Retrospective Study: Comparing Clostridium Botulinum Toxin Local Injection Efficacy to Galcanezumab

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Abstract:T he present study aims to compare between two medications, namely clostridium botulinum toxin and galcanezumab, in terms of efficaciousness in treating migraine. Topics of discussion in the study include the following: an overview of migraine, overview of botulinum toxin (botox) and galcanezumab, and effectiveness of the two medications. The study also involves conducting a head-to-head clinical trial to compare the efficaciousness of the two medications on a sample of (100) patients at one large university hospital in the Arab Republic of Egypt. Findings of the study include the following: administering galcanezumab was reported to yield better results in the possibility of achieving full recovery and addressing the symptoms of refractory migraine; unlike botulinum toxin, galcanezumab was not reported to result in worsening symptoms for any sample member. Through the findings, the study recommends conducting further research for comparing the efficaciousness of migraine medications other than those discussed in the present study.
Keywords: migraine, clostridium botulinum toxin, botox, galcanezumab.

***Introduction*:**

Migraine is among the most disabling disorders of all categories, and the leading among neurological disorder. The underlying biology of the disorder is complex and remains largely unclear, as it is presumed to be an outcome of a combination of biological and environmental factors that result in altering the way the brain processes sensory inputs. As a result, the received sensory inputs become perceived in a manner that is considered bothersome to the person who has margarine (Puledda et al., 2023, 3654).

Mitigating the symptoms and effects of migraine can be achieved through preventive interventions or treatments when migraine is a chronic medical condition. Treatments can have a variety of benefits for patients with migraine. Examples of such benefits include reduced frequency, duration, and severity of pain symptoms, general improvement of quality of life, and mitigation of impairments to functioning (Krymchantowski et al., 2023).

Nowadays, there is a variety of emerging therapies for migraine. Notable among these therapies is the use of botulinum toxin (botox). This compound was initially used for treating other medical conditions, such as blepharospasm and dystonia. However, clinical trials have generated evidence that it can be used for treating chronic migraine (Karaoğlan, 2023, 1).

Another prominent treatment for migraine is galcanezumab. It is a medication for preventing the development of migraine. Galcanezumab is distinctive among all treatments of the disorder is that it was not originally developed for treating other conditions, but was specifically designed for treating migraines (Urits et al., 2020, 406-407).

Overview of Migraine:

Migraine is a neurological disorder that has debilitating effects. The global prevalence rate of this disorder is estimated at approximately one in every ten individuals. The typical and most distinctive symptom of the disorder is having a headache that lasts for several hours; however, the symptoms vary from one individual to another. Episodes of migraine follow a consistent pattern consisting of four main phases (Atraszkiewicz, 2021, 422):

1. Prodromal phase: in this phase, early signs predicting the commencement of a migraine episode manifest. Symptoms experienced in this phase include altered mood, hyperosmia, hyperphotosensitivity, and depression.
2. Aura phase: the experiencing of perceptual disturbances are the distinctive symptoms of this phase. They often include visual disturbances, such as notably scotomas. Other symptoms that may be experienced in this phase include auditory disturbances, numbness, dizziness, and temporary aphasia.
3. Strong headache phase: the headache is accompanied by other symptoms such as phonophobia, osmophobia, photophobia, and nausea.
4. Postdromal phase: this is the phase of recovery from the migraine episode. Notable symptoms experienced in this phase include malaise, tiredness, soreness, and impaired cognition.

Migraine is significantly different from other types of headache, such as tension-type headache and cluster headache. The main differences between these types are summed up in Figure 1.

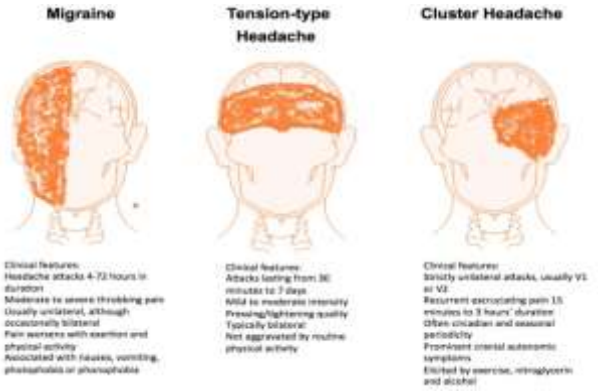

Figure 1. Comparison between migraine, tension-type headache, and cluster headache (Chong & Renton, 2016).

