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EPISODIC MIGRAINE (S NAHAS, SECTION EDITOR)

# Traditional and Novel Migraine Therapy in the Aging Population

Shema Mathew[1] · Jessica Ailani[1]

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**Abstract**
Migraine is a common disabling disorder that affects 36 million Americans. The clinical features of migraine are less typical in the people above age 60, making the diagnosis and treatment difficult in this group. In this review, we will discuss migraine-specific drugs and their use in populations about age 60 who suffer from migraine. This discussion will include an overview of traditional treatments for the acute and preventive treatment of migraine, and considerations for their use in patient populations above age 60. In addition, we will discuss newer agents that show a more promising safety profile.

**Keywords** Migraine · Aging population · Triptan · Gepant · Ditan

**Abbreviations**

| | |
|---|---|
| CGRP | Calcitonin gene related peptide |
| NSAIDs | Nonsteroidal anti-inflammatory drugs |
| TCA's | Tricyclic antidepressants |
| DHE | Dihydroergotamine |

## Introduction

Migraine is the most commonly diagnosed disabling disorder in the world, according to the Global Burden of Disease Survey 2015 [1]. Despite the high prevalence of migraine in the elderly population, it is poorly studied in people above age 60 [2]. Migraine causes a significant burden on the quality of life of the aging population [3]. In an epidemiological study by Waters, in people older than 75 years, 21% of the men and 55% of the women had recurrent headaches [4]. There are only a few studies investigating primary headache disorders in people above age 60 compared to the majority of studies that focus on secondary headaches in the aging [5–8].

Migraine in the aging population is mostly bilateral, and associated symptoms are fewer, making the misdiagnosis of tension type headache more common [9]. Other qualities of migraine, such as nature of pain, frequency of attacks, prodrome features, and aura are not different in migraine attacks in patients above age 60 [4]. As in other adult age groups, the most common associated migraine symptoms in the older age group are photophobia and phonophobia. As in children, migraine attacks in the aging population are reported to be shorter in duration [10].

Approximately 2% of patients report that their migraine onset is after age 50 [10]. A majority of migraineurs continue to have migraine attacks as they get older with rare cases of complete resolution of migraine, although frequency of attacks may decrease [11, 12]. It is also common for migraineurs with aura to experience aura without headache as they get older [6, 13].

Due to physiological and pathological changes that occur with aging, they are more susceptible to adverse effects of medication [14]. A majority of migraine trials exclude patients above age 60 or 65, so it is difficult to assess the impact of aging on medication efficacy and side effects [15]. Many elderly patients also have co-morbid diseases like atherosclerosis, hypertension, and diabetes which lead to heart disease and stroke and they influence the management of migraine in the elderly [16].

## Overview of Medications Used in Migraine

### Acute Migraine Medications

Patients with migraine should all have a treatment option to use for acute attacks. These can be non-specific medications, such as acetaminophen, non-steroidal anti-inflammatory

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✉ Shema Mathew
shema.mathew@gunet.georgetown.edu

[1] Department of Neurology, Med star Georgetown University Hospital, 3800 Reservoir Road NW, 7 PHC, Washington, DC 20007, USA

drugs (NSAIDs), or combination drugs. For more rapid onset attacks, attacks with significant nausea and/or vomiting, or more severe attacks, migraine specific medications should be considered.

Acetaminophen can be used in the older population but due to hepatic metabolism, liver function has to be monitored especially when it is taken in doses of > 3 g/day [17]. In patients with renal or hepatic dysfunction, it is advisable to reduce dose by 50–75% [15, 17].

NSAIDs should be used with caution in ages above 65 as there is risk of gastric ulcer or gastric bleeding [15]. As a result of gastrointestinal complications from NSAID therapy, thousands of patients above age 65 die annually [15]. NSAIDs are known to have interaction with anti-hypertensive agents, diuretics, hypoglycemic drugs, and digoxin. COX-2 inhibitors, which belong to the class of NSAIDs can increase the risk of stroke [18].

When NSAIDs are used in older population, renal function, liver function, and gastrointestinal adverse events should be monitored due to potential hepatotoxicity and nephrotoxicity [18].

The use of opioid analgesics is limited in the older population due to side effects like sedation and cognitive decline [19]. High doses of tramadol can cause seizures [17].

Neuroleptics are mainly used as antiemetics in acute migraine. They are also effective in relieving migraine pain [20]. They have to be used with caution in the older population as they can cause drug-induced Parkinsonism [21] and should be avoided in patients with Parkinson's disease which is common in this age group.

