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Injection-Based Therapies for Migraine in Older Adults: A Narrative Review of OnabotulinumtoxinA, Greater Occipital Nerve Block, and Anti-Calcitonin Gene-Related Peptide Monoclonal Antibodies

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ABSTRACT

As global populations age, the clinical approach to managing migraine must evolve. Migraine in older adults presents unique treatment challenges due to comorbidities, poor adherence to treatment, altered pharmacokinetics, and polypharmacy. Injection -based preventive treatments such as onabotulinumtoxinA (BoNT-A), greater occipital nerve blocks (GONB), and anti-calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) offer promising alternatives. This narrative review highlights the underrepresentation of older adults in migraine clinical trials and summarizes the effectiveness and safety of BoNT-A, GONB, and CGRP mAbs in patients over 65 years of age. To identify relevant studies addressing migraine management in the older adults, we conducted a comprehensive literature search of PubMed, Embase, and Cochrane Library. The search was limited from the past ten years, up to 5 April 2025. Studies were included if clinical trial, observational, real-world data, or review examined migraine treatment in adults over 65 years, with separate data according to age. A total of 22 studies were included: 4 on BoNT-A, 2 on GONB, 13 on anti-CGRP mAbs, and 3 reviews on injectable therapies. BoNT-A has shown significant benefits in reducing migraine frequency, acute medication use, and disability in real-world settings though randomized trials did not include older adults. GONB has demonstrated

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high response rates in older adults, although there was no separate analysis for patients over 65 years of age in randomized controlled trials. In contrast, CGRP mAbs have increasingly included in trials, with some trials enrolling patients up to 75 years. Subgroup analyses and real-world data support their comparable effectiveness and safety in older adults. BoNT-A, GONB and CGRP mAbs show effectiveness and are well tolerated for migraine prevention in older adults. Given the growing ageing population and their unique therapeutic needs, proactive migraine management in older migraine patients with injection-based and oral preventive is essential.

Keywords: Migraine Disorders; Older Adults; OnabotulinumtoxinA; Greater Occipital Nerve Block; Calcitonin Gene-Related Peptide Monoclonal Antibodies; Prevention

INTRODUCTION

As global populations age, migraine in older adults presents unique treatment challenges due to comorbidities, poor adherence to treatment, altered pharmacokinetics, and polypharmacy.[1] According to a Danish study, 38% of migraine patients aged 25–64 went into remission after 12 years of follow-up. In a US study, the estimated remission rate based on incidence and prevalence was 1.7% at age 20 and 7.1% at age 60, increasing with age.[2-4] Although the prevalence decreases after the fifth or sixth decade of life, it remains significant, affecting approximately 7% of women and 3% of men over 65 years of age. Additionally, the prevalence of migraine has been reported as 6% in women and 3% in men over 80 years of age.[5,6]

The clinical presentation of migraine in older adults often differs from that in younger populations, characterized by reduced attack frequency, decreased pain intensity, and sometimes late-onset aura with/without headache (migraine equivalent).[7] Such changes, combined with age-related comorbidities and an increased risk of secondary headache disorders with age, can complicate accurate diagnosis and effective management.[2,8,9] Furthermore, polypharmacy, physiological changes such as decreased drug clearance, and difficulty in obtaining the clinical information due to impaired cognition and mobility further compound the challenges of treatment.[10] While traditional prophylactics like tricyclic antidepressants, beta-blockers, and antiseizure medications remain common, they are often accompanied by adverse effects that limit their tolerability in older adults. Triptans are generally contraindicated in vascular diseases such as myocardial infarction and cerebral infarction, but their use in migraine patients has increased rapidly since the 2000s, with approximately 5% of migraine patients over the age of 60 using triptans.[11,12] Nonetheless, appropriate treatment is essential for older adults with migraine, as some individuals may be resistant to traditional treatments. In 2022, it was estimated that 10% of the global population was aged 65 and older, with this figure projected to rise to about 18% among OECD countries by 2025.[13] Although the World Health Organization and the United Nations announced the plan for “Decades of Healthy Ageing 2021–2030,” the consideration of headache or migraine is scarce in the document.[14]

The demand for treatment of migraine in older adults is increasing. Considering the high risk of adverse drug responses and multi-drug interactions, onabotulinumtoxinA (BoNT-A) has been recommended as a safe and useful option for older adults with chronic migraine by expert opinion, but there are very few reports on the actual outcomes of treatment in

older adults with migraine.[6,15] In addition, anti-calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) as migraine-specific treatments represent a paradigm shift in migraine management.[16] Greater occipital nerve block (GONB) with local anesthetics have been shown to be effective in prevention of migraine and the advantage of being relatively inexpensive and available at medical centers in a wide range of locations.[17-19] However, most randomized trials of Botox, GONB and CGRP mAbs are limited to patients aged 65 years or younger, making evidence-based treatment of older adults difficult.[20,21]

Recently, some randomized clinical trials (RCTs) of CGRP mAbs have begun to include participants up to 70[22-24] or 75[25-29] years of age. However, the proportion of people over the age of 65 is very small or unknown, so separate analysis for older adults with migraine is warranted.