With the manifestation of symptoms of migraine, an individual becomes significantly more likely to experience other comorbidities. For example, patients with migraine have an elevated risk of developing psychiatric disorders, such as depression and anxiety. The risk among this patient population is more than double that among patients without migraine. In fact comorbid symptoms of depression and anxiety are key factors responsible for the debilitating nature of the disorder as well as for the progression of the disorder over time (Smitherman et al., 2020, 2203).

Patterns of migraine vary from one person to another. However, they are grouped into two main categories (Herd et al., 2019, 1):

1. Chronic migraine: The medical definition of this type of migraine is that it is a headache that lasts for a minimum of 15 days per month; migraine symptoms manifest on 8 of those days.
2. Episodic migraine: this pattern of migraine occurs for less than 15 days per month.

The two types of migraine vary not only in symptom patterns but also in the effect on overall health outcomes. Patients with chronic migraine have generally poorer health status compared to those with episodic migraine. For example, patient with chronic migraine were found to be more likely to have not only anxiety and depression symptoms but also other physical medical conditions, such as stroke, heath disease, obesity, chronic obstructive pulmonary disease, and asthma (Escher et al., 2017, 128).

In addition to having poorer mental and physical health outcomes compared to those with episodic migraine, patients with chronic migraine have a lower socioeconomic status. This is largely attributable to the fact that chronic migraine interferes with one's ability to engage in employment and have a normal life. The adverse impacts of chronic migraine include the following (Escher et al., 2017, 128):

1. Reduced ability to secure employment:
    a. Lower levels of income.
    b. Reduced ability to find full- or part-time employment opportunities.
    c. Likelihood of becoming occupationally disabled.
2. Increased need for medical care:
    a. Increased need for primary care visits.
    b. Higher likelihood to require specialist visits.
    c. Elevated risk of requiring visits to hospital emergency departments.
    d. More frequent need for hospitalization.

Migraine is most prevalent among women, including both adult and young. In fact, migraine episodes often occur in concurrence with menstrual periods (Igarashi et al., 2023, 74).

Importance of Treating Migraine Treatment:

Individuals who experience four or more episodes of migraine headaches per month should be provided with preventive treatment (Kuruppu et al., 2021, 2). Preventive treatment of migraine is useful for mitigating its symptoms and adverse impacts on patients' lives. This treatment is recommended for patients with frequent or severe migraine symptoms. The main goals of this treatment include the reduction of the duration, intensity, and frequency of episodes; improving patients' responsiveness to medication and prevention of overdose of treatments; and enhancing patients' indicators of quality of life and overall functioning (Nissan et al., 2022, 2). The main goals of preventive treatment of migraine are summed up in Figure 2 below.

Figure 2. The main goals of the preventive treatment of migraine (Nissan et al., 2022, 2).

Overview of Clostridium Botulinum Toxin (Botox):

Botox is a neurotoxin complex that can be used for paralyzing muscles. It is derived from a type of bacteria known as Clostridium botulinum. Botox was accidentally found to be effective in treating migraine; this effect was discovered while using botox as a cosmetic treatment. Those who received botox injections were found to have significantly fewer occurrences of headaches (The Migraine Trust, 2023, 1).

The explanation of the effect of botox in treating migraine is that it blocks the production of neurotransmitters. Neurotransmitters are chemical compounds that transmit pain signals from the brain. Botox can also be used for treating a variety of other conditions, such as stroke, neuropathic pain, lower back pain, bladder pain, and cerebral palsy (The Migraine Trust, 2023, 1).

Eight types of Clostridium Botulinum toxin exist, coded by letters from A to H. From among these types, only two types are used for treating headaches, which are A and B (Kępczyńska & Domitrz, 2022, 2).

Botulinum toxins A and B have a variety of medical uses, which are illustrated briefly in Figure 3 below.

Figure 3. The most prominent medical uses of Clostridium Botulinum toxins A and B (Dima et al., 2019, 4).

Effectiveness of Clostridium Botulinum Toxin as a Migraine Treatment:

Evidence shows that Botulinum toxin A is effective in relieving pain associated with a variety of medical conditions, such as migraine. The explanation of this effect is that the toxin blocks the neural signals of sensory pain to the central nervous system; this results in reducing central sensitization (Shen & Wang, 2020, 201).

