the time between the onset and resolution of a headache; and change in the frequency of migraines, defined as percent reduction in the number of headache days with associated migraine features, such as nausea, vomiting, photophobia, or phonophobia. Outcomes will be collected via a migraine diary page patients fill out daily (Table 3).

Table 3. Example of a migraine diary for 1 week.

Day of the Week	Migraine (Y/N)	Pain Severity (scale 0-10)	Headache length (hrs)	Other symptoms	Abortive drug taken	Treatment day and side effects
Sunday						
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						

Recruitment

Patients will be recruited from Boston and surrounding areas within a 1 hour drive of Boston. Patients will be recruited via social media advertisements and flyers placed

around hospitals. Interested candidates will first complete a form with demographic information, as well as answer questions pertaining to the inclusion and exclusion criteria stated above. Candidates who meet the criteria will then be interviewed by phone to verify eligibility and be informed about the details of the study, including the requirement that patients travel to a facility once per month for 1 year, in order to receive injections, as well as complete a migraine diary to return once per month in order to measure outcomes.

Data collection

Researchers will note the date of each treatment administration throughout the course of the study, as well as any late or missed doses. For one month prior to the start of the study (month 0), patients will receive a migraine diary to record which days they experienced a headache, the length of time the headache lasted, the severity of pain experienced on a scale of 0-10 where 0 denotes no pain and 10 denotes the worst pain the patient can imagine, any associated migraine symptoms, if the patient experienced an aura, any migraine abortive medications taken, and any adverse effects the patient experienced that may be related to current treatment. This will be to obtain a baseline for the patients' symptoms before starting treatment. When the patients start treatment on month 1 and when they return each month for treatment, they will hand in their completed migraine diary and receive another blank diary for the subsequent month.

Data analysis

Patients will be stratified by demographics (age, sex, race, and ethnicity), which migraine abortive medication they are currently taking, how many headache days they experienced per month at baseline, and the severity of their headaches at baseline. The characteristics of each group will be compared to ensure that no group is significantly different from the other groups in regard to these baseline characteristics.

Data will be analyzed using ANOVA to determine if there is a statistically significant difference between the three groups using an alpha error of 0.05. Data will then be further analyzed using independent T-tests to determine if Emgality is superior to Botox for migraine prophylaxis. For T-test analysis, alpha error will be adjusted using the Bonferroni correction, in order to maintain an alpha error of 0.05.

Timeline and resources

This study will require one investigator to recruit patients, gather demographics and headache information, and separate them into groups randomly. Two separate medical providers will be required. The first provider will draw up medications and placebo to be administered and the second provider will administer Botox or monitor self-administrated Emgality, in order to maintain the double-blind design. A statistician will be required to analyze the data collected.

The study itself will require 17 months. Four months will be allotted for recruitment of patients for the study. One month will be allotted to obtain a baseline for each patients'

headaches via migraine diary as detailed above. Twelve months will be allotted for treatment.

Institutional Review Board

This study will be conducted in compliance with the protocol, regulatory requirements, and policies of the Boston Medical Center and Boston University Medical Campus Human Research Protection Program. This study will utilize de-identified data. An IND is not required for this study because the drugs that will be used are FDA-approved and will not be used for a new indication, will not be given at a new dose, or any other significant change in labeling. All applicable documentation will be submitted to the Boston Medical Center IRB for full board review according to section 12.1.1 of the Boston Medical Center IRB policy.

CONCLUSION

Discussion

Botox and CGRP antagonists have both been used for chronic migraine prophylaxis for patients who have failed first- and second-line prophylactic medications in the past. As of yet, there have been no studies directly comparing the two drugs. This study aims to compare the efficacy of Botox with Emgality, a CGRP antagonist, and determine if an agent that directly targets the CGRP receptor is superior to Botox for chronic migraine prophylaxis.

