

ABSTRACTS

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RATIONALE

Il 40° Congresso della Società Italiana per lo studio delle Cefalee chiuderà le celebrazioni del cinquantenario della SISC, introducendo temi attuali quali gli studi *real life* a sei anni dall'avvento delle terapie target, l'applicazione di metodi predittivi a supporto della clinica, quali gli algoritmi di intelligenza artificiale, le problematiche ancora irrisolte dell'emicrania refrattaria e delle forme rare e poco conosciute di cefalee primarie, i rapporti con il territorio, gli orizzonti ancora inesplorati delle diverse età della vita, dalla infanzia alla giovinezza fino alla senescenza.

Il Congresso si arricchirà di temi dal contenuto storico umanistico e al tempo stesso tecnologico, a sostegno di una cultura traslazionale nell'ambito della quale le cefalee rappresentano un complesso dalle mille sfaccettature dove diverse esperienze e sensibilità possono trovare spunti per interessanti e utili contributi.

La cornice del barocco leccese e delle più antiche tradizioni salentine farà da sfondo al contesto moderno della sede congressuale, con una distribuzione di spazi utile alla massima condivisione dei contenuti e alla ampia espressione dei vivaci contributi dei giovani soci nelle diverse discipline.

Marina De Tommaso - Presidente
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The 40th Congress of the Italian Society for the Study of Headaches (SISC) will bring the celebrations marking the Society's 50th anniversary to a close. The Congress will address current topics, including real-world studies six years after the advent of targeted therapies; the application of predictive methods to support clinical practice, such as artificial intelligence algorithms; unresolved issues in refractory migraine and rare, poorly understood forms of primary headache; the relationship with local healthcare services; and the still unexplored horizons of the different stages of life, from childhood and adolescence to old age.

The Congress will also explore topics combining historical and humanistic perspectives with technological advances, fostering a culture of translational research in which headache disorders represent a multifaceted field. Within this complex landscape, diverse experiences and perspectives can provide inspiration for valuable and meaningful contributions.

The setting of Lecce's Baroque architecture and Salento's oldest traditions will provide a backdrop to the modern congress venue, whose layout will be designed to maximise the sharing of knowledge and encourage the active participation of young Society members, fostering the broadest possible expression of their valuable contributions across the various disciplines.

Marina De Tommaso - President
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Franco Granella - Past President



ORAL COMMUNICATIONS



Decoding the biochemical signature of treatment-resistant migraine: searching for disease phenotypes and novel therapeutic targets.

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Background: Nearly 40% of migraine subjects fail to respond to monoclonal antibodies targeting the calcitonin gene related (CGRP) pathway (mAbs). We hypothesized that these subjects may bear a non-CGRP-dependent phenotype. Alterations in the endocannabinoid system (eCBome), reflected by changes in fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), have been previously demonstrated in migraine (1). The primary aim of the SPHERA project is to assess changes in gene expression of the eCBome catabolizing enzymes in migraine subjects who do not respond to mAbs treatment.

Methods: In this longitudinal prospective study, we enrolled 105 subjects (82.9% women, age 42.1±13.3 years), 55.2% with high frequency episodic migraine, and 44.8% with chronic migraine. We treated 40% of subjects with fremanezumab, 33.3% with galcanezumab, and 26.7% with erenumab. Participants were evaluated at baseline (T0) and after a 3-month mAbs treatment (T1). Subjects not achieving a reduction of at least 50% of monthly migraine days (MMDs) at T1 were classified as Non-Responders. At T0, we performed an extensive biochemical profiling including: gene expression of FAAH and MAGL and other metabolic enzymes of the eCBome system (DAGL, NAPE, NAAA) and microRNAs in peripheral blood mononuclear cells; plasma levels of eCBome associated lipids (PEA, AEA, 2-AG, OEA), neuropeptides (CGRP, PACAP, VIP), pro- and anti-inflammatory cytokines (IL-12, IL-10, TNF-alfa, IFN-γ, IL-2, IL-6), and kinurenic and quinolinic acids.

Results: At T1, 54 subjects (51.4%) classified as Responders. At T0, FAAH expression was higher in Responders (1.713±2.268 RQ) compared to Non-Responders (0.796±0.599 RQ; p=0.009). MAGL expression did not differ between the two groups (Responder: 9.615±6.294 vs. Non Responder: 8.156±5.556; p=0,310). No differences were observed in the remaining biochemical analyses between the two groups.

Conclusions: Non-responders showed reduced FAAH gene expression, consistent with previous evidence. This results in decreased endocannabinoid degradation and consequently higher compensatory eCBome levels aimed at maintaining an antinociceptive effect. Future Non Responders to mAbs treatment display reduced expression of FAAH. This may contribute to a non-CGRP-dependent migraine phenotype with selective eCBome involvement.



Multicenter study on the therapeutic management of pediatric migraine in SISC pediatric headache centers

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Background: Migraine in childhood and adolescence is a common clinical condition with a significant impact on the quality of life of patients and their families. Currently, there are no internationally shared therapeutic guidelines.

Methods: The aim of this survey was to describe the prescribing practices of the representatives of the Italian Society for the Study of Headaches (SISC) pediatric headache centers in the management of migraine during childhood and adolescence. An observational, multicenter, cross-sectional study was conducted using a questionnaire divided into two sections: (1) acute and preventive treatment (drugs, timing, selection criteria, and treatment duration); (2) management of seven clinical scenarios.

Results: The survey was completed by all representatives of the Italian pediatric headache centers (N=11). Acute treatment in children (6–11 years) and adolescents (>12 years) was mainly based (9/11) on paracetamol and ibuprofen or, after treatment failure, other NSAIDs, mainly ketoprofen (7/9) or naproxen (6/11). Triptans were infrequently prescribed in children (5/11) but more commonly in adolescents (8/11). For nausea and vomiting, most respondents prescribed antiemetics (9/11), mainly ondansetron (7/9). Preventive treatment was initiated according to shared criteria (10/11: >4 attacks/month for ≥3 months) and symptom severity (8/11), with homogeneous efficacy assessment (reduction in attack frequency and acute medication use, 11/11; pain intensity, 8/11). Differences persisted in treatment duration (3 months, 6/11; 6 months, 3/11; variable, 2/11) and reassessment timing. Across the seven clinical scenarios, management of high-frequency migraine and indication for preventive treatment were largely uniform (9–11/11), with a preference for nutraceuticals (7/11) in children. In adolescents with chronic migraine, greater heterogeneity emerged in preventive treatment, with amitriptyline (6/11), flunarizine (5/11), and topiramate (5/11) most frequently selected. In medication-overuse headache (MOH), withdrawal strategies differed (abrupt discontinuation 4/11; gradual withdrawal 5/11). In menstrual migraine, continuous preventive treatment was initiated by 2/11 centers, whereas perimenstrual mini-prophylaxis was adopted by 5/11.

Conclusions: The greatest differences emerged in the most complex clinical scenarios, where limited pediatric evidence and the lack of uniform recommendations lead to different therapeutic approaches. These findings identify the main areas of uncertainty in clinical practice and provide a basis for shared recommendations.



Plasma PACAP-38 Is Increased in Migraine Regardless of Clinical Phenotype: A Case-Control Study

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Background: Pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) has emerged as a key neuropeptide involved in migraine pathophysiology through its vasoactive, nociceptive, and neuroinflammatory effects. Although experimental evidence strongly supports its biological role, clinical studies evaluating circulating PACAP-38 concentrations have yielded inconsistent results. We aimed to compare plasma PACAP-38 concentrations between patients with migraine and healthy controls and investigate their relationship with migraine phenotype and clinical characteristics.

Methods: We conducted a single-center cross-sectional case-control study. Plasma PACAP-38 concentrations were measured using a commercially available sandwich ELISA (BlueGene Biotech; Cat. No. E01P0585). Patients were classified according to migraine phase (ictal/interictal), migraine subtype, presence of aura, medication-overuse headache (MOH), and sex. Associations with demographic and clinical variables were evaluated using non-parametric tests with correction for multiple comparisons.

Results: Eighty-five patients with migraine (70 females, 15 males; mean age 44.7 ± 14.7 years; 42 chronic and 43 episodic migraine) and 36 healthy controls (26 females, 10 males; mean age 45.3 ± 13.0 years) were included. Plasma PACAP-38 concentrations were significantly higher in patients with migraine than in healthy controls (234.86 vs 169.72 pg/mL; $p<0.001$). Increased PACAP-38 concentrations were observed both during migraine attacks (219.21 vs 169.72 pg/mL; $p=0.003$) and in the interictal phase (233.76 vs 169.72 pg/mL; $p<0.001$), whereas no significant difference was found between ictal and interictal samples ($p=0.443$). No significant differences were observed according to migraine subtype, presence of aura, medication-overuse headache, or sex. Furthermore, plasma PACAP-38 concentrations were not associated with clinical characteristics or measures of migraine severity after correction for multiple comparisons.

Conclusions: Plasma PACAP-38 concentrations are significantly increased in patients with migraine compared with healthy controls, supporting activation of the PACAP pathway as a biological hallmark of migraine. Circulating PACAP-38 concentrations appear independent of migraine phenotype and clinical severity, suggesting that PACAP-38 may represent a trait biomarker rather than a marker of disease activity. Larger prospective studies, particularly including more patients sampled during migraine attacks, are warranted to further clarify the diagnostic and pathophysiological significance of PACAP-38.



Moral Judgment in Migraine: A Case-Control Study

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Background: Evidence on decision-making processes in migraine suggests possible alterations in the evaluation of complex situations. However, their impact on moral judgment remains poorly explored. The aim of this study was to compare the frequency of utilitarian choices and response times to moral dilemmas in individuals with chronic migraine (CM), episodic migraine (EM), and healthy controls (HC), while considering the role of personality traits and clinical variables.

Methods: A total of 188 participants were included: 64 with CM (mean age 46.4 ±12.8), 50 with EM (mean age 48.5 ±12.3), both diagnosed according to ICHD-III criteria, and 74 HC (mean age 37.3 ±13.7). Participants completed a moral judgment task including dilemmas of different types and underwent assessment of personality traits and clinical history. For each participant, the proportion of utilitarian responses and the mean response time across moral dilemmas were calculated. Between-group differences were analyzed using ANOVA, ANCOVA adjusted for age and personality traits, Tukey post hoc comparisons, and mixed ANOVA with Group × Dilemma Type interaction. In participants with migraine, clinical indicators of disease severity were also considered.

Results: No statistically significant between-group differences emerged in the proportion of utilitarian choices; however, both ANOVA (p=.061) and adjusted ANCOVA (p=.054) showed a trend toward statistical significance. Descriptively, the CM group exhibited the highest proportion of utilitarian responses (48%), followed by EM (47.0%) and HC (44%). Mixed ANOVA revealed neither a main effect of dilemma type nor a Group × Dilemma Type interaction. Response time analysis showed a significant group effect (ANOVA: p=.046; ANCOVA: p=.041). Post hoc comparisons indicated significantly longer response times in participants with CM compared with HC (p=.041), whereas the comparison between CM and EM showed a trend toward significance (p=.051). Clinical analyses confirmed greater disease severity in participants with CM, with no evidence of independent associations between clinical indicators and moral judgment.

Conclusions: Findings suggest that migraine does not substantially alter the content of moral judgment but is associated with longer decision-making times, particularly in individuals with chronic migraine. Future studies should clarify whether these findings reflect differences in cognitive processing, disease severity, or treatment-related factors, and confirm the observed tendency toward a greater utilitarian orientation in chronic migraine.



Migraine monitoring and attack prediction in the preictal phase using machine learning approaches combining e-diaries and biological variables collected through wearable sensors: the MigraMeter study

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Background: Migraine is a disabling disorder characterized by recurrent and unpredictable attacks. Physiological and behavioral changes may occur hours before headache onset, even without prodromal symptoms, reflecting changes of the central and autonomic nervous system. We aimed to develop a machine learning model integrating e-diary and high-resolution wearable sensor data to identify early warning signs of the pre-ictal phase with the potential to support timely and personalized interventions and ultimately improve the quality of life of individuals with migraine.

Methods: Adults with episodic or chronic migraine underwent prospective monitoring for ≥28 days using a wearable device continuously recording pulse rate, electrodermal activity, skin temperature, actigraphy and sleep parameters, together with an e-diary (MigraMeter). Sensors data were processed into 10-minute segments and labelled according to migraine phases, as preictal, ictal, postictal and interictal, according to temporal proximity on migraine onset time, to enable a time-resolved characterization of interindividual changes. Machine learning models were trained and validated using 10-fold cross-validation. The primary outcome was the performance of the model to discriminate the interictal-pre-ictal phase transition within different time windows (6–48 hours).

Results: Nineteen participants (median age 41 years [IQR 30–45], 84.2% female, 73.7% with episodic migraine). were monitored for a median period of 39 days (IQR 22–49), with a median of 5 monthly migraine days (IQR 3–9). In the 12 hours window, CatBoost combined with Select K-Best feature selection achieved the best performance (AUC-ROC 0.88±0.10; balanced accuracy 0.71), demonstrating robust identification of physiological alterations preceding attacks. Electrodermal activity was the most informative feature, followed by pulse rate and skin temperature. The model consistently achieved AUC values >0.70 across individuals indicating robust discriminative ability in the preictal windows (6-48 hours). In contrast, F1-scores were more variable, suggesting differences in precision–recall balance related to individual physiological patterns and class distribution.

Conclusions: The CatBoost model showed the highest discriminative ability and robustness up to the 48 hours pre-ictal window, demonstrating good performance in detecting the interictal-to-pre-ictal transition, largely driven by autonomic physiological features. These findings support the feasibility of developing machine learning–based tools for the early prediction of migraine attacks through individualized risk estimation using continuous physiological data.



Unraveling the Spectrum of Migraine Resistant to Treatment: the role of MRI resting-state functional connectivity in migraine subjects treated with anti-CGRP monoclonal antibodies

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Background: Around 30% of individuals with migraine fail to achieve sufficient disease control (Non-responders) using monoclonal antibodies targeting the CGRP pathway (mAbs). Functional magnetic resonance imaging (fMRI) allows a non-invasive characterization of alterations in resting-state networks, including default mode network, salience, executive control, and sensory systems, defining migraine as a network-level brain disorder. fMRI has also been explored as a predictor of response to mAbs, but definite conclusions are lacking. Our aim was to assess if Non-responders bears a distinct functional connectivity fMRI profile.

Methods: Fifty-seven migraine individuals were enrolled (age 46.0 ± 14.0, 80% female). Subjects were evaluated with fMRI at baseline (T0), and after underwent a 3-month mAbs treatment (T1). Non-Responders were defined as those who did not achieve a reduction of at least 50% in monthly migraine days (MMDs) at T1. Resting-state fMRI was analysed using Independent Component Analysis (ICA) and graph theory, to identify resting-state networks and characterize functional connectivity patterns.

Results: At T1, 24 subjects were classified as Non-responders. At a global level, Non-responders showed stronger functional connectivity between the right superior frontal gyrus and the left cerebellar lobule VI/crus II ($p<0.01$, tfce corrected), whereas Responders exhibited higher connectivity between the right occipital pole, the right inferior frontal gyrus pars triangularis and the right insula ($p<0.01$, tfce corrected). Within resting-state networks, Responders showed increased connectivity in the right precuneus, the left cingulate gyrus, and the right intracalcarine cortex and lingual gyrus ($p<0.01$, tfce corrected), while Non-responders showed higher connectivity in the left paracingulate gyrus ($p<0.05$, tfce corrected). Graph-theoretical analysis indicated a diffuse, less segregated frontal organisation in Non-responders, whereas Responders showed greater thalamic centrality and a more efficient network architecture ($p<0.05$).

Conclusions: We identify a brain connectivity and organization of migraine individuals with a future meaningful response to mAbs treatment. Future Responders are characterized by a more efficient network architecture with the thalamus acting as central hub.



Long-term combination with onabotulinumtoxinA and atogepant to achieve higher standards of migraine control: a 52-week, prospective, real-world evaluation (SYNERGY study)

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Background: Patients with chronic migraine (CM) who remain inadequately controlled despite ongoing preventive monotherapy represent a particularly challenging population. Whether the clinical benefit achieved after adding a second preventive therapy can be maintained over the long term remains poorly understood. Herein, we evaluated the 52-week real-world effectiveness of onabotulinumtoxinA (BoNT-A) plus atogepant in the expanded SYNERGY study.

Methods: We prospectively analyzed 143 adults with CM receiving atogepant added to stable BoNT-A (prior exposure mean 11.8±6.7 months), regardless to prior anti-calcitonin gene-related peptide (CGRP) drugs exposure. Outcomes were assessed at baseline and weeks 12, 24, 36, and 52. Co-primary outcomes were change in monthly migraine days (MMDs) from baseline to week 52 and ≥50% MMDs response (RR50%). Secondary outcomes included monthly headache days (MHDs), acute medication days, HIT-6 and effectiveness using the IHS recommendations at 52 weeks. Sensitive analysis were performed including patients that discontinued treatment. All participants give written informed consent.

Results: Participants were mostly female (134/143, 93.7%, mean age±SD, 41.0±11.3) and 88/143 (61.5%) had prior anti-CGRP monoclonal antibody exposure. Baseline MHDs and MMDs were 22.9 ± 5.7 and 16.6 ± 6.6 days, respectively.
At week 52, in the 115 patients completing the follow up, MMDs decreased to 8.2±5.8 days ($\chi^2(4)=199.5$, $p<0.001$), with reductions versus baseline at all time points (all $p<0.001$) and RR50% was achieved by 63/108 patients (58.3%). IHS-defined modest or optimal control was achieved by 21/108 (19.4%) and 27/108 (25.0%) individuals respectively. None achieved migraine freedom. In prior anti-CGRP monoclonal antibody failures (n=88), MMDs decreased from 16.7±6.9 to 8.8±6.1 days and RR50% was achieved by 37/67 (55.2%). Discontinuation increased from 8/143 (5.6%) at week 12 to 35/143 (24.5%) at week 52, mainly due to ineffectiveness.

Conclusions: Atogepant add-on to BoNT-A was associated with sustained MMDs reductions over 52 weeks. IHS categories showed that one quarter of subjects achieved optimal control, supporting long-term evaluation of combination prevention in CM with high residual migraine burden.



Headache outcome after middle-meningeal artery embolization in subdural hematoma

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Background: Middle meningeal artery embolization (MMAE) has recently emerged as a promising adjunctive or alternative therapeutic strategy for chronic subdural hematoma (cSDH). Yet, beyond its role in cSDH, the MMA is also implicated in headache pathophysiology. Although MMA vasodilation alone does not fully explain migraine pain, modulation of dural vascular signaling may play a role in the pathogenesis of migraine.

Methods: We conducted a retrospective study including patients who underwent MMAE procedure pre- or post-surgical treatment for cSDH between December 2024 and February 2026.

Results: After applying the inclusion and exclusion criteria, a total of 24 patients (16.55%) out of 145 who underwent MMA embolization procedure for cSDH were included. Among these, 10/24 patients (41.7%) reported headache prior to treatment, whereas 14/24 (58.3%) were headache-free pre-procedure. Among patients with pre-existing headache, 5/10 (50.0%) had migraine and 4/10 (40.0%) had tension-type headache, while one patient presented with headache secondary to the cSDH; 2/5 patients with migraine exhibited a marked improvement of their primary headache disorder after the procedure (these cases were described in detail) and 1/4 with tension-type headache.

Conclusions: Although MMA embolization cannot be considered a treatment for primary headache disorders, the improvement observed in some patients with migraine or tension-type headache in our series may reflect modulation of shared meningeal mechanisms. Prospective studies will be necessary to clarify whether MMA embolization may influence meningeal nociceptive pathways beyond its established role in preventing hematoma recurrence and could be considered as an option for refractory migraine.



Tobacco/nicotine-related headache as a candidate phenotype for ICHD-4: Insights from the JASTIS study, a Japanese cross-sectional analysis

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Background: The International Classification of Headache Disorders (ICHD), 3rd edition, classifies headaches attributed to substance use or withdrawal as secondary headaches. However, headache related to smoking or nicotine has not been sufficiently established as an independent diagnostic entity. (A) Headache during or shortly after smoking, (B) headache worsening on days of smoking reduction, and (C) headache improvement after smoking avoidance are clinically observed, but their frequency and association with migraine remain unclear. This study aimed to examine smoking-related headache symptoms associated with heated tobacco products (HTPs) and conventional cigarettes, and their relationship with migraine.

Methods: We performed a cross-sectional analysis using data from the 2026 Japan Society and New Tobacco Internet Survey (JASTIS), an internet-based cohort survey. Participants were recruited from a nationally representative online panel comprising more than two million individuals. Among 30,000 respondents, 27,486 individuals with valid responses were included. For HTPs and conventional cigarettes, the three smoking-related headache symptoms were assessed separately: (A) headache during or shortly after smoking, (B) headache worsening on days of smoking reduction, and (C) headache improvement after smoking avoidance. Each symptom was evaluated using a four-point frequency scale: 1 = never, 2 = rarely, 3 = sometimes, and 4 = often. In the present analysis, each symptom was dichotomized into positive and negative responses; “sometimes” and “often” were considered positive, whereas “never” and “rarely” were considered negative.

Results: Among 3,889 respondents for HTPs, headache during or shortly after use was reported by 16.3% (632/3,889), headache worsening on days of reduced use by 12.0% (468/3,889), and headache improvement on days of reduced use by 12.7% (493/3,889). Among 9,061 respondents for conventional cigarettes, the corresponding frequencies were 11.2% (1,018/9,061), 7.7% (700/9,061), and 8.1% (733/9,061). Participants with migraine reported smoking-related headache symptoms more frequently than those without migraine.

Conclusion: Smoking-related headache symptoms were observed with both HTPs and conventional cigarettes and were more frequent among individuals with migraine. These findings suggest overlapping phenotypes of exposure-triggered, withdrawal-like, and exposure-sensitive headache, and may inform future classification of tobacco/nicotine-related headache in ICHD-4.



Effects of Receptive Music Therapy in addition to OnabotulinumtoxinA treatment for chronic migraine: a pilot study

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Background: Chronic migraine is a disabling condition with a significant impact on quality of life. OnabotulinumtoxinA is a recognized pharmacological treatment, consisting of injections in 31-39 sites over the scalp, neck and shoulders for a total dose of 155-195 UI, according to the standardized PREEMPT paradigm, repeated every 12 weeks. Treatment is generally effective and well tolerated, but pain related to the injection procedure is a frequent adverse event and may limit treatment tolerability in some patients. Integrative strategies such as music therapy may reduce pain, thereby improving treatment tolerability and effectiveness. This study evaluates the effect of receptive music therapy as an adjunct to onabotulinumtoxinA treatment for chronic migraine, both during treatment sessions and between sessions through remote delivery.

Methods: 54 patients with chronic migraine were involved in a randomized controlled trial. The experimental group received onabotulinumtoxinA treatment in addition to receptive music therapy before, during and after each injection sessions, whereas the control group received pharmacological treatment alone. Between sessions the intervention continued remotely through personalized relaxing playlists delivered to participants' mobile devices by a qualified music therapist. Control participants instead received emotionally neutral podcasts covering general-interest topics. Compliance with the remote listening protocol and participants' perceived benefit were assessed using a Google Forms questionnaire completed before and after each listening session. Categorical variables were analyzed using the Chi-square test or Fisher's exact test, whereas continuous variables were examined with parametric or non-parametric tests as appropriate. A two-sided p value < 0.05 was considered statistically significant.

Results: Receptive music therapy was associated with significant reductions in pain intensity (VAS) and anxiety (STAI-S8). Pain intensity (VAS) significantly decreased in the experimental group after both treatment sessions ($p=0.01$ and $p=0.003$), whereas no significant changes were found in the control group. Likewise, anxiety levels (STAI-S8) were significantly reduced only among participants receiving receptive music therapy ($p=0.006$). Preliminary findings also suggest that the remote listening program may provide additional emotional support and contribute to chronic migraine pain management.

Conclusion: The integration of receptive music into the PREEMPT protocol appears to improve pain perception, emotional well-being and the overall treatment experience in patients with chronic migraine.



A case report of galcanezumab-induced myastenia gravis-like symptoms

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Background: Over the past decade, new migraine treatments, blocking the calcitonin gene-related peptide (CGRP) pathway, have been approved and have demonstrated excellent efficacy and an optimal safety profile in both randomized controlled trials (RCTs) and real-world data (1,2). However, pharmacovigilance remains essential, especially for drugs that have been introduced so recently.

Methods: We present a clinical case of myasthenia gravis-like symptoms (MyG-l) during treatment with galcanezumab. A 52-year-old woman had suffered from migraine since adolescence, she had no other significant comorbidities; therefore, after failing several prophylactic medications, she began treatment with galcanezumab, achieving an optimal control of her migraine (3). Nevertheless, after 9 months of treatment, she developed right eyelid myoclonus, accompanied by fatigue during prolonged movements of her right hand, increased fatigue while walking, and occasional dysphagia with liquids. Myasthenia gravis was suspected, so several tests were performed. Both anti-acetylcholine receptor antibodies and anti-specific muscle kinase antibodies were negative. Laboratory workup, including thyroid function, was normal. A contrast-enhanced chest computed tomography (CT) scan revealed no abnormalities of the thymus. The brain magnetic resonance imaging (MRI) was normal; electroneurography (ENG), electromyography (EMG), repetitive nerve stimulation (RNS), and single-fiber electromyography (SFEMG) were negative. The patient was also prescribed an acetylcholinesterase inhibitor (pyridostigmine), without success. We ultimately decided to discontinue galcanezumab, and the patient reported a subjective improvement in her MyG-l, accompanied by a significant worsening of her migraine. The patient requested to resume treatment with galcanezumab, which led to the recurrence of MyG-l. We therefore decided to permanently discontinue the treatment and to try another preventive therapy.

Conclusions: Galcanezumab, fremanezumab, erenumab, and eptinezumab are monoclonal antibodies that target CGRP; gepants, on the other hand, are small molecules that target CGRP. All of these drugs are generally well tolerated, but postmarketing surveillance, as is well known, remains essential for identifying rare adverse events.
Our case report is not the only one in the literature that suggests the onset of neuromuscular manifestations following the initiation of therapy with a CGRP antagonist or a CGRP-receptor (CGRPR) antagonist. Another case report of MyG-I following initiation of galcanezumab has been published (4), and there are also two case reports of MyG-I following initiation of erenumab (5,6).
In our case, the positive results of both dechallenge and rechallenge are highly indicative of an adverse drug reaction (ADR). According to the Naranjo's ADR Probability Scale (7), we obtained a score of 8; therefore, this can be considered a probable ADR.
Numerous studies have examined the role of CGRP at neuromuscular junctions; most of them have shown that CGRP modulates synaptic transmission by interacting with acetylcholine or its receptor (8), but these findings need to be confirmed, and certainly scientific data are necessary to verify whether anti-CGRP/CGRPR drugs can influence neuromuscular transmission.



Headache-Attributed Burden in Italian Children and Adolescents: Findings from the REPICEF School-Based Study

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Background: Primary headaches are among the most common neurological disorders in children and adolescents, affecting school performance, emotional well-being, and social participation. Despite their high prevalence, population-based data on headache-attributed burden remain limited. The REPICEF (Registro EPIdemiologico delle CEFalee in età evolutiva) project evaluated the educational and psychosocial impact of primary headaches in a large school-based cohort of Italian children and adolescents.

Methods: REPICEF is a cross-sectional, school-based study conducted in L'Aquila, Italy, including students aged 6–17 years. Participants completed the Italian version of the Headache-Attributed Restriction, Disability, Social Handicap and Impaired Participation (HARDSHIP) questionnaire. Headache-attributed burden was assessed using HARDSHIP items evaluating vitality (Q35), emotional well-being (Q39–Q40), social participation (Q43), and school functioning (Q44). Data were analyzed using R (v4.3.0).

Results: Among 963 participants, 855 (89.1%) reported at least one headache episode during the previous year. Headache was associated with impairment across emotional, social, and school-related domains. Younger children (6–11 years) reported lower vitality than adolescents (mean Q35: 1.88 vs. 2.29), whereas adolescents reported higher fear scores (Q39: 1.58 vs. 1.29). Girls showed higher fear scores than boys (Q39: 1.90 vs. 1.54), while boys reported greater perceived social impact (Q43: 3.53 vs. 3.42) and greater difficulty with schoolwork (Q44: 1.60 vs. 1.78). Across headache diagnoses, probable medication-overuse headache showed the poorest quality-of-life profile, with the lowest vitality and emotional well-being scores, whereas undifferentiated headache was associated with reduced vitality and greater impairment in school functioning. Difficulties with homework and daily activities were observed across all headache subtypes.

Conclusions: Primary headaches impose a substantial educational and psychosocial burden in Italian schoolchildren, extending beyond clinically definite migraine and tension-type headache. The marked impact observed in probable headache categories highlights the importance of early identification and timely management, even before a definitive diagnosis is established, to reduce headache-related disability during childhood and adolescence.



Abnormal neurovascular coupling in the precuneus–posterior cingulate cortex may bridge simple and complex aura phenomena in the migraine brain: an arterial spin labelling investigation

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Background: Migraine aura is a heterogeneous phenomenon in which visual symptoms predominate, while a substantial proportion of patients also experience somatosensory and, more rarely, dysphasic or motor manifestations. While neurovascular coupling (NVC) abnormalities within the primary visual cortices in migraine with aura (MwA) have recently been implicated as a potential mechanism facilitating cortical spreading depression (CSD) ignition, it is still unclear whether impaired NVC extending beyond visual areas may contribute to CSD propagation and, therefore, to the broader symptomatology characterizing complex aura phenotypes.

Methods: Forty patients with MwA (21 simple visual MwA, 19 complex MwA), 30 patients with migraine without aura (MwoA), and 22 healthy controls (HC) underwent multimodal 3T MRI during the interictal period, including resting-state functional MRI and multi-delay arterial spin labeling. Regional NVC was estimated by computing the correlation coefficient between z-scored regional homogeneity (ReHo) maps from resting-state blood oxygen level dependent signals and z-scored cerebral blood flow (CBF) maps from multi-delay arterial spin labeling signals.

