

Emerging Treatment Options for Migraine

Yi Jing [Zhao](#),¹*MRCP*, Jonathan JY [Ong](#),^{2,3}*MRCP*, Peter J [Goadsby](#),⁴*MD, PhD*

Abstract

Migraine is one of top 5 medical conditions that contribute to Years Lived with Disability and affects approximately 1 billion people from around the world. To date, preventive treatment and acute therapies for migraine are limited, have undesirable side effects and are poorly tolerated in patients. In the last few decades, considerable advances in our understanding of migraine and its pathophysiology have paved the way for the development of targeted treatment options. Calcitonin gene-related peptide (CGRP) plays an integral role in the neurobiology of migraine, and new classes of drugs that target the CGRP pathway have included gepants and CGRP pathway monoclonal antibodies. Serotonin 5-HT_{1F} receptor agonists—namely ditans—have also been developed to treat acute migraine. Lastly, non-invasive neuromodulation offers another treatment option for migraine patients who prefer treatments that have fewer side effects and are well tolerated. In this review, we discussed emerging treatment options for migraine that were made available in recent years.

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Introduction

As 1 of the top 5 medical conditions that contribute to Years Lived with Disability,¹ migraine is estimated to affect 1 billion individuals from around the world. Despite the high cumulative lifetime risk that migraine poses to many people,² preventive treatment of the condition is still limited.

Currently, acute treatment options for migraine include analgesics such as acetaminophen, aspirin and non-steroidal anti-inflammatory drugs. These treatments are non-targeted and are associated with significant

side effects.³ Ergotamine preparations have been used for close to 100 years but are no longer considered good treatment option due to the many side effects associated with their use.⁴ Triptans, which are serotonin 5-HT_{1B/1D} receptor agonists,⁵ were the first group of drugs that were specifically designed to treat migraine.⁶ Triptans have important limitations, especially contraindications in patients with cardiovascular risk factors.⁷

Preventive medications for migraine faced similar problems. Conventional treatment options were

¹Department of Neurology, National Neuroscience Institute (Singapore General Hospital Campus), Singapore

²Division of Neurology, University Medicine Cluster, National University Hospital, Singapore

³Yong Loo Lin School of Medicine, National University of Singapore, Singapore

⁴NIHR-Wellcome Trust King's Clinical Research Facility, SLaM Biomedical Research Centre, King's College, United Kingdom

Address for Correspondence: Dr Zhao Yi Jing, Department of Neurology, National Neuroscience Institute (Singapore General Hospital Campus), Outram Road, Singapore 169608.

Email: zhao.yi.jing@singhealth.com.sg

serendipitously borrowed from treatments of other conditions that were not specifically developed to treat migraine. Consequently, the wide range of mechanisms of action had led to undesirable side effects. These factors undermined the efficacy of the drugs that were attributed to poor tolerability and resulted in poor adherence and persistence in patients.^{8,9} Studies have shown that up to 80% of patients discontinued their preventive migraine treatments within 1 year after they were started on them.¹⁰

The unmet needs and challenges faced by migraine patients and medical practitioners alike have led to a search for new treatment options. In the last few decades, considerable advances were made in our understanding of migraine and its pathophysiology,^{11,12} and they helped to pave the way for the development of targeted treatment options such as calcitonin gene-related peptide (CGRP) that targets the neurobiology of migraine.¹¹ The new classes of drugs that were developed specifically target the CGRP pathway and included small-molecule CGRP receptor antagonists or gepants and CGRP monoclonal antibodies.^{13,14} Both classes of drugs have emerged as frontrunners in acute and preventive treatment of migraine, respectively.

Non-triptan serotonergic agonists that have better cardiovascular safety profile—namely serotonin 5-HT_{1F} receptor agonists or ditans—were also developed.¹⁵ Additionally, non-invasive neuromodulation is a useful treatment in migraine patients who prefer treatments

that offer fewer side effects and tolerability issues¹⁶ or have contraindications to existing pharmacological options. In this review, we focus on emerging therapeutic options for acute treatment and prevention of migraine.