Potential limitations of the study include patient adherence, considering the length of the study and requiring multiple follow ups. In addition, because the data is reliant on patient reports, the accuracy of the results may be limited. Since this study will be performed in the Boston, MA area, results may not be generalizable to the entire population of migraine patients. This study uses one CGRP antagonist, Emgality, so results may not be generalizable to all CGRP antagonists, particularly those, such as Aimovig, whose mechanism of action differs from Emgality.

Summary

Migraines are a common pain disorder affecting roughly 20% of the US population at some point in their lives and is the fifth leading cause of YLDs worldwide. The etiology of migraines is unknown but current research suggests that it may be related to activation of CGRP receptors in the head, leading to sensitization of nociceptors and pain. For those

with chronic migraines, Botox and CGRP antagonists may effectively manage patients' pain when other drugs fail. The mechanism of action of Botox is by cleaving SNAREs and, thus, inhibiting acetylcholine release, while CGRP antagonists target the CGRP receptor or protein. However, both drugs are costly and require patients to come into the office for injections in the case of Botox or self-injections in the case of CGRP antagonists. Currently, there are no studies directly comparing the two drugs to each other and existing research indirectly comparing the two is conflicting with some results suggesting CGRP antagonists are superior to Botox or vice-versa. Thus, this study aims to directly compare the two agents for chronic migraine prophylaxis through a prospective, double-blind, head-to-head clinical trial. By determining which drug is superior, providers will be better able to discuss these two treatment options with patients and decide which to trial first. This may reduce healthcare costs and the possibility of failing treatment.

Clinical and/or public health significance

Migraines affect an estimated 44.5 million adults in the US and result in significant economic burden, costing an estimated \$36 billion annually. Although some patients receive relief from their symptoms through first- and second-line medications, many do not and require more expensive and time-consuming treatments, such as Botox and CGRP antagonists. Currently, there are no head-to-head studies directly comparing Botox and CGRP antagonists for chronic migraine prophylaxis and existing research indirectly comparing the two is conflicting. Determining if either of these medications is superior to

the other for chronic migraine prophylaxis can assist in guiding providers and patients in deciding between the two drugs, which may result in sooner pain relief and lower costs for patients.

LIST OF JOURNAL ABBREVIATIONS

Am Fam Physician	American Family Physician
Br J Pharmacol	British Journal of Pharmacology
Clin Neurol Neurosurg	Clinical Neurology and Neurosurgery
Cureus	The Cureus Journal of Medical Science
Expert Opin Ther Targets	Expert Opinion on Therapeutic Targets
Front Pharmacol	Frontiers in Pharmacology
Headache J Head Face Pain	Headache: The Journal of Head and Face Pain
J Headache Pain	The Journal of Headache and Pain
Otolaryngol Neck Surg	Journal of Otolaryngology – Head & Neck Surgery
Sci Rep	Scientific Reports
Ther Adv Chronic Dis	Therapeutic Advances in Chronic Disease