Ergotamine should be avoided or used with caution in patients above 65, particularly in those with pre-existing hypertension as it can cause coronary vasoconstriction and associated ischemic changes [22].

Triptans are selective agonists at 5HT1B and 5HT1D subtypes and have a more favorable risk profile as compared to ergot alkaloids [23]. In vivo, in human studies show that triptans induce vasoconstriction, increase blood pressure and decrease buffering capacity of conduit arteries after taking therapeutic dosages of triptans [24]. As a result, triptans are contraindicated in individuals who suffer from active cardiovascular disease and hypertension that is not under control [25]. As discussed previously, these conditions are common in the elderly population. However, a retrospective case-control study has shown that there was no increase in incidence of ischemic cardiovascular complications in patients with cardiovascular risk factors and is on triptans [26].

## Preventive Migraine Medications

Tricyclic antidepressants (TCAs) develop higher plasma drug concentrations and metabolites in patients who are older compared to younger patients [15]. Amitriptyline can cause cardiac conduction abnormalities, orthostatic hypotension, seizures, and confusion [22]. Due to glaucoma and urinary retention in the older population, TCAs are contraindicated in patients with these conditions [22].

With the exception of venlafaxine, the use of Selective serotonin reuptake inhibitors(SSRIs) and Selective norepinephrine reuptake inhibitors (SNRIs) for prophylactic treatment of migraine is not supported by evidence [27]. In the elderly, studies have shown that there is strong association of development of hyponatremia following treatment with SSRIs and venlafaxine. Sodium levels have to be monitored when older patients are being treated with these medications [28].

The use of beta blockers, a first-line medication for migraine prevention has to be limited in older population because they influence congestive heart failure, conduction abnormalities, asthma, glaucoma, depressive symptoms, and diabetes [22].

Sodium valproate causes many adverse events because of reduction of hepatic mass and blood flow in this age group. This drug can cause liver function disturbances, decreased bone marrow density, delirium, tremor, and ataxia [29–31].

There is moderate reduction in clearance of calcium channel blockers with aging [32]. These agents have to be used with caution in patients with congestive heart failure [22]. Verapamil has been associated with gastrointestinal bleeds because it has antiplatelet effects [33].

Lisinopril, candesartan and topiramate are medications that have good evidence for migraine prevention and have not shown to cause increased side effects in patients above 65 [34–36] (Table 1).

## Novel Medications in Migraine Treatment

5HT1F receptors have been shown to be associated with migraine pathophysiology and selective 5HT1F receptor agonists known as ditans have been created as an option for migraine treatment [37, 38].

**Table 1** Dosage and Titration of safe medications for use in older populations

| Medication | Dosage | Most common side effects |
|---|---|---|
| Lisinopril | 10 mg daily × 7 days, then 20 mg daily as tolerated | Dizziness, cough, syncope, and hypotension |
| Candesartan | 4 mg daily, increase by 4 mg every 3–5 days to a max of 16-32 mg/day | Dizziness and tiredness, Paresthesia |
| Topiramate | 25 mg daily, Increase by 25 mg every week to 100 mg as tolerated (max of 200 mg) | Paresthesia, taste disturbances, word-finding difficulty, and weight loss |

Lasmiditan is a 5-hydroxytryptamine(HT)1F receptor agonist. Preclinical models with lasmiditan have shown that it does not cause vasoconstriction and its antimigraine effects are probably mediated through neural modulation [39].

The results from a randomized, double blind, placebo controlled, parallel group, phase 3 trial of various doses of lasmiditan to placebo to treat a single migraine attack showed benefit [40]. The presence of cardiovascular factors did not exclude patients from the study. 2231 subjects with migraine with or without aura were enrolled and given 100 mg lasmiditan vs. 200 mg lasmiditan vs. placebo to treat a single migraine attack. Results found that 28.2% of patients were pain free at 2 h with 100 mg, 32.2% were pain free at 2 h with 200 mg and 15.3% were pain free at 2 h with placebo [40]. The most common side effects were paresthesia, somnolence, nausea, fatigue, and dizziness.

There are two other phase 3 trials evaluating the safety and efficacy of various doses of lasmiditan, which also met primary end points for doses of 100 mg and 200 mg [41•, 42•].

