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Advances in primary headache disorder management: A review of pharmacological and non-pharmacological strategies with emphasis on European evidence

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Abstract. Primary headache disorders – migraine, tension-type headache, and cluster headache – represented one of the leading causes of years lived with disability worldwide, imposing a substantial socioeconomic burden across Europe, with annual costs estimated in billions of euros owing to lost productivity and increased healthcare utilisation. The aim of research was to critically evaluate evidence on pharmacological and non-pharmacological management of primary headache disorders published between 2019 and 2024, with a specific focus on European clinical data and guideline recommendations, in order to provide practitioners with an immediately applicable, evidence-based update. CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab) demonstrated ≥50% responder rates of 40-60% and mean reductions of 3-8 monthly migraine days, with real-world European registry persistence exceeding 70% at 12 months – substantially outperforming traditional oral preventives. Oral gepants (atogepant for prevention; rimegepant for acute and preventive use) offered effective, cardiovascular-safe alternatives supported by both pivotal trials and European real-world cohorts. For cluster headache, high-flow oxygen (≥12 L/min) and subcutaneous sumatriptan 6 mg remained gold-standard acute treatments, while galcanezumab was the only biologic with strong evidence for episodic cluster headache prevention. Non-pharmacological interventions – cognitive behavioural therapy, biofeedback, structured aerobic exercise, and non-invasive vagus nerve stimulation – demonstrated moderate-to-high efficacy in reducing headache frequency and disability across all three disorders. Integrated multidisciplinary approaches combining pharmacological and behavioural strategies consistently showed superior long-term outcomes compared with monotherapy. European real-world data revealed meaningful improvements in quality of life, work productivity, and reductions in medication-overuse headache, confirming the applicability of guideline recommendations across diverse healthcare contexts. The findings provided neurologists, headache specialists, and primary care practitioners with a comprehensive, evidence-based synthesis of modern European management strategies, supporting a shift toward personalised, multidisciplinary headache care. Sustained implementation of European guidelines, harmonised cross-country access to novel therapies, and continued long-term safety monitoring remained essential priorities

Keywords: migraine; tension-type headache; preventive therapy; non-pharmacological interventions; evidence-based neurology

INTRODUCTION

Primary headache disorders were among the most prevalent and disabling neurological conditions worldwide. Understanding why these disorders demanded scientific attention had never been more critical: neurological diseases collectively represented the leading cause of disability-adjusted life years globally, and primary headaches – migraine, TTH (tension-type headache), and CH (cluster headache) – accounted for a disproportionate share of this burden. According to the GBD 2016 Headache Collaborators [1], migraine affected approximately 11-14% of the European adult population, with women experiencing the condition two to three times more frequently than men. M. Ashina *et al.* [2] documented that TTH, the most common

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headache disorder, affected up to 30-40% of the general population and remained substantially underdiagnosed. Though rarer (prevalence ≈ 0.1%), cluster headache caused one of the most severe pain syndromes. M. Linde *et al.* [3] established that these disorders collectively cost European economies billions of euros annually through lost productivity, absenteeism, and healthcare expenditure, with migraine accounting for the majority of the economic burden. Against the backdrop of an aging population and rising non-communicable disease burden, advancing the quality and consistency of headache management had become a public health imperative. Between 2019 and 2024, several pivotal developments fundamentally reframed the understanding and management of primary headaches. T.J. Steiner & L.J. Stovner [4] confirmed that migraine remained the second leading cause of years lived with disability worldwide, reinforcing the urgency of improving therapeutic access. W.K. Karlsson *et al.* [5] demonstrated that calcitonin gene-related peptide (CGRP)-targeted monoclonal antibodies outperformed traditional oral preventives across virtually all efficacy endpoints. S. Sacco *et al.* [6] formulated the landmark 2022 European Headache Federation (EHF) guideline recommending CGRP monoclonal antibodies as first-line preventive therapy for both episodic and chronic migraine, marking a paradigm shift in European clinical practice. E. Caronna *et al.* [7] further demonstrated in a real-world Spanish registry that early initiation of anti-CGRP therapy significantly enhanced the probability of sustained response, highlighting the importance of treatment timing. A. May *et al.* [8] updated the evidence base for this challenging condition, codifying the role of galcanezumab and non-invasive vagus nerve stimulation (nVNS). H.C. Diener *et al.* [9] articulated the prevailing European consensus on medication-overuse headache management, underscoring the critical interplay between pharmacological and behavioural strategies. K. Probyn *et al.* [10] and D. Onan *et al.* [11] published systematic analyses confirming clinically meaningful efficacy of self-management and physiotherapy interventions for TTH, respectively, strengthening the evidence base for non-pharmacological approaches across all headache subtypes.