Emerging Preventive Therapies

CGRP Pathway Monoclonal Antibodies

CGRP monoclonal antibodies were developed for preventive treatment of migraine. The early success of onabotulinumtoxin A in the prevention of chronic migraine suggested that peripheral drugs were effective as migraine therapy.¹⁷ However, the site of action of onabotulinumtoxin A in migraine remains unresolved. Since CGRP monoclonal antibodies have large molecular weight, it is postulated that they do not cross the blood-brain barrier substantially. Consequently, they are assumed to exert only a peripheral effect on the trigeminovascular structures.

As a class of drugs, CGRP monoclonal antibodies target either the CGRP receptor or its ligand. Hence, there are minimal unintended side effects with vastly improved tolerability. Additionally, their long half-lives make them ideal for dosing at longer intervals and obviate the need for daily dosing.¹⁴

Recently, 4 monoclonal antibodies—erenumab, fremanezumab, galcanezumab and eptinezumab—were developed and approved by the United States Food and Drug Administration (FDA) in the last 2 years (Table 1).^{18–20} Erenumab was the first monoclonal

Table 1. Summary of CGRP Monoclonal Antibodies

CGRP Monoclonal Antibody	Route of Administration	Target	Molecular Form	Recommended Dose and Frequency	Main Adverse Reactions
Eptinezumab (ALD-403)*	Intravenous	CGRP ligand	Humanised IgG1	100 mg or 300 mg every 3 months	Flu-like symptoms, fatigue, nausea/vomiting
Erenumab (AMG-334)†	Subcutaneous	CGRP receptor	Human IgG2	70 mg or 140 mg every month	Injection site reaction, flu-like symptoms, constipation
Fremanezumab (TEV-48125)‡	Subcutaneous	CGRP ligand	Humanised antiCGRP IgG2	225 mg every month or 675 mg every 3 months	Injection site reaction, pruritus
Galcanezumab (LY-2951742)§	Subcutaneous	CGRP ligand	Humanised antiCGRP IgG4	240 mg loading and 120 mg every month thereafter	Injection site reaction, flu-like symptoms, abdominal pain

CGRP: Calcitonin gene-related peptide; IgG1: Immunoglobulin G1; IgG2: Immunoglobulin G2; IgG4: Immunoglobulin G4

*Lipton R. Eptinezumab for Prevention of Chronic Migraine: Results of 2 Quarterly Intravenous Infusions in the Phase 3 PROMISE-2 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy-2) Trial. Scientific Presentation at the American Headache Society Annual Meeting, 28 June–1 July 2018, San Francisco, CA, USA.

†Shi L, Lehto SG, Zhu DXD, Sun H, Zhang J, Smith BP, et al. Pharmacologic characterization of AMG334, a potent and selective human monoclonal antibody against the calcitonin gene-related peptide receptor. *J Pharmacol Exp Ther* 2016;356:223–31.

‡Bigal ME, Escandon R, Bronson M, Walter S, Sudworth M, Huggins JP, et al. Safety and tolerability of LBR-101, a humanized monoclonal antibody that blocks the binding of CGRP to its receptor: results of the phase I program. *Cephalalgia* 2014;34:483–92.

§Benschop RJ, Collins EC, Darling RJ, Allan BW, Leung D, Conner EM, et al. Development of a novel antibody to calcitonin gene-related peptide for the treatment of osteoarthritis-related pain. *Osteoarthritis Cartilage* 2014;22:578–85.

antibody that was approved for use by the FDA in May 2018 (Table 2).¹⁸

Erenumab (AMG-334)

Erenumab differs from the other 3 monoclonal antibodies in that it is a fully human antibody and targets the canonical CGRP receptor, the calcitonin-like receptor/RAMP 1 complex.²¹ Erenumab is available in several countries since 2018.¹⁸ Results from initial phase 2 trials showed that it has good safety and tolerability profile in the treatment of chronic and episodic migraines.^{22,23} In episodic migraine, erenumab 70 mg was established as an effective dose in patients of a 5-year open-label extension study. An interim study published in 2017 also demonstrated favourable safety and tolerability profiles, including improved measurements across the primary and secondary endpoints.²⁴