One study evaluated three doses of lasmiditan (50, 100, and 200 mg) when compared to placebo in the treatment of acute migraine. This study did not exclude patients with coronary artery disease, cardiac arrhythmias, or uncontrolled hypertension. The study met its primary end-point of pain freedom in 2 h, with 28.6% of subjects taking 50 mg, 31.4% of subjects taking 100 mg, and 38.8% of subjects taking 200 mg of lasmiditan having pain freedom compared to placebo 21.3%, ($P < 0.005$) [41•].

There was a prospective, open label study evaluating the safety and tolerability of lasmiditan 100 mg vs. 200 mg [42•]. This study enrolled participants who completed the first two trials [40, 41•]. Subjects were randomized to receive either 100 mg or 200 mg of lasmiditan. The primary end points were the proportion of subjects who experienced adverse events, and the proportion of migraine attacks associated with adverse events. Approximately 20% of patients taking both doses experienced side effects. Dizziness was the most commonly reported side effect. No cardiovascular events or side effects have been reported [42•].

5HT1F receptor agonists can be considered as another type of specific acutely acting antimigraine drug with cardiovascular safety when compared to triptans and with a mechanism of action to be somewhat different from that of triptans. Due to the lack of vasoconstrictive properties, they have a better safety profile to be used in the elderly population with migraine.

## Small Molecule CGRP Antagonists (Gepants) and CGRP Mab (Calcitonin Gene-Related Peptide Monoclonal Antibodies)

CGRP is released in the perivascular space by trigeminal sensory neurons. It is a potent vasodilator and plays a central role in neurogenic inflammation [43]. CGRP receptor antagonists under the pharmacological class of "gepants" namely olcegepant and telcagepant have proven to show efficacy in treatment of migraine, but were discontinued due to hepatotoxicity with daily use [44–49].

Newer CGRP antagonist ubrogepant and rimegepant are in development for acute migraine treatment and atogepant is in development for migraine prevention [50–53].

In order to study the vasoconstrictive properties of small molecule CGRP receptor antagonists, ex vivo experiments were done on human coronary and cerebral arteries with sumatriptan and small molecule CGRP antagonists rimegepant [54•]. The results showed that rimegepant did not actively constrict human coronary or cerebral arteries when tested up to concentrations of 10um. Sumatriptan showed concentration–dependent active constriction of human coronary and cerebral arteries. This suggests that rimegepant may be free from the cardiovascular limitations seen with triptans [54•].

Monoclonal antibodies (mABs) to CGRP are macro molecules that are unlikely to cross the blood brain barrier [55]. They require parental administration, intramuscular, intravenous, or subcutaneous. CGRP mABs have been found to be efficacious in the prevention of migraine in adults [56]. Their mode of action is either through binding the CGRP ligand (eptinezumab, fremanezumab, galcanezumab) or the CGRP receptor (erenumab).

The effect of erenumab on exercise time during treadmill stress tests in patients with stable angina was studied [57•]. This study consisted of 89 patients with documented coronary artery disease. After two exercise tests, if the patient qualified, they were randomized 1:1 and administered either IV placebo or IV erenumab 140 mg with a third treadmill administered within 1 h. The primary end point was the change from baseline in exercise duration as measured by the total exercise time. The result was that the total exercise time change from baseline in the erenumab group was non-inferior to that observed in the placebo group. The secondary end point was time to onset of at least 1-mm ST segment depression and time to onset of exercise-induced angina during the treadmill. It was reported that there was no difference in erenumab and placebo groups for the secondary end points of time to exercise induced angina or time to onset of > 1-mm ST segment depression [57•].

The results of this study show that erenumab may be safe from a vascular stand point and may be considered for the use in elderly patients who may have stable angina. Larger studies on these populations would be needed to confirm results. It is of note that the original erenumab phase 2/3 trials did not include patients above the age of 65.

The above studies show that gepants and CGRP mabs are effective for migraine treatment, possibly without vasoconstrictor activity, and could be an option for migraine treatment in the elderly (Table 2).

**Table 2** ***Strategies to use medications that are risky in older populations

| | |
|---|---|
| Acetaminophen | Monitor liver function test (LFT) if given > 3 g/day. Limit intake to 15 days/month. |
| NSAIDs | Add proton pump inhibitor to avoid gastro-intestinal complications. Monitor LFT and kidney function test every 3 months. Limit intake to 10 days/month. |
| Triptans | Close monitoring of blood pressure, advisable to get cardiac clearance for coronary artery disease (CAD) if they are symptomatic/develop symptoms after initiating triptans. Limit intake to 2 days/week |
| TCA | Avoid in patients with orthostatic hypotension and cognitive decline, Administer small doses between 10 and 30 mg with slow titration |
| Sodium valproate | Monitor LFT and observation for side effects of tremors and ataxia |
| Beta blockers | Check blood glucose level every 3 months and regular follow up to monitor mood (depression) and blood pressure |