Despite these advances, several gaps remained. Evidence for TTH management lags considerably behind migraine, with fewer high-quality trials and greater heterogeneity in non-pharmacological research. Long-term safety data for novel biologic agents extended beyond 3 years in only a limited number of studies. Significant inter-country variation in reimbursement and access to CGRP therapies created inequities across European healthcare systems. Furthermore, existing reviews either focus narrowly on a single headache subtype or fail to incorporate the most current European guideline updates alongside real-world registry data. A comprehensive synthesis that integrated pharmacological strategies, non-pharmacological evidence, and a critical analysis of the European clinical landscape – spanning multiple headache disorders and guideline frameworks simultaneously – was therefore lacking. The objective of this review was to provide a comprehensive, evidence-based synthesis of pharmacological and non-pharmacological management strategies for primary headache disorders (migraine, TTH, and CH), with a specific focus on European clinical trial data, real-world registries, and guideline recommendations published between 2019 and 2024, in order to support neurologists and primary care practitioners in delivering optimised, personalised headache care across Europe. This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [12]. Comprehensive electronic searches were performed in PubMed/Medline, Embase, and the Cochrane Library, covering January 2019 to December 2024, supplemented by hand-searching of major European journals. Search terms combined headache subtypes ("migraine", "tension-type headache", "cluster headache") with management-related keywords and study designs, limited to human studies in English. Priority was given to studies with European authorship, multicentre European participation, or direct relevance to EAN and EHF recommendations, reporting clinical outcomes such as monthly headache days, ≥50% responder rates, disability scores (MIDAS, HIT-6), or safety data. Studies on secondary headaches only, exclusively pediatric populations, case reports with <10 patients, or non-management topics were excluded. From 2,856 identified records, 145 studies – comprising 25 guidelines/consensus statements, 45 systematic reviews/meta-analyses, 50 RCTs, and 25 real-world European cohorts – met all inclusion criteria.

PHARMACOLOGICAL STRATEGIES IN HEADACHE MANAGEMENT

The selection of acute migraine therapy depended on attack severity, the presence of cardiovascular comorbidities, prior treatment history, and patient preference. Current European practice stratified acute treatment into a step-wise approach: simple analgesics for mild attacks, triptans as first-line specific therapy for moderate-to-severe migraine, and gepants or lasmiditan as cardiovascular-safe alternatives, consistent with recommendations from the German Migraine and Headache Society [13]. W.K. Karlsson *et al.* [5] confirmed that eletriptan and rizatriptan provided the highest probability of 2-hour pain freedom among oral triptans, with odds ratios of approximately 3.5 and 3.2 versus placebo, respectively. Sumatriptan remained widely used due to its well-established efficacy, broad availability, and multiple formulations. The 2022 EHF consensus [6] operationalised the definition of "effective acute treatment" as restoration of well-being within 2 hours – encompassing

headache relief and resolution of associated symptoms – sustained for 24 hours without recurrence. Critically, when triptans failed to meet this standard across three separate attacks, they should be considered ineffective for the individual patient, and gepants represented the appropriate next step. Newer agents had substantially expanded options for patients with cardiovascular contraindications to triptans. Gepants – specifically ubrogepant and rimegepant – act as small-molecule CGRP receptor antagonists and had demonstrated high-quality efficacy evidence: rimegepant achieved pain freedom at 2 hours in approximately 21% of patients versus 11% for placebo in pivotal trials, with a particularly favourable tolerability profile and no associated medication-overuse headache risk. Real-world European cohort data corroborated high patient satisfaction and superior persistence with gepants compared with triptans, particularly among patients with prior triptan failure or cardiovascular risk factors [14].

Preventive therapy was indicated for patients with four or more migraine days per month causing significant disability, those who failed or cannot tolerate acute treatments, or those at risk of medication-overuse headache. The 2022 EHF guideline update [6] represented a landmark European consensus that has fundamentally restructured the preventive treatment hierarchy. CGRP monoclonal antibodies (mAbs) – erenumab, fremanezumab, galcanezumab, and eptinezumab – were recommended as first-line preventive options for both episodic and chronic migraine, on the basis of robust evidence from multiple Phase III RCTs and extensive real-world data. These agents worked by blocking either the CGRP ligand (fremanezumab, galcanezumab, eptinezumab) or its receptor (erenumab), thereby disrupting the key trigemino-vascular signalling pathway implicated in migraine pathogenesis. Pooled clinical trial data demonstrated ≥50% responder rates of 40-60% for CGRP mAbs, with meant reductions in monthly migraine days of 3-8 days – significantly superior to placebo and consistently outperforming oral preventives in head-to-head comparisons in terms of efficacy and tolerability [5]. Their subcutaneous or intravenous monthly/quarterly dosing regimens improved adherence compared with daily oral medications. In terms of tolerability, CGRP mAbs exhibited low rates of serious adverse events; constipation was the most notable side effect specifically associated with erenumab (up to 3-fold higher than placebo in some studies), while injection-site reactions were mild and transient across the class. Gepants had expanded into the preventive arena: atogepant (approved in Europe) and rimegepant (dual acute/preventive indication) offered effective oral alternatives for patients, who preferred or required tablet-based regimens. Their primary advantages included no injection requirement, a short half-life (reducing prolonged CGRP blockade), and – uniquely – no established medication-overuse headache risk, making them particularly valuable for patients with frequent acute treatment use. Network meta-analyses position oral gepants as comparably effective to some traditional preventives, with superior tolerability [5].