REFERENCES

1. Steiner TJ, Stovner LJ, Jensen R, Uluduz D, Katsarava Z, on behalf of Lifting The Burden: the Global Campaign against Headache. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. *J Headache Pain*. 2020;21(1):137. doi:10.1186/s10194-020-01208-0
2. Bonafede M, Sapra S, Shah N, Tepper S, Cappell K, Desai P. Direct and Indirect Healthcare Resource Utilization and Costs Among Migraine Patients in the United States. *Headache*. 2018;58(5):700-714. doi:10.1111/head.13275
3. Siddiqui M, Shah PV, Balani P, Lopez AR, Nobleza CMN, Khan S. Comparing the Efficacy, Safety, and Superiority of Calcitonin Gene-Related Peptide Monoclonal Antibodies and Botox in Preventing and Treating Migraines. *Cureus*. 2021;13(1). doi:10.7759/cureus.13002
4. paying for aimovig. Accessed June 19, 2022. <https://www.aimovig.com/paying-for-aimovig>
5. Migraine Headaches: Causes, Treatment & Symptoms. Cleveland Clinic. Accessed May 26, 2022. <https://my.clevelandclinic.org/health/diseases/5005-migraine-headaches>
6. What Is Chronic Migraine? American Migraine Foundation. Accessed May 26, 2022. <https://americanmigrainefoundation.org/resource-library/what-is-chronic-migraine/>
7. Weatherall MW. The diagnosis and treatment of chronic migraine. *Ther Adv Chronic Dis*. 2015;6(3):115-123. doi:10.1177/2040622315579627
8. Mayans L, Walling A. Acute Migraine Headache: Treatment Strategies. *Am Fam Physician*. 2018;97(4):243-251.
9. Becker WJ. Botulinum Toxin in the Treatment of Headache. *Toxins*. 2020;12(12):803. doi:10.3390/toxins12120803
10. Bérard A, Strom S, Zhao JP, Kori S, Albrecht D. Dihydroergotamine and triptan use to treat migraine during pregnancy and the risk of adverse pregnancy outcomes. *Sci Rep*. 2021;11(1):19302. doi:10.1038/s41598-021-97092-y
11. Lonati D, Schicchi A, Crevani M, et al. Foodborne Botulism: Clinical Diagnosis and Medical Treatment. *Toxins*. 2020;12(8):509. doi:10.3390/toxins12080509

12. Binder WJ, Brin MF, Blitzer A, Schoenrock LD, Pogoda JM. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: An open-label study. *Otolaryngol Neck Surg.* 2000;123(6):669-676. doi:10.1067/mhn.2000.110960
13. Botox (botulinum toxin type A) [package insert]. Irvine, CA: Allergan, Inc; 2011.
14. Lacković Z, Filipović B, Matak I, Helyes Z. Activity of botulinum toxin type A in cranial dura: implications for treatment of migraine and other headaches. *Br J Pharmacol.* 2016;173(2):279-291. doi:10.1111/bph.13366
15. Cernuda-Morollón E, Ramón C, Larrosa D, Alvarez R, Riesco N, Pascual J. Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: What happens after one year? *Cephalalgia.* 2015;35(10):864-868. doi:10.1177/0333102414561873
16. Magalhães E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. *Clin Neurol Neurosurg.* 2010;112(6):463-466. doi:10.1016/j.clineuro.2010.02.004
17. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the Trigeminal System in Migraine. *Headache.* 2019;59(5):659-681. doi:10.1111/head.13529
18. Wattiez AS, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): Role in migraine pathophysiology and therapeutic targeting. *Expert Opin Ther Targets.* 2020;24(2):91-100. doi:10.1080/14728222.2020.1724285
19. Reuter U. A Review of Monoclonal Antibody Therapies and Other Preventative Treatments in Migraine. *Headache J Head Face Pain.* 2018;58(S1):48-59. doi:10.1111/head.13302
20. Aimovig (erenumab-aooe) [package insert]. Thousand Oaks, CA: Amgen Inc; 2018.
21. Emgality (galcanezumab-gnlm) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2018.
22. Ashina M, Goadsby PJ, Reuter U, et al. Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine. *Cephalalgia.* 2019;39(11):1455-1464. doi:10.1177/0333102419854082
23. Lu J, Zhang Q, Guo X, et al. Calcitonin Gene-Related Peptide Monoclonal Antibody Versus Botulinum Toxin for the Preventive Treatment of Chronic Migraine: Evidence From Indirect Treatment Comparison. *Front Pharmacol.* 2021;12. Accessed May 26, 2022. <https://www.frontiersin.org/article/10.3389/fphar.2021.631204>

24. Frank F, Ulmer H, Sidoroff V, Broessner G. CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: A systematic review and meta-analysis. *Cephalalgia*. 2021;41(11-12):1222-1239.
doi:10.1177/03331024211018137

CURRICULUM VITAE