Two large phase 3 trials, ARISE and STRIVE,^{25,26} showed success in the primary endpoint of reduction in mean monthly migraine days. In ARISE, 577 patients who experienced episodic migraine were randomised to a placebo group and a treatment group that were given erenumab 70 mg; consequently, a reduction of -2.9 monthly migraine days was seen in the treatment group against -1.8 days in placebos.²⁵ In STRIVE, 955 patients with episodic migraine were randomised to 3 treatment arms comprising placebos, erenumab 70 mg and 140 mg who were treated for 6 months. Between 4–6 months, mean reduction in monthly migraine days was 3.2 in the 70 mg group, 3.7 in the 140 mg group and 1.8 in placebos. The study also achieved positive results in all secondary endpoints, including a reduction of 50% in mean monthly migraine days and mean number of days of taking acute migraine-specific medications.²⁶

In ARISE and STRIVE, patients who failed >2 migraine prevention treatments were excluded. A separate study, LIBERTY, addressed this issue by randomising these patients with episodic migraine to either placebos or erenumab 140 mg. The 50% responder rate for reduction in monthly migraine days was 30% in treated patients and 14% in placebos. This finding supported the efficacy of erenumab in a group of difficult-to-treat migraine patients.²⁷

Fremanezumab (TEV-48125)

Fremanezumab is a humanised, subcutaneous immunoglobulin G2 monoclonal antibody that targets the alpha and beta forms of the CGRP ligand.²⁸ It is the only CGRP monoclonal antibody that offers monthly

and quarterly dosing schedules, and was approved by the FDA in September 2018.¹⁹

In phase 3 of the HALO episodic migraine prevention trial, monthly and quarterly treatments with fremanezumab 225 mg and 675 mg reduced mean monthly migraine days by 3.7 and 3.4 days, respectively, compared to -2.2 days in placebos.²⁹ In phase 3 of the HALO chronic migraine prevention trial, the results in both treatment arms were also positive compared to placebos.³⁰ In both trials, injection site reactions were more commonly reported in treated patients than placebos.

Galcanezumab (LY-2951742)

Galcanezumab is one of 2 humanised, subcutaneous monoclonal antibodies that target the CGRP ligand.³¹ The results from 2 phase 3 randomised controlled trials, EVOLVE-1 and EVOLVE-2, that examined the effect of galcanezumab 120 mg and 240 mg on episodic migraine^{32,33} showed a reduction in mean monthly migraine days with good overall efficacy, safety and tolerability.

For chronic migraine, the REGAIN study also yielded positive results with galcanezumab 120 mg and 240 mg that showed a significant reduction in mean monthly migraine days compared to placebos.³⁴

Eptinezumab (ALD-403)

Eptinezumab is a 90% humanised, immunoglobulin G1 subtype monoclonal antibody that targets the CGRP ligand.³⁵ It was approved by the FDA in February 2020 for preventive migraine treatment in adults.³⁶ It is the only monoclonal antibody that is administered through infusion. Since it is administered on a quarterly basis, it has the additional advantage of reaching peak concentrations very quickly.^{35,37}

Pivotal trials of eptinezumab include 2 phase 3 trials, PROMISE-1 and PROMISE-2, in episodic and chronic migraine, respectively.^{38,39} Notably, both trials included a unique secondary outcome measure that scrutinised the probability of a migraine attack happening at day 1 post-infusion. In PROMISE-1, the probability of a migraine attack at day 1 was reduced by 45% to 53.6% in 3 treatment arms compared to 20.7% in placebos.³⁸ In PROMISE-2, the results were equally encouraging; the likelihood of migraine at day 1 was reduced by 51% and 53% for eptinezumab 100 mg and 300 mg, respectively, compared to 27% in placebos.³⁹ The quick onset of efficacy will likely confer an additional advantage on eptinezumab by helping it to gain wider use in acute treatment of migraine than other monoclonal antibodies.