OnabotulinumtoxinA retained a strong recommendation specifically for chronic migraine (≥15 headache days/month), where decades of European registry data confirmed persistent clinical benefit. Long-term follow-up data indicated that benefits were maintained or enhanced over multiple treatment cycles, and combination with CGRP mAbs had shown additive benefits in refractory chronic migraine cohorts – particularly for patients, who achieved partial but insufficient response to either agent alone [15]. Traditional oral preventives – propranolol, topiramate, and amitriptyline – maintained Level A evidence [16] and remained appropriate first-line options in settings, where access to or reimbursement for newer agents was limited. However, their long-term use was frequently constrained by tolerability issues (cognitive effects with topiramate, fatigue with propranolol, anticholinergic burden with amitriptyline), which explained why European registries document 12-month persistence rates of only 30-50% compared with >70% for CGRP mAbs [14, 15]. T.J. Schwedt *et al.* [17] further corroborated these persistence advantages in a large real-world analysis comparing onabotulinumtoxinA and CGRP mAbs, confirming that biologic agents demonstrated markedly superior adherence profiles. European real-world registries from Italy, Germany, Spain, and Scandinavia had been pivotal in confirming that pivotal trial results translated directly into clinical practice. Italian multicentre data from the RAMO study [18] demonstrated that anti-CGRP mAbs outperformed onabotulinumtoxinA in chronic migraine on several quality-of-life endpoints. Italian prospective registry data from A. Zovi *et al.* [19] further substantiated these findings across a broader patient population, while Spanish registry data showed that early treatment initiation was independently associated with superior and more sustained response [7]. Additional benefits documented in European registries included reduced acute medication consumption, fewer emergency department visits, and improved work productivity – outcomes with direct health-economic relevance. Table 1 summarised the key pharmacological agents for migraine management, their evidence levels, and European guideline recommendations.

Table 1. Key pharmacological agents for migraine management

Agent	Indication	Evidence level	EHF/EAN grade	Key notes (European data)
Eletriptan/ Rizatriptan	Acute (episodic)	High	Strong	Widely used first-line triptans for moderate-severe attacks

Table 1, Continued

Agent	Indication	Evidence level	EHF/EAN grade	Key notes (European data)
Subcutaneous sumatriptan 6 mg	Acute (episodic/CH)	High	Strong	Fast onset; standard therapy for acute CH
Ubrogepant/ Rimegepant	Acute (episodic)	High	Strong	Cardiovascular-safe; no overuse headache risk
Erenumab/ Fremanezumab/ Galcanezumab/ Eptinezumab	Preventive (episodic & chronic migraine)	High	Strong	First-line per EHF 2022; high adherence in European registries
Atogepant	Preventive (episodic migraine)	High	Strong	Oral CGRP antagonist; no overuse risk
Rimegepant	Acute & preventive	High	Strong	Convenient oral option; dual use
OnabotulinumtoxinA	Chronic migraine prevention	High	Strong	Established effectiveness in European registries; additive with CGRP mAbs
Propranolol/ Topiramate	Preventive (episodic migraine)	High	Moderate	Effective but limited by tolerability; second-line in Europe
Amitriptyline	Preventive (migraine & TTH)	Moderate	Moderate	First-line for TTH; long-term anticholinergic burden

Source: W.K. Karlsson *et al.* [5], S. Sacco *et al.* [6], A. May *et al.* [8], M.T. Corasaniti *et al.* [15], A. Zovi *et al.* [18], F. Vernieri *et al.* [20], S.D. Silberstein *et al.* [21]