This narrative review focuses specifically on treatment, exclusively injection-based preventive treatments, including BoNT-A injections, GONB, and CGRP mAb treatments for migraine patients over 65 years of age. We examined the age inclusion criteria for representative clinical trials and separate analysis for aged people. By consolidating evidence from recent real-world studies and clinical trials of these treatments, including their effectiveness, adverse events, and comparisons with younger patients, we aim to provide practical insights and expert opinions for optimizing care of migraine for older adults.

METHODS

To conduct a narrative review of migraine injectional preventive treatments in older adults over 65 years of age, a structured search strategy was employed using the PubMed, Embase, and Cochrane review database. The search strategy involved applying filters to limit studies published in the last 10 years, up to 4 April 2025 (Accessed from 4 April 2025 to 5 April 2025).

The search focused on identifying relevant articles and the search terms for PubMed and Cochrane review included combinations of keywords such as ((migraine) AND ((elderly) OR (older) OR (geriatric) OR (aged)) AND ((calcitonin-gene related peptide) OR (onabotulinumtoxinA) OR (occipital nerve block)). For the search through Embase, search terms included combination of keywords (treatment of migraine with calcitonin-gene related peptide monoclonal antibody or onabotulinumtoxinA or occipital nerve block) and (aged 65+ years).

Boolean operators (e.g., AND, OR) were used to refine the search results and ensure relevance to the topic (**Fig. 1**). The retrieved references were saved as files and imported to Rayyan, a web and mobile application for systematic review, for duplicate and relevance checking.[30] First, we evaluated the abstract to determine its relevance to the work and then reviewed the full text. We have checked the references of the selected articles to identify any other relevant publications.

SJC, BSK, SC, and MKK reviewed the initial research and selected the relevant articles. We included the studies that all meet the following criteria: 1) included or focused on older adults with migraines over 65 years of age, and 2) clinical trials, observational studies, or real-world evidence or important reviews of CGRP-targeted therapies, botulinum toxin, or GONB with local anesthesia. We excluded studies that did not have relevant search terms or did not include older adults over 65.

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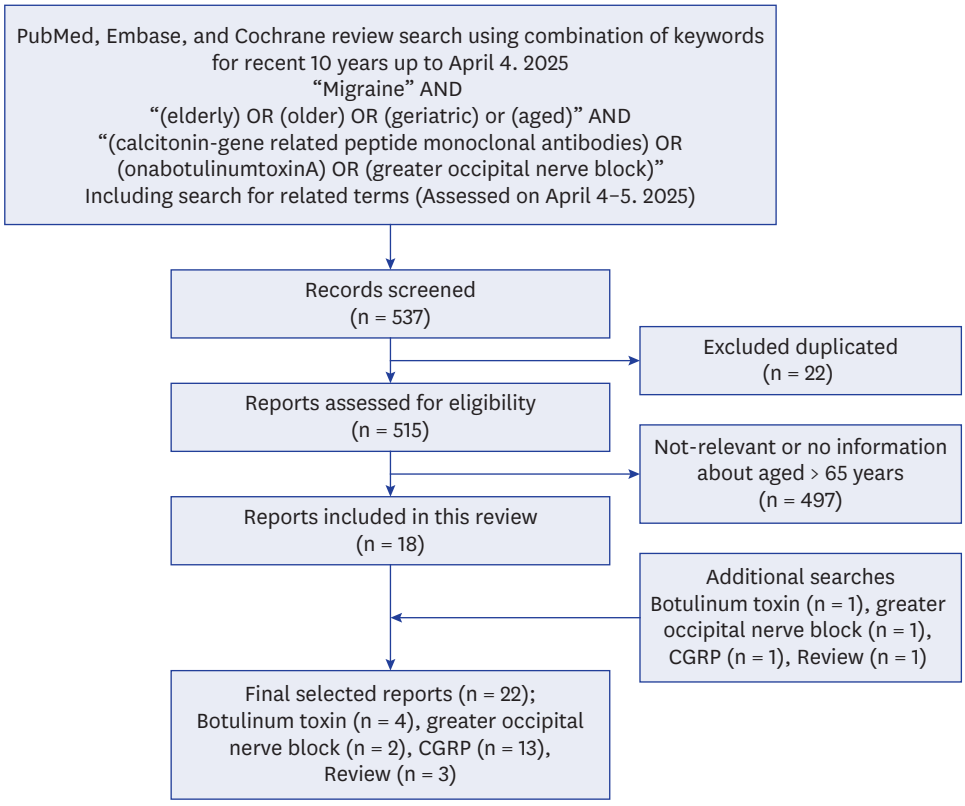

Fig. 1. Flow chart of the selection of reviewed articles.