Results: Voxel-wise analysis of CBF maps revealed that patients with cMwA showed a significant CBF increase in regions predominantly localized medially, within the precuneus–posterior cingulate cortex region, compared to both patients with MwoA and HC ($p<0.05$, TFCE corrected). Furthermore, a reduced NVC at the left and right precuneus - posterior cingulate cortex (pCUN-PCC-1 parcels) was observed in patients with cMwA compared with patients with svMwA, MwoA and HC (respectively $p=0.004$ and $p=0.048$, FDR corrected).

Conclusions: In patients with complex aura, neurovascular uncoupling extends beyond the visual cortex to involve the precuneus–posterior cingulate cortex, a central hub of the default mode network characterized by exceptionally high baseline metabolic demand and extensive structural and functional connectivity with somatosensory and motor cortices. Such impaired perfusion–function matching within this multimodal hub may reduce network metabolic resilience and facilitate anterior CSD propagation, thereby providing a plausible mechanistic substrate for the broader clinical manifestations of complex aura.



Migraine in Older Adults: A Multicenter Real-World Analysis from the Italian RICe Registry

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Background: Primary headaches, particularly migraine, are highly prevalent disorders that remain insufficiently characterized in the growing elderly population. This multicentre study evaluated headache diagnoses, with a focus on migraine, across different age groups in tertiary headache centres participating in the Italian Registry for Headache Disorders (RICe).

Methods: Using a post-hoc design, we evaluated 3,477 patients enrolled at 30 Headache centers between 2019 and 2025. Patients were stratified into four age groups: young adults (18–30 years), adults (31–45 years), middle-aged (46–59 years), and elderly (≥60 years). Migraine demographic and clinical characteristics were recorded. Preventive and acute treatment use was also reported. Statistical analyses included chi-square tests and Kruskal–Wallis ANOVAs.

Results: According to age stratification, 644 patients (18.5%) were elderly, 1,285 (36.9%) middle-aged, 990 (28.5%) adults, and 558 (16.1%) young adults. Focusing on patients with migraine (3,013, 86.7%), the distribution of headache diagnoses according to ICHD-3 differed across groups [$\chi^2(6)=71.5$, $p<0.001$]. Elderly patients were more likely to receive a chronic migraine (CM) diagnosis ($z=4.18$), whereas migraine with aura was more prevalent in younger and adult individuals ($z=3.62$ and 4.97, respectively). An additional diagnosis of medication-overuse headache (MOH) occurred more often in the elderly group ($z=3.56$). Consistently, elderly individuals reported a higher number of monthly migraine days, but lower pain intensity and fewer severe attacks (all $p<0.001$). Physical activity and stress were common triggering factors in the elderly. Other core migraine characteristics were largely comparable across groups. Preventive treatment patterns differed across groups, with greater use of beta-blockers and onabotulinumtoxinA in the elderly. No age-related differences were observed in the prescription of anti-CGRP monoclonal antibodies.

Conclusions: In elderly patients, CM predominates and is characterized by frequent attacks of less severe intensity with specific triggering factors as well as a higher presence of MOH, compared to younger individuals. Our findings underscore the importance of age-tailored diagnostic assessment and individualized therapeutic approaches, while supporting the use of contemporary preventive treatments, including anti-CGRP monoclonal antibodies, in older patients.



Central and peripheral contributions to fibromyalgia phenotypes: role of migraine comorbidity and small fibre pathology

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Background: Fibromyalgia (FM) is a heterogeneous chronic pain condition involving peripheral and central mechanisms. Migraine is a prototypical disorder of central nervous system dysregulation, while small fibre pathology (SFP) reflects peripheral nociceptive dysfunction. We investigated whether comorbid migraine and SFP identify different clinical phenotypes within the FM spectrum.

Methods: We examined 296 FM patients diagnosed according to the 2016 ACR criteria (1). Migraine was classified as episodic, high-frequency, or chronic according to IHS criteria. Clinical severity was evaluated using the Fibromyalgia Impact Questionnaire, Zung Anxiety and Depression scales, Multidimensional Assessment of Fatigue, and the Brief Pain Inventory. Skin biopsy assessed intraepidermal nerve fibre density (IENFD). A multivariate analysis of covariance (MANCOVA) tested the effects of migraine category and SFP (present/absent) on clinical variables, with age as covariate.

Results: Migraine was diagnosed in 46.6% of FM patients, including 50% with frequent or chronic forms. Reduced IENFD was observed in 64.5%. MANCOVA indicated a significant effect of migraine comorbidity ($p=0.047$) and a significant migraine × SFP interaction ($p=0.003$) on the multivariate clinical profile, whereas univariate ANOVAs were not individually significant. FM patients with chronic migraine showed higher anxiety and greater pain interference. SFP alone was associated only with higher symptom severity scores.

Conclusions: Migraine comorbidity, particularly chronic migraine, was associated with greater pain interference and higher anxiety in FM patients, whereas SFP alone did not define a distinct clinical phenotype. However, the significant migraine × SFP interaction suggests that the coexistence of central and peripheral abnormalities may contribute to the overall multidimensional symptom profile of FM. Migraine and SFP jointly influence the overall clinical expression of FM. Their coexistence delineates a mixed phenotype, supporting a model of FM as a disorder spanning central and peripheral pain mechanisms.



Gut Microbiota Functional Remodeling in Pediatric Migraine: A Multi-Omic Insight into Neuroactive and Immunometabolic Pathways

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Background: Pediatric migraine is increasingly linked to alterations of the microbiota–gut–brain axis, but the functional activity of the gut microbiota remains poorly characterized. We integrated fecal metaproteomics and untargeted metabolomics to investigate gut microbiota-associated functional and metabolic signatures in children with migraine.

Methods: Stool samples from 50 migraine patients and 24 healthy controls were analyzed by LC–MS/MS-based metaproteomics, while metabolomics was performed on 83 migraine patients and 41 controls. Microbial protein groups were functionally annotated using COG and KEGG-based approaches, and fecal metabolites were annotated from untargeted metabolomic profiles.

Results: Metaproteomics revealed selective remodeling of microbial pathways related to nitrogen metabolism, arginine/citrulline and glutamate–glutamine turnover, aromatic amino acid metabolism, and short-chain fatty acid-associated functions. These changes converged with fecal metabolomic alterations involving arginine-related metabolites, glutamate/GABA-associated compounds, tryptophan- and tyrosine/phenylalanine-derived metabolites, purine intermediates, and lipid-related molecules. The nitrogen and arginine/citrulline signature suggested a potential link with nitric oxide-related pathways, whereas glutamate/GABA and aromatic amino acid alterations pointed to remodeling of neuroactive microbial functions. Changes in lipid/acyl-CoA, butanoate/propanoate, and purine-related pathways suggested an altered intestinal immunometabolic environment potentially relevant to barrier integrity, mucosal immune regulation, purinergic signaling, and microbiota–gut–brain communication.

Conclusions: Integrated metaproteomic and metabolomic profiling identified selective remodeling of gut microbial functions and fecal metabolic outputs in pediatric migraine, supporting a functional microbiota signature potentially linked to nitric oxide-related metabolism, neuroactive amino acid pathways, purine signaling, and intestinal immunometabolic homeostasis.



Neurophysiological evaluation in hemiplegic migraine patients: a study with repetitive transcranial magnetic stimulation and sound induced flash illusions

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Background: Migraineurs show increased cortical excitability and dysfunction in intracortical inhibitory patterns. Furthermore, an increased visual excitability leads for to reduction of illusory phenomena when concurrently presenting visual and auditory stimuli (sound-induced flash illusions – SIFI). Hemiplegic migraine (HM) is a rare subtype of migraine with aura with striking motor manifestations. The aim of the study is to assess the neurophysiological correlates of HM patients.

Methods: Patients affected by HM and episodic migraine without aura (MwoA) were included, as well as healthy subjects (HS) of same age and sex. Repetitive transcranial magnetic stimulation (rTMS) was performed using trains of 10 stimuli at 120% of resting motor threshold at 5Hz. Motor evoked potentials (MEPs) were considered as % related to the first MEP. The response trends were distinguished into facilitatory, inhibitory, or flat. Regarding SIFI, fission illusions were evaluated delivering one flash (1F) with 2–4 beeps (B), while fusion illusions were induced delivering 2–4F with 1B.

Results: 9HM (4F), 13MwoA (11F) and 11HS (7F) were included. MEPs 2-10 were significantly higher in HS compared to HM and MwoA, with the facilitatory as the most represented trend (63.6%), while the most frequent in migraineurs was the inhibitory one (HM 88.9%, MwoA 84.6%, χ^2 comparing the three groups p=0.004). HM and MwoA perceived less fission illusions (1F3B HM 1.62±0.43, MwoA 1.45±0.35, HS 1.95±0.25, p=0.003; 1F4B HM 1.64±0.47, MwoA 1.52±0.37, HS 2.16±0.26, p=0.001), while only HM perceived significantly fewer fusion illusions than HS (3F1B HM 2.84±0.44, MwoA 2.52±0.53, HS 2.35±0.23, p=0.028).

Conclusions: HM showed rTMS results comparable to MwoA, confirming that a baseline increased cortical excitability may lead to protective inhibitory responses where HS show facilitatory ones. Both MwoA and HM showed a lesser extent of SIFI, but only HM presented a reduction in fusion illusions compared to HS, demonstrating how such population may show increased visual excitability that goes beyond MwoA patients.



Long-term effectiveness, safety and tolerability of atogepant in the prevention of migraine: a multicentric, prospective observational, real world study (the 48-week STAR study)

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Background: To investigate the long-term effectiveness, safety and tolerability of atogepant for migraine prevention after 48 weeks of treatment.

Methods: At baseline (T0), weeks 9–12 (T3), 21–24 (T6) and 45-48 weeks (T12), monthly migraine days (MMDs), and main patients' reported outcomes were assessed. The co-primary outcomes were changes in MMDs and the percentage of MMDs ≥50% responders (50%RR) at T3, T6, and T12 compared to baseline. We also reported the proportion of patients achieving migraine freedom according to the International Headache Society proposal.

Results*:* Three hundred and seventy (370) patients from 17 Italian centers were enrolled (female 311, 84.1%, age 47.7 SD 0.7). Of these, 57 patients (15.4%) dropped out of treatment within the first 12 weeks; 85 (23.0%) within

24 weeks; and 118 (31.9%) within 48 weeks. Nineteen participants (16,1%) dropped out because of adverse events, 43 (36,4%) for inefficacy, 14 (11,9%) for both adverse events and inefficacy, and 42 (35,6%) for other reasons.
In patients continuing therapy for 48 weeks, MMDs decreased from 16.5 (SD 0.5) to 7.8 (SD 0.5; $p<0.001$) at T3, 7.6 (SD 0.5) at T6, 7.9 (SD 0.5) at T12, while 50%RR was achieved in 52% of patients at T3, 48.1% at T6, and 43.3% at T12. At all evaluation times, patients affected by chronic migraine less frequently achieved 50%RR ($p<0.01$). Migraine freedom was achieved in 6.2% of patients at T3, 7.1%, at T6, and 8.4% at T12.
Pain NRS reduced from baseline (8 IQR 1) to T3 (6 IQR 2, $p<0.001$) and remained stable until T12. The MIDAS scores almost halved from 64.9 at baseline (SD 47.8) to 23.9 (SD 32.1) at T12.
Overall, patients' weight progressively decreased from baseline to T12 ($p<0.001$) and a clinically relevant (i.e.>7%) weight loss was observed in 43.9% of participants at T3, 47.2% at T6, and 50.0% at T12. No correlation was observed between clinical response and weight loss at all observation times.

Conclusions: The STAR study demonstrates the sustained effectiveness and tolerability of atogepant over 48 weeks. Discontinuations and weight loss support the need for long-term monitoring in clinical practice and treatment optimization.


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POSTERS



HEADACHES IN CHILDREN AND ADOLESCENTS

Effects of a mindfulness-based intervention on adolescents with high frequency primary headaches: a prospective multicenter study

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Background: Primary headache in childhood and adolescence is frequently associated with high disability and a complex psychological profile characterized by anxiety, depressive symptoms, pain catastrophizing, and difficulties in emotional regulation. These factors contribute significantly to headache chronification and to the functional impact of the condition. In addition to standard care, mindfulness is a feasible and effective behavioral approach, although data on the long-term effects of mindfulness in adolescents with headache remain limited.

Methods: This prospective study included 40 adolescents aged 11–18 years with high-frequency primary headache recruited from four pediatric headache centers. Participants attended a mindfulness program conducted by an experienced physician in small groups, consisting of eight weekly online sessions, combined with lifestyle education. Questionnaires were administered before treatment (T0), and 3 (T3) and 6 (T6) months after the end of treatment to assess headache-related disability (PedMIDAS), anxiety (MASC, STAI-C), depressive symptoms (CDI-2), pain catastrophizing (PCS), emotional dysregulation (DESR), alexithymia (TAS-20), and emotional and behavioral functioning (CBCL).

Results: The analyses showed a progressive reduction in monthly headache frequency (11.6 vs 9.1 vs 7.9 days/month at T0, T3, and T6), associated with a decrease in analgesic use (4.2 at T0, 3.1 at T3, and 2.8 at T6). An improvement in headache-related disability was also observed (PedMIDAS: 39.8 at T0, 23.0 at T3, and 19.0 at T6), together with a reduction in pain catastrophizing levels (PCS: 25.1 at T0, 24.7 at T3, and 19.5 at T6). A trend toward a reduction in state anxiety was also found (STAI-C1: 34.2 at T0 vs 33.5 at T3 and 32.3 at T6). Twelve-month assessments are still ongoing and appear to confirm maintenance of the benefit in patients who have completed follow-up.

Conclusions: The results of our study show that a mindfulness-based intervention, integrated into an educational-behavioral approach, may lead to an overall improvement in the clinical and psychological condition of adolescents with high-frequency primary headache. The benefit is particularly evident in domains related to emotional regulation and pain perception, with a positive impact on quality of life.



Headache and focal neurological deficits: diagnostic challenges between Hemiplegic Migraine and Ischemic Events in an adolescent

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Background: Differential diagnosis between hemiplegic migraine and cerebral ischemic events remains a clinical challenge, even in the pediatric population, particularly when patients present with transient focal neurological deficits and initially inconclusive neuroradiological findings.

Methods: We report the case of a 14-year-old adolescent with a family history of migraine who presented to the Emergency Department following an episode of loss of consciousness, subsequently developing aphasia, focal neurological deficits, and headache with migrainous features. Initial investigations, including electroencephalography (EEG), brain computed tomography (CT), echocardiography, and carotid and vertebral Doppler ultrasonography, were unremarkable, whereas brain magnetic resonance imaging (MRI) revealed transient vascular abnormalities that were not confirmed on follow-up imaging. The patient was discharged with a diagnosis of migraine with atypical aura. Clinical follow-up required repeated reassessments over time, both in the outpatient setting and during subsequent hospital admissions. Recurrent paroxysmal neurological manifestations prompted serial laboratory and instrumental investigations, including neuroradiological, ultrasonographic, and electrophysiological studies. As part of the diagnostic work-up, genetic testing was also initiated and is currently ongoing. These investigations progressively clarified the clinical picture, occasionally yielding unexpected findings, ultimately leading to an effective therapeutic strategy.

Results: Brain MRI performed during the second hospitalization demonstrated multiple bilateral subacute cerebellar ischemic lesions. Transcranial Doppler ultrasound revealed a grade III right-to-left shunt, highly suggestive of a patent foramen ovale (PFO), which was subsequently confirmed by echocardiography. This finding, together with mildly abnormal coagulation parameters, supported the initiation of antiplatelet therapy, initially as monotherapy and later as dual antiplatelet therapy. The patient subsequently underwent successful percutaneous PFO closure.

Conclusions: Overall, the clinical and instrumental findings were consistent with a cerebrovascular etiopathogenetic mechanism. However, the semiology of the recurrent neurological episodes was not entirely explained by the ischemic lesions detected on neuroimaging, leaving the initial diagnosis of hemiplegic migraine as a plausible concomitant condition. This case highlights the diagnostic challenges posed by recurrent focal neurological manifestations in patients with a migrainous phenotype. Appropriate clinical management therefore requires continuous diagnostic reassessment, integrating clinical evolution with instrumental findings to guide timely therapeutic decision-making.



Atypical Aura in Childhood: An Italian Multicenter Case Series and Narrative Review

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Background: Migraine with aura is a common neurological disorder in childhood, yet atypical aura presentations remain underrecognized and often pose a significant diagnostic challenge because they may mimic acute neurological disorders, including stroke, epilepsy, encephalitis, and demyelinating diseases. Current ICHD-3 criteria only partially reflect the broad clinical spectrum observed in pediatric patients. This multicenter collaborative study, involving 5 Italian pediatric headache centers, aimed to describe representative cases of atypical aura and to review the available literature on their clinical features, diagnosis, and management.

Methods: Three pediatric patients with atypical migraine aura were retrospectively collected from 5 Italian tertiary pediatric headache centers. Clinical presentation, diagnostic work-up, management, and outcomes were analyzed. A narrative review of the literature was also performed, focusing on confusional, hemiplegic, and prolonged aura in childhood.

Results: The case series included three distinct phenotypes: confusional aura with acute disorientation and altered awareness, hemiplegic aura with transient unilateral motor deficit and additional focal neurological symptoms, and prolonged aura with symptoms exceeding the duration defined by ICHD-3. In all patients, neuroimaging, electroencephalography, and laboratory investigations excluded alternative neurological conditions. Clinical outcomes were favorable, with complete symptom resolution and no structural abnormalities. The literature review confirmed that atypical aura is likely more common in children than currently recognized and is characterized by heterogeneous manifestations, including prolonged duration, bilateral or brainstem symptoms, and non-sequential progression of neurological deficits. Diagnosis remains primarily clinical after careful exclusion of secondary causes, while management is largely supportive, with specific therapeutic considerations in selected subtypes such as hemiplegic migraine.

Conclusions: Atypical migraine aura in childhood encompasses a wide spectrum of clinical presentations that frequently resemble neurological emergencies. Awareness of these uncommon phenotypes is essential to ensure prompt diagnosis, guide appropriate investigations, and avoid unnecessary interventions. This Italian multicenter experience, combined with a narrative review of the literature, highlights the need for greater recognition of pediatric atypical aura and supports future refinement of diagnostic criteria tailored to the pediatric population.



Secondary headache in the pediatric emergency departement: the crucial role of medical history

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Background: Headache is a common condition in children and a frequent cause of admission to the Emergency Department (ED); up to 0.5–1% of cases is associated to serious intracranial anomalies. The ED pediatrician must promptly recognize red flags for secondary headache to ensure the appropriate management.

Methods: We report the case of a girl admitted to the Pediatric ED of the Regina Margherita Children's Hospital of Turin, Italy, for a 4-day history of right temporal headache and one episode of vomiting, apparently without other symptoms.

Results: A twelve-year-old girl was admitted for right temporal headache that had been on for 4 days. She reported a single episode of vomiting, no fever, photophobia or phonophobia. She had a history of occipital headaches, the last episode occurring 2 months earlier. Physical examination was unremarkable, and symptoms improved with analgesic treatment, so she was discharged with an ophthalmologic evaluation the following day.
The fundus oculi was normal, showing “mild papillary asymmetry and slight temporal blurring of the left optic disc”; the visual field revealed left lateral homonymous hemianopia. The girl was then taken back to the ED, where urgent head CT scan showed right occipital intraparenchymal hemorrhage. Brain MRI angiography confirmed an acute right parieto-occipital lobar hematoma with suspected underlying arteriovenous malformation. However, cerebral angiography was negative for vascular malformations. She was admitted to the Neurosurgery Unit, where she underwent conservative treatment and an uneventful clinical course. Only then she report concomitant cervical pain, which had developed simultaneously with the headache.

Conclusions: This case emphasizes the importance of obtaining a detailed medical history, even in the ED setting. Cervical pain, a potential red flag for secondary headache due to intracranial hemorrhage, emerged only later. Patients may not report all relevant symptoms; therefore, targeted history-taking is essential, especially with children. It is the clinician’s duty to ask targeted questions aimed at identifying possible red flags, in order to identify severe forms of secondary headache early and prevent possible diagnostic delays.



Tolosa–Hunt syndrome in adolescence: a rare cause of secondary headache and painful ophthalmoplegia

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Background. Tolosa–Hunt syndrome (THS) is a rare cause of secondary headache and painful ophthalmoplegia attributed to idiopathic granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbital apex. Although well described in adults, pediatric-onset THS is exceptionally uncommon and represents a significant diagnostic challenge because of its rarity and broad differential diagnosis. We report the case of an adolescent with THS whose clinical presentation was characterized by unilateral headache, facial pain and diplopia.

Methods. We retrospectively reviewed the clinical, neuroradiological, laboratory, and therapeutic data of a 15-year-old girl referred to a tertiary Pediatric Headache Center for progressive unilateral headache, facial pain and diplopia. Diagnostic work-up included neurological and neuro-ophthalmological assessments, contrast-enhanced brain MRI, cerebrospinal fluid analysis, and investigations aimed at excluding infectious, autoimmune, vascular, neoplastic, and systemic causes.

Results. The patient presented with left frontotemporal headache, facial pain, and otalgia, followed within 24 hours by binocular diplopia. Initial neurological assessment in the emergency setting was unremarkable; however, subsequent evaluation revealed left ptosis, exotropia, anisocoria, and partial third cranial nerve palsy. Contrast-enhanced MRI demonstrated an area of enhancing inflammatory tissue involving the left cavernous sinus, extending to the orbital apex and adjacent dura, associated with mild ipsilateral proptosis. Diagnostic investigations excluded alternative causes. Based on the clinical presentation, neuroradiological findings, and exclusion of the main differential diagnoses, THS was diagnosed according to ICHD-3 criteria. Treatment with intravenous methylprednisolone (1 g/day for 5 days) resulted in complete pain resolution within 48 hours and progressive improvement of oculomotor dysfunction.

Conclusions. This case highlights the importance of considering THS in the differential diagnosis of adolescents presenting with unilateral headache and progressive painful ophthalmoplegia. Despite its exceptional rarity in pediatric patients, early recognition through dedicated imaging of the cavernous sinus region and systematic exclusion of alternative diagnoses is essential for prompt treatment and may reduce diagnostic delay.



Pain management for acute primary headache in a pediatric Emergency Department: a retrospective study

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Background: Headache is a common reason for pediatric emergency department (ED) attendance, but real-world data on analgesic use, dosing, timing and reassessment are limited. We evaluated acute primary headache management in a tertiary pediatric ED and factors associated with outcome at discharge.

Methods: We retrospectively included patients <18 years presenting with primary headache to the ED of Bambino Gesù Children's Hospital between January and December 2025. Secondary headaches were excluded. Demographic, clinical, diagnostic and treatment data were collected. Patients were grouped by headache status at discharge: unchanged, improved or resolved. Factors associated with outcome were assessed by bivariate analysis and ordinal regression.

Results: 471 patients were included: 267 (56.7%) were female and mean age was 11.2 years. Most were triaged as green (70.9%) or blue (25.7%). Associated symptoms were reported by 359 patients (76.2%), mainly phono/photophobia, nausea and vomiting. Brain CT was performed in 223 cases (47.3%) and hospital admission was required in 26 (5.5%). Only 166 patients (35.2%) received analgesic treatment in the ED, mainly ibuprofen, paracetamol or ketorolac; recommended weight-based dosing was achieved in 57 treated patients (36.7%). Headache reassessment was documented in 298 patients: pain was unchanged in 58 (19.5%), improved in 119 (39.9%) and resolved in 121 (40.6%). Treated patients were less frequent in the unchanged group. Higher ibuprofen dosage was independently associated with headache improvement in ordinal regression (OR 1.638, p=0.003), together with younger age (OR 0.894, p<0.001).

Conclusions: In this pediatric ED cohort, analgesic treatment, appropriate weight-based dosing and pain reassessment were suboptimal. Higher ibuprofen dosage was associated with better short-term outcome, supporting standardized, timely and adequately dosed analgesic pathways for children with acute headache.



Primary Headaches in Italian Children and Adolescents: Epidemiology and Clinical Profile from the REPICEF Study

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Background: Primary headaches are among the most common neurological disorders in children and adolescents, yet contemporary population-based epidemiological data from Italy remain limited. The REPICEF (Registro EPIdemiologico delle CEFalee in età evolutiva) study aimed to estimate the prevalence and clinical profile of primary headaches in a large school-based population using a standardized diagnostic instrument.

Methods: REPICEF is a cross-sectional, school-based study conducted in L'Aquila, Italy, including students aged 6–17 years. Participants completed the Italian version of the Headache-Attributed Restriction, Disability, Social Handicap and Impaired Participation (HARDSHIP) questionnaire, recently validated for the Italian pediatric population. Headache diagnoses were assigned according to the questionnaire algorithm based on ICHD-3 criteria. Demographic characteristics, headache phenotypes, and diagnostic distribution were analyzed using R (v4.3.0).

Results: A total of 963 students (mean age 13.7 ± 2.9 years; 50.3% female) were included. Overall, 855 participants (89.1%) reported at least one headache episode during the previous year. The most frequent diagnoses were probable migraine (28.4%), probable TTH (22.8%), undifferentiated headache (16.7%), TTH (13.7%), and migraine (11.4%). Moderate headache intensity was reported by 63.7% of participants, while photophobia and phonophobia were present in 66.5% and 83.9%, respectively. Adolescents showed a significantly higher prevalence of probable TTH than younger children (19.3% vs. 11.3%; $p < 0.001$), whereas definite TTH was more frequent in children (14.4% vs. 9.6%; $p = 0.008$). Females had a significantly higher prevalence of probable MOH than males (6.8% vs. 1.7%; $p < 0.001$), while probable TTH ($p = 0.014$) and undifferentiated headache ($p = 0.025$) also differed significantly by sex.

Conclusions: Primary headaches are highly prevalent among Italian children and adolescents, with probable migraine representing the most frequent diagnostic category. These findings support standardized school-based screening to improve the early identification of pediatric headache disorders.



Developmental differences in coping and pain catastrophizing in pediatric migraine: how patients and their mothers change across age

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Background: We aimed to: 1) explore coping strategies and pain catastrophizing in children and adolescents with migraine and their mothers; 2) investigate differences according to developmental stage, headache frequency, and pain intensity.

Methods: The study included 166 pediatric patients with migraine with and without aura (mean age 12.2 ± 2.6 years; 67 children and 99 adolescents) and their mothers. Patients were stratified according to: developmental stage (children vs adolescents), headache frequency (daily, high and low frequency), and pain intensity (severe and mild). Pain catastrophizing was assessed using the Pain Catastrophizing Scale/Child (PCS/PCS-C), while coping strategies were evaluated using the Pediatric Pain Coping Inventory (PPCI) in patients and the Coping Strategies Questionnaire-Revised, Italian version (CSQ-R-I) in mothers.

Results: Compared with adolescents, children showed higher scores in "Seeking Social Support" (p= <0.001) and lower scores in "Cognitive Self-Instruction" (p= 0.004). Mothers of children reported lower scores in "Praying/Hoping" (p= <0.001) and "Magnification" (p= 0.012) compared with mothers of adolescents. No significant differences according to headache frequency were found among children or their mothers. In contrast, adolescents with daily headache showed higher scores in "Magnification" (p= <0.001), "Helplessness" (p= 0.015), and "Total PCS-C" (p= 0.007), whereas those with lower headache frequency reported higher "Distraction" scores (p= 0.009). No significant frequency-related differences were observed among mothers of adolescents. Pain intensity was not associated with significant differences in children; however, mothers of children with severe pain showed higher "Magnification" scores (p= 0.043). Adolescents with severe pain reported higher "Seeking Social Support" scores (p= 0.036), with no corresponding maternal differences.

Conclusion: Developmental stage significantly influences coping and pain catastrophizing in pediatric migraine. Adolescents and their mothers exhibit a more maladaptive cognitive-emotional response to pain, especially when headache frequency is high. These findings support the integration of age-specific and family-oriented interventions into pediatric migraine care.



The use of drawing in pediatric headaches: a cross-cultural analysis of the literature.

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Background: The scientific literature reports several studies highlighting the usefulness of drawing in the diagnosis of primary headaches, demonstrating good sensitivity and specificity, especially in children under 10 years of age, where verbal methods are not always appropriate. (1)
Furthermore, in an outpatient setting, drawing facilitates the child's relationship with the clinician and allows for the exploration of emotions, moods, and fears.
However, when analyzing drawings, it seems reasonable to hypothesize the influence of various factors such as gender, age, cultural, and socio-geographical contexts.
The objective of this study was therefore to analyze published collections of pediatric headache drawings in the literature to identify geographical similarities and differences, on a symbolic and iconographic level, with further distinctions by age and gender.

Methods: The study material consists of scientific articles that were the subject of a recent study of ours (1) and which use drawing as an assessment tool. We selected studies on children and adolescents (0–18 years) that involved the production of spontaneous drawings referring to headache or related symptoms.

Results: The comparative analysis of the different studies indicates universal and consistent characteristics, including the depiction of the location, intensity, and pulsation of pain. However, three main factors—age, gender, and cultural context—influence this graphic representation. Age appears to be the primary factor, with more structured and detailed representations occurring with cognitive development. Gender differences are relatively limited, although females express the emotional aspects of pain more. It is interesting to note how cultural context influences the ways in which pain is symbolized and interpreted. Drawing appears more expressive in Anglo-Saxon and North American contexts, more communicative in Latin American contexts, more clinically and diagnostically oriented in European contexts, and more phenomenological and perceptual in Eastern European contexts.

Conclusions: The results suggest that interpretation of drawings should take into account the child's developmental level and cultural context to improve understanding of their subjective experience.