Analysis of the data presented in Table 1 revealed a clear stratification of the current therapeutic landscape. CGRP-targeted biologics and gepants represented a genuine step change in migraine management: they were the first treatments designed specifically around the core pathophysiology of migraine, offering superior efficacy-to-tolerability ratios compared with any prior pharmacological option. The availability of multiple mechanisms and delivery formats enabled genuinely individualised treatment selection, which the EHF 2022 guidelines explicitly advocated [6]. R.B. Lipton *et al.* [22] demonstrated that inadequate preventive treatment was independently associated with migraine progression and chronification, further underscoring the clinical imperative of early, effective intervention. Tension-type headache, though the most prevalent headache disorder, remained the least well-characterised in terms of pathophysiology. Modern evidence points to peripheral sensitisation of pericranial myofascial nociceptors in episodic TTH, with central sensitisation playing an increasingly important role in the transition to chronicity. For acute episodic TTH, simple analgesics – paracetamol and NSAIDs – remained first-line based on strong longstanding evidence. R. Xie *et al.* [23] confirmed in a 2024 network meta-analysis that ibuprofen, ketoprofen, and diclofenac provide superior pain relief compared with paracetamol for more severe episodic attacks, while the combination of paracetamol with caffeine demonstrated additive benefit. A network meta-analysis by L. Qin *et al.* [24] of complementary and alternative medicine approaches further confirmed mindfulness-based and manual therapy interventions as clinically meaningful adjunctive strategies for TTH management, providing an evidence base for integrating these modalities alongside conventional pharmacotherapy. Critically, European guidelines uniformly caution against overuse of any acute analgesic – defined as use on ≥10 days/month for combination analgesics or triptans – because medication-overuse headache was particularly prevalent in TTH, occurring in approximately 1-2% of the European general population [9]. For chronic TTH, amitriptyline 25-75 mg nightly remained the evidence-based first-line preventive, with meta-analyses showing reductions of approximately 30% in headache frequency. European guidelines recommended early integration of non-pharmacological strategies as co-interventions to prevent the transition from episodic to chronic TTH [9].

Cluster headache was characterised by strictly unilateral, periorbital attacks of excruciating severity (typically VAS 9-10/10) lasting 15-180 minutes, accompanied by ipsilateral cranial autonomic features. Its unique circadian and circannual rhythmicity, mediated through the hypothalamic clock, distinguished it from all other primary headaches and necessitated a distinct therapeutic approach, as reviewed by B. de Freitas Dias *et al.* [25]. The authors A. May *et al.* [8] provided the most current and authoritative European framework. For acute attacks, 100% oxygen at ≥12 L/min via non-rebreathing mask for 15 minutes achieved meaningful pain relief in approximately 75-80% of episodic CH patients, with complete safety and no systemic side effects. Subcutaneous sumatriptan 6 mg achieves pain freedom within 15 minutes in approximately 75% of attacks and was therefore the pharmacological first choice for acute treatment, when oxygen was unavailable or insufficient. Intranasal zolmitriptan and sumatriptan were recommended as alternatives, particularly for patients, who cannot self-inject. Preventive treatment was initiated simultaneously with acute therapy during cluster periods to abbreviate the bout duration. Verapamil, titrated to a minimum effective

dose of 240 mg/day (with electrocardiographic monitoring due to PR interval prolongation risk at higher doses), was the established first-line preventive across European centres. Transitional therapy with oral or intravenous corticosteroids bridges the 2-3-week latency before verapamil took full effect. Galcanezumab 300 mg monthly received a strong recommendation specifically for episodic CH based on pivotal RCT data from study of D.W. Dodick *et al.* [26] showing significant reductions in weekly attack frequency. The emerging therapeutic landscape in CH was comprehensively reviewed by M. Barbosa da Silva *et al.* [27], who highlighted the role of novel biologics and neuromodulation in refractory cases. For refractory cases, non-invasive vagus nerve stimulation (nVNS) was endorsed by EAN guidelines for both acute and preventive purposes in CH; it showed an acceptable side-effect profile and can be combined with pharmacological therapy. Sphenopalatine ganglion stimulation represented an invasive, but highly effective option for patients with chronic CH unresponsive to pharmacological management, with European multicentre data demonstrating acute attack relief rates of 30-45% and preventive benefits in more than half of implanted patients (Table 2).

Table 2. EAN 2023 recommendations for cluster headache management

Treatment	Acute/ Preventive	Recommendation	Evidence level	Notes
100% Oxygen	Acute	Strong	High	First-line; safe in all patients; effective in episodic CH
Subcutaneous sumatriptan 6 mg	Acute	Strong	High	Fast onset; first-line pharmacological option
Intranasal zolmitriptan	Acute	Strong	Moderate-high	Alternative, when self-injection not feasible
Verapamil	Preventive	Strong	Moderate-high	First-line preventive; ECG monitoring recommended; titrate gradually
Oral/IV corticosteroids	Transitional	Strong	Moderate	Bridge therapy until preventive effect achieved
Galcanezumab	Preventive (episodic CH)	Strong	High	Only biologic approved for episodic CH; rapid onset; confirmed by pivotal trial
Non-invasive VNS (nVNS)	Acute & preventive	Strong (consensus)	Low-moderate	Safe; useful for refractory cases; supported by trial evidence
Sphenopalatine ganglion stimulation	Preventive (chronic CH)	Conditional	Moderate	Invasive; reserved for chronic, pharmacotherapy-refractory CH

Source: A. May *et al.* [8], D.W. Dodick *et al.* [26], M. Barbosa da Silva *et al.* [27], S.D. Silberstein *et al.* [28], P.J. Goadsby *et al.* [29]

So, data in Table 2 illustrated the guiding principle of CH management: speed and mechanism specificity were paramount in acute care, while preventive therapy must balance onset speed, tolerability, and the episodic or chronic nature of the disorder. The addition of galcanezumab as the first biologic agent for episodic CH represented a clinically significant advance [26], providing an evidence-based option for patients, who cycle through frequent cluster bouts, or who responded inadequately to verapamil. The continued endorsement of nVNS, supported by the S.D. Silberstein *et al.* [28] and P.J. Goadsby *et al.* [29] randomised trials, reflected growing European clinical experience with neuromodulation as an adjunctive strategy particularly valued for its safety profile.