However, our literature review revealed a paucity of studies with comparable patient-reported outcome measures in older adults with migraines over 65 years of age. Therefore, a systematic review was not feasible, and we conducted a comprehensive narrative review of BoNT-A injections, GONB, and CGRP mAb treatments based on articles between April 2014 and March 2025.

The reviewed information was descriptively analyzed to identify trends, treatment effectiveness, safety profiles, and areas for further research.

RESULTS

A total of 537 records were screened. After removing 22 duplicates, 515 articles were assessed for eligibility. Among them, 396 articles were excluded due to irrelevance or lack of data on patients aged ≥ 65 years. Eighteen studies were included from the initial screening. Through additional searches, 4 more studies were identified (1 on BONT-A, 1 on GONB, 1 on CGRP mAbs, and 1 review article), resulting in a final inclusion of 22 articles: 4 on BONT-A, 2 on GONB, 13 on CGRP mAbs, and 3 review articles (**Fig. 1**).

OnabotulinumtoxinA

BoNT-A is an established treatment option for chronic migraine; however, there is no published RCT including migraine patients aged over 65 years.[31] Although BoNT-A has not been specifically tested in older adults for migraine prevention, it has been extensively

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used for cosmetic purposes, such as treating wrinkles in the elderly.[32] BoNT-A inhibits neurotransmitter release from the peripheral terminals of trigeminal neurons, reducing peripheral and central sensitization.[33] Its non-systemic action and long safety record make it particularly suitable for older adults with comorbidities and polypharmacy.

The use of BoNT-A can reduce the monthly frequency of migraine attacks, the severity of pain, and migraine-related disabilities in patients with chronic migraine.[34,35] Additionally, BoNT-A is a well-tolerated treatment that contributes to improving overall functional performance and health-related quality of life. Overall, BoNT-A has demonstrated significant effectiveness in the treatment of patients with chronic migraine as well as high frequency episodic migraine.[35-38]

There are three real-world studies examining the effectiveness of BoNT-A in older adults with migraine. Altamura et al.[15] evaluated the prophylactic effects of BoNT-A in older adults with chronic migraine through a real-life European multicenter study, focusing on a standard dose of 155–195 units over a period of 9 months. The study provided evidence that BoNT-A is effective across different age groups, with no significant differences in outcomes between older adults and younger patients. It demonstrated that BoNT-A treatment significantly reduced both monthly headache days and monthly acute medication days. The ≥ 50% responder rate was comparable between older adults and younger patients (38.7% vs. 42.4%, $P = 0.301$), and the reversion rate to episodic migraine was also similarly high in both groups (72.3% vs. 68.8%, $P = 0.416$). Similarly, Özön[39] conducted a small retrospective cohort study that demonstrated the effectiveness of low doses of BoNT-A in older adults, reducing both the frequency and severity of chronic migraine attacks. This study evaluated the effectiveness of lower doses (30 or 60 units) over 3 months and suggested significant benefits of even with reduced doses in this population. A study by Ceccardi et al.[40] further supports the use of BoNT-A in older adults with chronic migraine. This retrospective analysis included 24 patients aged over 60, many of whom had multiple comorbidities and had previously failed several preventive treatments. Over a 12-month follow-up period, patients experienced significant reductions in monthly headache days, high-intensity headache days, analgesic consumption, and MIDAS scores. BoNT-A was generally well tolerated, with only mild and transient adverse effects reported in 20% of patients, and no serious adverse events.[40] These findings suggest that BoNT-A is a safe and effective preventive option for chronic migraine in older adults with migraine, including those with complex medical conditions (**Table 1**).

Although age-related changes in drug metabolism and muscle mass are acknowledged, there are currently no specific recommendations regarding dosage adjustments or treatment schedules for older adults. The effectiveness of BoNT-A may be influenced by various factors, including the anatomical area being treated, gender, muscle mass, and skin thickness.[42] Therefore, patient-centered approaches for follow-up treatments are recommended.

In summary, real-world studies evaluating BoNT-A in older adults consistently demonstrate its effectiveness in reducing migraine frequency and acute medication use, though they vary in study design, dosing strategies, and the extent of functional improvement reported.[15,39,40] However, their study lacked a younger comparator group. These results suggest that while standard dosing remains effective, lower doses might be appropriate for selecting older adults. None of these studies reported serious adverse effects, supporting the safety of BoNT-A in older adults. Future prospective trials with head-to-head comparisons across

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Table 1. Summary of studies about botulinum toxin A and greater occipital nerve block