The different strains of Botulinum produce certain neurotoxins that have a blocking effect on the release of acetylcholine at neuromuscular junctions. This blocking mechanism results in a flaccid paralysis. Therefore, Clostridium Botulinum has been used as a treatment for conditions characterized by excessive contraction of muscles. Since its introduction into therapeutic use, Botulinum toxin has been speculated to have pain relieving effects other than those stemming from muscle contraction. Hence, interest in studying the impact of using Botulinum toxin on migraine has emerged. For the treatment of migraine, the Botulinum toxin is administered by injection into muscles located in the head and back of the neck. Regular administration of the Botulinum toxin is necessary for producing therapeutic effects (Herd et al., 2018, 7).

Figure 4 below illustrates how the Botulinum toxin produces the pain relieving effect.

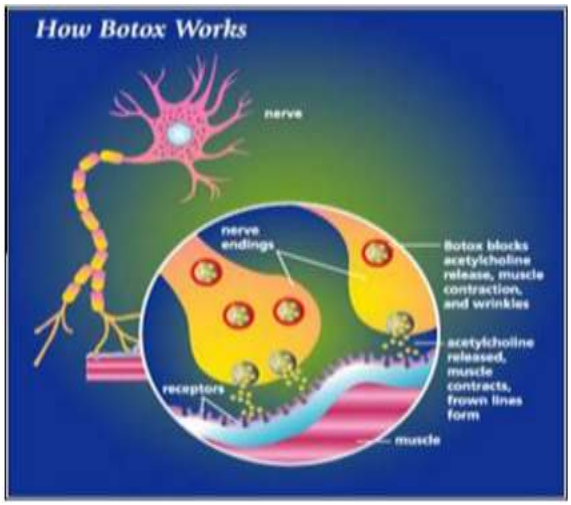

Figure 4. The mechanism of the effect of Botulinum toxin impacts on neuromuscular junctions (Alshadwi et al., 2015, 4).

Injection sites of botulinum are numbered at 31 sites distributed across the head and neck. The administered dose is 5 units per site (a total of 155 units). Retreatment is administered every 12 weeks (Lipton & Silberstein, 2015, 113). The injection sites of botulinum are illustrated in Figure 5 below.

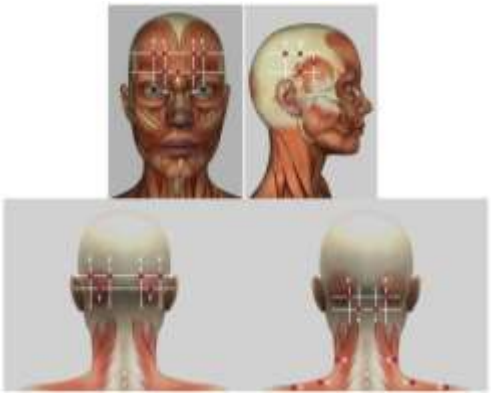

Figure 5. Botulinum toxin injection sites for treating migraine. (Lipton & Silberstein, 2015, 114).

In addition to the aforementioned clinical procedures, it would be of value to raise patients' awareness on the potential positive effects of keeping a diary that describes the symptoms experienced after receiving the treatment. Furthermore, injection should focus on the particular sites in which the pain is concentrated; these sites should be targeted with additional injections. This strategy is known as "follow the pain" (Kępczyńska & Domitrz, 2022, 4).

Despite its therapeutic benefits, the use of botulinum toxin type A can result in a variety of adverse effects. The most notable of these effects include facial paresis, migraine, headache, pruritus, neck pain, rash, muscle spasms, musculoskeletal stiffness, musculoskeletal pain, myalgia, muscular weakness, muscle tightness, and pain at injection sites. These effects typically occur within the few days following the administration of the treatment and are generally short lasting; however, with some patients, the side effects may be experienced for several months, or even years, following the administration (Dillon, 2012, 5).

Overview of Galcanezumab:

Galcanezumab is a monoclonal antibody that binds to and blocks calcitonin gene-related peptide (abbreviated at CGRP) (Lamb, 2018, 1769). It can be used for the prevention of chronic or episodic migraine. The importance of binding to CGRP is that it plays a significant role in nociceptive modulation, vasodilation, and neurogenic inflammation associated with migraine (Hirata et al., 2021, 721).