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Appropriateness and effectiveness of first-line analgesics in children with headache admitted to the Pediatric Emergency Department

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Background: Headache in children is a common reason for referring to the Pediatric Emergency Department (PED). Timely analgesic treatment is essential to achieve better outcomes; pain must be first appropriately and systematically assessed using validated scales. The main aim of this study was to evaluate the appropriateness and effectiveness of analgesics given for headache by caregivers before admission to the PED and by healthcare professionals in the PED. Second, we evaluated the use of validated pain scales by healthcare professionals at triage, on clinical evaluation, and on discharge.

Methods: Single-center, retrospective observational study on a representative sample of children <18 years-old admitted with non-traumatic headache to our tertiary PED between January and December 2024. Data from electronic medical records included demographics, headache type, analgesic use at home and in the PED, dosing accuracy, pain scale administration, pain response to treatment, and clinical outcomes. Descriptive analysis is reported.

Results: A total of 152 patients were included (median age 10 years; range 8-13 years). Analgesics were given at home to 112 of patients (73.7%): 77 (50.7%) received acetaminophen, 28 (18.4%) ibuprofen and 7 (4.6%) ketoprofen. Older children were significantly more likely to receive treatment at home (p=0.024). Acetanomiphen and ibuprofen were underdosed in 11.2% of children, with no difference between the two medications; ketoprofen was always given at the right dosage. In the PED, 90 children (60.5%) received analgesics at triage and showed greater reduction of pain scores compared to untreated patients (p<0.001). Pain assessment scales were used in 80.3% of patients at triage, 63.2% on medical evaluation, and 20.4% at discharge. Pain was never assessed using appropriate and validated scales in the PED in 11 children (7.2%).

Conclusions: Early analgesic treatment is essential to reduce effectively headache in children. Although significant progress has been made achieved on pain assessment, measurement and management in the recent years, there is still considerable room for improvement. Enhancing parental education on the proper management of headache at home including the correct choice of medication, the right timing of administration and the appropriate dosage represents a crucial objective for all healthcare professionals involved in pediatric care.



Psychological Correlates in Adolescents with Chronic and Non-Chronic Headache Attending the Regina Margherita Children's Hospital Headache Center of Turin, Italy (OIRM): A Preliminary Analysis

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Background: The OIRM Pediatric Headache Center provides multidisciplinary care for children and adolescents with primary headache disorders. Patients with chronic headache frequently require psychological assessment and intervention because of the substantial associated emotional burden. This study aimed to compare baseline levels of anxiety, depression, and anger between adolescents with chronic and non-chronic headache referred for psychological care.

Methods: Since January 2024, an integrated multidisciplinary care program has been implemented, including clinical triage, disability assessment with the Pediatric Migraine Disability Assessment (PedMIDAS), and structured screening for psychological comorbidities with the Children's Depression Inventory (CDI), the Children's Inventory of Anger (ChIA), and the Revised Children's Manifest Anxiety Scale (RCMAS-2). All the patients included in the program between January 2024 and March 2025 were included and divided in two groups: patients with chronic headache (Group A) and with non-chronic headache (Group B). Descriptive analysis is reported; significance for $p<0.05$.

Results: Overall, 126 patients (Group A: n=18; Group B: n=108) were included; mean age 11.9 years. In Group A, 44.44% of patients showed clinically significant anxiety scores and 33.33% reported clinically significant depressive symptoms. Clinically relevant anger was observed in 5.56% and was limited to the suppressed anger subscale. In Group B, clinically significant scores were found in 6.48% for anxiety, 10.19% for depression, and 30.56% for anger (9.26% expressed anger; 21.30% suppressed anger). Based on Fisher's exact test, Group A showed higher probability of clinically relevant anxiety ($p<0.0001$; OR=11.54) and depressive symptoms ($p=0.0145$; OR=4.41). Conversely, Group B showed a significantly higher probability of elevated anger levels ($p=0,0350$; OR=0,13).

Conclusions: A multidimensional care model integrating cognitive behavioural interventions, therapeutic education, and individualized pharmacological prophylaxis could be effective in reducing disability, improving psychological well-being, and promoting quality of life. Our findings suggest that chronic headache is associated with increased vulnerability to anxiety and depressive symptoms, supporting the need for early psychological assessment within multidisciplinary headache care. These preliminary findings should be confirmed by prospective studies on larger patient cohorts.



Beyond Words: Migraine Phenotype in Children and Adolescents with Autism Spectrum Disorder

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Background: Migraine is increasingly recognized as a relevant comorbidity in Autism Spectrum Disorder (ASD), yet its clinical phenotype in autistic children and adolescents remains poorly characterized. Shared neurobiological mechanisms, including neuroimmune dysregulation and altered excitatory-inhibitory neurotransmission involving GABAergic and glutamatergic pathways, have been proposed. In addition, communication difficulties, atypical pain behaviors, and sensory hyper-responsiveness may contribute to underrecognition of migraine in this population. We aimed to characterize the phenotype of migraine without aura and explore treatment response patterns in children and adolescents with ASD.

Methods: We conducted a retrospective observational study at the Headache Center of Bambino Gesù Children's Hospital, Rome. Clinical and demographic data collected between July 2011 and May 2026 were reviewed. Variables of interest included headache characteristics, associated symptoms, migraine equivalents, family history of migraine, sleep disturbances, and treatment response. Inclusion criteria were ASD diagnosis, age 5–18 years, and negative neuroradiological investigations.

Results: Twenty patients were included (65% males), with a mean age of 9.8 years at first headache assessment. Migraine attacks were equally distributed between moderate and severe intensity. Pain quality was undefined in 45%, constrictive in 30%, and pulsating in 25%, whereas pain location was unilateral in 35%, undefined in 35%, bilateral in 20%, and holocranial in 10%.
Combined photophobia and phonophobia were documented in 55% of patients and, in some additional cases, could be inferred from behavioral manifestations during attacks. Nausea and/or vomiting occurred in 25% and vertigo in 15%. Sleep disturbances were present in 55% and were associated with a higher monthly headache burden (6.6 vs 4.2 attacks/month). Positive family history of migraine and migraine equivalents were documented in 85% and 80% of patients, respectively. Acute treatment (ibuprofen) was effective in 85% of cases.
Preventive treatment was prescribed in 55% of patients (11/20), requiring a mean of 1.9 treatment attempts per patient. Preventive strategies included nutraceuticals, amitriptyline, flunarizine and topiramate. Nutraceuticals were the most frequently used first-line option (45.5%) but showed limited effectiveness, whereas topiramate was associated with clinical improvement in all treated patients (3/3).

Conclusions: Children and adolescents with ASD exhibit a distinctive migraine phenotype characterized by poorly defined pain descriptors, prominent sensory manifestations, frequent sleep disturbances, and strong familial aggregation. Behavioral manifestations may provide important clues for recognizing migraine-associated sensory symptoms and reducing underdiagnosis. Improved phenotypic characterization may facilitate earlier recognition and more individualized management in this understudied population.



Early Childhood Headache: Mapping Psychological, Cognitive, and Functional Impact

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Background: Although the literature on pediatric headache is extensive, evidence in young children remains limited, particularly regarding psychological, behavioral, attentional, and executive functioning, partly due to methodological challenges. This study examined these domains in children up to 8 years of age with headache.

Methods: Thirty children with headaches (mean age=5.8 years, SD=1.1; range=3.6-7.11 years; 15 F, 15 M) were included. Clinical variables included headache frequency, intensity, age at onset, medication use, migraine equivalents, and comorbidities. Behavioral functioning and quality of life were assessed through parent-report measures, including the CBCL 1.5-5 and 6-18, the BRIEF and BRIEF-P, and the PedsQL. Attention, executive functioning, and nonverbal reasoning were directly assessed using selected NEPSY-II subtests and Raven's CPM.

Results: Mean headache frequency was 5 attacks/month, with 83.3% in the low-frequency group (≤9/month). Symptom onset ranged from 1 month to 4 years pre-assessment. Migraine equivalents were present in 76.7% of children, while comorbidities were present in 57.7%, mainly language disorders. Borderline/clinical BRIEF scores were observed in 37.9% of children for Inhibition and in 41.4% for Emotional Regulation. Clinically significant internalizing problems were identified in 42.9% of patients. Quality of life was impaired in 50% of patients (cutoff <77), with the lowest mean score observed in emotional functioning (64.3%, <75). A total of 73.1% of patients scored ≥75th percentile on CPM. On NEPSY subtests, performance was heterogeneous: 23.8% and 25.0% showed above-average scores on Denomination and Inhibition tasks, respectively, while 33.3% and 25.0% demonstrated borderline or below-average performance.

Conclusions: Findings indicate a heterogeneous cognitive-behavioral profile in young children with headache, suggestive of emotional, attentional-executive vulnerabilities alongside preserved cognitive abilities.



How long do migraine attacks last in children and adolescents? Insights from a cohort of patients aged 6–18 years

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Background: Attack duration is a cornerstone of the diagnostic criteria for migraine without aura (MwA). Since publication of first International Classification of Headache Disorders (ICHD), this criterion has undergone several revisions, particularly in pediatric patients. Although evidence has consistently shown that migraine attacks in children are often shorter than in adults, the current ICHD-3 criteria still define attack duration as 2–72 hours. Consequently, some children with otherwise typical migraine features may not fully satisfy current diagnostic criteria. This study aimed to evaluate the duration of untreated migraine attacks in a cohort of pediatric patients with MwA.

Methods: We conducted a retrospective study including patients (6–18 years) with MwA and evaluated at the Headache Centers of Bambino Gesù Children's Hospital and the IRCCS Mondino Foundation. Data were retrospectively collected from the medical records of patients evaluated between January 2026 and early June 2026. Attack duration was assessed only for untreated attacks and categorized into four predefined, mutually exclusive intervals: ≤2 hours, >2 to ≤4 hours, >4 to ≤72 hours, and >72 hours. For attacks lasting ≤2 hours, duration was additionally recorded in minutes. Descriptive statistics were used to summarize demographic and clinical characteristics.

Results: A total of 150 patients met the inclusion criteria. Mean age was 12.3 ± 3.2 years, and 62.7% were female. Attack duration was ≤2 hours in 45 patients (30.0%), >2 to ≤4 hours in 45 patients (30.0%), >4 to ≤72 hours in 56 patients (37.3%), and >72 hours in 4 patients (2.7%). Among patients with attacks lasting ≤2 hours, mean attack duration was 59.1 ± 37.1 minutes (median 60 minutes; range 5–120 minutes). Of these 45 patients, 37 experienced attacks lasting <2 hours. Attacks lasting <2 hours were more frequently observed in younger children, with proportions progressively decreasing with age.

Conclusions: Nearly one-third of children and adolescents with MwA experienced attacks lasting no longer than 2 hours. These findings suggest that the current lower duration threshold may not fully capture the clinical spectrum of pediatric migraine and support reconsideration of pediatric-specific duration criteria in future revisions of the ICHD.



6 YEARS WITH TARGETED THERAPIES: REAL-WORLD EXPERIENCES

Improving Distress perception in caregivers of migraine patients with depressive symptoms treated with fremanezumab. The observational prospective real-life MI-DEAR study

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Background: To investigate whether the improvement in the migraine burden alleviates the distress of informal caregivers of patients affected by high-frequency episodic (HFEM) or chronic migraine (CM) with depressive symptoms.

Methods: Consecutive adult patients with HFEM or CM and depressive symptoms who received a prescription of fremanezumab were considered, along with their caregivers. The enrolled dyads have been evaluated before and after 6 months since treatment initiation. In patients, we evaluated monthly migraine days (MMDs), monthly use of acute medications, pain intensity, migraine-related disability (MIDAS) integrated into the composite 4D score, and depressive symptoms (Patient Health Questionnaire-9; PHQ-9). Caregivers filled in the Relative Stress Scale (RSS). The mutuality scale (MS) was also collected in the dyads.

Results: 154 dyads were enrolled (patients aged 42.6 ±12.7 years; 80.5% female; and caregivers aged 48.1±12.2 years; 36.4% female). Of these, 150 completed the 6-month follow-up. After six months of treatment with fremanezumab, MMDs reduced from 15.3±6.5 to 6.3±5.5, the 4D Score from 54.3±11.7 to 30.7±16.9 ($p < 0.001$), and the PHQ-9 score from 11.4±5.1 to 7.6±4.6 ($p < 0.001$). PHQ-9 and 4D score variations resulted highly correlated ($r = 0.373$; $p < 0.001$). In parallel, caregivers showed a significant reduction in RSS score from 20.0±10.9 to 16.7±11.7 ($p < 0.001$). Multiple regression analysis showed that the reduction in RSS is primarily related to PHQ improvement ($p<0.001$) rather than to 4D score improvement ($p=0.703$). The mutuality scale (MS) scores did not significantly change from T0 to T6 in patients and caregivers

Conclusions: The MI-DEAR study highlighted that caregivers' elevated perceived stress improves after effective migraine management in patients. The improvement in the migraine burden was associated with a reduction in depressive symptoms in patients, which in turn was the main factor alleviating caregivers' stress.



Effectiveness and safety of monthly versus quarterly Fremanezumab for Migraine Prevention: a 12 months Italian, Multicenter, Real-life Study

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Background: Fremanezumab, an anti-CGRP monoclonal antibody, is available as either a 225 mg monthy injection or a 675 mg quartery injection for migraine prevention. Both regimens were effective in randomized controlled trials, but real world evidence is lacking. Our purpose was assessing whether the two regimens have comparable efficacy and tolerability.

Methods: This is a prospective observational study involving four Italian headache centers. Eligible patients were assigned to the monthly or quarterly regimen based on their preference. Patient characteristics were collected at baseline, and then reassessed at 3, 6 and 12 months after starting fremanezumab. We collected data about monthly headache days (MHD), monthly migraine days (MMD), acute medication days (AMD), acute medication pills (AMP) and adverse events (AE). Migraine disability assessment score (MIDAS), Headache Impact Test (HIT-6), Allodynia Symptoms Checklist (ASC12) were completed at each timepoint.

Results: Two-hundred twenty-two patients chose monthly administration and 165 patients chose quarterly administration. Data were available for 347 patients at 3 months, for 377 patients at 6 months and for 298 patients at 12 months. Patients in the monthly group were 80,8% female and had a median age of 49 (IQR 38-58), 57,1% had episodic migraine with 15 (IQR 11-23) MHD and 15 (IQR 10-20) MMD at baseline. Patients in the quarterly group were 79,8% female and had a median age of 51 (IQR 41-58), 66.3% had episodic migraine with 16 (IQR 12-25) MHD and 15 (IQR 10-20) MMD at baseline. There was no significant difference at baseline between the two groups. Both regimens proved effective and safe, with no difference between the two groups at each timepoint in responder rates and AE. Both groups showed similar reductions in MHD, MMD, AMD and AMP, as well as in MIDAS and HIT-6 scores.

Conclusions: Our data confirm the effectiveness of fremanezumab in improving both frequency of headache and disability metrics in migraine patients, along its general safety and tolerability. Choice of monthly or quarterly administration does not appear to influence any outcome measure, and should therefore be individualized based mainly on patients preference and ease of administration.



Long-term effectiveness and persistence of anti-CGRP monoclonal antibodies in migraine: a prospective real-world study

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Background: Anti-CGRP monoclonal antibodies (mAbs) are widely used for migraine prevention, but real-world long-term effectiveness data accounting for treatment discontinuation and switching remain limited. We assessed 12-month outcomes using per-protocol and modified intention-to-treat (mITT) analyses, including intra-class comparisons.

Methods: We conducted a prospective observational study of 223 migraine patients initiating anti-CGRP mAbs (erenumab 70mg n=14, erenumab 140mg n=55, fremanezumab n=38, galcanezumab n=58) at a tertiary headache centre. Outcomes included monthly migraine and headache days, MIDAS, HIT-6, HADS, and 50% responder rates. Between-group differences were tested with Kruskal-Wallis tests at T12. Attrition and switching rates were tracked. For comparison, botulinum toxin (n=28) and oral prophylaxis (n=63) outcomes were drawn from a parallel headache cohort.

Results: Baseline headache frequency was 18.7±7.3 days/month, with rapid reduction to 8.9±6.8 at T3 and sustained effectiveness at T12 (8.1±6.3). MIDAS decreased from 80.4±59.1 to 29.8±37.2, and HIT-6 from 66.1±9.3 to 56.5±11.7. HADS anxiety improved from 9.2±4.4 to 7.2±4.2, and depression from 7.2±4.2 to 5.4±3.8. Attrition was 30% by T12, with 33 patients (14.8%) switching or stopping treatment (18 stop, 15 switch to another mAb). Per-protocol 50% responder rate at T12 was 67.9% (106/156). No significant intra-class differences emerged (Kruskal-Wallis $p>0.05$ at all timepoints), though erenumab 140mg showed numerically higher response rates (60.0% at T12, n=50). Compared with the parallel cohort, botulinum toxin showed lower per-protocol responder rates (42.9% at T12, n=7) but with substantial attrition (75%), while oral prophylaxis showed 61.5% (n=13, 79% attrition).

Conclusions: Anti-CGRP mAbs demonstrated sustained real-world effectiveness over 12 months with a per-protocol responder rate of 67.9% and treatment persistence of 85.2%. No clinically meaningful intra-class differences were identified, though larger head-to-head studies are needed. Comparison with other prophylactic classes was limited by small sample sizes and differential attrition.



Looking at adherence to treatments targeting the calcitonin gene-related peptide pathway from the lens of pharmacoutilization: real-world data

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Background: The real-world use of treatments targeting the CGRP pathway might deviate from physicians' prescriptions. We aimed to report the use of treatments targeting the CGRP pathway in relation to their effectiveness using pharmacoutilization data.

Methods: We collected prescription and dispensing data from a single center within the Italian Headache Registry (RICe). Clinical outcomes were assessed at each follow-up visit using MIDAS scores and monthly disabling headache days from medical records. We included only patients with a complete 12-month follow-upò. Therapeutic adherence was assessed using the Proportion of Days Covered(PDC), calculated as the ratio between days covered by dispensed medication and expected coverage days over 12 months for each drug. Changes from baseline were calculated as the difference between follow-up and baseline. Responders were defined as patients with a ≥50% reduction in monthly disabling headache days at months 10–12 compared with baseline. Correlation analyses assessed the relationship between adherence and reduction in monthly disabling headache days.

Results: The study included 127 patients, 104 women(81.9%) and 23 men(18.1%), with a mean age of 51.2±12.0 years (range 20–76). Fremanezumab was the most prescribed treatment (n=43,33.9%), followed by erenumab (n=39;30.7%), galcanezumab (n=28;22%) and eptinezumab (n=17;13.4%). Mean PDC to CGRP-targeting treatments was 86.3%, with 88 patients (69.3%) achieving ≥80% PDC. Subcutaneous therapies showed similar PDC (erenumab 90.7%, fremanezumab 86.6%, galcanezumab 89.9%), and higher adherence than eptinezumab (69.1%), which was the only treatment with adherence significantly below the 80% threshold (p=0.026). Overall, 80 patients (63%) were responders and 47 (37%) non-responders. During follow-up, 20 patients (15.7%) discontinued treatment due to inefficacy or intolerance. No significant correlation was found between adherence and clinical improvement, for either monthly disabling headache days or MIDAS score. Similarly, no differences were observed between high (≥80%) and low (<80%) adherence groups in the reduction of monthly disabling headache days (−8,4±9,8vs−8,9±11,1;p=0,888) or MIDAS score (−34,2±40,5vs−23,0±40,3;p=0,217).

Conclusions: Our observational study, based on pharmacoutilization data, suggests high adherence to self-administered CGRP-targeting treatments in real-world practice, irrespective of the degree of response. The lower adherence observed with eptinezumab may be related to the logistical demands of hospital-based intravenous administration compared with subcutaneous self-administration.



Familial aggregation of response to CGRP monoclonal antibodies in migraine: preliminary clinical evidence of inherited treatment susceptibility

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Background: Drugs targeting the calcitonin gene-related peptide (CGRP-mAbs) have demonstrated efficacy in randomized clinical trials and real-world studies. Nevertheless, approximately one-third of patients fail to achieve a clinically meaningful response, suggesting substantial biological heterogeneity in the contribution of CGRP-dependent mechanisms to migraine pathophysiology. Given the well-established familial aggregation of migraine, we investigated the familial aggregation of therapeutic response to CGRP-mAbs, hypothesizing that responsiveness to CGRP-targeted therapies may aggregate within families, putatively reflecting shared inherited biological determinants.

Methods: This is a prospective, single-center observational study including patients with migraine and at least one first-degree relative also treated with CGRP-mAbs. The primary outcome was familial aggregation of treatment response, evaluated as the change in monthly headache days from baseline to 6th month. A linear mixed-effects model including family as a random intercept was used to partition treatment-response variability into between-family and within-family components, with the intraclass correlation coefficient (ICC) quantifying familial clustering after adjustment for age, sex, baseline headache frequency, migraine subtype, medication-overuse headache, and previous preventive treatment failures. As a secondary analysis, response was dichotomized as a ≥50% reduction in monthly headache days. Families were classified as concordant responders, concordant non-responders, or discordant, and the observed concordance was compared with that expected under independent treatment responses.

Results: Fifty patients from 23 families completed the six-month follow-up. After adjustment for demographic and clinical covariates, family membership accounted for a substantial proportion of treatment-response variability (ICC = 0.57), indicating that more than half of the residual variability was attributable to between-family differences. Twenty of the 23 families (87.0%) showed concordant treatment response, including 16 concordant responder families and four concordant non-responder families, whereas only three families were discordant. The observed concordance markedly exceeded the 65.7% expected under the assumption of independent treatment responses.

Conclusions: Treatment response to CGRP-mAbs shows a high degree of intrafamilial concordance that remains largely independent of established clinical predictors, suggesting that shared familial determinants contribute to treatment response. The marked familial aggregation observed in our cohort provides a strong rationale for pharmacogenetic studies aimed at identifying the molecular determinants of treatment response and advancing precision medicine in migraine prevention.



Atogepant as Add-on Therapy to OnabotulinumtoxinA in Chronic Migraine: A Real-World Study

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Background: OnabotulinumtoxinA (BoNT-A) is a well-established preventive treatment for chronic migraine (CM). Given the high burden of CM, many patients require additional preventive therapy for adequate disease control. Although BoNT-A plus anti-CGRP treatments may provide synergistic benefits, real-world evidence remains limited. We evaluated atogepant as add-on therapy to BoNT-A in patients with CM.

Methods: This single-center, real-world study included patients with CM receiving BoNT-A for at least 2 cycles who had achieved only a partial response. Oral atogepant 60 mg once daily was added to ongoing BoNT-A treatment. Patients were assessed at T0 (immediately before first BoNT-A cycle), T1A (initiation of combination therapy), and T6A (after six months of combination therapy). Demographic characteristics and CM duration were recorded. Outcomes included monthly headache days (MHDs) and changes in MHDs between timepoints (ΔMHD), monthly acute medication use, migraine-related disability assessed using the Migraine Disability Assessment (MIDAS), and the proportions of patients achieving 50% and 75% reduction in MHDs at T6A.

Results: Twenty patients were included: 18 women (90%) and 2 men (10%), with a mean age of 47.45 ± 12.12 years and a mean CM duration of 7.10 ± 3.39 years. Mean MHDs decreased from 22.45 ± 7.38 at T0 to 17.65 ± 7.01 at T1A and 9.60 ± 8.40 at T6A. Mean ΔMHD was −4.80 from T0 to T1A and −8.05 from T1A to T6A. Mean monthly acute medication use decreased from 17.30 ± 12.58 at T0 to 9.80 ± 5.81 at T1A and 3.90 ± 2.29 at T6A. Mean MIDAS score decreased from 78.35 ± 54.55 at T0 to 52.82 ± 27.48 at T1A and 22.10 ± 17.16 at T6A. 14 patients (70%) achieved a ≥50% reduction in MHDs and 8 (40%) achieved a ≥75% reduction at T6A. Ten patients (50%) met the criteria for episodic migraine at T1A, increasing to 15 patients (75%) at T6A.

Conclusions: In patients with CM and a partial response to BoNT-A, adding atogepant was associated with further reductions in MHDs, acute medication use, and migraine-related disability, with clinically meaningful responder rates. These findings support a benefit
of combining treatments with complementary mechanisms of action for suppression of CM.



Five-Year Real-World Effectiveness and Treatment Persistence of Erenumab in Migraine.

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Background: Erenumab is a monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) receptor and has consistently demonstrated efficacy and a favourable safety profile in patients with chronic migraine and high-frequency episodic migraine refractory to first-line preventive therapies. However, most available clinical and real-world studies have focused on observation periods of approximately two years, while evidence from longer follow-up remains scarce. This study aimed to evaluate the persistence of erenumab effectiveness in a selected real-world cohort over an extended follow-up of up to five years.

Methods: This observational real-world study included 22 patients with migraine treated with erenumab. Monthly migraine days (MMD), Migraine Disability Assessment Scale (MIDAS), Headache Impact Test-6 (HIT-6), medication-overuse headache (MOH), treatment persistence, and adverse events were assessed at baseline and at Months 4, 12, and 60. Changes from baseline were analysed using non-parametric paired tests. A ≥50% or ≥75% reduction in MMD defined treatment response.

Results: Mean age was 52.3±9.3 years and 72.7% of patients were female. Mean MMD decreased from 18.3±6.3 at baseline to 9.8±6.9 at Month 4, 9.5±5.7 at Month 12, and 10.3±7.1 at Month 60; all reductions versus baseline were significant ($p \leq 0.00117$). At Month 60, 10/19 patients (52.6%) achieved a ≥50% response and 4/19 (21.1%) a ≥75% response. MIDAS and HIT-6 improved significantly through Month 60: mean MIDAS declined from 69.3 to 38.7 and HIT-6 from 67.9 to 63.0. MOH prevalence declined from 76.2% at baseline to 31.3% at Month 60. At Month 60, 12/22 patients (54.5%) remained on Erenumab. Adverse events occurred in 7/22 patients (31.8%); 3/22 (13.6%) discontinued treatment because of adverse events or safety concerns.

Conclusions: In this five-year real-world cohort, Erenumab was associated with an early, sustained reduction in migraine burden, alongside improvements in disability and headache impact. Long-term persistence and reduced MOH support its clinical relevance. Larger prospective studies are needed to confirm these findings.



Real-World CGRP-targeted Therapy Outcomes in High-Frequency Migraine: Implications for the 2025 position statement of HIS

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Background: An International Headache Society position statement was proposed in 2025 to state migraine prevention targets: 1. Migraine Freedom (elimination of migraine days) 2. Optimal Control (<4 days/month) 3. Modest Control (4–6 days/month) 4. Insufficient Control (>6 days/month). We evaluated the real-world effectiveness and tolerability of CGRP-targeted therapies in patients with high-frequency episodic migraine (HFEM) and chronic migraine (HFCM) and assessed treatment outcomes according to the IHS higher standards' framework.

Methods: A single-center, real-world, observational study was conducted at a third-level Headache Center (Policlinico Umberto I, Rome). 330 patients diagnosed with HFEM (n=224) or HFCM (n=106) according to ICHD-3 criteria received CGRP monoclonal antibodies or gepants. Treatment effectiveness was assessed using monthly migraine days recorded in headache diaries and the Patient Global Impression of Change (PGIC). 325 were eligible (268 female, 57 male; mean age 48.3 years). Mean follow-up was 27.8 (SD ±19).

Results: 26 patients (8%) achieved "Migraine Freedom", 177 (54.5%) "Optimal Control", 69 (21.2%) "Modest Control", and 53 (16.3%) "Insufficient Control". Notably, approximately 10% of patients who improved from near-daily headache to 4–6 monthly migraine days experienced marked gains in daily functioning, work productivity, and quality of life despite not meeting the highest therapeutic target. Many patients also reported reduced attack severity and duration, improved response to acute medication and greater functional recovery.

Conclusions: CGRP-targeted therapies provide sustained long-term benefits in high-frequency migraine. While the IHS framework promotes ambitious treatment goals, rigid frequency-based thresholds may underestimate clinically meaningful improvement in partial responders. Integrating patient-reported outcomes with objective measures may provide a more comprehensive assessment of treatment success and better reflect the multidimensional impact of migraine.



Sustained Clinical Response to Atogepant After Failure of Four Anti-CGRP Monoclonal Antibodies in Highly Resistant Chronic Migraine

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Background: Chronic migraine (CM) resistant to multiple preventive therapies remains a major therapeutic challenge, particularly in patients with medication overuse headache (MOH) and psychiatric comorbidities. Although monoclonal antibodies (mAbs) targeting the calcitonin gene related peptide (CGRP) pathway have significantly improved migraine prevention, some patients show inadequate or transient responses. Atogepant may provide clinical benefit after mAb failure owing to their distinct pharmacological profile.

Methods: We report the case of a 51-year-old man with highly resistant CM, MOH, and psychiatric comorbidities, including anxiety disorder and mood disorder with obsessive compulsive features and dysphoric mood. Previous preventive treatments included topiramate, valproate, propranolol, flunarizine, amitriptyline, onabotulinumtoxinA, and four anti-CGRP mAbs (galcanezumab, fremanezumab, erenumab, and eptinezumab), all with inadequate efficacy. Peripheral nerve blocks, repetitive transcranial magnetic stimulation, behavioral therapies, and medical cannabis were also unsuccessful. Eptinezumab (October 2024–July 2025) produced only partial and transient benefit. From August 2025, migraine frequency progressively worsened, with near-daily attacks and severe disability (MIDAS 90). Atogepant 60 mg once daily was initiated in October 2025. Outcomes included monthly migraine days (MMDs), pain intensity (Numerical Rating Scale, NRS), MIDAS score, and acute medication use.

Results: At baseline, the patient reported 28 MMDs, severe disability (MIDAS 90), and triptan use on 15 days/month, consistent with MOH. After three months of atogepant, MMDs decreased to 9, mean pain intensity improved to 6/10, MIDAS score decreased to 30, and triptan use was reduced to 6 days/month. Treatment was well tolerated, with no adverse events. Clinical benefits were sustained throughout follow-up.