Source	Setting	Sample size	Mean age, yr	Headache type	Management	Duration	Outcomes, mean (SD)	Outcome measure	Key findings
Altamura et al., 2023[15]	16 European multicenter study Prospective real-life studies, Italy	≥ 65 yr: 235 < 65 yr: 2,596	69.6 (SD 4.7)	Chronic migraine	BoNT-A 155–195 units	9 mon	In elderly, at three treatment cycles MHD: 24.8 (6.2) to 11.9 (7.9), $P = 0.001$ DAM: 19.2 (9.8) to 9.6(7.4), $P = 0.049$ ≥ 50% responder rate: 30.7% to 38.7%	Changes in MHDs and DAMs ≥ 50% responder rate Compared between old and non-old patients	Old age did not influence the outcome
Özön et al., 2020[39]	Retrospective cohort study, Turkey	≥ 65 yr: 26 < 65 yr: 27	68 (min–max 65–73)	Chronic migraine	BoNT-A 60 units (5 unit each muscle[a]) 30 units (2.5 units each muscle)	3 mon	Comparison between elderly and non-elderly 60U: 7.8 (4.8) vs. 8.3 (3.8), $P < 0.01$ 30U: 7.5 (4.1) vs. 4.1 (2.7), $P < 0.01$	Difference in MHDs before and after treatment Comparison between individuals aged ≥ 65 and those aged < 65 yr	60U were effective treatment in both young and old 30U were superior in the elderly population
Ceccardi et al., 2022[40]	Headache centre of Spedali Civil of Brescia, Italy	≥ 60 yr: 24	64.9 (SD 5.4)	Chronic migraine	BoNT-A	12 mon	Baseline to 3-, 6-, 12-mon Total HDs (23.6 vs. 17.1 vs 18.1 vs. 15.7, $P < 0.0001$) Total HDs (high intensity) (11.9 vs. 9.2 vs. 7.6 vs. 3.5, $P = 0.002$ Total AMs (36.1 vs. 20.1 vs. 22.4 vs. 12.3, $P = 0.003$) MIDAS (78.6 vs. 48.6 vs. 45,3 vs. 36.2, $P = 0.05$) Side effects in 20% without serious adverse event	Reduction in total HDs, total AMs, MIDAS scores Safety by side effects	Over 60 yr old with chronic migraine, affected by systemic comorbidities, onabotulinumtoxin A seems to be a safe and well tolerated therapeutic strategy
Allen et al., 2018[41]	Retrospective cohort study at the Mayo Clinic in Arizona, USA	≥ 65 yr: 233 < 65 yr: 329	NA	Migraine	Received at least 1 GONB	At least 1 follow up visit	≥ 65 yr 54% had a significant response < 65 yr 61% had a significant response ($P = 0.03$) Across the different age categories, patients who underwent 2 GONB procedures responded equally well, with an odds ratio of 4.9 to 5.0 ($P < 0.001$).	The percentage reduction from baseline pain score using the 11-point NPRS Minimal < 30% Moderate 31–50% Significant > 50%	Older patients also demonstrated a significant response to treatment

SD = standard deviation, MHD = monthly headache days, DAM = days with acute medication use, AM = acute medication, NPRS = Numeric Pain Rating Scale, GONB = greater occipital nerve block.
[a]The injections were applied bilaterally to the following muscles: frontal muscles, temporal muscles, occipital muscles, semispinalis capitis, splenius capitis, trapezius muscles (cervical region).

different age groups and dosing regimens are needed to optimize BoNT-A protocols tailored for the older adults.

Greater occipital nerve block

Peripheral nerve block procedures have been used for both the acute and preventive treatment of migraine.[17,43] These techniques involve blocking the greater and lesser occipital nerves, as well as specific branches of the trigeminal nerve, including the supraorbital, supratrochlear, and auriculotemporal nerves.[44] Among these methods, the weekly or monthly repeated GONB is one of the most commonly employed approaches for prevention of migraine.[43] GONB blocks nociceptive input through local anesthetic action on the greater occipital nerve, thereby reducing afferent stimuli from the regions it innervates.[45] This provides an inexpensive, minimally invasive option with few systemic side effects, making it well suited for older adults with limited treatment tolerance. However, recent RCT excluded individuals over 65 years, resulting in limited data for this age group.[18] A randomized controlled trial by Dilli et al.[46] planned to include patients aged up to 75 years but did not perform a separate analysis for the older adults. The mean age of participants

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was 44 years (standard deviation = 11), suggesting that older adults were underrepresented in the study cohort.[46]

A retrospective study at the Mayo Clinic revealed that, as an acute treatment, 54% of 233 migraine patients aged 65 years or over showed a ≥ 50% improvement in their numeric pain score immediately after GONB treatment, compared to 61% of 329 patients under 65 years of age ($P = 0.03$, **Table 1**).[41] Furthermore, patients who underwent two or more repeated GONBs responded equally well across all age groups, with an odds ratio of significant response (50% reduction in pain intensity) of 4.9 to 5.0 compared to the single GONB. There were no reports of lasting complications or side effects during follow-up visits.[41]

A clinical trial investigating four-weekly GONB injections for 12 weeks showed a significant reduction in headache days among younger adult populations (40.9% vs. 9.1%, representing a 50% reduction, mean age 28.5).[47] The use of single GONB with lidocaine and methylprednisolone was reported to lead complete or partial pain relief in 48% of patients, with benefits lasting up to two months, suggesting a potential preventive effect.[48] Similarly, another study (mean age 45.8 years, range 19–68) found that 52% of patients with chronic migraine experienced a ≥ 50% reduction in headache days one month after the procedure.[49] However, these studies focused on younger participants, and evidence in this demographic has largely been limited to acute treatment responses. The current findings suggest that GONB may offer comparable acute efficacy in older adults, so further research evaluating the preventive effectiveness and safety of GONB specifically in older adults is warranted.