NON-PHARMACOLOGICAL MANAGEMENT STRATEGIES

Non-pharmacological interventions constituted an essential pillar of European headache management, valued not only for their intrinsic efficacy, but for their capacity to reduce pharmacological burden, prevented medication-overuse headache, and addressed the behavioural and psychological dimensions of chronic pain. European guidelines across all three headache disorders explicitly recommended integrating these strategies alongside pharmacological care [9, 30], reflecting both patient preference for drug-sparing approaches and the mechanistic rationale for multimodal treatment. Cognitive behavioural therapy (CBT) addressed the maladaptive thought patterns, catastrophising, and avoidance behaviours that characterised and perpetuated chronic headache. Its proposed mechanisms included modification of pain-related cognitions, improvement of self-efficacy, and reduction of psychophysiological arousal – all of which contributed to headache chronification. K. Probyn *et al.* [10] demonstrated that non-pharmacological self-management programmes, including CBT-based approaches, produced statistically significant and clinically meaningful reductions in headache frequency and disability for TTH and migraine, with effects sustained at 6-12 months of follow-up. Mindfulness-based stress reduction (MBSR) and acceptance and commitment therapy (ACT) had demonstrated similar but somewhat smaller effects, with the additional benefit of improving psychological wellbeing and quality of life. These approaches were particularly recommended for patients

with comorbid anxiety or depression, which affect approximately 30-40% of chronic migraine patients in European populations.

Biofeedback trained patients to consciously regulate physiological parameters – most commonly frontalis muscle EMG activity (for TTH) and finger skin temperature or heart rate variability (for migraine) – associated with headache triggering. The technique exploits neuroplasticity: with repetitive practice, patients learn to downregulate sympathetic arousal and muscular tension that preceded or accompanied headache. Y. Nestoriuc & A. Martin [31] confirmed that thermal and EMG biofeedback produced significant reductions in migraine frequency (effect size d = 0.59) and TTH frequency (effect size d = 0.73), with response rates of 45-55% after a standardised 8-12-session protocol. Importantly, these effects were maintained over 12 months in studies with follow-up data, and biofeedback was the only psychological intervention with high-quality evidence specifically supporting pediatric and adolescent headache, making it valuable across the age spectrum. Physical therapy targeting pericranial and cervical musculature – through manual therapy, myofascial release, and therapeutic exercise – addressed the peripheral sensitisation of pericranial nociceptors that underlied TTH and contributed to migraine chronification via cervicotrigeminal convergence. D. Onan *et al.* [11] demonstrated that combined physiotherapy approaches (manual therapy plus exercise) reduced chronic TTH frequency by a mean of 4.2 days/month, with 60% of participants achieving a ≥50% reduction – an effect size comparable to preventive pharmacotherapy. R. Souren *et al.* [32] demonstrated in a tertiary headache centre observational study that adherence to headache-specific multidisciplinary treatment recommendations achieves significantly greater headache frequency reductions and better long-term outcomes than unimodal approaches, confirming the superiority of integrated care models.

Structured aerobic exercise programmes (3 sessions per week, 30-45 minutes at moderate intensity) had accumulated substantial evidence for migraine prevention specifically. European guidelines specifically recommended aerobic exercise as a first-line lifestyle intervention for migraine prevention, as it reduced monthly migraine frequency by approximately 0.6 days and improved both MIDAS and HIT-6 scores, likely through modulation of endogenous opioid systems, β-endorphin release, and CGRP levels. The randomised controlled evidence base for exercise as migraine prophylaxis continues to grow, with outcomes comparable to some pharmacological options in terms of frequency reduction [30, 33]. Non-invasive vagus nerve stimulation (nVNS) – delivered via a handheld device applied to the neck – modulated pain processing through projections from the nucleus tractus solitarius to the trigeminal nucleus caudalis, reducing central sensitisation and trigeminovascular activation. For acute CH, the ACT1 [28] and ACT2 [29] randomised trials established nVNS as an effective acute treatment in episodic CH, with pain-free response rates of 34% versus 15% for placebo at 15 minutes – a significant and clinically meaningful difference. For migraine, nVNS had demonstrated preventive efficacy in the PREMIUM and EVENT trials, as reviewed by F. Puledda & K. Shields [34], with monthly migraine day reductions of 2.3-2.9 days. European real-world data confirmed sustained use and patient-reported benefit across neuromodulation devices, with low rates of adverse events (mild application-site discomfort in <5% of users) and no drug interactions, making them suitable add-on therapies for patients with polypharmacy or contraindications to pharmacological treatment. Lifestyle modifications – encompassing consistent sleep hygiene, adequate hydration, regular meal timing, structured stress management, aerobic exercise, and systematic trigger identification [35] – were foundational across all European headache guidelines. While individual lifestyle factors had modest individual effect sizes, their systematic adoption as a package of behavioural change produced meaningful cumulative benefits in reducing headache frequency and severity. Wearable technology and smartphone-based headache diary applications had emerged as powerful tools for trigger identification and behavioural monitoring, with evidence from real-world studies supporting improved treatment adherence [36].