Conclusions: This case demonstrates the effectiveness of atogepant in a patient with highly resistant CM after failure of multiple preventive therapies, including four anti-CGRP mAbs. The observed clinical benefit may reflect its distinct mechanism of action, characterized by sustained intracellular inhibition of CGRP receptor signaling following receptor co-internalization. These findings suggest that switching to a gepant may represent an effective, mechanism-based strategy for patients with refractory CM, particularly in the presence of MOH and psychiatric comorbidities.



Profiling Eptinezumab long-term effectiveness and dose-response in patients with chronic migraine and medication overuse headache: a real-world longitudinal study

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Background: Eptinezumab, an intravenous anti-CGRP monoclonal antibody, has demonstrated rapid and sustained efficacy in clinical trials. This real-world, longitudinal study aims to evaluate the long-term effectiveness of Eptinezumab in patients with chronic migraine (CM) and medication overuse headache (MOH), stratifying clinical outcomes between the 100 mg and 300 mg dosing regimens.

Methods: We conducted a prospective longitudinal study on a cohort of patients diagnosed with CM or MOH treated with Eptinezumab. Clinical parameters—including monthly migraine days (MMDs), monthly acute medication intake, Visual Analogue Scale (VAS) score, and disability scales - MIDAS, SF-36 VAS, HIT-6 , BDI- were collected at baseline (T0) and multiple subsequent timepoints up to 12 months. Patients were stratified based on the received dose (100 mg vs. 300 mg) a T3. Repeated measures analyses and mixed-effects models were utilized to examine trajectories over time.

Results: A total of 77 patients were analyzed. Both the 100 mg and 300 mg cohorts exhibited a robust, statistically significant reduction in MMDs and acute medication consumption starting from the first post-infusion evaluation ($p < 0.001$ compared to baseline), which was maintained throughout the 12-month follow-up. Patients in the 300 mg group presented with higher baseline disease severity and a greater prevalence of MOH. Despite a more severe baseline profile, the 300 mg dose led to a significantly higher proportion of ≥50% and ≥75% responders over time compared to the 100 mg dose, particularly in difficult-to-treat and MOH subgroups, showing superior long-term stability and prevention of medication overuse relapse.

Conclusion: In a real-world setting, Eptinezumab demonstrates exceptional and rapid effectiveness in reducing migraine burden and facilitating acute medication withdrawal. While both doses are highly effective, the 300 mg regimen provides substantial additional clinical benefit for patients with higher baseline severity and comorbid medication overuse, offering a personalized therapeutic target for refractory migraine management.



Pain Relief after 30 minutes Predicts Complete acute Treatment Success at 12 Hours: A Real-World Analysis of Intravenous Eptinezumab infusion in Highly Refractory Migraine Patients.

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Background: Eptinezumab is the intravenous anti-CGRP monoclonal antibody approved for the prevention of episodic and chronic migraine. Data from the RELIEF and the BE-FREE studies demonstrated its rapid onset of action. The BE-FREE is an ongoing Italian observational, prospective, multicenter, real-world study exploring the very early changes in migraine pain intensity and associated symptoms from 30 minutes (T30) to 48 hours after eptinezumab infusion, when an acute migraine attack is ongoing.
In this analysis of the BE-FREE study we evaluated whether a very early pain intensity reduction predicts the 12 hours (T12) treatment success.

Methods: We evaluated 22 patients undergoing eptinezumab infusion (100 mg or 300 mg) during an acute migraine attack. Baseline (T0) data included socio-demographic and clinical variables as diagnosis, monthly migraine days (MMDs), presence of Medication Overuse Headache (MOH), headache pain intensity (Numeric Rating Scale, NRS) and previous failed preventives. We also analyzed the time interval between the onset of the migraine attack and the infusion. Painkillers were prohibited in the previous 24 hours.
For this analysis we focused on the variation of NRS score at T30, accordingly patients were classified as: i) Rapid Responders (RRs) defined as those with a >50% NRS reduction at T30, ii) Delayed Responders/Non-Responders (DRs) those without. The NRS variation from T0 to T12 in the 2 groups was also evaluated. Statistical comparisons of NRS score at T12 was performed using the non-parametric Mann-Whitney U test.

Results: The cohort (n=22, 86.4%F, median age of 43.3, SD15 years) presented a highly refractory clinical profile, with a baseline MMDs of 20.0 (IQR: 15-30), a mean of 4.8 prior preventive treatment failures, a high prevalence of chronic migraine (72.7%) and 59% of MOH. Data were collected at different eptinezumab infusions, mainly at

I infusion (15 patients, 68.2%); the attack had started 3.9 ± 2 h before the infusion. Eptinezumab was administered at a dose of 100 mg in 17 patients (77.3%) and of 300 mg in 5 patients (22.7%). At 30 minutes, 7 patients (31.8%) achieved a > 50% pain reduction and were classified as RRs. Strikingly, at 12 hours, 100% of RRs (7/7) achieved a complete pain-free status (NRS = 0). In contrast, the DR group (N=15) exhibited a slower, heterogeneous recovery, with a mean NRS of 3.7 at 12 hours. The RRs experienced a significantly lower pain intensity from T0 to T12 ($p = 0.0244$) and a significantly greater absolute pain reduction at 12 hours ($p = 0.0417$), with an average decrease of 5.86 points vs 2.57 points in DRs. Eptinezumab dosage (100 mg vs 300 mg) did not correlate with the very early response at 30 minutes.

Conclusions: These findings suggest that in highly refractory migraine patients undergoing eptinezumab treatment during a migraine attack, a NRS score reduction of >50% within 30 minutes of infusion is not merely an indicator of immediate relief but may be a prognostic marker predicting a complete pain-free status at 12 hours.



Atogepant in clinical practice: 6-month real-world data on effectiveness and safety in migraine prevention from a third level headache center

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Background: Atogepant is an oral calcitonin gene-related peptide receptor antagonist approved for migraine prevention in adults. We evaluated its 6-month real-world effectiveness and tolerability across multiple dimensions of migraine burden.

Methods: Fifty-seven patients treated with atogepant at the Headache Center of Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, were included (mean age 43.65 ± 15.09 years; 48 female). Diagnoses included high-frequency episodic migraine (n=42), chronic migraine (n=11), and low-frequency episodic migraine (n=4). Monthly migraine days (MMD), migraine acute medication (MAM), Migraine Disability Assessment (MIDAS), 6-item Headache Impact Test (HIT-6), 12-item Allodynia Symptom Checklist (ASC-12), Pain Catastrophizing Scale (PCS), Migraine Interictal Burden Scale-4 (MIBS-4), and Migraine Treatment Optimization Questionnaire (mTOQ) were assessed at baseline and after 3 (T3) and 6 months (T6).

Results: Of 57 patients, 51 were evaluated at T3 and 39 at T6. At T6, 10 patients were still awaiting their 6-month follow-up visit, while 8 had discontinued treatment (n=3 loss to follow-up, n=3 treatment intolerance, n=2 lack of efficacy). MMD decreased from 10.68 ± 4.57 at baseline to 3.76 ± 3.49 at T3 and 4.72 ± 5.28 at T6 (both $p<0.001$ versus baseline). MAM decreased from 12.97 ± 12.08 to 4.38 ± 3.98 and 4.85 ± 5.73, respectively ($p<0.001$). MIDAS decreased from 56.09 ± 61.77 to 12.60 ± 18.61 and 9.65 ± 12.98, while HIT-6 decreased from 67.00 ± 5.06 to 56.69 ± 8.54 and 53.94 ± 13.53 (both $p<0.001$ over time). PCS and MIBS-4 scores decreased, while the mTOQ score increased (all $p<0.001$). The ASC-12 score decreased over time, with a more pronounced improvement at T3 ($p=0.044$).

Conclusions: Atogepant was associated with an early clinical benefit at 3 months that was sustained through 6 months. In addition to reducing migraine frequency and acute medication use, treatment improved migraine-related disability, headache impact, pain catastrophizing, interictal burden, and acute treatment optimization. The favorable tolerability profile observed supports the use of atogepant in clinical practice and suggests a multidimensional reduction in migraine burden.



Long-Term Response and Treatment Persistence in the Anti-CGRP Era: A Real-World Study

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Background: New therapies targeting the calcitonin gene-related peptide (CGRP) pathway have transformed migraine prophylaxis by addressing the limitations of standard preventives, with efficacy that appears stable across successive treatment cycles. In this registry-based study, we aimed to evaluate the long-term response and treatment persistence of patients receiving anti-CGRP therapies in a real-world setting throughout the extended period following their introduction into routine clinical practice.

Methods: We retrospectively analyzed patients followed at our headache center and treated with anti-CGRP preventive therapies. We assessed reduction in monthly headache days (MHDs) and monthly analgesic medications (MAMs) from baseline, focusing on response stability and treatment persistence. We also evaluated the occurrence of a reduction in treatment efficacy over time based on changes in headache frequency. Reasons for treatment discontinuation were recorded.

Results: 132 patients were included: 114 (87%) were women; the mean age was 46±12.7 years. At baseline, 71 (62.3%) patients were affected by chronic migraine, while 62 (60.2%) had medication overuse headache. The mean disease duration was 29.2±13.6 years. The mean treatment duration was 27.5±13.9 months: 64 patients achieved a ≥75% reduction in MHDs, 33 achieved a ≥50% reduction, whereas only 3 achieved a ≥30% reduction from baseline. Only 6 patients experienced no benefit. Notably, 26 patients were lost to follow-up, and 12 of them did not attend the first scheduled 3-month visit after prescription. 10 patients experienced a gradual reduction in efficacy over time. Compared with those with a sustained response, patients with a partial loss of efficacy had higher baseline MHDs ($p=0.02$), higher baseline MAMs ($p=0.01$), and a higher prevalence of psychiatric comorbidities and chronic pain syndromes ($p<0.05$). Finally, 4 subjects discontinued anti-CGRP therapies after prolonged remission and 2 because of pregnancy planning.

Conclusions: This study confirmed the long-term effectiveness of anti-CGRP therapies even in a difficult-to-treat population, such as our cohort. A reduction in treatment efficacy over time appears uncommon and might be associated with less favourable baseline characteristics. Despite the availability of effective and well-tolerated therapeutic options, a substantial proportion of patients were lost to follow-up, possibly reflecting concerns about potential adverse events and barriers to accessing outpatient headache care.



Worsening of migraine after discontinuation of anti-CGRP monoclonal antibodies: patients without recurrence for at least 6 months

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Background: Monoclonal antibodies targeting CGRP or its receptor are widely used for migraine prevention. However, the optimal timing of treatment discontinuation and the subsequent clinical course remain unclear. This study evaluated the frequency of worsening after discontinuation and associated factors among responders, defined as patients who achieved a ≥50% reduction in monthly headache days (MHD), and who discontinued treatment after shared decision-making.

Methods: We conducted a retrospective analysis at two specialized-headache clinics. Patients with migraine were included if they had received anti-CGRP monoclonal antibodies for at least 3 months, achieved a ≥50% reduction in MHD, discontinued treatment at the patient's request and in agreement with the physician, and were followed for at least 6 months after discontinuation. The primary endpoint was the proportion of patients with an increase of at least 2 MHD from the final MHD value within 6 months after discontinuation. We also examined potential associated factors, including age, sex, episodic or chronic migraine, treatment duration ≥6 months, pre-treatment MHD, final MHD <4 days, and failure of at least three previous preventive treatments.

Results: Among 1,900 patients treated with anti-CGRP monoclonal antibodies, 75% (1,423/1,900) achieved a ≥50% reduction in MHD. Of these, 24% (335/1,423) discontinued treatment after clinical improvement; 292 patients had at least 6 months of follow-up. Within 6 months after discontinuation, 52% (152/292) showed an increase of at least 2 MHD from the final value, whereas 48% did not experience worsening. The mean time to worsening was 7 months; some patients remained stable for up to 39 months. Treatment duration ≥6 months and final MHD <4 days were associated with a favorable outcome.

Conclusion: In the Japanese clinical setting, the therapeutic effect may persist for at least 6 months after discontinuation in approximately half of patients with migraine who respond to anti-CGRP monoclonal antibodies.



Sustained Effectiveness of CGRP Monoclonal Antibodies Over Four Consecutive Years: A Prospective Real-World Study

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Background: Long-term real-world data on continuous treatment with calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) beyond three years remain scarce. We evaluated the effectiveness and safety of four consecutive years of CGRP-mAb therapy in patients with high-frequency episodic migraine (HFEM) and chronic migraine (CM).

Methods: In this prospective real-world observational study, we included 52 patients (78.8% women; 86.5% CM) who initiated CGRP-mAbs between 2021 and 2022 and prospectively completed headache diaries throughout 48 months of continuous treatment. The primary outcome was the change from baseline in monthly headache days (MHDs). Secondary outcomes included monthly migraine days (MMDs), attack intensity and duration, and acute treatment effectiveness assessed by 2-hour pain freedom and pain relief.

Results: CGRP-mAbs produced a rapid and sustained reduction in headache burden that remained stable throughout four consecutive years of treatment. Mean MHDs decreased from 22.6 (SD 7.1) at baseline to 8.7 (SD 7.1) at 6 months and remained consistently low through years 1 (8.3), 2 (6.9), 3 (6.8), and 4 (7.3) (all $p<0.001$ vs baseline). Significant improvements were likewise observed for MMDs, attack intensity, and attack duration from month 6 onward and were maintained throughout follow-up. The proportion of patients achieving 2-hour pain freedom after acute medication increased from 11.5% at baseline to 76.9% after four years of treatment ($p<0.001$). No evidence of progressive loss of treatment effectiveness was observed over time.

Conclusions: Continuous treatment with CGRP-mAbs provides durable clinical benefits for up to four years in patients with HFEM and CM, with sustained reductions in headache burden and persistent improvement in acute treatment response. These findings support the long-term maintenance of CGRP-targeted therapies without evidence of waning effectiveness in routine clinical practice.



Premonitory episodes without headache during anti-CGRP preventive treatments: a cross-sectional multicenter study

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Background: Calcitonin gene-related peptide (CGRP) is central to migraine pathophysiology, but the main site of action of CGRP-targeted preventive therapies remains uncertain. Patients receiving anti-CGRP treatments may experience non-headache symptoms that do not progress to pain (premonitory episodes without headache), which have not yet been characterized. This study investigated the frequency, phenotype, and clinical correlates of these episodes in migraine responders to anti-CGRP preventive treatments, including their association with treatment type and responder status.

Methods: A cross-sectional multicenter study was conducted in two independent cohorts of migraine responders to anti-CGRP preventives. One cohort included patients receiving anti-CGRP mAbs at King's College Hospital, UK, and the other included patients receiving atogepant at the Florence Headache Centre, Italy. Responders were defined as patients achieving at least a 50% reduction in monthly migraine days (MMD). Demographic and clinical data were extracted from medical records, and an ad hoc structured questionnaire assessed the occurrence and features of premonitory episodes without headache. Associations were tested using chi-square or Fisher's exact tests, and multivariable logistic regression examined predictors of episode occurrence.

Results: Overall, 213 patients were included (84% female 21% chronic migraine). 144 were on anti-CGRP mAbs, and 69 were on atogepant. Premonitory episodes without headache were reported by 114 patients (54%), with a median of 4 symptoms, and most episodes lasted 1-24 hours. The most frequent symptoms were difficulty concentrating (58%), neck stiffness (54%), fatigue (49%), mood changes (49%), photophobia (45%), and phonophobia (41%). Symptom frequencies were similar across treatment cohorts despite differences in baseline clinical characteristics. Higher responder-rate categories were independently associated with lower odds of premonitory episodes without headache (OR 0.67, 95% CI 0.46-0.99; P=0.047), whereas treatment type was not associated with episode occurrence (OR 0.72, 95% CI 0.39-1.33; P=0.290).

Conclusions: Premonitory episodes without headache were common in migraine responders receiving anti-CGRP preventive treatments and showed a symptom profile overlapping the classical migraine premonitory phase. Whether premonitory episodes without headache reflect activation of CGRP-independent pathways, or whether there is a limited effect on central non-headache symptoms, or a downstream interruption of progression to the pain phase, remains to be determined.



Anti-CGRP Monoclonal Antibodies for Chronic Migraine Prevention: A Critical Synthesis of Evidence from Randomized and Real-World Studies

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Background: Chronic migraine is one of the leading causes of neurological disability. Monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or its receptor have introduced a mechanism-based preventive strategy, although an integrated appraisal of evidence from randomized trials and real-world studies remains warranted.

Methods: A systematic review was conducted according to PRISMA 2020 guidelines and registered in PROSPERO (CRD420261284751). PubMed, Scopus, and Web of Science were searched through July 2025. Randomized controlled trials and real-world observational studies evaluating erenumab, fremanezumab, galcanezumab, or eptinezumab in adults with chronic migraine were included. Primary outcomes were changes in monthly migraine days (MMDs) or monthly headache days (MHDs), ≥50% responder rates, and safety.

Results: Of 1,688 retrieved records, 11 studies met the inclusion criteria. Anti-CGRP monoclonal antibodies consistently reduced migraine frequency, increased ≥50% responder rates, and showed favorable tolerability compared with placebo and, in comparative studies, conventional preventive therapies. Real-world evidence confirmed effectiveness in heterogeneous and treatment-resistant populations, with high treatment persistence. However, methodological heterogeneity, particularly regarding outcome definitions (MMDs versus MHDs), limited direct quantitative comparisons across studies.

Conclusions: Anti-CGRP monoclonal antibodies represent an effective and well-tolerated preventive option for chronic migraine, with clinically meaningful benefits consistently demonstrated in both randomized and real-world settings. Further long-term prospective studies and standardized outcome measures are needed to optimize treatment positioning and support personalized migraine management.

Improvement in Depressive and Anxiety Symptoms During Eptinezumab Treatment: a post-hoc analysis from the TACHIS Study

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Background: Depression and anxiety disorders are common migraine comorbidities contributing substantially to disease burden. Whether mood improvement during anti-calcitonin gene related peptide pathway treatments is entirely attributable to reductions in headache frequency remains unclear. We evaluated longitudinal changes in self-reported depressive and anxiety symptoms during eptinezumab treatment and their relationship with clinical outcomes.

Methods: This post-hoc analysis of the TACHIS study, a prospective, multicenter, real-world study, included patients with episodic or chronic migraine who started eptinezumab across 23 Italian headache centers. Depressive

and anxiety symptoms were assessed at baseline and after 12 and 24 weeks using the validated Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). Migraine outcomes included monthly headache days (MHDs), acute medication days (AMDs), the Migraine Disability Assessment (MIDAS), the Headache Impact Test-6 (HIT-6) and the Migraine-Specific Quality of Life Questionnaire (MSQ). Longitudinal changes were evaluated using mixed-effects models adjusted for demographic and clinical covariates.

Results: A total of 128 patients were included (82.0% female; mean age 46.9±12.4 years). 24 patients (18.8%) had pre-existing psychiatric comorbidities, including depression, anxiety, personality disorders, and bipolar disorder. Linear mixed-effects models demonstrated significant reduction in MHDs and AMDs, migraine-related disability (MIDAS and HIT-6 questionnaires), and migraine-specific quality of life (MSQ) during eptinezumab treatment (all $p<0.001$ compared to baseline).
Mean HAM-D scores decreased from 14.6±6.4 at baseline to 11.7±7.3 at 12 weeks and 11.6±7.3 at 24 weeks ($p<0.001$), while HAM-A scores decreased from 17.5±10.2 to 11.8±9.8 and 11.2±8.9, respectively ($p<0.001$). Most of the improvement in depressive and anxiety symptoms occurred within the first 12 weeks of treatment and was maintained through week 24. After adjustment for clinical covariates, changes in MHDs were not independently associated with changes in HAM-D and HAM-A scores. Conversely, a weak but significant association was observed between reductions in HAM-D and MIDAS scores ($\rho=0.294$; $p=0.045$).

Conclusions: Eptinezumab treatment was associated with early and sustained reduction in depressive and anxiety symptoms. These improvements were not independently associated with reductions in MHDs, suggesting that mood changes may not be solely driven by headache frequency. Further studies are needed to clarify the mechanisms underlying this association.



Early successful response to Atogepant in pharmacoresistant male and female migraine patients in a real-life setting

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Background: The aim of this study is to assess in a real-world setting efficacy, tolerability and improvements in measures of daily and night functioning just after the first 4 weeks of treatment with Atogepant in a sample of resistant high frequency or chronic migraineurs.
Due to possible gender differences in the expression of Calcitonin Gene Related Peptide (CGRP), in this study we also evaluated early response to Atogepant in subgroups of patients according to sex.

Methods: In a prospective monocentric real-life study, we evaluated the efficacy of Atogepant in a sample of 56 migraineurs (F:M 46:10, mean age 44.55) resistant to at least three standards of care antimigraine preventive oral drugs. We evaluated at baseline and after 4 weeks of therapy mean changes in mean monthly migraine days (MMD), in mean monthly use of painkiller drugs (MDI), in mean severity of pain (using VAS score), in migraine related disability according to HIT-6 score and allodynia (ASC-12 score).

Results: After 4 weeks of treatment we observed a significant decrease in MMD (17.54 vs 11.43, $p<0.01$), in MDI (19.57 vs 9.98, $p<0.01$), in VAS score (8.23 vs 6.38, $p<0.01$), in HIT 6 score results (67.66 vs 61,82, $p<0.01$) and in ASC-12 results (6.96 vs 5.86, $p = 0.018$). Moreover 41.1% of the sample resulted at least 50% responders and 26.8% resulted at least 75% responders.
As a subgroups analysis we divided our population by sex. At baseline our subgroups did not differ for MMD, MDI and VAS, while HIT6 score and ASC12 score were statistically significant higher in the female group [GP1.1][SG1.2]. After 4 weeks of treatment, we observed a statistically significant improvement in all assessed parameters in both groups, with no significant differences between them, except for ASC-12 score, which showed a greater reduction in males (male 1.10 vs female 6.89, $p<0.01$).

Conclusions: The study suggests in a real-life setting a very early clinical improvement of migraine even in resistant patients treated with Atogepant prevention in both sex. The significant quick decrease in symptomatic drugs emphasizes the possible role of Atogepant in cessation of medication overuse.



Body Weight Changes During Atogepant Therapy: A Case Report and Narrative Review of the Metabolic Role of CGRP

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Background: Calcitonin gene-related peptide (CGRP) receptor antagonists (gepants) have expanded therapeutic options for migraine prevention. Although randomized clinical trials have demonstrated favorable efficacy and safety, emerging evidence suggests that atogepant may be associated with modest weight loss.

Methods: We report the case of a woman with resistent chronic migraine and medication-overuse headache who experienced body weight changes during preventive treatment with atogepant. Clinical features, anthropometric data, headache outcomes and concomitant medications potentially affecting body weight were reviewed. A narrative review of randomized clinical trials, pooled analyses, long term extension studies and experimental evidence on the metabolic effects of CGRP receptor antagonism was also performed.

Results: Before atogepant, the patient had approximately 20 monthly migraine attacks (NRS 9/10), poorly responsive to NSAIDs, bronchial asthma and gastroesophageal reflux disease. Topiramate was discontinued due to paresthesias, memory impairment, limited efficacy and worsening of mood, while pregabalin was discontinued following a 5-kg weight gain over three months and insufficient therapeutic response; duloxetine was subsequently added to the treatment regimen for concomitant anxiety and depressive symptoms. Atogepant was introduced in July 2024, with eletriptan as acute treatment. Headache frequency improved to 6–7 monthly attacks (NRS 6–7/10), no longer associated with photophobia or phonophobia, with only mild nausea and consistent response to eletriptan. Body weight was 72 kg (BMI 28.1 kg/m²) at baseline, decreased to 70 kg (BMI 27.3 kg/m²) after 12 months and increased to 74 kg (BMI 28.9 kg/m²) after 24 months.

Conclusions: Pregabalin is commonly associated with weight gain and long-term duloxetine treatment may also contribute to modest weight increase, so these concomitant factors should be considered when interpreting weight changes. Nevertheless, available evidence suggests that rimegepant and ubrogepant are weight neutral, whereas atogepant is associated with a modest, dose- and duration-dependent reduction in body weight (approximately 1.5–2 kg after 52 weeks). The mechanisms underlying this differential effect on body weight between gepants remain unclear, although a specific metabolic effect cannot be excluded. This case highlights the complexity of interpreting body weight changes during long-term atogepant treatment in the presence of potential confounding medications. Nevertheless, the transient weight reduction observed after one year is consistent with published evidence and supports prospective monitoring of body weight during atogepant therapy. Further studies are needed to clarify the metabolic effects of CGRP receptor antagonism. References of 1. Peterlin BL, Bond DS, Ailani J, et al. Weight loss with atogepant during the preventive treatment migraine: A pooled analysis. Cephalalgia. 2024;44(12). doi:10.1177/03331024241299753 2. Bond DS, Smith JH, Sinclair A, et al. Weight loss with atogepant in the long-term treatment of migraine: An interim analysis of a safety endpoint from a phase 3, multicenter, open-label, 156-week extension study. Headache. Published online July 3, 2026. doi:10.1111/head.70162 3. Rizzoli P, Marmura MJ, Robblee J, et al. Safety and tolerability of atogepant for the preventive treatment of migraine: a post hoc analysis of pooled data from four clinical trials. J Headache Pain. 2024;25(1):35. Published 2024 Mar 11. doi:10.1186/s10194-024-01736-z



Atogepant for the Prevention of Migraine in Difficult-to-Treat Patients: Multidimensional Outcomes from a Single-Center Experience

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Background: Migraine is a highly disabling neurological condition, particularly in "difficult-to-treat" populations with multiple prophylactic failures. This clinical complexity is often exacerbated by medication overuse (MO), which further impairs quality of life. Atogepant, an oral calcitonin gene-related peptide (CGRP) receptor antagonist, represents a promising targeted therapeutic option for migraine prevention.
Objective: To evaluate the short-term, real-world efficacy of atogepant on multidimensional Patient-Reported Outcomes (PROs) in a difficult-to-treat migraine cohort characterized by several prophylactic failures and a high prevalence of MO.

Methods: This prospective, single-center study enrolled 42 patients (36 females; mean age 45.7 years) with an average of 4.9 previous prophylactic failures. Notably, 55% had previously failed anti-CGRP monoclonal antibodies, 67% failed onabotulinumtoxinA, and 71% exhibited MO at baseline. Clinical evaluations at baseline and 3 months measured Monthly Migraine Days (MMD), Monthly Days of Intake of symptomatic drugs (MDI), pain intensity (VAS), and validated PROs assessing disability (MIDAS, HIT-6), depression and anxiety (PHQ-9, GAD-7), sleep (PSQI, ESS), fatigue, and allodynia.

Results: After 3 months of treatment, the cohort demonstrated highly significant reductions in mean MMD (17.9 to 11.1), MDI (23.1 to 12.1), VAS, MIDAS, and HIT-6 scores. Significant secondary improvements occurred in depressive symptoms (PHQ-9) and sleep quality (PSQI). A ≥50% responder rate was achieved by 50% of the sample. Notably, 35% of patients who previously failed anti-CGRP monoclonal antibodies achieved ≥50% response. Responders and non-responders differed at baseline only by MMD and the number of prior prophylactic failures. While responders experienced broader improvements in multidimensional parameters like mood and fatigue, non-responders still exhibited mild but significant decreases in acute medication intake, VAS, and MIDAS. Furthermore, atogepant drastically reduced MO, with the number of abusers dropping from 30 to 14.

Conclusions: Atogepant demonstrates robust real-world efficacy in a difficult-to-treat migraine population, successfully reducing disease burden and facilitating the cessation of medication overuse. Multidimensional assessments reveal that atogepant's benefits extend beyond headache frequency reduction, positively impacting mood, sleep, and fatigue, thereby substantially improving overall quality of life.

BEYOND CGRP: FROM NEW PHARMACOLOGICAL TARGETS TO NON-PHARMACOLOGICAL THERAPY

Role of Specific microRNAs in Cluster Headache: Association with Disease Phenotype and Neuropeptide Levels

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Background: Increasing evidence supports the role of epigenetic mechanisms in primary headaches. microRNAs (miRNAs) may be involved in pain generation and migraine chronification, but their involvement in cluster headache (CH) is yet to be elucidated. This study evaluated the expression of selected miRNAs and pain-related neuropeptides in episodic cluster headache (eCH) during the active (AeCH) and remission (ReCH) phases, and in chronic cluster headache (cCH).

Methods: Fasting peripheral blood samples were collected to isolate peripheral blood mononuclear cells (PBMCs) and serum. Expression of miR-382-5p, miR-34a-5p, and miR-155 was assessed in PBMCs using Relative Quantification (RQ) normalized to the U6 housekeeping gene. We measured serum levels of alpha and beta calcitonin gene-related peptide (CGRPα, CGRPβ), pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP) using validated ELISA kits in AeCH and cCH patients outside an acute attack.

Results: We enrolled 39 AeCH patients (age: 45.7±11.6 years, 31 males), 27 ReCH patients (age 47.4±11.6 years, 23 males), 19 cCH patients (age: 50.8±14.4 years, 16 males) and 23 healthy controls (HCs: age: 40.5±15.3 years, 15 males). No differences in miRNA expression were observed between CH participants and HCs. However, miR-155 expression was significantly lower in eCH compared to cCH (eCH: 0.18±0.12 RQ vs. cCH: 0.32±0.14 RQ, $p=0.001$), a finding confirmed when comparing AeCH with cCH (AeCH: 0.15±0.12 RQ vs. cCH: 0.32±0.14 RQ, $p<0.001$). CGRPα and PACAP levels were significantly higher in both AeCH and cCH groups compared to HCs. As regards CGRPα: AeCH 443.88±218.22, cCH 400.74± 201.67, HCs 214.35±114.89 (AeCH vs HCs $p<0.001$; cCH vs HCs, $p =0.017$). For PACAP: AeCH 50.57± 17.42; cCH 53.89±17.68; HCs: 35.93± 10.85 (AeCH vs HCs $p<0.005$; cCH vs HCs, $p =0.03$). No differences were found for CGRPβ or VIP levels.