In a fashion similar to that of botulinum toxin, galcanezumab focuses in treating migraine on CGRP biding (Gklinos & Mitsikostas, 2020, 1). Galcanezumab's initial entrance into the markets was in the United States in September 2018 (Kuruppu et al., 2021, 1616). The main features of galcanezumab are outlined in Figure 6 below.

Features and properties of galcanezumab	
Alternative names	Galcanezumab-gnlm; Emgality; LY2951742
Class	Antimigraines; monoclonal antibodies
Mechanism of action	Humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the receptor
Route of administration	Subcutaneous
Pharmacodynamics	Binds to calcitonin gene-related peptide (CGRP) with high affinity (K_D 31 pmol/L); neutralizing CGRP-induced receptor activation; inhibits capsaicin-induced dermal blood flow response
Pharmacokinetics	Linear pharmacokinetics; slow absorption (time to maximum concentration ≈ 5 days) and long elimination half-life (≈ 27 days)
Adverse reactions	Injection-site reactions (including pain, erythema and pruritus)
ATC codes	
WHO ATC code	N02C-X08 (galcanezumab)
EphMRA ATC code	N2C (anti-migraine preparations)
Chemical name	Immunoglobulin G4, anti-(human calcitonin gene-related peptide) (human-Mus musculus clone III heavy chain), disulfide with human-Mus musculus clone III kappa chain, dimer

Figure 6. Features of galcanezumab (Lamb, 2018, 1771).

Effectiveness of Galcanezumab as a Migraine Treatment:

Galcanezumab is one of the drugs that rely in controlling migraine on targeting CGRP or its receptor. These drugs are classified by the mechanisms by which they make effect into the following categories (Rivera-Mancilla et al., 2020, 1238):

1. Gepants: these drugs take effect by direct blocking of the CGRP receptor only.
2. Monoclonal antibodies: the main effect mechanism of these drugs is the direct blocking of the CGRP or its receptor. Galcanezumab is an example of an antibody that targets the CGRP.

The mechanisms by which gepants and monoclonal antibodies relieve the pain associated with migraine are illustrated in Figure 7 below.

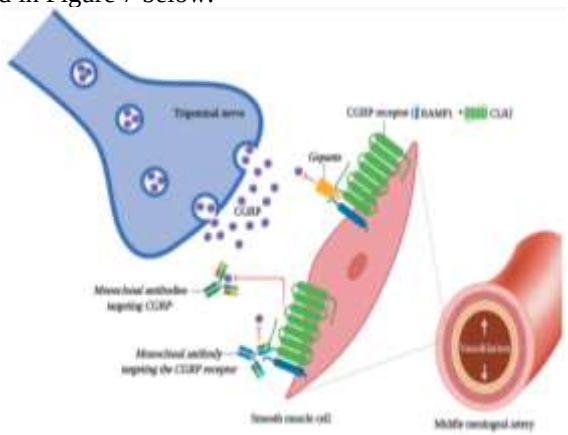

Figure 7. The mechanisms by which gepants and monoclonal antibodies relieve the pain associated with migraine (Rivera-Mancilla et al., 2020, 1238)

Compared to Botulinum toxin, evidence available supporting the effectiveness of galcanezumab as a migraine treatment is still limited, as of the time of writing this article. This paucity of evidence is largely attributable to the fact that the treatment is still under development. The mechanism by which galcanezumab treats migraine revolves around binding to CGRP, but without blocking the CGRP receptor (Rosen et al., 2018, 1348).

Galcanezumab is administered only once month via prefilled syringes or auto-injectors. The recommended doses of galcanezumab are as follows (Kuruppu et al., 2021, 1616):

1. An initial dose of 240 mg. This dose is administered as two consecutive 120 mg injections. Injection is performed using a prefilled syringe or an auto-injector.
2. One dose per month following the initial injection. Each dose is an injection of 120 mg.
3. It is preferable to administer 120 mg rather than 240 mg, as the latter has not been proven a superior approach over the former.

According to Igarashi et al. (2023, 74), global trials of galcanezumab show that the treatment has a significant effect in reducing the number of days in which moderate-to-severe and severe migraine occurs as well as the number of days in which other symptoms associated with migraine occur, including aura, prodromal symptoms, phonophobia, photophobia, and vomiting.