ANALYSIS OF EUROPEAN DATA AND RECOMMENDATIONS IN THE CONTEXT OF CLINICAL PRACTICE

European guidelines – principally those issued by the European Academy of Neurology (EAN) and the European Headache Federation (EHF) – represented the authoritative frameworks that shape clinical decision-making for neurologists and primary care practitioners across the continent. The 2022 EHF guideline update on CGRP-targeted therapies [6] and the 2023 EAN cluster headache guidelines [8] reflected a synthesis of the highest-quality available evidence and have had tangible impacts on prescribing practices. Real-world surveys across Germany, Italy, Spain, France, and Scandinavia conducted between 2022 and 2024 document a rapid uptake of CGRP mAbs in specialist headache centres: in Germany, for example, more than 60% of eligible patients at certified headache centres received biologic preventive therapy by 2023, compared with fewer than 10% in 2019. In Italy, the RAMO multicentre cohort [18] enrolled over 1,000 patients across 14 centres within 18 months, reflecting both the practical feasibility of European collaborative research and the clinical appetite for comparative effectiveness data. These registry findings were essential precisely because they complemented RCT evidence with real-world generalisability, including populations typically excluded from trials – elderly

patients, those with significant comorbidities, and those previously exposed to multiple treatment failures.

EAN and EHF recommendations influenced clinical decision-making not only through their official adoption but through structured educational initiatives, European headache specialist networks, and integration into national clinical guidelines. Countries with well-developed specialist headache infrastructure – Germany, Italy, Denmark, Spain – demonstrated the greatest alignment with European recommendations and correspondingly better patient outcomes, as measured by validated disability scales [38]. Italian real-world data from A. Zovi *et al.* [19] further corroborated the superiority of CGRP mAbs over traditional preventives across diverse patient populations in European specialist settings. In contrast, countries with limited access to specialist care or restricted reimbursement pathways showed lower adoption of guideline-recommended therapies, highlighting the persistent challenge of harmonising care quality across EU member states [22]. EHF had specifically highlighted this inequity in position papers, calling for EU-level health technology assessment processes to facilitate equitable access.

Non-pharmacological therapies had also matured considerably within the European evidence base. Network meta-analyses confirmed that CBT and physiotherapy deliver clinically relevant reductions in TTH and migraine frequency, often comparable to pharmacological options but without systemic side effects [10, 24, 37]. A particular European strength had been the integration of digital therapeutics: high smartphone penetration across Western Europe and telemedicine infrastructure expanded during the COVID-19 pandemic had enabled the scalable deployment of digital CBT programmes, digital biofeedback, and remoted headache monitoring. Preliminary evidence from European pilot studies (2022-2024) suggested that digital therapeutic platforms can achieve CBT-comparable outcomes for headache reduction with improved accessibility and lower cost [36] – findings with significant implications for healthcare system planning. Consensus statements on integrating new treatments into clinical practice, such as that by J. Ailani *et al.* [38], provided practical frameworks for implementing these digital approaches alongside pharmacological strategies.

Health-economic considerations were central to European implementation of novel therapies. While CGRP mAbs carried higher upfront annual costs (approximately EUR 6,000-EUR 12,000 per patient per year across different European pricing systems), real-world economic analyses from Germany, Italy, and the United Kingdom demonstrated favourable cost-effectiveness ratios, when total disease burden – including emergency department visits, hospitalisation, lost productivity, and acute medication expenditure – was incorporated into the model. A pharmacoeconomic analysis from Spain [39] demonstrated that preventive therapy with CGRP mAbs reduced indirect costs (productivity loss, absenteeism) by approximately 35% over 12 months among chronic migraine patients, resulting in a net cost-effectiveness ratio well within the acceptecompared with onabotulinumtoxinA in terms of persistence and overall treatment costs. However, reimbursement criteria remained highly variable: while Germany, France, and Spain had broad coverage for all four approved mAbs in both episodic and chronic migraine, several Eastern European countries restricted coverage to chronic migraine only or required documented failure of three prior preventive agents – a requirement that delayed access to effective treatment by years in some cases [22].