Conclusions: Our data support the involvement of miR-155 and neuropeptides in CH pathophysiology. Our results confirm data from literature supporting a pro-inflammatory state in chronic CH, when considering that a higher miR-155 expression is consistent with an activation of the inflammatory pathway.



Accelerated DLPFC-tDCS as an Adjunctive Treatment for Chronic Migraine Unresponsive to Monoclonal Antibodies: Preliminary Findings from a Sham-Controlled Pilot Study

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Background: Chronic migraine can remain highly disabling despite preventive treatment with monoclonal antibodies, with some patients continuing to experience frequent attacks. In this clinical population, transcranial direct current stimulation (tDCS) targeting the dorsolateral prefrontal cortex (DLPFC) may represent an adjunctive therapeutic strategy through the modulation of neural circuits involved in pain processing.

Methods: Eight patients diagnosed with chronic refractory migraine (7 women; 47.9±9.9 years) were enrolled in the study and assigned to one of two treatment sequences: sham–active (n = 4) or active–active (n = 4). Assessments were conducted at baseline (T0), one month after the first cycle (T1), and one month after the second cycle (T2). The primary outcome was the monthly number of migraine days; secondary outcomes included days of symptomatic medication use, HIT-6, MIDAS, and BDI-II. The comparison between real and sham stimulation was based on the changes observed between T0 and T1. Active versus sham stimulation during T0–T1 was assessed using ANCOVA on T1 migraine days adjusted for baseline.

Results: Repeated-measures ANOVAs showed significant time effects for monthly migraine days ($p=.007$), medication-use days ($p<.001$), and BDI-II scores ($p<.001$), with significant T1–T2 reductions in migraine and medication-use days. No Time×Group interactions emerged. Baseline-adjusted ANCOVA showed no active-versus-sham difference in migraine days at T1 ($p=.639$, $\eta^2=.046$).

Conclusions: These preliminary results highlight the potential of tDCS applied to the DLPFC as an adjunctive strategy in refractory patients. The outcomes observed encourage further study in a larger sample, which is necessary to define its specific effect relative to sham stimulation.



Real-world effectiveness and safety of rimegepant as preventive treatment for episodic migraine: study protocol of an ongoing prospective single-center observational study

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Background: A significant proportion of patients with episodic migraine either do not receive appropriate prophylaxis or discontinue treatment early due to insufficient efficacy or adverse events [1]. This study aims to evaluate the real-world effectiveness and safety of Rimegepant as a preventive treatment in adult patients with episodic migraine.

Methods: This prospective, observational study is conducted in a tertiary headache center, including adult patients with migraine with or without aura according to the International Classification of Headache Disorders, 3rd edition criteria, presenting an indication for preventive treatment, and with documented failure, intolerance, or contraindication to at least three classes of conventional preventive therapies. Patients receive rimegepant 75 mg every other day. Follow-up visits are performed every 3 months for 12 months using headache diaries and validated patient-reported outcome questionnaires, including Headache Impact Test-6 items (HIT-6), Migraine Disability Assessment (MIDAS) and Migraine-Specific Quality of Life Questionnaire (MSQ). The primary endpoint is the change in MMD at 3 months compared with baseline. Secondary endpoints include ≥50% responder rates, changes in monthly headache days, acute medication use, headache-related disability, quality of life, and safety outcomes.

Results: The study is currently ongoing. Preliminary data from the first patients who completed the 3-month follow-up showed a reduction in MMD. At baseline, the median number of MMD was 7, decreasing to 4 at 3 months, corresponding to a median reduction of 3 days ($p = 0.031$). No serious adverse events or discontinuations due to tolerability were recorded in this preliminary cohort.

Conclusions: Preliminary real-world data suggest that rimegepant may represent an effective and well-tolerated preventive treatment option for patients with episodic migraine and multiple prior preventive treatment failures. Early findings indicate a clinically meaningful reduction in monthly migraine days at 3 months, with a favorable safety profile. Although limited by the small sample size and the ongoing nature of the study, these results provide encouraging early evidence and warrant further evaluation in the full study cohort.



Gut-brain axis alterations in a nitroglycerin model of migraine: from microbiota dysbiosis to trigeminal sensitization

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Background: Growing evidence implicates the gut–brain axis in migraine pathophysiology; however, the mechanisms linking gut microbiota (GM) dysbiosis, microbial metabolites, intestinal inflammation, and trigeminal nociception remain poorly understood. Here, we investigated these mechanisms in a nitroglycerin (NTG)-induced chronic migraine model.

Methods: Adult male rats received five injections of NTG (5 mg/kg, i.p.) or vehicle every other day over a 9-day period. Trigeminal nociceptive sensitization was assessed 4 hours after the last administration, using the orofacial formalin test. Gut microbiota composition was analyzed in fecal samples by 16S rRNA gene sequencing. Differential abundance analysis was assessed using DESeq2, while PICRUSt2 was used to predict microbial functional profiles. Fecal and serum short-, medium-, and long-chain fatty acids were quantified by GC–MS. Inflammatory markers were evaluated in ileum, colon, and cervical spinal cord by RT-qPCR.

Results: Compared with controls, NTG-treated rats exhibited significant trigeminal hyperalgesia at the orofacial formalin test. Alpha diversity of the gut microbiota was unchanged, whereas beta diversity analysis revealed a distinct microbial community structure in NTG-treated rats. Differential abundance analysis showed a reduction in specific Firmicutes taxa and an enrichment of Bacteroidota-associated taxa, including members of the Rikenellaceae family and the Clostridia_vadinBB60_group genus. Functional prediction indicated an increased representation of microbial pathways involved in fatty acid biosynthesis. Among the measured metabolites, fecal propionic acid levels were significantly elevated in NTG-treated animals, while other fatty acids remained unchanged. Intestinal inflammation was characterized by increased expression of IL-1β and IL-6 in both the ileum and colon. At the central level, NTG induced an upregulation of IL-6 and downregulation of IL-4 expression in the cervical spinal cord.

Conclusions: Chronic NTG exposure induces trigeminal nociceptive sensitization accompanied by gut microbial dysbiosis, selective elevation of fecal propionate, intestinal inflammation, and central neuroimmune activation. These findings support the involvement of gut–brain axis-related mechanisms, whereby microbiota-associated metabolic and immune alterations may contribute to migraine-related trigeminal sensitization.



Probiotic supplementation alleviates migraine-like pain by restoring intestinal barrier integrity and endocannabinoid homeostasis

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Background: Gut microbiota and the endocannabinoid system (ECs) play a key role in regulating body homeostasis and nociceptive information. Intestinal dysbiosis can compromise the gut barrier integrity, leading to a systemic pro-inflammatory response. We previously observed an increase in serum lipopolysaccharide-binding protein levels, indicative of intestinal barrier impairment and alterations in gut microbiota composition in the nitroglycerin (NTG)-induced animal model of chronic migraine. The present study aimed to investigate whether probiotic-mediated restoration of gut microbiota attenuates migraine-like pain by improving intestinal barrier integrity and modulating ECs signalling.

Methods: Adult male Sprague-Dawley rats were treated with NTG (5 mg/kg i.p.) or vehicle every other day for nine days (5 injections). A subgroup of NTG animals received a multistrain probiotic in their drinking water for the entire period duration, whereas rat without the probiotic treatment were provided with plain drinking water. On day 9, 4 hours after the last administration of NTG (or vehicle) trigeminal hyperalgesia was assessed using the orofacial formalin test. All animals were then euthanized. Ileum and colon tissues, along with the trigeminal ganglia (TG) and cervical spinal cord, were used to assess the gene expression of tight junctions (TJs) and ECs components. In a separate cohort of rats, colon samples were collected for the immunohistochemical assessment of ZO-1 and occludin expression.

Results: Probiotic supplementation alleviated NTG-induced trigeminal hyperalgesia, significantly reducing nociceptive behaviour in the orofacial formalin test. NTG treatment compromised the integrity of the intestinal barrier, as evidenced by reduced expression of TJs in both colon and ileum. Probiotic supplementation restored these changes. NTG also induced region-specific changes in ECS components, including reduced expression of monoacylglycerol lipase (MAGL) in the ileum and the TG, increased cannabinoid receptor 2 expression in the ileum, and decreased diacylglycerol lipase (DAGL) expression in the colon. Probiotic supplementation restored MAGL gene expression in the ileum and TG and increased DAGL gene expression in the TG, suggesting a partial normalization of ECs signaling.

Conclusion: Chronic NTG-induced dysbiosis is associated with impaired intestinal barrier integrity and altered endocannabinoid signaling. Probiotic supplementation attenuates trigeminal hyperalgesia, restores ZO-1 expression, and normalizes MAGL levels in the intestine and TG, suggesting that modulation of 2-AG signaling contributes to gut-trigeminal communication.



Who takes care of patients suffering from migraine? The caregiver's identikit study. A MI-DEAR sub-analysis

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Background: Migraine represents one of the leading causes of health loss globally, impacting on patients and family members. Despite its clinical relevance, the specific impact of migraine on informal caregivers remains poorly investigated in the literature. This study aimed to investigate the socio-demographic and occupational profiles of migraine caregivers, identify their specific characteristics, and evaluate the factors influencing their burden.

Methods: We conducted a multicenter Italian cross-sectional sub-analysis utilizing data from the MI-DEAR database. Caregiver's detailed data (demographic characteristics, comorbidities and specific work activities) and the Relatives Stress Scale (RSS) were systematically collected. The geographic location of the headache centers was also evaluated.

Results: 154 caregivers of patients with migraine (F 64%, mean age 48.1 yrs +SD12.2) were enrolled. Most caregivers reported being employed full-time (71%), 9% were employed part-time, the remaining 12% comprised non-working individuals. The most represented professional categories were clerical support workers (20% total: 11% male, 9% female), technicians and associate professionals (17% total: 12% male, 5% female), and specialized professionals (15% total: 8% male, 7% female). RSS score was not influenced by the type of work ($p = 0.506$), and no significant difference emerged between working and non-working caregivers ($p = 0.712$). Caregivers' RSS scores remained consistent regardless of job-related responsibility level (High vs Low $p = 0.506$), significantly higher in caregivers of migraine patients attending a headache center in major metropolitan areas ($p = 0.015$).

Conclusions: Our findings characterize the common migraine caregiver profile as predominantly a middle-aged male employed in professional or high-responsibility administrative roles with a higher burden in those living in metropolitan areas, which could be crucial features for further psychosocial interventions.



Inhibition of PEA degradation via NAAA blockade modulates migraine-related pathways without reversed trigeminal hyperalgesia in female rats in the NTG-based migraine model

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Background: Increasing evidence supports the involvement of the endocannabinoid system (ECS) and related lipid mediators in migraine pathophysiology. Palmitoylethanolamide (PEA) is an endocannabinoid-like lipid with anti-inflammatory and analgesic effects, acting predominantly through PPAR-α receptors. Its bioavailability is primarily regulated by enzymatic degradation mediated by N-acylethanolamine acid amidase (NAAA). NAAA inhibition may represent a strategy to enhance endogenous PEA signaling and counteract migraine-related neuroinflammatory and nociceptive mechanisms. Here, we assessed the effects of the selective NAAA inhibitor ARN726 on trigeminal hyperalgesia in the nitroglycerin (NTG) migraine model in female rats and investigated its effects on inflammatory and endocannabinoid-related pathways, and on CGRP levels in migraine-relevant areas of the nervous system.

Methods: Female Sprague-Dawley rats (170–200 g) received NTG (10 mg/kg, i.p.) or vehicle 4h before the orofacial formalin test. ARN726 (3 mg/kg, i.p.) or vehicle was administered 2 h before behavioral testing. Gene expression of inflammatory mediators was analyzed in the medulla, whereas the ECS-related components were assessed in the medulla and TG by real-time PCR. In a separate cohort of animals, CGRP levels were quantified in the cervical spinal cord, medulla and TG by ELISA.

Results: The NTG-induced trigeminal hyperalgesia was not reversed by ARN726. In the medulla, NTG increased IL-1β and IL-6, while reducing IL-4 expression, whereas ARN726 selectively increased IL-4 compared with NTG-treated rats. ARN726 also reduced NAAA expression and increased PPAR-α expression in the medulla relative to both control and NTG groups. In the TG, NTG increased FAAH and PPAR-α expression compared with controls, whereas ARN726 reversed these changes. Additionally, ARN726 significantly reduced TRPV1, NAPE-PLD, and NAAA expression compared with both NTG and control groups. Notably, NTG did not alter basal CGRP levels in any region, whereas ARN726 significantly reduced CGRP levels in the cervical spinal cord and increased it in the medulla.

Conclusion: In a migraine specific animal model, the inhibition of PEA degradation in female rats induced a wide range of effects over mediators of inflammation, nociception and endocannabinoid function, without interfering with trigeminal hyperalgesia. Further studies are needed to optimize the targeting of the NAAA–PEA axis and to clarify its therapeutic potential in female models of migraine.



Beyond medications: Mindfulness practice for patients with high-frequency migraine without aura

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Background: Migraine is a complex neurological disorder with relevant epidemiological and social impact. Although pharmacological preventive therapies have improved migraine management, a strictly medical approach may not fully address the emotional, psychological and behavioral dimensions of the disease. A biopsychosocial model supports the integration of non-pharmacological strategies to improve pain coping and disease management. The aim of this study was to evaluate the effectiveness of an online mindfulness program in patients with high-frequency migraine without aura and to assess its impact on clinical outcomes and psychological variables related to pain coping.

Methods: Twenty-six patients with migraine without aura according to International Classification of Headache Disorders, 3rd edition (ICHD-3) were included. Mean age was 37.3 ± 12.2 years; 22 patients were female and 4 were male. Patients completed questionnaires assessing disability, pain catastrophizing, anxiety and depression. Patients attended an online mindfulness-based program delivered in small groups. The program consisted of eight weekly sessions, each lasting 75 minutes. During the sessions, patients were instructed in mindfulness practice and were asked to perform daily home practice for 12 minutes using a pre-recorded session. Clinical follow-up was performed at 3 and 6 months after the end of the program using headache diaries. The following questionnaires were administered: Pain Catastrophizing Scale (PCS), State-Trait Anxiety Inventory and Beck Depression Inventory (BDI).

Results: At 6-month follow-up, monthly migraine days decreased from 7.28 ± 1.72 to 3.5 ± 3.5. PCS score significantly decreased from 26.2 ± 9.9 to 20.9 ± 8.5 ($p = 0.01$). BDI score decreased from 10.6 ± 8.6 to 6.4 ± 7.3, trait anxiety decreased from 47.4 ± 8.0 to 43.9 ± 9.8.

Conclusions: The reduction in monthly migraine days and in psychological measures suggests that mindfulness may have a positive effect on both clinical burden and pain-related coping strategies in patients with high-frequency migraine. Mindfulness practice may represent a useful non-pharmacological strategy for patients with high-frequency migraine without aura, potentially improving disease awareness, psychological coping and clinical outcomes within an integrated biopsychosocial approach.



Combination Therapy with Atogepant and OnabotulinumtoxinA in Chronic Migraine: Preliminary Real-World Evidence from an Ongoing Study

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Background: Chronic migraine (CM) is a highly disabling neurological disorder associated with substantial functional impairment and healthcare burden. Preventive therapies targeting calcitonin gene-related peptide (CGRP) pathways and onabotulinumtoxinA have demonstrated efficacy in CM management. This ongoing real-world study aims to evaluate the effectiveness and tolerability of atogepant, onabotulinumtoxinA, and their combination in patients with CM.

Methods: The study is planned to enroll 30 patients with CM, allocated to three treatments groups: atogepant (n=10), onabotulinumtoxinA (n=10), and combination therapy (n=10).
Clinical evaluations were performed at baseline and after 1, 3, 6, 9, and 12 months. Outcome measures included monthly migraine days (MMDs), monthly headache days (MHDs), mean headache intensity, monthly acute medication use, and treatment-emergent adverse events. Disease burden and disability were additionally assessed using validated questionnaires, including the Migraine Disability Assessment Scale (MIDAS) and the Headache Impact Test-6 (HIT-6).

Results: At the time of this preliminary analysis, 22 patients had been enrolled. Preliminary analyses showed reductions in migraine burden across all treatment groups. Improvements were observed in MMDs, MHDs, headache intensity, and acute medication use. MIDAS and HIT-6 scores also showed clinically meaningful reductions during follow-up. Patients receiving combination therapy appeared to experience greater overall clinical improvement compared with those receiving either monotherapy, although interpretation is limited by the small sample size. Reported adverse events were generally mild and consistent with the established safety profiles of the respective treatments.
These preliminary real-world findings support the effectiveness and tolerability of both atogepant and onabotulinumtoxinA in CM prevention. The combination of the two therapies may provide additional clinical benefit in selected patients with CM, potentially suggesting a synergistic effect through complementary modulation of trigeminovascular pathways.

Conclusions: All evaluated therapies showed favorable efficacy and tolerability profiles in CM prevention. The combination of the two therapies may provide additional clinical benefit in selected patients with CM. Further analyses in a larger cohort and after completion of patient recruitment are needed to confirm these observations.



Clinical and Neurophysiological Effects of Anodal Transcranial Direct Current Stimulation in Patients with Refractory Chronic Cluster Headache

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Background: Chronic cluster headache (CCH) is a disabling disorder that remains refractory to available preventive therapies in a substantial proportion of patients. Growing evidence suggests that dysfunctional pain-processing networks and abnormal cortical excitability contribute to its pathophysiology (1). Anodal transcranial direct current stimulation (tDCS) may modulate these dysfunctional networks through changes in cortical excitability and neuroplasticity (2). We investigated the clinical and neurophysiological effects of anodal tDCS using high-density electroencephalography (HD-EEG).

Methods: Fifteen patients with ICHD-3 refractory chronic cluster headache underwent ten sessions of anodal tDCS (2 mA, 20 min, five sessions/week for two weeks), with the anode positioned over C3 (targeting the left dorsolateral prefrontal cortex) and the cathode over FP2. Clinical outcomes and resting-state HD-EEG were assessed at baseline (T0), immediately after treatment (T1), and one month later (T2). Functional connectivity (FC) was analysed using Network-Based Statistics, as previously described (3).

Results: Significant clinical improvement was observed after treatment. MIDAS scores decreased from 31.8 ± 18.4 to 23.2 ± 7.1 (p=0.01), and HIT-6 scores from 66.7 ± 0.7 to 60.2 ± 7.8 (p=0.01). Significant improvements were also observed in CHIQ (p=0.03), BDI (p=0.02), ESS (p=0.04), and PSQI (p=0.04). Clinical benefits persisted at one-month follow-up, with further improvement in MIDAS (p=0.04 vs T1; p=0.006 vs T0) and sustained reductions in HIT-6 (p=0.009), CHIQ (p=0.04), and BDI (p=0.02) compared with baseline. HD-EEG revealed frequency-specific FC modulation, with reduced theta connectivity across occipital, parietal, and limbic regions, increased alpha connectivity within temporal, prefrontal, and insular networks persisting at follow-up, and enhanced low-gamma connectivity immediately after treatment with partial persistence at one month.

Conclusions: Anodal tDCS over the left dorsolateral prefrontal cortex was associated with sustained clinical improvement and reorganization of cortical functional connectivity in patients with refractory CCH. The observed increase in alpha and low-gamma connectivity together with reduced theta synchronization suggests adaptive neuroplastic changes within pain-processing networks. These preliminary findings suggest that tDCS may represent a promising adjunctive treatment for refractory CCH and warrant confirmation in larger randomized sham-controlled trials.



From triggers to patterns: the role of nutrition in migraine susceptibility — a narrative review.

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Background: Migraine attacks typically emerge in predisposed individuals following exposure to heterogeneous stimuli that vary widely across patients. A system-level perspective frames migraine as a disturbance of homeostasis and allostasis: the brain integrates multiple inputs and generates adaptive responses to maintain physiological stability, but sustained physiological or paraphysiological stressors may impose excessive allostatic load, ultimately culminating in an "allostatic reset" clinically manifesting as a migraine attack. Within this framework, dietary triggers are better conceptualized as threshold modulators rather than deterministic causes. Nutrition figures among the most frequently implicated domains, encompassing fasting, dehydration, specific foods and additives, and overall dietary patterns.

Methods: This narrative review synthesizes current evidence on dietary exposures as potential precipitants and modulators of migraine course, through a systematic search of the MEDLINE database up to July 2025.

Results: The most frequently reported food-related triggers include fasting, dehydration, alcohol, coffee, caffeine withdrawal, chocolate, milk and dairy products, processed and cured meats rich in nitrates and nitrites, citrus fruits, tea, onions, tomatoes, ice cream, nuts, spicy foods, and ultra-processed foods. Additives such as monosodium glutamate, aspartame, sulfites, and other artificial sweeteners have been repeatedly implicated, alongside dietary histamine and biogenic amines. Importantly, a discrepancy emerges between self-reported triggers and results from blinded provocation studies, underscoring the roles of recall bias, expectancy effects, and prodromal symptoms — particularly food cravings — misattributed to causation. Several studies further suggest that overall dietary patterns characterized by high glycemic load, irregular meal timing, excessive sugar and saturated fat intake, or ultra-processed food consumption may exert a greater influence on migraine susceptibility than individual food items. Inter- and intra-individual variability — shaped by genetic background, metabolic state, gut microbiome composition, and comorbidities — contributes additional complexity to the phenomenon.

Conclusions: Available evidence remains fragmented and frequently contradictory. Broad dietary exclusion strategies are inappropriate and risk reinforcing patients' cognitive biases, with potential negative consequences on quality of life and dietary diversity. Current evidence instead supports a personalized approach to trigger identification, prioritizing protective dietary patterns, adequate hydration, and consistent meal timing. Future research integrating omics technologies, digital tracking, and personalized nutrition strategies holds promise for developing individualized preventive interventions.



OnaBotulinumtoxin-A effectiveness evaluation in CHronic migraine patients with short or long disease history and psychiatric comorbidities: an Italian multicentric study (the BACH study)

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Background: Onabotulinumtoxin-A (OBT-A) is a worldwide approved preventive treatment for patients suffering from Chronic Migraine (CM). The aim of the study was to o investigate whether the disease duration for over or less than 10 years can predict OBT-A effectiveness in patients with CM and to evaluate if psychopathological profile may influence their outcome.

Methods: We considered consecutive CM patients undergoing OBT-A treatment for the first time and collected Monthly Headache Days (MHDs), number of Monthly Acute Medications (MAMs), pain intensity by Numerical Rating Score (NRS), Head Impact Test (HIT-6) and Migraine Disability Assessment questionnaire (MIDAS) scores at baseline and after 3, 6, 9 and 12 months. The psychopathological profile was evaluated by Beck Depression Inventory (BDI-II), State-Trait Anxiety Inventory (STAI-Y), Toronto Alexithymia Scale (TAS-20) at baseline, 6 and 12 months. Effectiveness of OBT-A was also evaluated by the 4D Migraine composite scale, including 4 parameters: MHD, MAMs, NRS and MIDAS scores.

Results: We enrolled 183 patients (mean age 46.8 yrs, SD 15.7; 158 female); at baseline 67% had a CM history longer than 10 years, 37% were affected by depression, 36% by alexithymia and 9% by anxiety. The MHD, MAMs, MIDAS, HIT-6, NRS and 4D scores significantly decreased ($p<.001$) across the follow-up in the whole sample. In almost all cases, the trend was not influenced by disease duration, psychiatric comorbidities, or by their combination ($p>0.05$). Also TAS, STAI and BDI scores decreased during the one-year follow-up, suggesting a positive effect of OBT-A treatment also on psychiatric comorbidities. Those three scores decreased more in alexithymic, anxious and depressed patients beyond what expected for the regression-to-the-mean effect. However, those patients who presented BDI higher scores at 12 months in our sample tended to have lower benefit from the OBT-A treatment in the long term.

Conclusions: In our study OBT-A effectiveness was neither affected by disease history nor by psychiatric comorbidities. People with higher BDI scores at 12 months tended to have less benefit from the treatment.



THE PATHOPHYSIOLOGY OF MIGRAINE IN THE CGRP ERA

Plasma GFAP Levels in Patients with Migraine: Lack of Association with Clinical Phenotype and Disease Burden

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Background: Growing evidence highlights the role of astrocytic activation and subsequent neuroinflammation in migraine pathophysiology, particularly in driving trigeminovascular sensitization. As a major intermediate filament protein of astrocytes Glial Fibrillary Acidic Protein (GFAP) directly reflects glial response and neuroinflammatory changes. Although GFAP is widely utilized to monitor neurodegenerative conditions, evidence regarding its correlation in migraine patients remains uncertain. This study aimed to evaluate plasma GFAP levels in migraine patients compared to healthy controls, and to investigate its association with specific clinical phenotypes, disease burden, and attack phases.

Methods: We conducted a cross-sectional observational study in patients with migraine and controls. Plasma GFAP concentrations were quantified using the fully automated Lumipulse® G1200 platform (Fujirebio, Ghent, Belgium). Clinical variables included monthly migraine days (MMD), pain intensity, migraine-related disability (MIDAS), headache impact (HIT-6), disease duration, migraine subtype (episodic or chronic), migraine with aura, medication-overuse headache (MOH), and ictal/interictal status. Group comparisons, Spearman correlation analyses, and multivariable linear regression analyses were performed.

Results: Seventy-one patients with migraine and 26 healthy controls were included. Plasma GFAP concentrations showed no statistically significant difference between cases and controls (18.40 [IQR 11.80–28.70] vs 18.10 [12.05–20.60] pg/mL; $p=0.372$); with no difference after adjustment for age. No significant differences were observed according to migraine chronicity, presence of aura, MOH, attack phase, sex or disease severity indices. A positive correlation was observed between plasma GFAP levels and age both in patients with migraine ($\rho=0.470$, $p<0.001$), and in the overall population ($\rho=0.422$, $p<0.001$). In multivariable analysis, age was the only independent predictor of plasma GFAP levels.

Conclusions: Our study showed that Plasma GFAP concentrations did not differ between migraine patients and controls, and were not associated with migraine phenotype, attack phase, or disease burden. The consistent association with age, observed both in patients and in the overall population, indicates that age is the main determinant of circulating GFAP levels, consistent with the established age-related increase of this marker. Overall, our findings do not support plasma GFAP as a biomarker of migraine phenotype or severity.



SIFI Fission Profile in Migraine Prophylaxis: Mixed ANOVA Results

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Background: Changes in cortical excitability have been extensively described in migraine and may represent an expression of pain sensitization, potentially contributing to migraine chronicization. Anti-calcitonin gene-related peptide monoclonal antibodies (anti-CGRP mAbs) and anti-CGRP small molecules, such as atogepant do not cross the blood-brain barrier and are thought to act predominantly at the peripheral level, with no evidence of direct effects on the central nervous system (CNS). The sound-induced flash illusion (SIFI) paradigm provides a simple and affordable method to assess visual cortical excitability, as illusion perception depends on cortical excitability: fewer illusions occur when visual cortex excitability is increased. The aim of this study was to evaluate changes in cortical excitability in patients treated with anti-CGRP therapies.

Methods: Sixty-two migraine patients treated with anti-CGRP monoclonal antibodies or atogepant were enrolled: 14 received fremanezumab, 15 galcanezumab, 18 erenumab, and 15 atogepant. Patients were assessed at treatment initiation (T0) and after three months (T3) using the SIFI paradigm. Paired comparisons between T0 and T3 were performed using paired t-tests or Wilcoxon signed-rank tests, with statistical significance set at $\alpha = 0.05$.

Results: A significant increase in illusion perception was observed at T3 in the 1F4B condition (1.95 vs. 2.66, p=.002). A significant increase was also found in the 1F3B condition (1.86 vs. 1.97, p=.006). Restoration of visual illusion was more pronounced in the atogepant-treated group.

Conclusion: These preliminary findings suggest that anti-CGRP therapies induce measurable changes in visual cortical excitability, consistent with a reduction in cortical hyperexcitability. Atogepant appears to produce a greater effect than the other treatments. Further studies are warranted to confirm these findings and clarify their clinical relevance.



Migraine prodromal symptoms and their clinical manifestations, an observational multicenter study

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Background: Migraine prodromal symptoms typically emerge 2–48 hours before headache onset and include cognitive, affective, and homeostatic disturbances. Although widely described in the literature, their reported prevalence varies considerably, likely due to methodological differences in symptom assessment. This multicenter observational study aimed to evaluate the prevalence, characteristics, timing, and distribution of prodromal symptoms across migraine subtypes in routine outpatient clinical practice.

Methods: Consecutive adult patients diagnosed with migraine without aura, migraine with aura, or chronic migraine according to ICHD-3 criteria were enrolled at multiple Italian headache centers between January and June 2025. Patients reporting prodromal symptoms constituted the study group, while those not reporting prodromal symptoms served as controls for prevalence analysis. An interviewer-administered questionnaire assessed symptom type, timing, duration, and recurrence. Descriptive statistics were performed; group differences were evaluated using t-tests and chi-square tests, with significance set at $p<0.05$.

Results: Among 3,711 migraine patients (mean age 41.3 ± 13.4 years; 86.0% female), 122 (3.3%) reported prodromal symptoms. Prevalence differed significantly across migraine subtypes ($\chi^2=7.67$, $p=0.02$): 3.5% in migraine without aura, 5.3% in migraine with aura, and 2.2% in chronic migraine. The most frequent prodromal manifestations were yawning/asthenia (37.7%), difficulty concentrating (33.6%), anxiety (26.2%), hunger (21.3%), and depressive symptoms (18.9%). Mean prodromal onset occurred 9.9 ± 11.4 hours before headache onset, with a mean duration of 6.3 ± 8.9 hours. Female patients reported significantly longer prodromal duration than males (6.9 ± 9.3 vs 1.1 ± 1.9 hours; $p<0.001$). Prodromal symptoms recurred in approximately 30% of attacks within the same patient and remained clinically consistent over time.