Calcitonin gene-related peptide monoclonal antibodies

CGRP mAbs have revolutionized migraine prevention due to their target specificity and favorable safety profiles for both episodic and chronic migraine. CGRP mAbs blocks CGRP or its receptor involved in migraine pathophysiology. Unlike traditional preventive treatments, CGRP mAbs demonstrate minimal drug interactions and superior adherence rates—attributes that are particularly valuable for older adults with migraine who often manage multiple medications.

Although CGRP mAbs are considered effective and safe, age-related changes of CGRP may influence treatment outcome. Research indicates that CGRP levels may decrease with age, potentially affecting the clinical presentation and treatment response of migraine in older adults.[50] However, no long-term prospective studies have measured CGRP levels in older adults.

Older adults have commonly been excluded from the RCTs or constituted only a small proportion of study populations. However, some recent CGRP mAb trials, particularly those involving patients with previous preventives failure, have expanded the study population to include individuals up to 75 years of age (**Table 2**). Among the available randomized trials, only a pooled subgroup analysis of three phase III fremanezumab studies specifically evaluated adults aged 60 years or older.[23] The treatment-by-age interaction was not statistically significant for key outcomes such as monthly migraine days (MMDs) ($P = 0.63$), ≥ 50% responder rate ($P = 0.58$), or Headache Impact Test-6 (HIT-6) score reduction ($P = 0.71$), indicating that age did not significantly influence treatment response. Both older and younger subgroups achieved comparable reductions in headache frequency and disability, with no increase in adverse events among older adults.

Recent real-world evidence has also begun to address this critical knowledge gap. Real-world studies have examined this population: one study focused on erenumab, another on

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Table 2. Published randomized clinical trials of calcitonin gene-related peptide monoclonal antibody for migraine

Migraine prevention treatment	Name of trial	Inclusion	Inclusion age	Published years	Separate analysis for older adults
Erenumab	STRIVE,[51] ARISE[21]	Episodic migraine	18–65 yr	2017–2018	NA
Eptinezumab	PROMISE-1[26]	Episodic migraine	18–75 yr	2020	NA
	PROMISE-2[52]	Chronic migraine	18–65 yr	2020	NA
	DELIVER[25]	Migraine with previous preventive medication failure	18–75 yr	2022	NA
Fremanezumab	HALO EM[53]	Episodic migraine	18–70 yr	2018	Pooled analyses from HALO EM, HALO CM, and FOCUS included participants aged ≥ 60 yr[23]
	HALO CM[24]	Chronic migraine	18–70 yr	2017	
	FOCUS[22]	Migraine with previous preventive medication failure	18–70 yr	2019	
Galcanezumab	EVOLVE-1,[54] EVOLVE-2[55]	Episodic migraine	18–65 yr	2018	NA
	REGAIN[56]	Chronic migraine	18–65 yr	2018	NA
	CONQUER[28]	Migraine with previous preventive medication failure	18–75 yr	2020	NA

NA = not applicable.

fremanezumab, and other studies evaluated patients treated with erenumab, fremanezumab, or galcanezumab (**Table 3**).[9,10,57-59] Two retrospective observational real-world studies suggest that erenumab, fremanezumab, and galcanezumab exhibit comparable effectiveness and safety profiles in older migraine patients, similar to those seen in younger patients.[9,10] Another prospective observational study of patients treated with erenumab demonstrated a significant reduction in MMDs and a low incidence of adverse effects among older migraine patients compared to their younger counterparts.[57] Meanwhile, a small case series has highlighted the feasibility of fremanezumab in patients aged ≥ 70 years, reinforcing its potential as a viable preventive option.[58]