***The strategies mentioned are not evidence based, but based on the personal opinion of authors after review of the appropriate literature cited in this article

## Botulinum Toxin (BoNT)

Onabotulinum toxin A (BoNT/A) is approved for the prevention of chronic migraine (CM) in adults [58]. The mechanism of action of BoNT/A in headache is uncertain. Rat models suggest that pericranially injected BoNT/A is taken up by local sensory nerve endings, axonally transmitted to the trigeminal ganglion and transcytosed to dural afferents [59]. Co-localization of synaptosomal-associated protein (SNAP-25) and the migraine mediator CGRP in dura suggests that BoNT/A may prevent dural neuro inflammation by suppressing transmission by CGRP. This might explain the effects of BoNT/A in headache disorders like migraine [59].

As it lacks the medication side effects, it is a safe option to be used in the older population.

## Noninvasive Neuromodulation

As glutaminergic neurotransmission and cortical excitability are linked to migraine and cortical spreading depression, neuromodulation is a key concept in migraine. There are currently several neuromodulation devices available to treat migraine in adults.

Transcutaneous supraorbital nerve stimulation (TSNS) is an external stimulator for treatment of migraine [60]. A sham controlled study of TSNS showed that it reduced the number of headache days > 50% in patients with episodic migraine (with and without aura) by the third month of use [61]. The adverse effects of TSNS appear to be mild and transient, which were intolerance to paresthesia, drowsiness, worsening of headache, and reversible forehead irritation [62]. A sham controlled study with TSNS to assess the safety and efficacy of the device for acute pain relief during migraine attacks resulted in significant pain relief with the use of TSNS when compared to sham stimulation and was well tolerated suggesting that it may be safe and effective acute treatment for migraine attacks [63].

Transmagnetic stimulation (TMS) is known to induce depolarization which disrupts the cortical spreading depression associated with migraine and therefore prevents migraine propagation [64]. A sham controlled study on sTMS in the acute treatment of migraine with aura, reported a pain-free response rate higher in those with active compared with sham treatment [65].

Noninvasive vagal nerve stimulation (nVNS) device is another device that is used in headache treatment. nVNS stimulates low threshold myelinated A fibers through 90-s pulses [66]. There are two small open label studies and a prospective study for nVNS showing efficacy in the treatment of acute migraine pain [67, 68•].

Since neuromodulation devices have no major side effects, they can be an effective treatment option to treat migraine in the older population.

## Conclusion

Migraine presents with less typical features in people above age 60, making the diagnosis more difficult in this age group. It is important to rule out secondary causes of headache, especially when they present with visual symptoms in the absence of headache. It is important to remember that comorbid conditions play a role in the diagnosis and treatment of migraine in general population, but more so in the older age group and medications have to be chosen carefully for the acute as well as preventive treatment.

Medications that are used for acute and preventive treatment like Acetaminophen, Nonsteroidal anti- inflammatory drugs, Ergotamine, Triptans, Tricyclic Antidepressants, Sodium valproate, Calcium channel blockers, beta blockers

should be used with caution due to adverse events related to physiological and pathological changes in older subjects.

For preventive treatment, medications namely lisinopril, candesartan, and topiramate can be used in the older age group as they have good evidence to be effective for prophylactic treatment of migraine and have not shown to cause increased side effects in patients above age 65.

It is important to start medications at a very low dose and titrate slowly, monitor side effects and obtain lab work as needed on a regular basis.

Other non-medication options that are safe to be used in the older age group are Botulinum toxin injections, noninvasive neuromodulation devices like cefaly, trans magnetic stimulation device, and noninvasive vagal nerve stimulation device.

Although the side effect profile is good for the recently FDA-approved CGRP mab group of medications, they have not been studied in the older age group.

While there are some options for prophylactic management of migraine in the older age group, medications for acute treatment are sparse. It is controversial if the most commonly used traditional antimigraine-specific triptans can be used in the older age group.

Some of the noninvasive neuromodulation devices mentioned above which are approved for acute management of migraine can be used safely in the older age group.

With current studies, thus far lasmiditan, which is a 5HT1F receptor agonist and small molecule CGRP antagonists or gepants have shown promising safety profile for the acute treatment of migraine in the elderly.

## Compliance with Ethical Standards

**Conflict of Interest** Shema Mathew and Jessica Ailani declare no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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