Conclusions: In this large outpatient cohort, migraine prodromal symptoms were infrequently reported, particularly in chronic migraine, suggesting substantial underrecognition in routine clinical practice. Prodromal manifestations were more common in episodic migraine and were mainly characterized by non-specific cognitive, affective, and homeostatic symptoms. Their variable recurrence and duration highlight the heterogeneity of the migraine prodrome and support the need for improved recognition to facilitate earlier therapeutic intervention.



Neurovascular decoupling links metabolic demand to cortical spreading depolarization susceptibility in migraine with aura

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Background: Although neuroimaging investigations have consistently demonstrated that "hyperresponsive" and "hyperconnected" visual cortices may represent the functional substrate of cortical spreading depolarization (CSD) in patients with migraine with aura (MwA), the mechanisms underpinning the brain "tendency" to ignite the cortical spreading depolarization and, consequently, aura phenomenon are still matter of debate. Considering that triggers able to induce aura phenomenon constrain brain to increase global (such as physical activity, stressors and sleep abnormalities) or local (such as bright light visual stimulations) energy demand, a vascular supply unable to satisfy the increased energy requirement could be hypothesized in these patients.

Methods: Forty patients with MwA (21 simple visual MwA, 19 complex MwA), 30 patients with migraine without aura (MwoA), and 22 healthy controls (HC) underwent multimodal 3T MRI during the interictal period, including resting-state functional MRI and multi-delay arterial spin labeling. Regional NVC was estimated by computing the correlation coefficient between z-scored regional homogeneity (ReHo) maps from resting-state blood oxygen level dependent signals and z-scored cerebral blood flow (CBF) maps from multi-delay arterial spin labeling signals.

Results: Voxel-wise analysis of CBF maps revealed that patients with MwA as a whole group showed a significant CBF increase in multiple regions encompassing the visual network (along the fusiform and lingual giri), compared with both patients with MwoA and HC ($p<0.05$, TFCE corrected). Furthermore, applying the cortical parcellation to both CBF and ReHo z-normalized maps, we found a reduced NVC at the VIS-4 and VIS-5 left parcels (within the visual network) in patients with both svMwA and cMwA compared with both patients with MwoA and HC (respectively $p=0.040$ and $p=0.025$, FDR corrected).

Conclusions: The coexistence of increased perfusion and reduced NVC in the visual cortex of patients with MwA may indicate that, although more blood is available overall, it is not optimally distributed according to local functional requirements. The dysregulated or inefficient allocation of CBF relative to locally coordinated neural dynamics (neurovascular "decoupling") may represent a critical pathophysiological element linking the exposure to trigger factors for MwA (associated with further increases in brain metabolic demand) and the ignition of CSD.



A Patient-Specific Human Trigeminal Neuron Model for the Study of Migraine Mechanisms

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Background: Reliable animal models have been critical to the understanding of the mechanisms underlying migraine pain. However, species differences in trigeminovascular biology and CGRP signaling limit clinical translatability. Induced pluripotent stem cells (iPSCs) offer a promising avenue, as they allow the generation of patient-specific cells while preserving each individual's genetic background intact. This approach is amenable to study individual vulnerability as well as the factors underlying migraine occurrence and severity at the cellular and molecular levels.

Methods: Peripheral blood mononuclear cells (PBMCs) were obtained from two subjects with chronic migraine (CM) and one healthy control (HC) and reprogrammed into iPSCs. The iPSC lines were subsequently differentiated into trigeminal sensory neurons and subjected to gene expression profiling, immunocytochemistry, and electrophysiological characterization.

Results: All lines differentiated efficiently into mature neurons, as confirmed by expression of neuronal markers (TUBB3, MAP2, NEFH) and trigeminal markers (BRN3A, ISL1) by RT-qPCR. Distinct neuronal subtypes were also identified, including GABAergic ($GABA^+$) and glutamatergic ($vGLUT1^+$) populations. The analysis of nociceptive markers confirmed that the neurons expressed CGRP and TRPV1. Interestingly, CM-derived neurons showed reduced expression of both markers compared to the HC line, suggesting an altered nociceptive phenotype consistent with chronic receptor depletion and desensitization.

Conclusions: These very preliminary findings pave the way for the establishment of the first patient-specific in vitro model of human trigeminal neurons for CM. Additional iPSC lines derived from a large number of donors will be required to validate and strengthen the robustness of this platform. Future investigations will focus on characterizing intrinsic neuronal excitability, calcium dynamics, and the functional integrity of CGRP-mediated signaling pathways.



Long-term effectiveness and safety of fremanezumab for migraine prevention: 24-month outcomes from the Italian cohort of the PEARL study

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Background: Fremanezumab is a calcitonin gene-related peptide pathway monoclonal antibody approved for the prevention of episodic (EM) and chronic migraine (CM). In Italy, fremanezumab reimbursement is subject to Italian Medicines Agency criteria (≥8 monthly migraine days [MMD], a Migraine Disability Assessment [MIDAS] score of ≥11 before treatment and ≥3 prior preventive treatment failures). Here, we report effectiveness and safety of fremanezumab for migraine prevention in Italian participants enrolled in the observational, Phase 4 Pan-European Real Life (PEARL; EUPAS35111) study after 24 months of follow-up.

Methods: Eligible participants were adults with high-frequency EM (HFEM) and CM receiving monthly (225 mg) or quarterly (675 mg) fremanezumab in routine clinical practice. A mandatory ≥1 month treatment discontinuation period occurred following 12 months of continuous treatment. The primary endpoint was the proportion of participants achieving ≥50% reduction in MMD during the 6 months following fremanezumab initiation. Secondary endpoints included mean change from baseline in MMD at Months 1 and 24, and mean MIDAS scores over 24 months. Safety was assessed through adverse event (AE) reporting.

Results: This analysis included 354 participants (HFEM, n=125; CM, n=229) from 30 Italian centres (female, 82.2%; CM, 64.7%; baseline MMD, 15.6 days). In total, 61.9% (n=219/354) of participants achieved ≥50% reduction in MMD during the 6-month period after fremanezumab initiation. Mean change from baseline in MMD was sustained from Month 1 (total, –8.2; HFEM, –5.4; CM, –9.8) to Month 24 (total, –10.5; HFEM, –6.5; CM, –12.7). In participants with documented cessation and reinitiation, mean MIDAS scores decreased from 93.7 at baseline (HFEM, 67.8; CM, 107.8) to 22.0 at Month 12 after fremanezumab initiation (HFEM, 14.0; CM, 26.0), and from 37.5 at baseline of reinitiation (HFEM, 29.9; CM, 42.6) to 25.3 at Month 12 after reinitiation (HFEM, 11.7; CM, 31.5). Drug-related AEs were reported in 62/354 (17.5%) participants, with 2/354 (0.6%) reporting drug-related serious AEs and 4/354 (1.1%) reporting AEs that led to discontinuation.

Conclusions: These results underscore the long-term effectiveness and safety of fremanezumab for the preventive treatment of HFEM and CM and the importance of continued treatment now that treatment pauses are no longer mandated.



Excitation/inhibition imbalance in migraine patients assessed by electroencephalography

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Background: Migraine has been linked to an imbalance between excitation and inhibition (E/I) at both electrophysiological and molecular levels [1]. The exponent of the aperiodic component of the power spectrum of the electroencephalography (EEG) signal is regarded as a proxy of the E/I balance in human brain [2] and can be assessed in a non-invasive and cost-effective way.

Methods: We recorded resting-state activity with 32-channel cap EEG in 11 migraine patients and 8 healthy controls. We extracted the exponent of the aperiodic fit of the power spectrum computed on source-reconstructed signals down-sampled to 68 regions of interest (ROI) according to Desikan-Killiany atlas. Group comparisons were performed, followed by 5,000 random permutations and FDR correction.

Results; We observed a steeper slope of the aperiodic component of the power spectrum in several cerebral ROIs, including left entorhinal cortex, left fusiform gyrus, left isthmus of the cingulate gyrus, and left parahippocampal gyrus.

Conclusion: These preliminary data show evidence of abnormal E/I balance from EEG recordings of migraine patients. Reduced excitability is particularly concentrated in ROIs belonging to left medial temporal regions and implicated in the Default Mode Network.



Delta-band hyperconnectivity as a potential marker of migraine severity and chronification: a resting-state high-density EEG study

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Background: Increasing evidence suggests that migraine is characterized by altered brain network dynamics and dysfunctional thalamo-cortical communication. Resting-state EEG studies have identified abnormal slow-frequency oscillatory patterns consistent with the Thalamo-Cortical Dysrhythmia (TCD) model (1). However, the relationship between these oscillatory abnormalities and alterations in functional connectivity across migraine phenotypes remains unclear. Notably, HD-EEG functional connectivity has recently proved sensitive to treatment-related cortical network modulation in migraine, with early changes in delta-band connectivity observed after both atogepant and onabotulinumtoxinA (2,3). We investigated resting-state high-density EEG (HD-EEG) functional connectivity in chronic migraine (CM), high-frequency episodic migraine (HFEM), and healthy controls (HCs) to characterize frequency-specific network alterations associated with migraine.

Methods: In this retrospective cross-sectional study, interictal resting-state HD-EEG recordings were obtained from patients with migraine (HFEM n=22; CM n=12) and healthy controls (HCs n=30). Clinical migraine burden and disability were assessed using validated questionnaires. Source-space functional connectivity was computed using the weighted phase-lag index (wPLI) across δ, θ, α, β, low-γ, and high-γ frequency bands after artifact removal and source reconstruction. Between-group differences were assessed using Network-Based Statistics (NBS), adjusting for age and sex. Correlations between connectivity measures and clinical variables were explored.

Results: Thirty-four patients with migraine (HFEM n=22; CM n=12) and 30 HCs were included. Source-space analyses revealed significant alterations in resting-state functional connectivity, predominantly within the δ band. δ-band hyperconnectivity involved temporo-parietal, orbitofrontal, insular, and limbic regions, showing a progressive increase across groups, with the highest mean network connectivity in CM, intermediate values in HFEM, and the lowest values in HCs (CM > HFEM > HC). Within the migraine cohort, δ-band mean network connectivity was positively correlated with MIDAS score.

Conclusions: Resting-state HD-EEG identified a progressive increase in δ-band functional connectivity across migraine phenotypes, with the greatest abnormalities observed in CM. The association between δ-band hyperconnectivity and clinical disability supports a relationship between slow-frequency network hypersynchronization and migraine severity. These findings suggest that δ-band connectivity may represent a potential neurophysiological marker of migraine chronification and warrant validation in larger longitudinal studies.



Migraine Subgroups Defined by Associated Symptoms and Alleviating Strategies: A Cross-Sectional Study of 3275 Patients with Episodic Migraine

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Background: Migraine still lacks an objective biomarker. We explored potential subgroups of migraine based on phenotypic characterisation of symptoms (premonitory, ictal, and postdromal), pediatric prodromes and alleviating strategies.

Methods: Data were collected cross-sectionally across 15 years (2008-2023) from a specialized tertiary headache center. Patients with episodic migraine, with or without aura, were included. Premonitory (8 symptoms), ictal (12 symptoms) and postdromal (3 symptoms) symptoms, as well as alleviating strategies during attacks (7 strategies) and pediatric prodromes (2 symptoms) were collected through a semi-structured interview. Latent class analysis (LCA) was performed to identify subgroups, using sex, migraine diagnosis and age groups as covariates.

Results: A total of 3275 patients (77% female; mean age 38.4±12.1) with episodic migraine were included. LCA identified 4 latent classes. Class 1 was characterized by premonitory cervical stiffness and irritability, multiple ictal symptoms (including asthenia, yawning, dizziness and unilateral autonomic signs) and postdromal asthenia, with attacks relieved by application of heat or sleep. Class 2 had a symptom profile similar to Class 1 but was distinguished by relief with application of cold. Class 3 had a milder ictal symptom profile and low frequency of premonitory symptoms and postdromal asthenia. Class 4 exhibited marked sensory hypersensitivity, with severe ictal photophobia and phonophobia, fewer non-headache ictal symptoms and relieving strategies. Male sex and age >55 years were strongly associated with Class 3 (male sex: OR 2.90, 95% CI 2.30–3.65; $P < 0.001$; age >55 years: OR 1.58, 95% CI 1.05–2.38; $P = 0.029$).

Conclusions: This study identified 4 latent classes representing distinct phenotypic profiles of migraine based on associated symptoms and attack-relieving strategies. Two classes showed a similar multisymptom profile but were distinguished by different alleviating strategies (application of heat or sleep versus application of cold), suggesting potentially distinct underlying mechanisms in pain control. In contrast, one phenotype was characterized by a low overall symptom burden, whereas another was dominated by severe sensory hypersensitivity despite relatively few other associated non-headache symptoms. These findings highlight the clinical heterogeneity of migraine and provide a framework for future biomarker discovery and precision medicine.

Modulation of cerebral hemodynamics by atogepant in episodic migraine: a transcranial Doppler follow-up study

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Background. Migraine is characterized by dynamic neurovascular dysregulation, with endothelial dysfunction and impaired cerebrovascular reactivity (CVR) contributing to disease expression and progression. Calcitonin gene-related peptide (CGRP) plays a central role in both vascular modulation and trigeminovascular activation. However, the hemodynamic effects of CGRP receptor antagonism remain incompletely explored. Objective is to evaluate changes in cerebral hemodynamics and vasoreactivity in patients with episodic migraine treated with atogepant.
Methods. Twenty-three patients with episodic migraine underwent transcranial Doppler (TCD) examination at baseline (T1) and after 3 months of preventive treatment with atogepant (T2). Mean flow velocity (MFV), pulsatility index (PI), and breath-holding index (BHI) were assessed in the middle cerebral artery. A paired t-test was used for longitudinal comparisons. Patients were also assessed using the MIDAS scale.
Results. The study initially enrolled a population of 28 subjects, subsequently reduced to 23 evaluable patients (mean age approximately 41 years, predominantly female) following careful selection aimed at excluding potential cardiovascular confounding factors. The sample appeared clinically homogeneous, with a clear predominance of migraine without aura (96%).
In the left hemisphere, a statistically significant reduction in the Breath-Holding Index (BHI) was observed, decreasing from 0.76 ± 0.26 to 0.61 ± 0.26 ($p = 0.011$). In parallel, the left side showed an increase in the Pulsatility Index (PI) ($p = 0.0027$) and a reduction in the baseline–post-apnea peak velocity variation (from 17.47 to 14.21 cm/s; $p = 0.026$), along with an increase in baseline velocity at T2, particularly on the left. Taken together, these parameters suggest a restoration of basal vascular tone and an increase in peripheral resistance in a vascular territory previously characterized by hemodynamic instability. In contrast, the right hemisphere exhibited less pronounced changes, confirming an asymmetric response to treatment.
Conclusions. The integration of the analyzed hemodynamic parameters (BHI, PI, and ΔV) supports an adaptive modulation of the cerebrovascular network induced by treatment with atogepant. After a three-month follow-up, a shift toward greater stability and reduced dynamic variability of flow is observed, particularly within the vascular territory of the dominant (left) hemisphere. This phenomenon is consistent with a restoration of homeostatic control of basal vascular tone.
From a pathophysiological perspective, this hemodynamic pattern suggests a potential endothelial-protective effect of the molecule. Antagonism of the CGRP receptor appears to mitigate oxidative stress and neurovascular inflammatory processes, which are key elements in the migraine chronification. The more pronounced response observed in the left hemisphere reflects the known hemodynamic vulnerability of regions with higher synaptic density and elevated metabolic turnover, which in these patients benefit from a functional reorganization of flow regulation.
In line with current theoretical models in the literature, the results indicate that atogepant acts by attenuating the hyper-reactivity of the trigeminovascular system to vasodilatory stimuli (such as hypercapnia). The reduction in the Breath-Holding Index (BHI) and ΔV, together with the increase in the Pulsatility Index (PI), should therefore not be interpreted as a depletion of hemodynamic reserve, but rather as a normalization of endothelial reactivity. In conclusion, the treatment promotes stabilization of cerebrovascular dynamics, optimizing autoregulatory efficiency and reducing susceptibility to dysfunctional hyperemic responses. CGRP receptor blockade with atogepant is associated with a favorable modulation of cerebral hemodynamics in episodic migraine. These findings support the vascular safety of gepants and suggest a potential indirect restoration of endothelial-dependent vasoreactivity.



Autonomic evaluation in episodic migraine with a comprehensive assessment

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Introduction: Evidence suggests that migraine patients experience a certain degree of autonomic nervous system (ANS) dysfunction both during attacks and interictal period. The study aims to evaluate the autonomic function in migraine patients compared to healthy controls.

Methods: Patients affected by episodic migraine (EM) were selected for an autonomic evaluation during the interictal phase. In addition, healthy subjects (HS) with similar age and sex distribution were selected for comparison. The subjects did not suffer from conditions (and were not on any therapy) influencing the ANS. Systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) were recorded using an automatic sphygmomanometer, while live HR variations were evaluated with an ECG chest band. The Composite Autonomic Symptom Score (COMPASS-31) was administered to investigate autonomic symptoms. The following autonomic function tests (AFT) was administered: Standing Up Test (SUT–10min), Isometric Handgrip Test (IHT–3min), Mental Arithmetic Test (MAT–2min), Cold Pressor Test (CPT–90sec), and Hyperventilation Test (HVT–60sec) assessing BP and HR variations from baseline. Moreover, respiratory sinus arrhythmia (RSA) during Deep Breath Test (DBT–1min) was evaluated.

Results: 20EM (17F) and 18HS (12F) have been included. SBP variation at CPT was slightly higher in EM than in HS (2.7 ±5.6 vs -0.8 ±4.7, p-value 0.043). HVT revealed a significantly lower HR variation in EM patients compared to HS (4.4 ±6.4 vs 14.3 ±9.8, p-value 0.001). The other AFTs did not reveal significant differences. Conversely, at the COMPASS-31 EM subjects reported a higher autonomic burden compared to HS (24.9 ±16.9 vs 11.2 ±8.3, p-value 0.008).

Conclusions: Sympathetic pressor response at CPT was greater in EM compared to HS, suggesting a potentially higher sensitivity to external stimuli. Hyperventilation produced a lower HR variation in EM subjects, implying that vagal withdrawal is more evident in HS. Despite a significant autonomic burden at COMPASS-31, no other AFT showed alterations in EM. The present data suggest mild interictal alterations in cardiovascular regulation, but further studies during the ictal phase are requested to appreciate any other autonomic alteration in migraine subjects.



DIFFICULT HEADACHES: RESOLVED AND UNRESOLVED CASES

Switching between anti-CGRP monoclonal antibodies in a CADASIL patient: Four-Year Evidence of Safety and Efficacy

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Background: CADASIL is an autosomal dominant cerebral small-vessel arteriopathy caused by pathogenic NOTCH3 variants. Migraine, frequently with aura, is a common inaugural manifestation.
Although monoclonal antibodies targeting the calcitonin gene-related peptide pathway have transformed migraine prevention, CGRP blockade in a chronically hypoperfused brain raises a theoretical hemodynamic concern, given the peptide's role as a compensatory vasodilator. Accordingly, patients with cerebrovascular disease were generally excluded from pivotal trials, and direct evidence in the use of anti CGRP monoclonal antibodies in CADASIL remains limited to isolated short-term reports, mostly involving erenumab.

Methods: We report a 35-year-old woman with CADASIL due to the heterozygous NOTCH3 p.Cys222Tyr variant, with arterial hypertension and depressive disorder and with childhood-onset chronic migraine with aura refractory to several preventive classes.

Results: Brain MRI showed confluent periventricular and subcortical bihemispheric leukoencephalopathy, with diffusely enlarged Virchow–Robin perivascular spaces and bilateral anterior temporopolar involvement. Because of near-daily attacks and marked disability, erenumab had been prescribed elsewhere, reducing attacks from daily to 7-15 days/month. At first evaluation in our center, given a stable clinical picture, a switch from erenumab to onabotulinumtoxinA was attempted; monotherapy with onabotulinumtoxinA was, however, followed by a relapse (MIDAS 103) that resolved only after reintroduction of erenumab (140 mg every 4 weeks) combined with botulinum toxin treatment according to PREEMPT protocol (MIDAS 10). In early 2025, owing to further loss of efficacy and a concomitant rise in diastolic blood pressure, treatment was switched to the anti-CGRP ligand antibody galcanezumab (120 mg every 4 weeks), achieving stable headache control (4–5 days/month) and satisfactory blood-pressure control. Serial brain MRI (every 6–12 months) confirmed morphological stability of the leukoencephalopathy throughout the four-year period (2022–2026), without new ischemic or microhemorrhagic lesions or cerebrovascular events.

Conclusions: Through four-year clinical-radiological monitoring, this work documents the safety and efficacy of a switch from an anti-CGRP receptor antibody to an anti-CGRP ligand antibody, combined with botulinum toxin A, in genetically confirmed CADASIL with resistant chronic migraine. Despite its single-case design, prolonged CGRP-pathway modulation proved effective and was not associated with structural cerebrovascular progression, supporting individualized strategies and prospective validation.



Clinical characterization of a novel de novo mutation in the CACNA1A gene (c.3277del) associated with migraine without aura and episodic ataxia

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Background: Hemiplegic migraine (HM) is a rare form of migraine with motor aura, associated with pathogenic variants in genes involved in ion transport, including CACNA1A, which encodes the α1A subunit of the voltage-gated P/Q-type calcium channel. Variants in CACNA1A are responsible for a spectrum of paroxysmal neurological disorders, including familial hemiplegic migraine type 1, episodic ataxia type 2, and spinocerebellar ataxia type 6, now considered a clinical continuum rather than distinct nosological entities.

Methods: A 42-year-old man with a long-standing history of episodic vertigo, transient dysarthria, gait disturbance, and migraine without aura was evaluated. Targeted next-generation sequencing (NGS) of SCN1A, CACNA1A, SCN2A, ATP1A2, and ATP1A3 was performed, with complete coverage of exons and flanking intronic regions. The identified variant was confirmed by Sanger sequencing, and segregation analysis was performed in four first-degree relatives (parents and two brothers).

Results: Neurological examination revealed inexhaustible horizontal and vertical gaze-evoked nystagmus, while brain MRI and prolonged video-EEG were unremarkable. Paroxysmal episodes occurred in clusters of up to six per month, while migraine attacks were daily. NGS analysis identified a heterozygous frameshift variant in CACNA1A, c.3277del (p.Ser1093Alafs*93), resulting in protein truncation and loss of function of the P/Q-type channel. Segregation analysis confirmed the de novo origin of the variant, which was absent in both parents. Based on ACMG/AMP criteria, the variant was classified as pathogenic due to loss-of-function mechanism, absence from population databases (gnomAD v4.1), location within a CACNA1A hotspot region, and de novo origin. Initial preventive therapy with acetazolamide, poorly tolerated, was replaced with topiramate with partial benefit; subsequent reintroduction of acetazolamide, in combination with topiramate, resulted in a further reduction in attack frequency.

Conclusions: This case expands the phenotypic spectrum associated with CACNA1A-related channelopathies, showing how migraine without aura and episodic ataxia may represent atypical manifestations within the same clinical continuum. Recognition of such presentations, even in the absence of overt motor aura, is relevant for early diagnosis and for guiding personalized therapeutic strategies.



Intracranial Hypertension Mimicking Pseudotumor Cerebri as the Primary Manifestation of JAK2-Positive Myeloproliferative Neoplasms: A Two-Case Series.

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Background: Idiopathic intracranial hypertension (IIH) is a rare condition (0.9-2/100.000 persons) that affects mainly obese young women. Secondary intracranial hypertension due to cerebral venous sinus thrombosis (CVST) is far rarer condition (0.5/100,000 persons). However, chronic, oligosymptomatic CVST can perfectly mimic the clinical phenotype of IIH. In young adults carrying the JAK2V617F mutation, these clinical presentation and condition can represent the primary herald manifestation for an underlying myeloproliferative neoplasm (MPN). We present the cases of two women both born in 1983 affected from severe intracranial hypertension driven by this mechanism.

Case Presentations:

- Case 1: A normal-weight female developed in 2018 a clinical picture characterized by tinnitus, negative scotomas, and severe headache. Patient was hospitalized elsewhere and bilateral papilledema was ascertained. Also MRI was performed and reported empty sella, and optic hydrops; colleagues started acezolamide without clinical changes. We evaluated patients few weeks later since persistence of headache condition and we performed a second MRI/MRV study confirming previous reports, but also showing extensive chronic parcellar thrombosis in the right transverse/sigmoid and superior sagittal sinuses. Patient affected from JAK2-positive PMF was treated with acetazolamide and warfarin. Visual symptoms resolved by November 2019, but a high frequency/chronic migraine-like headache persisted. The introduction of ruxolitinib in 2022 marked a turning point, relieving pain symptoms and allowing acetazolamide discontinuation by 2023, though sporadic perimenstrual headache episodes persist. Follow-up imaging up to 2025 demonstrated a stable, unresolved, chronic thrombotic framework.
- Case 2: A female with class I obesity presented in late 2025 with recent abrupt onset headache, bilateral peripheral distorted vision, marked bilateral papilledema, and an elevated opening pressure of 350 mmH2O. MRI/MRV confirmed optic hydrops and a less extensive parcellar thrombotic defect in the right transverse-sigmoid sinus. Subsequent workup revealed a JAK2V617F-positive unclassifiable MPN. Driven by acetazolamide, rapid weight loss via semaglutide, and edoxaban, she achieved rapid clinical resolution, with mid-2026 neuroimaging confirming near-complete sinus recanalization.

Conclusions: While sparse literature reports link between intracranial hypertension conditions and essential thrombocythemia or polycythemia vera, cases secondary to primary myelofibrosis (PMF) or unclassifiable MPNs remain exceptionally rare. In our cases, lower initial thrombotic burden early managed with edoxaban favored complete radiologic resolution, whereas extensive organized and more lasting thrombosis condition resulted in a chronic headache phenotype where targeted JAK1/2 inhibition, rather than standard pressure-lowering agents or anticoagulant, resulted essential for long-term clinical compense.



Post-Dural Puncture Headache After Diagnostic Lumbar Puncture: Incidence, Clinical Presentation, and Associated Factors in a Neurological Cohort

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Background: Post-dural puncture headache (PDPH) is a common complication of lumbar puncture. This study assessed its incidence, clinical features, treatment response, and factors associated with headache occurrence.

Methods: We retrospectively analyzed clinical and CSF data from patients undergoing diagnostic lumbar puncture at the Neurology Clinic of Fondazione Policlinico Universitario A. Gemelli IRCCS (Rome) between December 2024 and April 2026, with a minimum follow-up of 3 months. Patients were categorized according to post-procedural headache occurrence and fulfillment of ICHD-3 criteria for PDPH. Demographic, clinical, and CSF variables were compared using the Mann-Whitney U or Fisher's exact test, as appropriate. Patients requiring symptomatic treatment rated medication effectiveness on a 0–10 numerical scale.

Results: Among 54 patients, 37 (68.5%) developed headache after lumbar puncture, and 35/37 (94.6%) fulfilled ICHD-3 criteria for PDPH (64.8% of the cohort). Mean headache onset was 18.8 ± 16.6 hours after procedure and mean duration was 8.3 ± 8.8 days. Orthostatic headache was reported by 97.1% of patients, followed by neck pain/stiffness (65.7%), nausea (44.4%), photophobia (41.7%), vomiting (25.0%), and phonophobia (25.0%). Thirty patients (81.1%) required symptomatic treatment. Paracetamol alone was the most frequently used medication (15 patients; mean effectiveness score 4.83/10), followed by ibuprofen (4 patients; 4.50/10). Combinations of analgesic (most commonly paracetamol) and caffeine were used by 11 patients and showed significantly greater perceived effectiveness than paracetamol alone (mean score 6.82 vs 4.83; $p = 0.046$). Several patients also reported benefit from caffeine alone. Emergency department visits for headache within 3 months occurred in 14.3% of patients. Patients developing PDPH were significantly younger than those without headache (35.3 ± 11.4 vs 49.7 ± 12.0 years; $p = 0.0002$), whereas sex, pre-existing primary headache, headache subtype, and CSF parameters were not associated with PDPH.

Conclusions: PDPH was frequent despite standardized lumbar puncture procedures. Younger age was the only significant predictor of headache occurrence. Treatments containing caffeine provided greater patient-reported symptom relief than paracetamol alone, supporting a possible role of caffeine in modulating mechanisms involved in PDPH. Larger prospective studies are needed to confirm these findings and better define caffeine's therapeutic role.



Integrated Management and 24-month Follow-up of Complex Medication Overuse Headache (MOH): Impact of Continuous Psychoeducational Support on Relapse Prevention.

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Background: Medication Overuse Headache (MOH) is a chronic secondary headache disorder resulting from the overuse of analgesics (≥15 days/month for over 3 months). In cases defined as "complex" (type 2), the patients' psychopathological profile is particularly complicated: the presence of psychiatric comorbidities, such as anxiety and depression, predicts worse treatment outcomes and higher relapse rates. The abuse of specific substances, is further linked to an unfavorable prognosis. Given the multifactorial nature of the disorder, the integration of different therapeutic strategies is necessary to improve clinical outcomes.

Methods: Two patients—a 48-year-old man and a 69-year-old woman—suffering from chronic migraine and MOH were followed through psychological counseling. At baseline, the female patient consumed an average of 45 opioid medications/month, while the male patient consumed approximately 90 combination drugs/month. Both presented psychiatric comorbidities (depression, generalized anxiety disorder, bulimia) and a history of failed prior detoxification attempts. The protocol involved a new detoxification process combined with anti-CGRP monoclonal antibodies (eptinezumab) and an educational psychological support program focused on pain awareness and medication management.

Results: At the end of the first year, both patients had successfully interrupted the abuse behavior, achieving a better differentiation between the migraine pain dimension and the emotional dimension. At the 24-month follow-up, clinical trajectories diverged:
Female Patient: Continued monthly psychoeducational sessions, maintaining an episodic migraine diagnosis (4 attacks/month) and total abstinence from opioids.
Male Patient: Continued exclusively with pharmacological prophylaxis. During the second year, a progressive increase in the intake of combination symptomatic medications and attack frequency was recorded, reaching 30 symptomatic drugs per month. This resulted in a new MOH diagnosis and the need for a new detoxification protocol.