Real-world studies consistently demonstrate comparable effectiveness between older and younger migraine patients. In a large-scale analysis by Salim et al.,[9] no significant difference was observed in MMD reduction between the two age groups, with both experiencing a reduction of 10.0 days ($P = 0.57$). Similarly, Cetta et al.[57] found equivalent reductions in MMDs and monthly headache days among matched cohorts of older and younger patients. Additionally, a multicenter study by Muñoz-Vendrell et al.[10] reported a significant reduction in MMDs (–10.1 ± 7.3 days) among older adults, with 57% achieving ≥ 50% reduction in migraine frequency. Safety analyses indicate generally favorable outcomes in older adults, including blood pressure monitoring over one-year period.[60] A real-life multicenter study reported adverse events in 25.3% of older adults, all of which were mild in nature.[10] Interestingly, Salim et al.[9] observed slightly lower rates of adverse events in older adults compared to younger patients (22% vs. 28%, respectively).[10] The most common adverse events in both age groups were injection site reactions and constipation. Notably, two cases of elevated blood pressure were reported among older adults, highlighting the need for cardiovascular monitoring in this population.[10] Treatment continuation rates were comparable between age groups, with approximately 73% of older adults maintaining treatment at six months, as noted in the Muñoz-Vendrell study.[10] Both age groups demonstrated significant improvements in quality-of-life measures, including HIT-6 scores.[9,10,57]

In summary, real-world studies have shown the effectiveness and safety of anti-CGRP monoclonal antibodies in patients aged ≥ 65 years. Cetta et al.[57] and Salim et al.[9] both showed comparable reductions in headache frequency and disability between older and younger groups. Muñoz-Vendrell et al.[10] reported significant clinical improvements and mild adverse effects in a large multicenter cohort. Although Gonzalez-Martinez et al.[59] observed a slightly delayed early response in older adults, the 6-month responder rates were similar to

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Table 3. Summary of real-world studies about calcitonin gene-related peptide monoclonal antibody

Source	Setting	Sample size	Mean age, yr	Headache type	Management and duration	Outcomes, mean (SD)	Outcome measure	Key findings
Cetta et al., 2022[57]	Prospective, single-center, observational study, Italy	≥ 65 yr: 15 < 65 yr: 15	≥ 65 yr: 70 (65–76) < 65 yr: 45 (19–55)	Migraine CM (60%)	Erenumab 70 (dose increased 140 mg after 3 m) or erenumab 140 6 mon	MHDs (mean, range) Baseline ≥ 65 yr: 20 [6.30] < 65 yr: 20 [6.30] After 3 m, ≥ 65 yr: 15 [1.30] < 65 yr: 14 [0.30] P = 0.881 btw groups After 6 m, ≥ 65 yr: 13 [2.30] < 65 yr: 16 [3.30] P = 0.514 btw groups	Difference in MHDs before and after treatment	After 3 and 6 mon of treatment, both groups had a reduction of all clinical features under examination, without statistically significant differences between groups. A similar proportion of patients in each group complained of AEs (M3 and M6, *P* = 1.0).
Katsuki et al., 2023[58]	Retrospective, single-center, case-series, Japan	≥ 70 yr: 6	Median age 78 (range: 71–99)	CM (n = 1), EM+TTH (n = 2), CM+MOH (n = 3)	Fremanezumab 225 mg monthly 3 mon	1) MHDs (median, range) Baseline, 30 (4–30) After 1 m, 30 (4–30) After 3 m, 29 (15–30, n = 4) 2) MAMIs Baseline, 17 (0–30) After 1 m, 9.5 (0–30) After 3 m, 1 (0–28)	Difference in MHDs and MAMI before and after treatment	Six migraine patients aged over 70 yr old treated with fremanezumab. Two (33.3%) of the six patients experienced therapeutic effectiveness
Muñoz-Vendrell et al., 2023[10]	Observational retrospective study of prospectively collected data from 18 different Spanish headache centers, Spain	≥ 65 yr: 162	Median age 68 (range: 65–87)	Migraine (80.9% CM)	Erenumab (n = 38) Galcanezumab (n = 85) Fremanezumab (n = 39) 6 mon	1) MMDs (median, range) Baseline, 18.0 ± 7.5 After 3 m, 9.8 ± 9.0 After 6 m, 7.3 ± 7.6 (*P* = 0.0001 from the baseline) 2) MHDs Baseline, 23.3 ± 6.9 After 3 m, 15.0 ± 10.5 After 6 m, 12.5 ± 10.0 (*P* < 0.001 from the baseline) 3) MAMIs Baseline, 18.9 ± 8.0 After 3 m, 11.1 ± 9.3 After 6 m, 9.4 ± 8.9 (*P* < 0.001 from the baseline)	Primary endpoints: 1) Reduction in monthly migraine days after 6 mon of treatment 2) Presence of adverse effects. Secondary endpoints 1) Reductions in headache and medication intake frequencies by months 3 and 6 2) Response rates 3) Changes in patient-reported outcomes 4) Reasons for discontinuation	Anti-CGRP mAbs are safe and effective treatments for migraine patients over 65 yr in real-life clinical practice. Treatment with fremanezumab had fewer adverse effects in our cohort. No differences were observed in patients with and without concomitant oral treatment, concomitant BTX treatment and medication overuse at baseline. I6

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Table 3. (Continued) Summary of real-world studies about calcitonin gene-related peptide monoclonal antibody