Table 2. Key Trials in Calcitonin Gene-Related Peptide (CGRP) Development

CGRP Monoclonal Antibody and Trial	Active Arm Dose and Frequency	Sample Size	Target Population	Treatment Duration	Change in Mean Monthly Headache Days		Treatment Difference (P Value)	≥50% Response Rate	P Value	
					Active	Placebo				
Erenumab										
ARISE*	70 mg every 4 weeks	577	Episodic migraine	12 weeks	-2.9	-1.8	-1.0 (<0.001)	39.7	29.5	0.010
STRIVE†	Arm 1: 70 mg every 4 weeks Arm 2: 140 mg every 4 weeks	955	Episodic migraine	6 months	-3.2	-1.8	-1.4 (<0.001)	43.3	26.6	<0.001
Fremanezumab										
HALO‡	Arm 1: 225 mg every 4 weeks Arm 2: 675 mg, single dose	875	Episodic migraine	12 weeks	-4.0	-2.6	-1.4 (<0.001)	47.7	27.9	<0.001
HALO II§	Arm 1: 675 mg, single dose Arm 2: 675 mg at baseline followed by 225 mg at weeks 4 and 8	1130	Chronic migraine	12 weeks	-4.3	-2.5	-1.8 (<0.001)	38	18	<0.001
Galcanezumab										
EVOLVE¶	Arm 1: 120 mg every 4 weeks Arm 2: 240 mg every 4 weeks	858	Episodic migraine	6 months	-4.7	-2.8	-1.9 (<0.001)	62.3	38.6	<0.001

*Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia* 2018;38:1026–37.

†Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med* 2017;377:2123–32.

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Table 2. Key Trials in Calcitonin Gene-Related Peptide (CGRP) Development (Cont'd)

CGRP Monoclonal Antibody and Trial	Active Arm Dose and Frequency	Sample Size	Target Population	Treatment Duration	Change in Mean Monthly Headache Days		Treatment Difference (P Value)	≥50% Response Rate		P Value
					Active	Placebo		Active (%)	Placebo (%)	
EVOLVE 2 [†]	Arm 1: 120 mg every 4 weeks	915	Episodic migraine	6 months	-4.3	-2.3	-2.0 (<0.001)	59.3	36	<0.001
	Arm 2: 240 mg every 4 weeks				-4.2		-1.9 (<0.001)	56.5		<0.001
REGAIN [#]	Arm 1: 120 mg monthly with loading dose of 240 mg	1113	Chronic migraine	3 months (9-month open-label extension)	-4.8	-2.7	-2.1	27.6	15.4	<0.001
	Arm 2: 240 mg for 3 months				-4.6		-1.9	27.5		<0.001
Eptinezumab										
PROMISE 1 ^{**}	Arm 1: 30 mg every 4 weeks	888	Episodic migraine	12 weeks	-4.0	-3.2	-0.8 (0.0045)	50.2	37.4	
	Arm 2: 100 mg every 4 weeks				-3.9		-0.7 (0.0179)	49.8		
	Arm 3: 300 mg every 4 weeks				-4.3		-1.1 (0.0001)	56.3		
PROMISE 2 ^{**}	Arm 1: 100 mg every 4 weeks	1022	Chronic migraine	6 months	-7.7	-5.6 (at months 1-3)	-2.1 (<0.0001)	61	44	
	Arm 2: 300 mg every 4 weeks				-8.2 (at months 1-3)		-2.6 (<0.0001)	64		

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Emerging Acute Therapies

5-HT_{1F} Receptor Agonists

Triptans are serotonin 5-HT_{1B/1D} receptor agonists and have remained the mainstay of acute migraine treatment since their introduction.⁴⁰ Despite evidence to the contrary,⁴¹ the potential for vasoconstriction associated with their use has curbed their widespread usage over concerns of cardiovascular and cerebrovascular risks.

Ditans are a new class of serotonin 5-HT_{1F} receptor agonists that were developed to treat acute migraine. Lasmiditan was the first medicine to be introduced and approved by the FDA for the acute treatment of migraine with or without aura.⁴² Preclinical studies have demonstrated that 5-HT_{1F} receptor agonists can inhibit trigeminocervical nociceptive traffic independent of any vascular effect.⁴³ Lasmiditan acts by reducing plasma protein extravasation at the trigeminal ganglion.⁴⁴ It selectively targets 5-HT_{1F} receptors—which are not expressed in the vasculature⁴⁵—and inhibits trigeminocervical nociceptive transmission. Its expression in the trigeminovascular system provides relief from migraine pain without the vasoconstrictor effects associated with triptans, potentially benefitting migraine patients who have concomitant cardiovascular or cerebrovascular conditions.⁴⁶