Methodology:

- **Research Design:**

The present study adopts a descriptive research design. This research design was selected because it is ideal for analyzing data collected from multiple independent groups and identifying/measuring similarities and differences between investigated groups (Lynch-Phillips, 2019, 60). The study compares the efficacy of botulinum toxin to that of galcanezumab in a sample of patients with chronic margarine, based on patients' reporting.

- **Sampling Method:**

The researcher adopts the random sampling method. Based on this technique, all members of the population have equal chances of being selected in the final sample. The purpose of using the random sampling method is to maintain the objectivity of sample selection.

- **Ethical Considerations:**

The researcher obtained consent from sample members prior to conducting the clinical trial. Collected data will not be disclosed or shared with any third party and will only be used for scientific research purposes.

- **Research Population and Sample:**
  - **Population:**

The population of the study consisted of patients who presented to one university hospital located in a large city in the Arab Republic of Egypt during the period spanning from January 1, 2023 to June 30, 2023. Data was retrieved from the hospital's data records.

  - **Sample:**

The researcher randomly selected a total of (100) patients from the population. The sample was selected using the random sampling method. The sample was randomly divided into two groups that received different therapies for migraine: the first group included (48) patients and received a galcanezumab-based therapy, while the second group included (52) patients who were treated using botulinum toxin (botox).

- **Data Collection:**
  - **Data Collection Instrument:**

In order to arrive at an appropriate design for the present study's data collection instrument, the researcher reviewed relevant literature with similar topics and clinical trial goals. The designed questionnaire focused on the aspects of quality of life outlined below:

1. Number of episodes of migraine.
2. Severity of episodes migraine.
3. Number of work days missed.
4. Number of attendances to emergency departments.

  - **Data Collection Procedures:**

Baseline data was collected on July 1, 2023. This was followed by the administration of the two therapies for the study groups. The processes of data collection and therapy administration were repeated over on a monthly basis over a period of six months starting from the time of collecting baseline data. The final questionnaire was distributed on January 1, 2024, but no additional administration of therapies was carried out.

- **Statistical Techniques:**

The study uses simple descriptive statistical techniques in order to formulate clear descriptions of changes/improvements and compare between the two study groups in terms of extent of change.

Findings and Discussion:

- **Overall Improvement Percentage:**

The overall improvement percentage scores for the study groups, based on sample members' responses, are illustrated in Table 1.

Table 1. Overall improvement percentages for study groups.

Study Group	Overall Improvement Percentage
Botulinum toxin	70%
Galcanezumab	80%

Table 1 shows that both therapies were strongly perceived by sample members to have a significant impact in addressing migraine symptoms. However the table highlights the superiority of galcanezumab.

- **Indicators of Improvement:**
  - **Number of Episodes:**

According to sample members' responses, the administration of the botulinum toxin and galcanezumab was associated with improvement in the number of episodes. Table 2 illustrates the extent of improvement in both groups in that regard.

Table 2. Improvement in number of episodes for the study groups.

Study Group	Improvement in Number of Episodes
Botulinum toxin	70%
Galcanezumab	80-85%

Table 2 shows that galcanezumab was more strongly perceived compared to botulinum toxin as an efficacious treatment for improving the number of episodes of migraine. While members of the botulinum toxin group reported that the number of episodes was reduced for the botulinum toxin group by 70%, members of the galcanezumab group reported that their therapy reduced the frequency of migraine episodes by 80-85%.

  - **Symptom Severity:**

The administration of the botulinum toxin and galcanezumab was perceived by sample members to be associated with improvement in the symptom severity. Table 3 illustrates the extent of improvement in both groups in that regard.

Table 3. Improvement in symptom severity for the study groups.

Study Group	Improvement in Symptom Severity
Botulinum toxin	80%
Galcanezumab	70%

Table 3 shows that botulinum toxin was more strongly perceived compared to galcanezumab as an efficacious treatment for improving the severity of symptoms of migraine. While members of the galcanezumab toxin group reported that the severity of symptoms was reduced for by 70%, members of the botulinum toxin group reported that their therapy reduced the severity of symptoms by 80%.

However, some members of the botulinum toxin group reported feeling changes in the nature of symptoms, such as feeling more frequency bilateral headaches; this indicates that sample members started experiencing tension-type instead of migraine headaches.