Source	Setting	Sample size	Mean age, yr	Headache type	Management and duration	Outcomes, mean (SD)	Outcome measure	Key findings
Gonzalez-Martinez et al., 2024[59]	Multicenter, real-world, observational case-control study, Spain	228 total (114 patients ≥ 65 yr, 114 matched controls < 55 yr)	≥ 65 yr: 70.1 (range 66–86) < 55 yr: 42.9 (range 38–49)	EM 20.2% CM 79.8%	Erenumab, Galcanezumab, Fremanezumab 12 wk	1) 50% responder rate (MHD): 8–12 wk: ≥ 65 yr: 31.6% < 55 yr: 48.2% (P = 0.015) 20–24 wk: ≥ 65 yr: 57.5% < 55 yr: 60.8% (P = 0.811) 2) MHD reduction (mean [SD]) 8–12 wk: ≥ 65 yr: 5.0 [7.2] < 55 yr: 8.8 [9.1] (P = 0.001) 20–24 wk: ≥ 65 yr: 8.9 [8.1] < 55 yr: 10.4 [7.7] (P = 0.591) 3) MMD reduction (mean [SD]) 20–24 wk: ≥ 65 yr: 10.7 [9.1] < 55 yr: 9.2 [7.7] (P = 0.040)	50% reduction in MHDs at 20–24 wk	Anti-CGRP mAbs are effective and well-tolerated in patients ≥ 65 yr. The older adults achieved similar 50% responder rates at 6 mon as younger controls, though early response (at 3 mon) was slower. TEAEs were mild and similar between groups (32% overall; most common: constipation). Predictors of 50% response in older patients included EM diagnosis and lower baseline MHD.
Salim et al., 2025[9]	Retrospective real-world analysis, USA	Total 3,011, ≥ 65 (n = 304) < 65 yr (n = 2,707)	≥ 65 yr: median 69.5 [IQR 67.3–73.3] yr < 65 yr: median 45.4 [IQR 35.8–53.8] yr	≥ 65 yr: EM 52 (17.1%), CM 252 (82.9%) < 65 yr: EM 543 (20.1%), CM 2164 (79.9%)	Erenumab, Galcanezumab, Fremanezumab 3 mon	1) MMDs (median IQR) ≥ 65 yr: 25 (15–30) to 8 (3–22) after 3 m < 65 yr: 20 (15–30) MMD to 8 (3–16) after 3 m P = 0.57 2) HIT-6 ≥ 65 yr: 64 (60–67) to 56 (48–63) < 65 yr:, 66 (62–69) to 56 (49–64) P = 0.27 3) MMDs changes in daily and non-daily migraine (post hoc analysis) daily migraine (change from baseline; U65, 15 (0–25); O65, 12 (0–25), P = 0.59) non-daily migraine (changes from baseline: U65, 9 (4–13); O65, 8 (3–12), P = 0.82)	The reduction in MMD and HIT-6 scores from anti-CGRP mAb treatment between O65 and U65 was compared using a nonparametric two-tailed Mann-Whitney test	There is no difference in the efficacy and tolerability of treatment with erenumab, fremanezumab, and galcanezumab in patients O65 when compared with patients U65 both with daily or nondaily migraine.

SD = standard deviation, CM = chronic migraine, MHD = monthly headache days, AE = adverse effect, MAMI = monthly acute medication intake, CGRP mAb = calcitonin gene-related peptide monoclonal antibody, IQR = interquartile range.

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Table 4. Comparative summary of three injectable preventive treatments for migraine in adults aged 65 years and older

Treatment	Evidence in ≥ 65 yr	Mechanism of action	Key advantages for older adults	Considerations in older adults
BoNT-A	Real-world studies only (no RCTs); favorable efficacy & safety	Inhibits neurotransmitter release from the peripheral terminals of trigeminal neurons	Widely available; long safety track record; non-systemic	Lack of RCTs; may require repeated injections; injection technique-sensitive
GONB	Limited data; mostly observational and acute studies	Local anesthetic blocks nociceptive input via the greater occipital nerve	Inexpensive; minimally invasive; low systemic side effects	Short duration of effect; lack of robust evidence in ≥ 65; technique-dependent
CGRP mAbs	Some RCTs and multiple real-world studies include ≥ 65; efficacy comparable to younger patients	Blocks CGRP or its receptor involved in migraine pathophysiology	High efficacy; minimal drug interactions; well tolerated	Cost; insurance access; long-term safety in frail older adults not fully established

BoNT-A = onabotulinumtoxinA, RCT = randomized controlled trial, GONB = greater occipital nerve block, CGRP mAb = calcitonin gene-related peptide monoclonal antibody.

younger patients. These findings support the use of anti-CGRP mAbs as a safe and effective option in older adults with migraine, even in those with comorbidities.