A phase 3 placebo-controlled randomised trial, SAMURAI, that investigated lasmiditan 100 mg and 200 mg in acute treatment of migraine found that pain relief at 2 hours was 59% compared to 43% in placebos. Also, 41% of patients experienced relief from their most bothersome symptoms with lasmiditan 100 mg and 200 mg compared to 30% in placebos.⁴⁷ Similarly, phase 3 of the SPARTAN trial demonstrated positive results for lasmiditan 50 mg, 100 mg and 200 mg in providing relief from pain at 2 hours and from most bothersome symptoms.⁴⁸

Lasmiditan was generally well tolerated, with paraesthesia and dizziness reported as the most frequent adverse events.⁴⁹ This finding was consistent with preliminary results reported in the open-label study, GLADIATOR, which ended recently and the publication of its results are currently pending.⁵⁰

CGRP Receptor Antagonists and Gepants

In the 1990s, a class of serotonin 5-HT_{1B/1D} receptor agonists, the triptans, were introduced as acute therapy in migraine management.⁵¹ However, the potential vasoconstrictor effects associated with their use in patients with cardiovascular and cerebrovascular diseases had prevented their widespread use.^{7,52} Studies had shown that CGRP levels were elevated

in the jugular vein during spontaneous and provoked migraine attacks. Provocation studies that used CGRP had shown that it could induce migraine-like attacks in migraineurs that subsided after they were given triptans.^{53–5} Against this background, interest turned to the development of gepants.

The first proof of concept study drug, BIBN 4096 BS (olcagepant), proved effective in the acute treatment of migraine attacks. Since it was administered intravenously,^{56,57} it was never commercialised. Subsequently, gepants were developed as oral medications including BI 44370 TA, telcagepant, MK-3207, rimegepant and ubrogepant. The initial development of this class of drugs was temporarily halted after concerns were raised over the hepatotoxicity of telcagepant and MK-3207.^{58,59} Apart from atogepant that was developed as preventive migraine therapy, most trials on gepants focused mainly on acute migraine treatment (Table 3).¹³

Ubrogepant

Ubrogepant has completed 2 positive phase 3 studies (ACHIEVE I and II). In Achieve I, 1327 patients were randomised to placebos, ubrogepant 50 mg and 100 mg.⁶⁰ The study met the primary endpoints of relief from pain for 2 hours and absence of most bothersome symptoms for both doses compared to placebos. Achieve II randomised 1355 patients to a lower dose of 25 mg and 50 mg.⁶¹ Both doses showed statistically significant results in providing relief from pain for 2 hours compared to placebos, while the 50 mg dose provided absence of most bothersome symptoms for 2 hours.

An open-label extension study also demonstrated that the treatment arm had a similar adverse event profile as the care arm.⁶² Ubrogepant was recently approved by the FDA for acute treatment of migraine with or without aura in adults.⁶³

Rimegepant

The findings of the latest phase 3 trial that assessed the efficacy of rimegepant in the treatment of acute migraine against placebos were published in July 2019. The results were positive: 19.6% of patients were pain-free for 2 hours after taking rimegepant compared to 12.0% in placebos. Likewise, for freedom from most bothersome symptoms at 2 hours post-dose, it was 37.6% in rimegepant patients compared to 25.2% in placebos.⁶⁴

Safety and tolerability were similar between treated patients and placebos, with nausea and urinary tract

Table 3. Migraine Drugs Approved in Last 5 Years

Drug Class and Name	Pharmaceutical Company	Brand Name	FDA Approval	Indication	Completed Phase 3 Trials
CGRP monoclonal antibodies					
Erenumab	Amgen/Novartis	Aimovig	17 May 2018	Preventive treatment of migraine in adults	ARISE* STRIVE† Liberty‡
Fremanezumab	Teva Pharmaceuticals	Ajovy	14 September 2018	Preventive treatment of migraine in adults	HALO I§ HALO II¶
Galcanezumab	Eli Lilly and Company	Emgality	27 September 2018	Preventive treatment of migraine in adults	EVOLVE 1¶ EVOLVE 2# REGAIN**
Eptinezumab	Alder Biopharmaceuticals/ Lundbeck	Vyepti	21 February 2020	Preventive treatment of migraine in adults	PROMISE-1†† PROMISE-2‡‡
5-HT_{1F} receptor agonists					
Lasmiditan	Eli Lilly and Company	Reyvow	11 October 2019	Acute treatment of migraine with or without aura in adults	SAMURAI§§ SPARTAN GLADIATOR¶¶
CGRP receptor antagonists					
Ubrogepant	Allergan	Ubrovelvy	23 December 2019	Acute treatment of migraine with or without aura in adults	ACHIEVE I## ACHIEVE II***