Conclusions: These observations, while limited to two cases and requiring more structured future studies, suggest that the continuity of psychoeducational support represents a determining factor in preventing behavioral relapses and consolidating therapeutic success in patients with high psychopathological complexity.



Migraine history in patients with aneurysmal subarachnoid hemorrhage developing cerebral vasospasm and delayed cerebral ischemia: a case series

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Objective: to describe the characteristics of patients with a history of migraine developing cerebral vasospasm and/or delayed cerebral ischemia (DCI) following aneurismal subarachnoid haemorrhage (aSAH).

Background: Cerebral vasospasm and DCI are major secondary vascular complications of aSAH. Migraine, a recognized cerebrovascular risk factor, may share pathophysiological mechanisms with vasospasm and DCI.

Methods: we retrospectively reviewed consecutive patients admitted to the Stroke Unit of Tor Vergata University Hospital with a diagnosis of aSAH between January 2022 and December 2025. Among these, we identified migraineurs who developed cerebral vasospasm and/or DCI. Collected data included demographics, vascular risk factors, aneurismal and aSAH features, clinical severity at admission with WFNS and Hunt-Hess scales, radiological severity assessed using the modified Fisher scale (mFS). Cerebral vasospasm was assessed by transcranial doppler ultrasound; patients with symptoms consistent with vasospasm underwent digital subtraction angiography.
Results: among 96 patients, 5 migraineurs (4 episodic, 1 chronic; none with aura; all female, mean age 35.2 years) developed vasospasm and/or DCI. Smoking was the only vascular risk factor identified. At admission, all patients had WFNS and Hunt-Hess grade 1-2; 3 patients presented with mFS grade 1-2 and 2 with grade 4. Cerebral vasospasm was documented in 4 patients, 3 of whom symptomatic. Three patients fulfilled criteria for DCI, including 1 without evidence of macrovascular vasospasm. All patients achieved favorable 3-month outcomes.

Results: Neurovascular complications occurred despite mild clinical presentation and low radiological burden in most of selected patients.
Although current evidence doesn't support a clear association between migraine and cerebral vasospasm after aSAH [1], previous studies have suggested a higher occurrence of DCI among migraineurs [2]. Metabolic and vascular dysfunction of the migrainous brain may represent a potential vulnerability factor for secondary neurovascular complications following aSAH, possibly through shared mechanisms [3] involving altered cerebrovascular reactivity, endothelial dysfunction, neuroinflammation and cortical hyperexcitability. Notably, the occurrence of DCI in 1 patient without angiographic vasospasm further supports the multifactorial pathophysiology of DCI.

Conclusions: It could be interesting to investigate with prospective studies whether migraine history could independently increase the susceptibility to secondary vascular complications post-aSAH, especially in patients with a high migraine burden.



Anti-CGRP Monoclonal Antibody Response in Chronic Migraine with Severe Neuropsychiatric Comorbidity: A Case Report and Pathophysiological Insights

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Background: Chronic migraine is frequently associated with psychiatric disorders and central sensitization, both of which may influence the response to preventive treatments. Anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies represent an effective preventive strategy; however, the determinants of treatment response in patients with high clinical complexity remain poorly understood. We describe the case of a patient with chronic migraine and severe neuropsychiatric comorbidity, proposing an integrated model of symptom amplification.

Methods: We analyzed the case of a 49-year-old woman with chronic migraine, bipolar disorder, and obsessive-compulsive disorder, treated with galcanezumab while receiving stable psychiatric therapy with olanzapine, aripiprazole, lamotrigine, paroxetine, and alprazolam. The assessment included neurological, psychiatric, neuropsychological, and psychometric evaluations using the Beck Depression Inventory-II (BDI-II), State-Trait Anxiety Inventory (STAI), Central Sensitization Inventory (CSI), Montreal Cognitive Assessment (MoCA), Brief Cognitive Status Exam (BCSE), Minnesota Multiphasic Personality Inventory-3 (MMPI-3), Morisky Medication Adherence Scale (MMAS), and Patient Health Engagement Scale (PHE-S). Clinical follow-up was performed after treatment discontinuation and subsequent reintroduction.

Results: The patient exhibited a clear "on-off-on" pattern. Treatment with galcanezumab reduced migraine attacks from more than seven episodes per month to 1–2 episodes/month. Treatment discontinuation was followed by headache recurrence, whereas reintroduction of the drug restored the clinical benefit. The multidimensional assessment revealed severe depression (BDI-II = 59), marked anxiety (STAI = 77/80), pronounced central sensitization (CSI = 100), multidomain cognitive impairment (MoCA = 19; BCSE = 18), and an MMPI-3 profile characterized by high negative emotionality, social withdrawal, and thought dysfunction. Overall, the findings suggest that treatment response is modulated by the interaction among peripheral mechanisms, central sensitization, psychiatric comorbidity, and brain networks involved in pain processing.

Conclusions: This case supports a biopsychosocial model of chronic migraine in which the effectiveness of anti-CGRP monoclonal antibodies is also influenced by the functional state of central pain modulation systems. A multidisciplinary approach integrating neurological, psychiatric, and neuropsychological perspectives may facilitate a more personalized treatment strategy for patients with high clinical complexity.



A carotid–cavernous fistula mimicking hemicrania continua

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Background: A 78-year-old woman presented with a 3-month history of recurrent attacks of excruciating, strictly left-sided headache involving the periorbital region. Her family and physiological history were unremarkable. Her past medical history was notable only for treated arterial hypertension. The pain was pulsating, rated 10/10 on the Numerical Rating Scale, lasted approximately 12 hours, occurred 3–4 times per week, and showed poor response to NSAIDs. Each attack was accompanied by ipsilateral ptosis and lacrimation. Between attacks, she experienced a continuous mild left frontal pulsating headache, which consistently worsened in the supine position. She denied visual loss, diplopia, and jaw claudication.

Methods: Routine laboratory investigations, including ESR and CPR, were unremarkable. An initial non-contrast brain MRI and doppler ultrasonography of the temporal arteries were both reported as normal. Neurological examination revealed left-sided fixed miosis with absent direct and consensual pupillary light reflexes and ipsilateral ptosis. Based on the overall clinical phenotype, characterized by a continuous unilateral headache with superimposed exacerbations and ipsilateral cranial autonomic symptoms, together with the unrevealing initial diagnostic work-up, hemicrania continua was initially suspected. However, an indomethacin trial (100 mg/day) was completely ineffective, making this diagnosis unlikely.

Results: Given the presence of objective focal neurological signs, brain MRI with gadolinium enhancement and dedicated intracranial MR angiography was subsequently performed. Imaging revealed progressive thickening of the left cavernous sinus with abnormal high-flow signal on time-of-flight sequences and early contrast enhancement on dynamic acquisitions, without significant dilatation of the ipsilateral superior ophthalmic vein. These findings raised the suspicion of a carotid–cavernous fistula, which was subsequently confirmed by digital subtraction angiography. The patient underwent endovascular treatment, resulting in complete resolution of the headache and the associated cranial autonomic signs.

Conclusions: This case highlights that secondary headache disorders involving the cavernous sinus may resemble primary trigeminal autonomic cephalalgias. Although cranial autonomic symptoms are highly suggestive of TACs, their presence should not preclude careful evaluation for structural causes, particularly when atypical features or neurological signs are present. Brain MRI should be considered mandatory in patients presenting with a new-onset TAC-like phenotype, preferably including gadolinium-enhanced sequences and dedicated vascular imaging (MR angiography).



Familial hemiplegic migraine type 2 in an Italian family: a complex phenotype with focal epilepsy and neurodevelopmental disorders

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Background: Familial hemiplegic migraine (FHM) is a monogenic subtype of migraine with aura, characterized by transient motor weakness associated with other reversible aura symptoms. FHM is genetically and clinically heterogeneous, and is associated with pathogenic variants in CACNA1A, ATP1A2, and SCN1A. ATP1A2-related FHM (FHM2) may be associated with a broader neurological phenotype. Here, we report an Italian family carrying an ATP1A2 variant and presenting with a complex phenotype of hemiplegic migraine, focal epilepsy, and cognitive and neurodevelopmental features.

Methods: We describe a 41-year-old woman with recurrent hemiplegic migraine evaluated at the Headache Center, Department of Neuroscience "Rita Levi-Montalcini", University of Turin. Personal and family history were reviewed, focusing on neurological manifestations, cognitive and neurodevelopmental features, and genetic counselling.

Results: The patient reported recurrent migraine with visual aura beginning at 6 years of age. During the disease course, attacks evolved to include right-limb paresthesias and weakness, expressive aphasia. Symptoms lasted 30 minutes and were followed by right-sided temporal headache associated with nausea/vomiting, photophobia, and phonophobia. One prolonged episode of limb weakness lasting several days occurred, with negative neuroradiological investigations. Recently, she developed disabling migraine without aura. Her history included focal epilepsy and mild intellectual disability. Serial brain MRI showed no progressive abnormalities. Family history revealed hemiplegic migraine in her mother and maternal aunt. One sister had autism spectrum disorder, while another deceased sister had severe intellectual and motor disability. Genetic testing identified the heterozygous ATP1A2 variant NM_000702.4:c.2723G>A (p.Arg908Gln), shared by affected family members, confirming FHM2. This variant affects a conserved residue in the C-terminal transmembrane region and has been shown to impair α2 pump function. Chromosomal analysis and FMR1 premutation testing were normal. Triptans were avoided; prophylaxis was attempted with lamotrigine and then topiramate.

Conclusions: To our knowledge, this is the first Italian family carrying the ATP1A2 p.Arg908Gln variant, previously reported in one patient with sporadic hemiplegic migraine and in two unrelated German and Russian families with FHM2. The co-occurrence of hemiplegic migraine, focal epilepsy, intellectual disability, and neurodevelopmental disorders further supports the broad phenotypic spectrum of FHM2.



Episodic Cluster Headache: High efficacy of the combined therapy with high-dose intramuscular methylprednisolone and high doses of verapamil on stopping single clusters

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Background: Following our previous study on combined therapy of high-dose intravenous methylprednisolone (MP) and high-dose oral verapamil (V) in Episodic Cluster Headache (ECH), here we report the results of combined treatment with high-dose intramuscular MP and high-dose oral V.

Methods: A series of 19 patients, 17 male and 2 female (50.4±17.2 years) affected by ECH was followed during 26 active cluster periods (CP). Patients were recruited within 2 weeks from the beginning and more than a month before the expected spontaneous end of CP. Patients received 120 mg intramuscular MP daily for 4 days, then 80 mg/day for 3 days, then 40 mg/day for 3 days; concomitantly, oral V was started or incremented 40 mg daily up to 320-400 mg/day; a subsequent titration up to 520 mg/day has been recommended in selected cases.

Results: A complete resolution of CP was documented in 21/26 (81%) cases: 18/26 (69%) CP stopped within the first days from the start of MP/V administration; other 3/26 (12%) CP ended during the first month without any V increment; 5/26 (19%) CP failed to achieve complete resolution at one month. Among these, a 50% reduction of frequency and intensity of attacks was obtained with V escalation up to 560 mg/day, whereas the duration of the CP was comparable to previous ones.
When stratified according to the initial V dose (<400 vs ≥400 mg/day, 11 vs 15 CP), complete response at one month was observed in 5/11 CP (45%) and in 10/15 CP (67%) respectively, suggesting a trend toward higher efficacy with higher V starting doses.

Conclusions: In our previous study the combination of high-dose intravenous MP and of oral V proved crucial in the stopping of CP, with a higher rate of positive results than those reported in the literature either with the combination of low doses of MP and V, or with a high-dose MP or V administered alone. In this preliminary study, the combination of high-dose intramuscular MP and oral V revealed similar efficacy to the combination of high-dose intravenous MP and of oral V, with the advantage of avoiding Day Hospital admission.



Early Reversal of Brain Sagging After Epidural Blood Patch in Spontaneous Intracranial Hypotension: Evidence from Basal Cistern Morphometry

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Background: Spontaneous intracranial hypotension (SIH) is characterized by cerebrospinal fluid (CSF) leakage leading to intracranial CSF volume depletion and downward displacement of the brain ("brain sagging"). Although epidural blood patch (EBP) is considered the first-line invasive treatment, the timing of anatomical reversal after EBP has not been systematically investigated. We describe two SIH patients demonstrating very early radiological improvement of brain sagging quantified by basal cistern morphometry.

Methods: Two women with definite spontaneous intracranial hypotension (SIH) were consecutively evaluated at the Intracranial Pressure Disorders Clinic, Headache Center, AOU Renato Dulbecco, Catanzaro (Italy) and underwent non-targeted lumbar epidural blood patch after unsuccessful conservative management. The first patient, aged 25 years, presented with severe orthostatic headache associated with neck pain, photophobia, phonophobia, nausea and aural fullness. The second patient, aged 63 years, developed orthostatic headache with cervical pain, vertigo and bilateral abducens nerve palsy causing diplopia. Pre-treatment brain MRI showed typical SIH findings, including diffuse pachymeningeal enhancement, bilateral subdural collections and marked brain sagging. Brain CT was performed the day after EBP in both patients, while one patient also underwent follow-up brain MRI 48 hours after treatment. Midsagittal measurements of the interpeduncular, prepontine and cisterna magna were obtained before and after EBP according to a previously described morphometric method (Table 1).

Results: Both patients experienced rapid resolution of orthostatic headache within 24 hours after EBP. Imaging obtained the day after demonstrated early upward repositioning of the brainstem with measurable enlargement of the basal cisterns compared with pre-treatment studies, indicating prompt reversal of brain sagging (Figure 1). In the patient who underwent MRI 48 hours after EBP, these findings were confirmed, despite persistence of residual subdural collections, suggesting that restoration of brain position may precede complete resolution of other SIH-related imaging abnormalities.

Conclusions: This case series provides preliminary evidence that reversal of brain sagging may occur within the first 24 hours following EBP. Quantitative assessment of basal cistern dimensions appears to be a simple, reproducible imaging biomarker for documenting early treatment response in SIH and may complement conventional MRI findings during post-treatment follow-up.

HEADACHES AND NEUROPATHIC PAIN

Trigeminal Neuralgia secondary to solitary pontine lesion: case series of a proposed new diagnostic entity

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Background: Trigeminal neuralgia associated with a solitary pontine lesion is a new, recently described entity, characterized by the radiological evidence of a single pontine T2-hyperintense lesion affecting the intraxial course of primary trigeminal afferents in patients without a diagnosis of white matter disease. Although this new entity has received increasing attention, its underlying pathophysiology remains poorly understood.

Methods: In this multi-centre, retrospective study, we set out to determine the occurrence of TN related to solitary pontine lesion providing a systematic description of clinical features and the neurophysiological evidence of trigeminal afferent disfunction.

Results: From total of 200 patients with a definite diagnosis of TN, solitary pontine lesion was identified in 5% of cases.

Conclusions: The application of trigeminal reflex testing revealed the damage of primary trigeminal afferents. The high frequence of refractoriness to first line-drugs and surgical treatment suggests a more severe phenotype in comparison with classical TN and the need of tailored treatment.



Neuropathic pain: the stigmata of migraine

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Background: Neuropathic pain depends on dysfunction/alteration along sensory pathways. Its pivotal feature is central sensitization generating semiotics as hyperalgesia/allodynia
Migraine (M) is a neuropathic pain in itself as stressed by our group since the beginning of 1980
Aim A) Possible existence in M of peculiar central set-up predisposing migraineurs to suffer from differently classified neuropathic pain both in cephalic and extra-cephalic areas. B) Possible analgesia of selective anti-primary headache drug in neuropathic acute pain in M via boosting action on maladaptative central plasticity, transitorily

Methods: Epidemiology: Cross sectional. Enrolled patients underwent eye ball enucleation or avulsion of 2 contiguous teeth or traumatic/surgical limb amputation
Clinical Pharmacology: Sumatriptan 6 mg subcutaneously in both a) pre-treatment argon laser trabeculotomy and b) post photorefractive keratectomy in M versus controls, rating 0-10 VAS
Statistic: T-Test, MANOVA, Prevalence Ratio, Poisson Regression

Results:
Deafferentation Pain in Cephalic-area

Eye ball enucleation-			PRs
M	(n = 89 age 6-55)	Controls (n= 101 age 7-56)	4.7
Phantom eye	56	14	
Avulsion 2 contiguous teeth			
M	(n = 190 age 19-60)	Controls (n= 230 age20-60)	infinity
Phantom Tooth	118	0	

Deafferentation Pain in Extra-Cephalic-area

Limb Amputation (traumatic/surgical) –Phantom limb			
M	(n = 459 age 19-50)	Controls (n= 441 age 18-53)	1.8
Phantom Limb	451	225	

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6 mg Sumatriptan versus no treatment

Sumatriptan Pre Argon-laser

M	n=26 age 60-65	Controls n=36 age 60-65	
VAS	6.2+1.8SD /1.1+1.3SD*	1.8+1.4SD/1.6+1.1SD	p> 0.0001

Sumatriptan 6mg Post Keratectomy

M	n= 26 age 30-32	Controls n=36 age 30-32	
VAS	8.2+3.6SD /1.2+1.5SD*	1.5+1.6SD/1.8+1.3SD	p>0.0001

Conclusions: The outcomes enlighten high scores of positive correlations for deafferentation pain some of which are not so frequent in Italy. The fact enhances positivity of relationships. Also, it is evident an "unexpected" analgesia induced by a selective anti M in acute neuropathic pain
All together the outcomes seemingly propose M sufferers are a "race" endowed with a peculiar "neuromatrix" characterized by central sensitization, hyperalgesia/allodynia which might be boosted acutely.



QZU® in the dissuasion of the misuse/abuse of analgesics in a group of patients with chronic migraine

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Background: One of the most interesting and studied properties of kudzu is its ability to alleviate addictions to smoking, alcohol and other substances thanks to the active ingredients contained in its roots.
The aim of the study is to demonstrate the efficacy of QZU®, at a dosage of 2 capsules/day, in the prophylaxis of chronic migraine with improper use/abuse of analgesics.

Methods: Between January and June 2025, 12 patients (all women) with chronic migraine were treated with QZU® 2 capsules/day for 2 months, recruited from various neurological outpatient facilities; all patients completed the diary and the data collection form (ICHD-III criteria).
Patients were evaluated at baseline and after 2 months of treatment for the number of attacks, migraine days and VAS (Visual Analogue Scale). Patient characteristics: 12 patients (mean age 37.8 (24-63) with chronic migraine (> 14 migraine days/month): the mean number of attacks/month was 7.2 (5-10), migraine days/month 17.4 (15-21) mean VAS 8.1 (7-10) and number of analgesics taken: 28 (18-40).

Results: QZU® was well tolerated: on a numeric scale of 1-10 the average score was 9.5 (8-10); patient compliance was excellent, no related side effects were reported. The results were significant: the average number of attacks/month was 3.6 (1-4), migraine days/month 9 (5-14), the average VAS 3.5 (2-5) and the number of analgesics taken 12 (6-14).

Conclusions: Our study, which confirmed preliminary data, clearly demonstrated the benefits, safety, and good tolerability of QZU® in the prophylaxis of chronic migraine.



Dolomy Fibro® in the prophylaxis of fibromyalgia syndrome: preliminary data from an observational study

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Background: The exact cause of fibromyalgia is unknown. It is believed to be multifactorial because several factors (biochemical, genetic, neurochemical, environmental, hormonal, psychological, etc.) are involved.
DOLOMYFibro® is a specific product for fibromyalgia. The active ingredients in Dolomy Fibro are: CRONILIEF® INDENA, CASPEROME® INDENA, Quercetin Phytosome® INDENA, Bromelain 2500 GDU, Coenzyme Q10, Zinc, Selenium.

Methods: As of May 31, 2026, three patients with fibromyalgia were recruited, treated with DOLOMYFibro® 1+1 capsules/day for 3 months, from a neurology clinic dedicated to fibromyalgia. Patients completed the Decalogue and the data collection form and were administered various questionnaires, including: FIQR (Fibromyalgia Impact Questionnaire Revised); PFS (Piper Fatigue Scale); DN4 (Neuropathic Pain); Quality of Life Questionnaire (SF-12), and VAS/NRS (Visual Analogue Scale/Numerical Rating Scale). Patients were evaluated at baseline and after 3 months of treatment.

Results: The three patients examined showed a mild-moderate improvement in the questionnaires they were administered, but the most interesting result was the improvement in the FIQR (Fibromyalgia Impact Questionnaire Revised) questionnaire. Based on the assigned score, fibromyalgia will be recognized as a chronic and disabling disease, limited to very severe forms. Treatment tolerability was excellent.

Conclusions: In conclusion, based on the limited preliminary data, it can be stated that Dolomy FIBRO capsules can be used to treat the symptoms of fibromyalgia syndrome, even in the medium to long term, due to their efficacy and tolerability. The possibility of combining Dolomy FIBRO with other types of pharmacological and non-pharmacological treatments needs to be tested.



Efficacy of Repetitive Great Occipital Nerve Blocks in Episodic Cluster Headache: A Retrospective Real-World Study from a Tertiary Headache Center

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Background: Cluster headache (CH) is one of the most severe forms of primary headache, characterized by excruciating unilateral pain and autonomic symptoms. While preventive medications require weeks to titrate, rapid transitional therapies are crucial to provide immediate relief. Greater occipital nerve (GON) blocks have emerged as a valuable short-term intervention; however, evidence regarding standardized repetitive protocols in real-world tertiary care settings remains to be fully elucidated.

Methods: we collected the data of 106 episodic cluster headache patients (58.0□14.1 years old) treated with great occipital nerve blocks from January 2012 to march 2026 in our headache tertiary center (ASUFC, Ospedale S. maria della misericordia Udine, Clinica Neurologica). Each patient was treated with 4 GON nerve blocks (Bupivacaine 30mg and triamcinolone 20mg), each one spaced one week apart.
We collected demographic data at baseline and, at each assessment, data regarding mean attack intensity, number of attacks per week, and attack duration were also collected. FSS, ESS, PSQI scales at the baseline and after the fourth treatment was also collected. The mean bout duration was 49.3□19.0 days, the patients were treated 21.4□12.5 days after the start of the bout. 51 patients were on medications (verapamil or corticosteroids).

Results: The repeated measure anova showed a significant reduction in headache attacks per week mean headache NRS intensity, and mean duration of the headache attacks ($p<0.001$). There was a significant improvement in sleep quality (PSQI 7.1□4.3 vs5.2□3.4, p 0.005), while there were no significant differences regarding ESS and FSS scales. No differences were found between the patients on medication and those drugs free.

Conclusions: A protocol of four weekly great occipital nerve blocks is highly effective in reducing the frequency, intensity, and duration of attacks in patients with episodic cluster headache, while significantly improving sleep quality. Notably, its efficacy is independent of concomitant preventative medications, supporting its use as a powerful transitional or standalone treatment in tertiary care.



Dolomy Fibro® in the Treatment of Orofacial Pain: Case Report.

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Background: The nasal and oral mucosa, the tongue, and the teeth are structures that can cause facial pain, as can dental treatments that lead to the onset of so-called "atypical" facial pain. The IHS classification establishes the diagnostic criteria in Chapter 13, dedicated to Cranial Neuralgia and Central Facial Pain.

Methods: A 67-year-old female patient presented with orofacial pain and right hemifacial edema following a right upper premolar avulsion due to a granuloma. Treatment with Dolomy FIBRO® 1+1 capsules/day was initiated to control the edema and orofacial pain, with neuralgic symptoms affecting the second branch of the right trigeminal nerve. The patient kept a diary of her clinical progress and, in particular, monitored her pain using a VAS (Visual Analogue Scale). Efficacy and tolerability data were also collected.

Results: The patient reported a reduction in edema after 7 days, with its elimination after 14 days of administration of Dolomy FIBRO® 1+1 capsules/day. Pain intensity in the first 14 days was significantly reduced (VAS: 8 at T0; VAS: 2 at T1 – 14 days). The patient continued therapy with Dolomy FIBRO® 1+1 capsules/day for another 60 days until the orofacial pain resolved.

Conclusions: As can be seen from the case report, Dolomy FIBRO® cps can be used to treat orofacial pain, especially in the presence of edema. Future research will explore the possibility of combining Dolomy FIBRO® cps with antiepileptic drug therapy, which is commonly used to treat typical and atypical neuralgia.



DOLOMY FIBRO® in the Treatment of Fibromyalgia Syndrome: Case Report.

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Background: The exact cause of fibromyalgia is unknown. It is believed to be multifactorial because several factors (biochemical, genetic, neurochemical, environmental, hormonal, psychological, etc.) are involved.

Methods: A 33-year-old female patient with fibromyalgia syndrome. Tests: Blood tests with inflammatory markers (ESR, CRP, C3, C4) and autoantibodies (ENA, ANA, p-ANCA), rheumatoid arthritis test: all negative. Clinical psychological interview + projective personality tests: anxious symptoms in a patient with a personality profile characterized by a tendency to project a conformist image of herself and to express her conflicts in physical forms. She responded positively to 6 out of 10 questions on the Fibromyalgia Syndrome Questionnaire (Decalogue). The patient kept a diary on her clinical evolution and, in particular, monitored her pain using the VAS (Visual Analogue Scale). Data on efficacy and tolerability were also collected. The patient was administered Dolomy Fibro capsules 1+1 capsules/day away from meals for 3 months.

Results: The patient reported a reduction in fibromyalgia symptoms, with elimination of asthenia and a 70% reduction in muscle tension, chronic and widespread pain, and hyperalgesia, as well as an improvement in sleep disturbances (Phase II). Pain intensity was significantly reduced (VAS: 9 at T0; VAS: 2 at T1 – 90 days). The patient continued therapy with Dolomy FIBRO 1 capsule/day.

Conclusions: As can be seen from the description of the case report, Dolomy FIBRO can be used in the treatment of the symptoms of fibromyalgia syndrome, even in the medium-long term due to its efficacy and tolerability.



REFRACTORY MIGRAINE: HOW TO PREDICT AND TREAT IT

Unraveling the Complexity of Medication-Overuse Headache: Clinical and Behavioral Predictors of 12-Month Outcomes.

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Background: Medication-overuse headache (MOH) is a complex neurological condition that, once treated, is associated with relapse risk. This study aims to identify factors associated with relapse into MO at 12 months.

Methods: We analyzed a single-center cohort of 217 MOH patients treated in our Headache Unit with a detoxification protocol. Twelve-month follow-up data were available for 175 patients. Categorical variables were compared using Fisher's exact test, with odds ratios (ORs) reported where appropriate, while continuous variables were compared using the Mann–Whitney U test and summarized as median and interquartile range or mean ± standard deviation. The Holm correction was applied separately to the multiple univariate comparisons performed for each outcome. Two multivariable logistic regression models identified factors independently associated with relapse into medication overuse and chronic headache recurrence. The models included age, sex, duration of chronicity, a medium/high Leeds Dependence Questionnaire (LDQ) score, depressive spectrum, and previous exposure to advanced preventive therapies. Multivariable analyses used a complete-case approach, and adjusted odds ratios (aORs), 95% confidence intervals (CIs), and p-values were reported.

Results: A total of 175 patients (94.09%) completed the one-year follow-up (150 females and 25 males with a mean age of 48.14±12.62 years). At this point, 49 patients (28.0%) relapsed into medication overuse (MO), while 71 (40.6%) experienced a chronic headache pattern recurrence. Multivariable analysis showed MO relapse was independently associated with a longer duration of chronicity (aOR 1.069 per year; 95% CI 1.02–1.12; p=0.0085), a medium/high LDQ score (aOR 3.229; 95% CI 1.43–7.27; p=0.0047), and previous exposure to advanced preventive therapies – botulinum toxin A, anti-CGRP mAbs, gepants (aOR 2.870; 95% CI 1.22–6.77; p=0.016). For chronic headache recurrence, a longer duration of chronicity was the only independently associated factor (aOR 1.044 per year; 95% CI 1.00–1.09; p=0.0484).

Conclusions: Relapse into MO at 12 months is driven by chronicity duration (cross-cutting risk of persistence), a medium/high LDQ score (indicating pharmacological dependence), and exposure to advanced therapies (a marker of clinical severity and refractoriness). The identified complex profiles require a multidimensional approach that includes detoxification, patient education, preventive treatment, structured monitoring, and psychological support.



The patient journey of resistant and refractory migraine: results from the refine study

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Background: Migraine patients often experience long treatment journeys marked by multiple preventive treatment failures. We aimed to analyze treatment failures across the three European Headache Federation (EHF) categories: resistant migraine (ResM), refractory migraine (RefM), and non-resistant/non-refractory migraine (NRNRM).
Methods: The multicenter, prospective, international REFINE study evaluated the EHF definitions of resistant and refractory migraine in a real-world setting. The number and sequence of preventive treatment failures were assessed and compared among patients with NRNRM, ResM, and RefM.
Results: Among 689 participants, 570 (82.8%) were women, with a median age of 47 years (IQR 38–56). Overall, 73 patients (10.4%) had RefM, 262 (38.0%) ResM, and 354 (51.4%) NRNRM. Patients with RefM and ResM had a longer migraine history than those with NRNRM (median 34, 31, and 24 years, respectively; $p<0.001$).
The median number of preventive treatment failures was 8 in RefM, 4 in ResM, and 2 in NRNRM ($p<0.001$). In the ResM group, 4.7% had 0–2 failures, 63.0% had 3–5, and 32.3% had >6 failures. Corresponding proportions in RefM were 0.0%, 12.0%, and 88.0%, while in NRNRM they were 51.2%, 37.2%, and 11.8%.
The most common first treatment failure was amitriptyline (38.2% of ResM, 32.8% of RefM, and 39.0% of NRNRM patients), followed by topiramate (25.8%, 28.4%, and 23.9%, respectively).
Discussion: These findings highlight the prolonged treatment journey experienced by patients with resistant and refractory migraine and underscore the need for earlier and more effective preventive therapies.
Conclusions: Although preventive treatment failure burden was greatest in ResM and RefM, patients with NRNRM also frequently experienced multiple treatment failures, reflecting a substantial unmet need across the migraine spectrum.