Older adults frequently present with comorbidities, particularly cardiovascular conditions (40–57%).[9,10] A retrospective cohort study of Medicare beneficiaries with migraine compared the cardiovascular outcomes in 5,153 patients with CGRP-mAb (mean age 57.8 years) and 4,000 patients with BoNT-A (mean age 61.9 years). CGRP-mAbs were not associated with an increased risk of cardiovascular events including stroke, compared to BoNT-A.[61] The older adults often requires multiple medications, making the favorable drug-drug interaction profile of CGRP mAbs particularly advantageous.[10] Some studies suggest potential differences in tolerability among different CGRP mAbs in older adults, with fremanezumab demonstrating a potentially better safety profile in certain studies.[10,58]

A comparative summary of the three injectable preventive treatments discussed above is presented in **Table 4**, highlighting their respective strengths, mechanisms, and considerations in older adults.

CONCLUSION

As the global aging population continues to grow, the demand for effective migraine treatments in older adults is also rising. Recent studies, including real-world data and observational analyses, have provided evidence regarding the safety and effectiveness of injectable treatments such as CGRP mAbs, GONB, and BoNT-A. These three injectable treatments each have their strengths and weaknesses; therefore, the clinician's expertise and decision-making are crucial for enhancing the quality of life of older adults suffering from migraines (**Fig. 2**).

The treatments options discussed in this review appear to be well tolerated, with studies demonstrating their effectiveness across various populations aged ≥ 65 years. However, due to the limited number of studies specifically focusing on older adults, further research is necessary to evaluate long-term safety, effectiveness, and the influence of age-related factors on treatment response. To ensure optimal migraine management in older adults, clinical trials that specifically include this demographic must be prioritized. Such studies will help establish robust evidence and develop treatment guidelines tailored for older adults. Additionally, older adults often have multiple comorbidities (e.g., hypertension, cardiovascular disease, diabetes) and are at a higher risk of complications related to polypharmacy. Therefore, a cautious approach that includes a baseline workup to assess for pre-existing conditions is essential when formulating treatment strategies for this population.

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		Strengths	Weaknesses	Opportunities	Threats	Key advantages
CGRP mAbs	 SC on abdomen or IV CGRP ligand or receptor	Proven efficacy	Cost↑↑	Increasing demand in aging population	Limited insurance coverage	High efficacy
		Adherence↑ (monthly or every 3 months injection)	Lack of long-term safety data (in elderly)	Elderly non-responder to traditional oral medications	Low accessibility in certain institutions or countries	Minimal drug interactions
		Low drug interaction	Caution required in patients with cardiovascular disease		Relatively new agents that require long-term follow-up	Well-tolerated
GONB	 Blocking GONs and LONs	Simple preparation (weekly or monthly injection)	Temporary effect, required repeated procedures	Alternative for elderly patients with medication limitations	Risk of procedural complications (bleeding, anaphylaxis, etc.)	Inexpensive
		Effective in acute pain control	Limited effectiveness in some patients	Can be combined with physical therapy or rehabilitation	Relative paucity in randomized controlled trial	Minimally invasive
		Relatively low cost	Requires skilled practitioner		Lack of standardized protocol	Low systemic side effects
BoNT-A	 Injection, 31 sites, 155 u CGRP release in C-fibers↓	Proven effectiveness for CM	Cost↑ Uncertain efficacy for EM	Useful for patients concerned with drug side effects	Limited insurance coverage	Widely available
		Adherence↑ (every 3 months injection)	Requires skilled practitioner	Expansion of access due to increasing availability	Low accessibility in certain institutions or countries	Long safety track record
		Additional cosmetic benefits for wrinkles	Risk of muscle weakness in sarcopenic elderly			Non-systemic

Fig. 2. SWOT analysis (Strengths, Weaknesses, Opportunities, and Threats) of three injectable treatments for migraine prevention in older adults. The table compares CGRP mAbs, GONB, and BoNT-A based on efficacy, safety, accessibility, and practical considerations. Each treatment modality presents distinct advantages and limitations, which should be carefully considered when selecting therapy for older adults with migraine.
CGRP mAb = calcitonin gene-related peptide monoclonal antibody, SC = subcutaneous, IV = intravenous, GONB = greater occipital nerve block, GON = greater occipital nerve, LON = lesser occipital nerve, BoNT-A = onabotulinumtoxinA.

Current methods for assessing the effectiveness of migraine treatments may not fully capture the benefits experienced by older adults with migraine. Therefore, it is essential to develop evaluation tools tailored to older adults that incorporate facial expressions assessed by artificial intelligence as a pain score, along with functional improvements and quality-of-life measures as key assessment parameters.[62,63]

By adopting a comprehensive approach that includes targeted research, personalized treatment strategies, and improved assessment methods, healthcare providers can optimize migraine management in older adults. This ensures both effectiveness and safety while ultimately enhancing patients' quality of life.

It is recommended that future clinical research include migraine patients over 65 years of age, taking into account their health status, and that data from older people be analyzed separately to improve the quality of treatment for older adults with migraine.

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