Safety profiles of novel agents remaind EU threshold of EUR 30,000 per quality-adjusted life year. T.J. Schwedt *et al.* [17] further confirmed the real-world economic advantages of CGRP mAb therapy ed reassuring based on accumulated European and global evidence. CGRP pathway therapies showed low rates of serious adverse events across all approved agents. The most common issues – constipation (primarily with erenumab, reported in 3-5% of patients), injection-site reactions (typically mild and transient), and mild fatigue – rarely necessitate treatment discontinuation. Long-term European registry data extending to 3 years confirmed cardiovascular safety: while CGRP played a physiological vasodilatory role, no increase in cardiovascular events had been documented in real-world populations, including those with hypertension or controlled coronary artery disease [40]. Post-marketing pharmacovigilance systems across European national regulatory authorities continued active monitoring, with quarterly aggregated safety reports providing robust population-level signal detection. For CH preventives, standard ECG monitoring before and during verapamil titration was well-established in European practice to detect the PR interval prolongation and rare atrioventricular block that can occur at doses above 480 mg/day [8]. Taken together, the European headache management landscape in 2019-2024 was characterised by three defining trends: 1) a shift from empirical, trial-and-error preventive strategies to mechanism-based precision medicine; 2) a strong movement toward integrated, multidisciplinary care models; 3) an increasing reliance on real-world registry data – a domain in which Europe leads globally – to complement and extend RCT findings.

CONCLUSIONS

This systematic review synthesised evidence from studies – comprising guidelines, meta-analyses, randomised controlled trials, and real-world European cohorts – on the management of migraine, tension-type headache, and cluster headache, with a specific focus on European clinical data and guideline recommendations. The strongest and most practice-changing evidence concerned calcitonin gene-related peptide-targeted

therapies. Monoclonal antibodies against calcitonin gene-related peptide or its receptor had demonstrated consistent, clinically meaningful efficacy in migraine prevention – with ≥50% responder rates of 40-60%, reductions of 3-8 monthly migraine days, and real-world persistence rates exceeding 70% at 12 months – establishing them as the new first-line standard per the 2022 European Headache Federation guideline. Oral gepants offer effective, cardiovascular-safe alternatives for both acute and preventive use. For cluster headache, it was confirmed high-flow oxygen and subcutaneous sumatriptan as gold-standard acute treatments, while galcanezumab was the only biologic with evidence in this indication. Non-pharmacological strategies – cognitive behavioural therapy, biofeedback, structured aerobic exercise, physiotherapy, and neuromodulation (nVNS) – individually demonstrated moderate-to-high efficacy across headache subtypes, with multidisciplinary combinations producing superior long-term outcomes compared with monotherapy. European real-world registries from Italy, Germany, Spain, and Scandinavia confirmed that guideline-concordant, multidisciplinary management produced meaningful improvements in quality of life, work productivity, and healthcare utilisation. Health-economic analysed support the cost-effectiveness of calcitonin gene-related peptide-targeted therapies, when total disease burden was considered, though substantial inter-country variation in reimbursement remained a significant barrier to equitable care. Limitations included the comparatively underdeveloped tension-type headache evidence base, limited long-term data beyond 3 years for novel agents, underrepresentation of pediatric and elderly populations, and potential publication bias toward positive calcitonin gene-related peptide results. Future research should prioritise head-to-head comparative trials, long-term safety registries beyond 5 years, and harmonised EU health technology assessment processes to ensure equitable access to effective headache care across Europe.

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Баштапкы баш ооруну дарылоодогу жетишкендиктер: европалык маалыматтарга жана сунуштамаларга негизделип даярдалган фармакологиялык жана фармакологиялык эмес стратегияларга сереп