CGRP: Calcitonin Gene-Related Peptide; FDA: Food and Drug Administration

*Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia* 2018;38:1026–37.

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§Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. *JAMA* 2018;319:1999–2008.

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††Saper J, Lipton R, Kudrow D, Hirman J, Dodick D, Silberstein S, et al. Primary results of PROMISE-1 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy-1) trial: a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of eptinezumab for prevention of frequent episodic migraines. *Neurology* 2018;90:S20.001.

‡‡Lipton R. Eptinezumab for Prevention of Chronic Migraine: Results of 2 Quarterly Intravenous Infusions in the Phase 3 PROMISE-2 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy-2) Trial. Scientific Presentation at the American Headache Society Annual Meeting, 28 June–1 July 2018, San Francisco, CA, USA.

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infections reported as the most common side effects. Specifically, issues with liver safety were not reported.⁶⁵ Currently, rimegepant is undergoing a phase 2 trial for migraine prevention. Should it prove successful, rimegepant will become the first gepant that is clinically proven to be effective in the treatment of acute migraine and prevention.

Atogepant

Atogepant is a novel, oral CGRP receptor antagonist that was designed to prevent migraine onset. It was described at the Scientific Meeting of the American Academy of Neurology and American Headache Society in 2018 and the results in patients with episodic migraine were reported to be promising. A total of 834 subjects were randomised across 5 different doses of atogepant and placebo. The findings included a mean reduction of 4 days in monthly migraine days in patients treated with atogepant.⁶⁶ At the time of writing, the findings have not been published. A phase 3 trial on prevention of chronic migraine is ongoing.⁶⁷

Neuromodulation

Non-invasive neuromodulation represents a non-pharmacological modality of treatment. It modulates the pain experienced by migraine patients, but without any of the side effects associated with medication-taking in acute and preventive migraine therapy.

Single-Pulse Transcranial Magnetic Stimulation

Transcranial magnetic stimulation is widely used by neurologists for diagnostic and therapeutic purposes,⁶⁸ and is deemed safe and non-invasive. By leveraging on the concept of electromagnetic field, neurologists are able to deploy fluctuating magnetic waves to reach the cerebral cortex to induce weak electric currents that can modify the excitability of neurons.⁶⁹ Initially, this intervention was piloted in animal models to inhibit cortical spreading depression and modulate thalamocortical signalling.⁷⁰ With the development of single-pulse transcranial magnetic stimulation (sTMS), its use in migraine patients was evaluated in a sham controlled trial⁷¹ and open-label trial⁷² for acute therapy.

In the sham-controlled trial, a total of 164 patients were treated with sTMS. The study reported that the pain-free response rate at 2 hours was significantly better at 39% in the sTMS group compared to 22% in the sham group. Adverse events were comparable between sTMS and sham groups.⁷¹

In the open-label trial, ESPOUSE, the efficacy of sTMS in preventive migraine therapy was evaluated

in 132 patients.⁷³ The findings of the study included a mean reduction of 2.75 headache days from a baseline of 9.06 days. Additionally, all pre-specified multiplicity-protected, secondary endpoints were met. The adverse events commonly reported in the study included light-headedness, tingling, tinnitus and dizziness. sTMS was approved by the FDA and the National Institute for Health and Care Excellence in the United Kingdom for acute and preventive treatment of migraine with and without aura.⁷⁴

Conclusion

Over the last 3 decades, considerable progress was made to understand the pathophysiology of migraine. This led to a burgeoning tide of new treatment options that are mechanism-based and targeted. The recent introduction of pharmacological and non-pharmacological treatments described in this review offer millions of migraine patients from around the world hope of more effective and lasting relief from the condition.

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