- **Missing Work Days:**

The administration of the botulinum toxin and galcanezumab was perceived by sample members to be associated with improvement in missing work days. Table 4 illustrates the extent of improvement in both groups in that regard.

Table 4. Improvement in missing work days for the study groups.

Study Group	Improvement in Missing Work Days
Botulinum toxin	60%
Galcanezumab	90%

Table 4 shows that galcanezumab was significantly more strongly perceived compared to botulinum toxin as an efficacious treatment for reducing missing work days. While members of the botulinum toxin group reported that the number of missing work days was reduced by 60%, members of the galcanezumab group reported that their therapy reduced the number by 90%.

- **Emergency Department (ED) Visits:**

The administration of the botulinum toxin and galcanezumab was perceived by sample members to be associated with improvement in ED visits. Table 5 illustrates the extent of improvement in both groups in that regard.

Table 5. Improvement in ED visits for the study groups.

Study Group	Improvement in ED Visits
Botulinum toxin	60%
Galcanezumab	75%

Table 5 shows that galcanezumab was more strongly perceived compared to botulinum toxin as an efficacious treatment for reducing ED visits. While members of the botulinum toxin group reported that the number of ED visits was reduced by 60%, members of the galcanezumab group reported that the number was reduced by 75%.

- **Patients with Complete Recovery:**

An important area of comparison between the botulinum toxin and galcanezumab is the number of patients who perceived achieving full recovery from migraine. Table 6 compares between the two groups in the regard.

Table 6. Number of fully recovering patients from the study groups.

Study Group	Number of Fully Recovering Patients
Botulinum toxin	0
Galcanezumab	4

Table 6 shows that galcanezumab was more strongly perceived compared to botulinum toxin as an efficacious treatment for achieving full recovery. While no member of the botulinum toxin group included reported achieving full recovery, four members of the galcanezumab group reported perceiving the effect.

- **Patients with Poor Recovery Outcomes:**

Findings show perceived poor outcomes reported by some members from both study groups. These outcomes are as follows:

1. Three patients from the galcanezumab group reported feeling no improvement (0%) after the intervention.
2. Six patients from the botulinum toxin group reported feeling worsening symptoms after the intervention.

- **Effect of Medication Overdose:**

The study investigated the perceived effect of overdose on the study groups. The percentages of reported improvement resulting of overdose on headache symptoms in study groups are illustrated in Table 7 below.

Table 7. Improvement resulting from overdoses of the therapies.

Study Group	Improvement Resulting from Medication Overdose
Botulinum toxin	70%
Galcanezumab	70%

Table 9 shows that overdose of botulinum toxin is almost equally strongly perceived is efficacious in mitigating the severity of migraine symptoms as overdose of galcanezumab. Overdose of both medications was perceived to be associated with reducing symptom severity by 70%.

The researcher believes that this finding warrants further research for more conclusive findings. Conducting conventional blind injections may be of value in obtaining findings that help in arriving at better insights and understanding of how botulinum toxin and galcanezumab address the symptoms of migraine.

- **Refractory Migraine:**

Five sample members (from both groups) reported having refractory migraine prior to the administration of the medications. Treatment was perceived to be efficacious for addressing the symptoms. The percentages of improvement ranged between 40 and 60%.

Conclusion:

This study has provided a brief discussion of two of the most promising medications for treating migraine, namely botulinum toxin (botox) and galcanezumab. Topics of discussion in the study included an overview of migraine, overview of botulinum toxin (botox) and galcanezumab, and effectiveness of the two medications. The researcher also conducted a head-to-head clinical trial to compare the effects of the two medications on a sample of patients with migraine from one large university hospital in Egypt.

Findings of the study highlight evident therapeutic superiority of galcanezumab compared to botulinum toxin, based on sample members' perceptions. Galcanezumab was perceived to be more effective overall and on indicators of improvement (number of episodes, symptom severity, missing work days, emergency department (ED) visits). Findings show that administering galcanezumab was felt to yield better results in the possibility of achieving full recovery and addressing the symptoms of refractory migraine. Moreover, unlike botulinum toxin, galcanezumab was not reported to result in worsening symptoms for any sample member.

Through the findings, the study recommends conducting further research for comparing the efficaciousness of migraine medications other than those discussed in the present study.

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