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Аннотация. Баштапкы баш оорулары – шакый, чыңалуудан пайда болгон баш ооруу жана кластердик баш ооруу – дүйнө жүзү боюнча майыптык менен өткөрүлгөн жылдардын алдыңкы себептеринин катарына кирип, Европа үчүн олуттуу социалдык-экономикалык көйгөй болуп саналат: эмгекке жарамдуулуктун жоголушунан жана саламаттыкты сактоо чыгымдарынын өсүшүнөн улам жыл сайынкы чыгымдар миллиарддаган еврого бааланат. Изилдөөнүн максаты – 2019-2024-жылдары жарыяланган, баштапкы баш ооруларын дарылоонун фармакологиялык жана фармакологиялык эмес ыкмалары боюнча маалыматтарды сынчыл баалоо, европалык клиникалык маалыматтарга жана колдонмо сунуштамаларга басым жасоо менен, адистерге практикада колдонсо боло турган далилдерге сереп берүү. Талдоонун жыйынтыгында CGRP моноклоналдык антителолору (эренумаб, фреманезумаб, галканезумаб, эптинезумаб) бейтаптардын 40-60 пайызында ≥50 % жооп берүүнү жана айына мигрень күндөрүнүн санын 3-8 күнгө азайтууну көрсөткөнү, ал эми европалык реалдуу клиникалык практика реестрлеринде 12 айдан кийин тартиптүү колдонуу көрсөткүчү 70 пайыздан ашканы аныкталды. Оралдык гепанттар (атогепант – алдын алуу үчүн; римегепант – өткүр жана алдын алуу максатында колдонуу үчүн) натыйжалуу жана жүрөккө коопсуз альтернатива болуп саналды. Кластердик баш ооруда кычкылтек (≥12 л/мин) жана тери астына сайылуучу суматриптан 6 мг өткүр дарылоонун «алтын стандарты» статусун сактап калды, ал эми галканезумаб – эпизоддук кластердик баш ооруну алдын алуу үчүн жогорку далилдик базасы бар жападан-жалгыз биологиялык препарат болуп чыкты. Фармакологиялык эмес аракеттер – когнитивдик-жүрүм-турум терапиясы, биологиялык тескери байланыш, аэробдук көнүгүүлөр жана вагус нервин инвазивдик эмес стимуляциялоо – үч оорунун баарында тең баш ооруунун жыштыгын жана күчүн азайтууда орточо жана жогорку натыйжалуулукту көрсөттү. Европалык реестрлердин маалыматтары заманбап комплекстүү дарылоону алып жаткан бейтаптардын жашоо сапатынын, эмгек өндүрүмдүүлүгүнүн олуттуу жакшыргандыгын жана абузустук (медикаментоздук) баш ооруу тобокелдигинин азайгандыгын күбөлөндүрдү. Серептин жыйынтыктары невролог, баш ооруу боюнча адис жана биринчи звенонун дарыгерлерин биринчилик баш ооруларды дарылоодо заманбап европалык стратегияларды колдонуу үчүн далилдик база менен камсыз кылып, персоналдаштырылган, көп тармактуу жардамга өтүүнү колдоду. Европалык колдонмолорду туруктуу ишке ашыруу, инновациялык дарылоо ыкмаларына жетүүнү гармониялаштыруу жана коопсуздукту узак мөөнөттүү мониторинг жүргүзүү артыкчылыктуу маселе бойдон калууда

Негизги сөздөр: шакый; чыңалуудан пайда болгон баш ооруу; алдын алуучу терапия; фармакологиялык эмес кийлигишүүлөр; далилдүү неврология

Достижения в лечении первичных головных болей: обзор фармакологических и нефармакологических стратегий с акцентом на европейские данные и рекомендации

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Аннотация. Первичные головные боли – мигрень, головная боль напряжения и кластерная головная боль – входили в число ведущих причин лет, прожитых с инвалидностью, во всём мире и представили значительную социально-экономическую проблему для Европы: ежегодные затраты, обусловленные потерей трудоспособности и ростом расходов на здравоохранение, которые оцениваются в миллиарды евро. Цель исследования – критически оценить данные о фармакологических и нефармакологических методах лечения первичных головных болей, опубликованные в 2019-2024 годах, с акцентом на европейские клинические данные и рекомендации руководств, чтобы предоставить специалистам применимый в практике обзор доказательств. В результате анализа данных было установлено, что моноклональные антитела к CGRP (эренумаб, фреманезумаб, галканезумаб, эптинезумаб) продемонстрировали ответ ≥50 % у 40-60 % пациентов и снижение числа дней мигрени в месяц на 3-8, при этом показатели приверженности в европейских реестрах реальной клинической практики превышали 70 % через 12 месяцев. Оральные гепанты (атогепант – для профилактики; римегепант – для острого и профилактического применения) являлись эффективной и кардиологически безопасной альтернативой. При кластерной головной боли кислород (≥12 л/мин) и подкожный суматриптан 6 мг сохранили статус «золотого стандарта» острого лечения, а галканезумаб – единственный биологический препарат с высокой доказательной базой для профилактики эпизодической кластерной головной боли. Нефармакологические вмешательства – когнитивно-поведенческая терапия, биологическая обратная связь, аэробные упражнения и неинвазивная стимуляция блуждающего нерва – продемонстрировали умеренную и высокую эффективность в снижении частоты и интенсивности головной боли при всех трёх нозологиях. Данные европейских реестров свидетельствовали о значительном улучшении качества жизни, производительности труда и снижении риска абузусной головной боли у пациентов, получающих современное комплексное лечение. Результаты обзора обеспечили неврологов, специалистов по головной боли и врачей первичного звена доказательной базой для применения современных европейских стратегий лечения, поддерживая переход к персонализированной, мультидисциплинарной помощи при первичных головных болях. Устойчивое внедрение европейских руководств, гармонизация доступа к инновационным методам лечения и долгосрочный мониторинг безопасности остались приоритетными задачами

Ключевые слова: мигрень; головная боль напряжения; профилактическая терапия; нефармакологические вмешательства; доказательная неврология