The role of gut microbiota in migraine subjects treated with anti-CGRP monoclonal antibodies: results the SPHERA project

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Background: Gut microbiota plays an important role in the pathophysiology of different neurological disorders via the gut-brain axis. Approximately 40% of migraine subjects do not achieve a meaningful benefit with anti-CGRP monoclonal antibodies (mAbs). We hypothesized that gut microbiota composition may differ between Responders and Non-Responders to mAbs and serve as one of the determinants of therapeutic outcome.

Methods: We enrolled 93 individuals treated with mAbs (age 41.2 ± 13.3 years) 82.9% females, with 15.0 ± 6.8 monthly migraine days (MMDs) at baseline and a previous failure of 3.1±1.3 preventive medication classes. Responders were defined as subjects achieving at least 50% reduction in MMDs after a 3-moth treatment with mAbs. Fecal samples were collected before mAbs treatment and analyzed by means of 16S rRNA gene sequencing, followed by the evaluation of alpha and beta diversities and the application of the ANCOM-BC2 statistical approach.

Results: After a 3-month treatment period with mAbs, 48 participants qualified as Responders and 45 as Non-Responders. Regarding overall microbial diversity, no differences were observed between the two groups, with comparable alpha-diversity and beta-diversity profiles. However, the ANCOM-BC2 approach demonstrated specific alteration between Responders and Non-Responders in gut microbiota composition at both the genus and species levels. Specifically, at the species level, Responder subjects exhibited a significantly higher abundance of Coprococcus eutactus (LogFC 1.89, $p < 0.001$), Marseilla massiliensis (LogFC 2.15, $p < 0.001$), Paraprevotella xylaniphila (LogFC 2.08, $p < 0.001$), Parasutterella secunda (LogFC 1.95, $p < 0.001$), Clostridium carnis (LogFC 1.43, $p = 0.001$). Conversely, Responder subjects showed a lower abundance of Rikenellaceae (LogFC -3.45, $p < 0.001$), Megamonas rupellensis (LogFC -2.24, $p < 0.001$), Coriobacteriia (LogFC -1.41, $p < 0.001$), Megasphaera massiliensis (LogFC -2.08, $p < 0.001$).

Conclusions: Future mAbs Responders exhibited a distinct microbiota composition associated with an anti-inflammatory profile, featuring a significant enrichment of butyrate-producing bacteria; by contrast, Non-Responders were characterized by a predominantly pro-inflammatory intestinal microbiome. These differences suggest that gut microbiota may act as a biological regulator capable of modulating the therapeutic response. Targeted interventions aimed at restoring intestinal eubiosis may represent a strategy to enhance the clinical response to mAbs.



Refractoriness of chronic migraine: possible risk factors and some way-out

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Background: Migraine (M) refractoriness might depend on prolonged exposure to receptor agonist/ antagonist. The condition results in compensatory changes in receptor number/affinity, say up or down-regulation. The latter leads to tolerance and partakes into iatrogenic refractoriness.
Aim: Non-iatrogenic refractoriness might be linked to epigenetic-polygenic factors routed by stress

Methods: Epidemiology: cross-sectional observation in Italian ethnicity subjects: 270 chronic refractory M, 270 severe M without aura (7-8 attacks/month), 274 controls, recruited in religious, cultural circles
Biochemistry: Samples obtained from 75 chronic M (age mean 35.2+2.8SD) versus 80 controls (age 35.3+2.9SD). Sampling follows 7-days wash-out or 2-months wash-out in case of anti-CGRP mAbs, Rescue Treatment: Diclofenac orally or muscularly
Statistic: T-Test, MANOVA, Prevalence Ratio, Poisson Regression

Results:
Epidemiology

	Controls	Refractory Chronic M	Severe M	PRs
Age mean	33.4+4.3	33.5+5.4	33.2+4.8	
PTDS (PCL-5 cut-off 43 IES cut-off 33)	2%	85% *	17%	4.7
Obesity – BMI >35	15%	70% *	28%	2
Eating Disorders Eating disorder Scale cut-off 3) Eat 26 cut-off 28)	3.3%	86% *	15%	2.6
Severe Insomnia (ISI test cut-off 22)	10%	90% *	40%	1.8

Biochemistry: basic of bio-rhythm and stress

	Controls	Refractory Chronic M
Serum hr8.00 a.m.		
Cortisol µg/dL	6.8+3.3SD	5- 122 interindividual variations >20 times
Melatonin pg/mL	28.5+6.2SD	11.3+4.8SD p>0.0001
Urine 8 am-8 pm 6-sulfatoxymelatonin		
(Elisa) ng/mL	47.5+19SD	4-48 inter-individual variations >10 times

Conclusions: PTSD and Eating disorders are not frequent pathologies, say >5% in general population, and have high score in positive correlations, which seemingly indicate they are real risk factors. Both significances of positive ratios of relationships and very wide inter-individual variations of both cortisol and 6-sulfatoxymelatonin seem to indicate a role for stress-routed epigenetic-polygenic factors in chronic M refractoriness.



Connectomics and Personality Profiles in Refractory Migraine

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Background: Chronic non-responsive migraine (CRM) is a neurological syndrome characterized by headache attacks lasting more than 15 days per month for at least three consecutive months, unresponsive to both traditional and innovative pharmacological treatments (diagnostic criteria of the International Classification of Headache Disorders, ICHD-beta III revision). Although the etiology is multifactorial, psychological factors and personality traits appear to play a crucial role in the chronicity of pain symptoms and are co-responsive to medication failure. This study aims to evaluate the personality profile and morphostructural study of the brain using 3 Tesla brain MRI (connectomics) in a sample of patients with refractory migraine who were unresponsive to both traditional and innovative medications (Botox, Monoclonal Antibodies, and Gepants) on prophylaxis, and to explore their correlation with disease severity.

Methods: Starting from 1 June 2026, patients affected by ECNR will be recruited to participate in a single-centre observational study who attend the Regional Headache Centre A.O. U. R. Dulbecco". Twenty non-responders participating in the study who meet the ICHD-beta diagnostic criteria for ECNR will be recruited; the diagnosis was performed at the Headache Center of our hospital (DH Therapeutic Drug Dependence and Treatment with Monoclonal Antibodies and Gepants). The identified patients will be sent to the neuroimaging unit of the IBSBC-CNR at Mater Domini in Catanzaro for a 3Tesla MRI examination. They will undergo a psychodiagnostic assessment of personality traits using validated psychometric tools (MMPI-2, PID-5). In addition, 20 healthy patients will be recruited who will undergo brain MRI and psychological testing for a case-control comparison.

Results: The sample analysis will assess the significant prevalence of specific personality traits, with particularly high scores in some dimensions and a correlation with the connectome characteristics of the reward system areas of ECNR patients. with a group of 20 healthy subjects.

Conclusions: The results suggest that specific personality profiles not only coexist with refractory migraine but can negatively influence clinical outcome and response to pharmacological treatments. Identifying these characteristics early would allow us to move beyond the traditional, purely biomedical approach, supporting the integration of psychotherapy pathways to improve the clinical outcome of these complex patients. Furthermore, the connectomic study will provide us with potential indications of reward system dysfunction.



COGNITIVE DEFICIT AND MIGRAINE

Characterizing Social Cognition Across Migraine Frequency Using the Story-Based Empathy Task and the Reading the Mind in the Eyes Test

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Background: Social cognition impairments have been increasingly reported in migraine, particularly in Chronic Migraine (CM), although their profile remains poorly characterized. The Story-Based Empathy Task (SET) has never been investigated in migraine. This validated non-verbal measure assesses cognitive and affective Theory of Mind (ToM) including a Causal Inference control condition. Our study investigated social cognition across migraine frequency groups combining the SET with the Reading the Mind in the Eyes Test (RMET) to explore distinct dimensions of Theory of Mind and their relationship with migraine burden.

Methods: participants were classified according to monthly migraine days (MMD), into Low-Frequency Episodic Migraine (LFEM; 0-7 days, n=26), High-Frequency Episodic Migraine (HFEM; 8–14 days, n=12), and Chronic Migraine (CM; 15 days, n=22). Group comparisons were performed using non-parametric tests, associations with MMD were explored using Spearman's correlations, and multivariable regression models adjusted for age and education were fitted. Performances were also compared with published normative data.

Results: SET data were available for 53 patients and RMET data for 44 patients. Among the SET domains, Intention Attribution showed the strongest association with migraine severity, correlating negatively with MMD ($\rho = -0.338$, $p = 0.015$), and remaining independently associated with MMD after adjustment for age, education, and HIT-6 score ($\beta = -0.059$, $p = 0.042$). Emotion Attribution was not associated with MMD, whereas Causal Inference scores were lower than published normative values in HFEM and CM. RMET performance was lower in CM than in HFEM (20.9 ± 3.8 vs 23.7 ± 3.7, $p = 0.045$). Compared with normative data, Intention Attribution showed a progressive decline from LFEM to HFEM and CM, whereas Emotion Attribution remained comparable with normative values. Overall, both continuous and categorical analyses consistently suggested poorer cognitive Theory of Mind performance with increasing migraine burden.

Conclusion: Preliminary findings suggest a differential Theory of Mind profile across migraine frequency groups. Although previous studies have mainly emphasized affective ToM alterations, Intention Attribution emerged as the component most closely associated with migraine frequency, possibly reflecting the greater executive demands of cognitive ToM. Larger studies are needed to confirm our findings and better define the social cognition profile across the migraine spectrum.



Effect of Atogepant on Cognitive Function Following Acute Treatment of Migraine Across Multiple Attacks: Results from the ECLIPSE trial

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**This individual has been added to this publication author by-line, with the permission of the original authors, for the express purpose of conducting the presentation at a local congress or in a local language. He did not contribute to the content of the publication.*

Background: Atogepant is approved for the preventive treatment of migraine in adults and has recently demonstrated its efficacy and safety for the acute treatment of migraine. This analysis evaluated the impact of atogepant 60mg administered as needed (PRN) for acute treatment of migraine on cognitive function assessed by the ability to think clearly.

Methods: ECLIPSE was a double-blind (DB), placebo-controlled, multiple-attack, crossover trial evaluating atogepant's efficacy, safety, and tolerability for acute migraine treatment. Adults with 2-8 monthly moderate-to-severe attacks were randomised to receive atogepant for three qualifying attacks and placebo for one attack during the up to 16-week DB period. Cognitive function scale is a single-item, patient-reported questionnaire measuring participants' difficulty in ability to think clearly, rated from 0 (not difficult at all) to 3 (very difficult). The proportion of participants achieving the ability to think clearly at 2-, 4-, and 8-hours postdose across attacks 1-4 was an additional (exploratory) efficacy endpoint. Data for atogepant and placebo are presented with nominal P-values.

Results: Atogepant treatment resulted in a nominally significant higher proportion of participants achieving the ability to think clearly compared with placebo as early as 2-hours postdose in the first treated attack (OR: 1.78); this effect increased over time through 4- and 8-hours postdose (OR: 3.39, 3.73, respectively). A similar reliable response was observed across attacks 2-4 ().

Conclusions: A greater proportion of participants treated with atogepant achieved the ability to think clearly compared to placebo as early as 2-hours and up to 8-hours postdose across multiple attacks.



Neuropsychological and psychological characterization of patients with migraine: preliminary results from the CogMig Study

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Background: Migraine is a complex neurological disorder frequently associated with cognitive difficulties and psychological symptoms, which may contribute to disease burden. This observational study aimed to investigate the cognitive and psychological features associated with migraine.

Methods: 39 patients with a confirmed diagnosis of migraine and at least four attacks per month attending the Headache Center of the Carlo Besta Neurological Institute were enrolled. A multidimensional assessment was performed using validated instruments assessing migraine-related disability and impact (MIDAS, HIT-6), anxiety and depression (HADS), pain catastrophizing (PCS), worry (PSWQ), coping strategies (COPE-NVI), sleep quality (PSQI), and global mental state (GEMS). The assessment have been performed in inter-ictal migraine period (48 hours).

Results: Participants had a mean age of 43.03 years (SD = 12.6); 36 were women (92.3%). The sample showed good cognitive functioning (89.12 ± 6.66), and all participants fell within the normal GEMS range. Patients were further divided into those with performance below the expected level (GEMS−; n = 15) and those with performance in line with or above expectations (GEMS+; n = 24) based on GEMS scores adjusted for demographic profile and cognitive reserve. The GEMS− group showed significantly lower performance in immediate recall (p = .023), months backwards (p = .001), the clock drawing test (p = .026), and metaphor comprehension (p = .008). In the overall sample (n = 39), high levels were observed for HADS-A (8.59 ± 4.17), PCS (25.41 ± 11.81), PSWQ (51.33 ± 12.0), and PSQI (8.13 ± 3.83), alongside a clinically significant headache impact (MIDAS: 36.21 ± 29.0; HIT-6: 65.36 ± 6.79)

Conclusions: The results showed that a subgroup of patients (GEMS−) exhibited lower-than-expected performance in specific cognitive domains (immediate verbal recall, attention–executive functions, and pragmatic–abstract processing) despite overall cognitive functioning within the normal range. The comparable clinical and psychological profiles of the GEMS− and GEMS+ groups indicate that cognitive difficulties may reflect multifactorial mechanisms beyond the assessed variables, suggesting a potentially underrecognized burden of migraine.



Impact of Prophylactic Treatment on Cognitive Function in Migraine: a clinical evaluation using the I-MIG-SCOG Scale

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Background: Migraine is frequently accompanied by cognitive issues that significantly reduce patients' quality of life. In this regard, we aimed to evaluate the subjective cognitive burden related to migraine in a real-world cohort of patients attending a specialized headache center under advanced prophylaxis, and to analyze the correlation between the I-MIG-SCOG scale score and the residual monthly attack frequency.

Methods: A cross-sectional analysis was conducted based on data recorded during outpatient follow-up visits in migraine patients undergoing prophylactic treatment with subcutaneous monoclonal antibodies or gepants. All migraine patients who had a fully completed 9-item I-MIG-SCOG scale at their last visit were included. The severity of the subjective cognitive impairment was quantified using the scale's total score (range 0–18) and correlated with the monthly headache frequency recorded at that visit.

Results: The preliminary analysis included 62 patients. The data confirmed a clear positive linear correlation between a high residual attack frequency and a more severe cognitive burden. Patients with a higher frequency of attacks per month showed significantly greater cognitive dysfunction on the I-MIG-SCOG scale (characterized by severe concentration deficits, slowed problem-solving, and anomia), with peak scores ranging between 10 and 15 points. Conversely, patients who achieved optimal clinical control thanks to prophylaxis, with minimal residual frequency (0 to 2 attacks/month), recorded minimal or zero I-MIG-SCOG scores, ranging between 0 and 3 points.

Conclusions: The preliminary results of this study consolidate the evidence that the transient attentive and executive difficulties associated with migraine are strictly dependent on the clinical control of attack frequency. An effective prophylactic therapy not only reduces physical pain but is also associated with a drastic reduction in subjective cognitive deficit, substantially improving the patient's global functional status.



HEADACHES AND CENTRAL SENSITIZATION DISORDERS

Bilateral Classical Trigeminal Neuralgia with Concomitant Continuous Pain in Crouzon Syndrome: A Case Report

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Background: According to ICHD-3 criteria, classical trigeminal neuralgia with continuous pain is characterized by recurrent unilateral paroxysms accompanied by persistent background pain within the affected trigeminal distribution. Peripheral and/or central sensitization may underlie the continuous pain component. Bilateral involvement is exceedingly rare, particularly in the context of craniosynostosis. Crouzon syndrome is a rare syndromic craniosynostosis caused by mutations in FGFR2 or FGFR3. Proposed mechanisms for trigeminal nerve involvement include skull base and posterior fossa abnormalities, hydrocephalus, intracranial hypertension, and vascular variants, all of which may lead to nerve distortion or compression.This case is notable for subsequent contralateral involvement of the second trigeminal branch, supported by MRI findings.

Case Report: A 30-year-old woman with Crouzon syndrome underwent right ventriculoperitoneal shunting for hydrocephalus at 6 months of age and a Le Fort III advancement osteotomy with external distraction at age 10 due to severe left visual impairment. Since 2019, she had experienced persistent right maxillary pain associated with gingival swelling and hyperemia in the setting of diffuse periodontal disease, impacted third molars, and prior maxillary fixation hardware. The pain was continuous, exacerbated by chewing and speaking, and partially responsive to pregabalin. In 2023, hardware removal led to a two-month remission. The patient first presented to our clinic in September 2024, when pregabalin was increased to 150 mg/day. In February 2026, she reported new pain involving the contralateral maxillary division; duloxetine 60 mg/day was added.Blink reflex testing was normal. Brain MRI showed ventricular asymmetry, possible aqueductal stenosis, marked posterior fossa hypoplasia, and severe narrowing of the prepontine cistern, where the trigeminal nerves were poorly visualized and partially indistinguishable from adjacent vessels, particularly the right superior cerebellar artery. Treatment was subsequently switched to carbamazepine, with only mild clinical benefit.

Conclusions: This case highlights the diagnostic complexity of facial pain in syndromic craniosynostosis. Although anatomical abnormalities in Crouzon syndrome may predispose to trigeminal neuralgia, bilateral involvement has not been previously reported.



Baseline sleep quality predicts differential response to migraine prophylaxis: an interaction analysis on mood outcomes

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Background: Preventive migraine treatments may differentially affect psychiatric comorbidities, such as anxiety and depression. However, comparative data across oral preventive therapies, botulinum toxin type A (BoNT-A), and anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) are lacking. We hypothesized that baseline sleep quality may modify the relative effectiveness of these therapeutic classes on mood outcomes, particularly in patients with comorbid insomnia.

Methods: We prospectively evaluated a cohort of 148 patients initiating preventive migraine treatment at baseline and after 6 months of therapy. Patients were grouped according to the preventive treatment received: antidepressants (amitriptyline, n=15), antiseizure medications (topiramate, n=16), beta-blockers (propranolol, n=14), calcium channel blockers (flunarizine, n=12), BoNT-A (n=21), and anti-CGRP monoclonal antibodies (erenumab, n=21; fremanezumab, n=22; galcanezumab, n=27).
Changes in anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) and its anxiety (HADS-A) and depression (HADS-D) subscales, as well as the Beck Depression Inventory-II (BDI-II). Multivariable linear regression models were used to examine the interaction between treatment class and baseline Pittsburgh Sleep Quality Index (PSQI) score, adjusting for baseline mood scores, headache frequency, sex, and age. Analyses were further stratified according to a clinically relevant PSQI cutoff (≥10 vs. <10).

Results: After 6 months, a significant interaction between oral preventive therapies and baseline PSQI was observed for BDI-II scores ($\beta = -0.93$, $p = 0.029$), with a trend toward significance for HADS-D ($\beta = -0.37$, $p = 0.092$). For each one-point increase in baseline PSQI score, oral preventive therapies were associated with an additional 0.93-point reduction in BDI-II score compared with anti-CGRP mAbs. Among patients with insomnia (PSQI ≥10), oral preventive therapies produced greater improvements in depressive symptoms than anti-CGRP mAbs (ΔBDI-II: −10.7 vs. −6.4; $p = 0.05$). Conversely, among patients without insomnia, anti-CGRP mAbs yielded greater improvements (ΔBDI-II: −4.7 vs. +1.9 with oral preventive therapies; $p = 0.006$; ΔHADS-D: −2.0 vs. +2.1; $p = 0.001$).

Conclusions: Baseline sleep quality significantly modifies the comparative effectiveness of preventive migraine treatments on mood outcomes. In patients with good sleep quality, anti-CGRP monoclonal antibodies were the most effective treatment for improving all mood-related outcomes.



Sleep-circadian mechanisms and CGRP signaling in TACs and hypnic headache: a systematic review

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Background: Trigeminal autonomic cephalalgias (TACs), particularly cluster headache (CH), are closely linked to sleep, circadian rhythmicity, and hypothalamic regulation. Hypnic headache, although not classified among TACs, is also defined by an exclusive sleep-related occurrence and probable hypothalamic involvement. Calcitonin gene-related peptide (CGRP) has a well-established role in CH pathophysiology and may represent a key mediator connecting trigemino-autonomic activation with sleep–circadian dysregulation. However, the extent to which CGRP interacts with sleep and circadian mechanisms across TACs and hypnic headache remains incompletely defined.

Methods: We conducted a systematic review of PubMed/MEDLINE, Scopus, and Web of Science from inception to April 2026. Search terms combined CGRP, CGRP-targeted therapies, TACs, cluster headache, paroxysmal hemicrania, SUNCT/SUNA, hypnic headache, sleep, insomnia, and circadian rhythm. Original studies, randomized trials, observational studies, case series, case reports, mechanistic studies and neuroimaging studies, reporting data on CGRP, sleep, or circadian outcomes were considered eligible. This systematic review was conducted in accordance with PRISMA 2020 recommendations. Given the heterogeneity of study designs, populations, and outcomes, no quantitative synthesis was performed.

Results: Overall, 18 original studies were included. Evidence for the CGRP–sleep/circadian interface was strongest in CH, where CGRP-mediated trigemino-autonomic activation overlaps with nocturnal attack clustering, circadian and circannual rhythmicity, impaired sleep efficiency, altered melatonin and cortisol rhythms, and posterior hypothalamic activation. CGRP levels increase during CH attacks and decrease after effective acute treatment, supporting its role in attack generation within a temporally regulated hypothalamic–trigeminal network. However, whether CGRP directly modulates sleep or circadian stability remains unknown, as trials of CGRP-targeted therapies have not systematically assessed polysomnography, actigraphy, or circadian biomarkers. For paroxysmal hemicrania and SUNCT/SUNA, evidence was indirect and mainly based on shared hypothalamic and trigemino-autonomic involvement. For hypnic headache, no direct CGRP data were identified.

Conclusions: Current evidence supports a shared sleep-circadian-trigeminal framework linking TACs and hypnic headache, with CGRP acting as a potential downstream mediator. However, its direct role in sleep-circadian regulation remains insufficiently demonstrated. Future studies should systematically integrate objective sleep measures and CGRP assays to clarify whether CGRP contributes only to attack generation or also to sleep-circadian dysregulation in TACs and related sleep-linked headache disorders.



Preliminary Validation of the Italian Version of the Utah Photophobia Symptom Impact Scale (UPSIS-2) in Patients with Migraine

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Background: Photophobia is one of the most debilitating non-pain symptoms of migraine attack and may persist beyond the ictal phase. Despite its clinical and research relevance, photophobia is often assessed using dichotomous questions, which may underestimate its functional burden. The Utah Photophobia Symptom Impact Scale version 2 (UPSIS-2) was developed to provide a multidimensional assessment of photophobia severity and its impact on daily functioning. To date, no Italian version of the scale is available. This study aims to perform a preliminary validation of the Italian UPSIS-2.

Methods: The UPSIS-2 was translated and culturally adapted into Italian following International Guidelines by two independent bilingual translators and evaluated in adults with episodic (EM) or chronic migraine (CM) enrolled in the Italian Headache Registry (RICe). Internal consistency was assessed using Cronbach's alpha and McDonald's omega. Structural validity was investigated through exploratory factor analysis (EFA), Kaiser–Meyer–Olkin (KMO) measure and Bartlett's test. Convergent validity was examined using Spearman's correlations with monthly headache days (MHDs), headache-related disability (MIDAS), headache impact (HIT-6) and mean pain intensity (NRS). Known-groups validity was tested across clinical migraine subgroups. Sensitivity analyses evaluated the contribution of the two optional items (items 16–17).

Results: The study included 110 participants (mean age 40.1±12.5 years); 84.5% were female, 32.7% had CM. The mean UPSIS-2 score was 27.4±17.5. Internal consistency was excellent (Cronbach's α=0.95; McDonald's ω=0.96), with no improvement after item removal. Structural analyses supported a predominantly unidimensional construct (KMO=0.92; Bartlett's $\chi^2(105)=1573.17$, $p<0.001$). UPSIS-2 scores showed moderate correlations with MIDAS ($\rho=0.34$, $p<0.001$), MHDs ($\rho=0.34$, $p<0.001$), and HIT-6 ($\rho=0.26$, $p=0.005$), whereas no association emerged with mean NRS. Patients with CM reported higher UPSIS-2 scores than patients with EM (35.0±17.3 vs 23.7±16.5; $p=0.002$). Sensitivity analyses showed comparable performance with and without optional items.

Conclusions: The Italian UPSIS-2 showed excellent internal consistency and preliminary evidence of structural and convergent validity. Higher UPSIS-2 scores in CM and associations with migraine frequency and disability support the use of this scale for multidimensional assessment of photophobia in clinical practice and research. Further studies should evaluate its test–retest reliability and responsiveness.



Integrated multidisciplinary approach in migraine management: a case report

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Background: Migraine is a multifactorial neurological disorder in which congenital predisposition and environmental factors contribute to neurological dysfunction and potentially disabling headache attacks. Alongside pharmacological therapies, there is growing interest in multidisciplinary approaches aimed at managing modifiable factors associated with migraine. Chronic stress, persistent cognitive patterns, difficulties in emotional regulation, and dysfunctional lifestyle habits may contribute to the persistence of this condition by increasing susceptibility to stimuli involved in triggering and maintaining migraine attacks.

Methods: We report the case of a 43-year-old woman with a neurologist-confirmed diagnosis of migraine without aura and a 10-year history of the disease. At baseline, the patient reported daily background headache with migrainous features and moderate intensity, associated with 6–7 severe migraine attacks per month (Monthly Migraine Days [MMD] = 7), frequently leading to significant limitations in daily activities (MIDAS score: 48) and prolonged bed rest. Pain intensity was rated as 10/10 on the Visual Analogue Scale (VAS), while the monthly pain medication intake (MPI) was 27. The patient underwent a 5-month integrated multidisciplinary program including osteopathic treatment, nutritional assessment, individualized physical activity, neurocognitive education focused on emotional and behavioral factors, mindfulness, autogenic training, guided imagery, and home-based exercises. Preventive pharmacological therapy remained unchanged during the first three months and was subsequently reduced under neurological supervision.

Results: After the 5-month intervention, the patient showed complete resolution of the daily background headache and a marked reduction in severe migraine attacks. Pain intensity decreased from a VAS score of 10/10 to a mean VAS score of 4/10, while monthly pain medication intake decreased from 27 to 4. The patient also resumed physical activity, travelling, and social activities, with a substantial improvement in disability (MIDAS score: 5). Clinical benefits were maintained at the 6-month follow-up after completion of the multidisciplinary program.

Conclusions: This case suggests that an integrated multidisciplinary approach may represent a valuable supportive strategy in migraine management, being associated with reduced attack frequency and pain intensity, lower use of acute medications, decreased migraine-related disability, and improved quality of life.



Relationship between pain processing and thalamocortical activity: a study of high-frequency somatosensory oscillations and pressure pain threshold.

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Background: It has been hypothesised that the thalamocortical network plays an important role in processing and integrating nociceptive information from the cranial meninges with sensory information from the skull and pericranial tissues. To test this hypothesis, we investigated whether thalamocortical activity levels correlate with pressure pain thresholds (PPTs) in cranial and pericranial muscles in patients with episodic migraine without aura (MO). Somatosensory evoked potentials (SSEPs) were recorded during the interictal period, and subjective pressure pain sensitivity was quantified using an algometer.

Methods: Twenty-three patients with MO and 29 healthy subjects (HS) underwent SSEP recording after median nerve stimulation at the wrist. During the same session, PPTs were assessed in all participants using a digital algometer at six bilateral sites: the frontal, temporal, masseter, semispinalis capitis, sternocleidomastoid, and trapezius muscles. After digital filtering, we analysed the amplitudes of pre-synaptic (reflecting thalamocortical activation) and post-synaptic (reflecting primary cortical activation) high-frequency oscillatory (HFO) SSEP activity.

Results: Compared with HS, patients showed lower PPTs in all muscles bilaterally, except the trapezius, as well as reduced thalamocortical high-frequency activity and habituation. In HS, HFO cortical activity correlated positively with PPTs in the right semispinalis capitis and left sternocleidomastoid muscles. In the same group, habituation correlated negatively with PPTs in the left masseter and sternocleidomastoid muscles. By contrast, no significant correlations were found in patients with MO.

Conclusions: Our results suggest that, in both HS and patients with MO, HFO thalamocortical drive does not contribute to pressure pain sensitivity in cranial and pericranial muscles. Primary cortical activation and habituation appear to influence PPT levels in HS, but not in patients with migraine during the pain-free phase.



DIAGNOSTIC ALGORITHMS AND ARTIFICIAL INTELLIGENCE

A practical domain-specific Retrieval-Augmented Generation framework for headache research

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Background: Headache medicine is characterized by rapidly expanding and heterogeneous scientific literature, particularly on pharmacological treatments. This creates practical difficulties for clinicians and researchers who need rapid, reliable, and source-traceable answers to focused and detailed scientific questions. Although large language models can support biomedical summary, their unguided use is limited by the risk of inaccurate, outdated, or non-verifiable statements. Retrieval-Augmented Generation (RAG) offers a practical solution by linking generative models to a selected, personalized and controlled scientific corpus. Herein we describe the development and practical use of a domain-specific RAG system designed to support headache research.

Methods: A personalized RAG workflow was developed using a local library of headache-related studies selected and controlled by the researcher. Documents were ingested through a Python-based pipeline that extracted full text and metadata, corrected or integrated bibliographic information when available, removed duplicates, and organized the corpus into structured libraries with searchable metadata.
Full texts were divided into overlapping chunks, embedded using OpenAI text-embedding-3-small, and stored in a Supabase PostgreSQL database with pgvector indexing. Rule-based topic classification enabled optional category-restricted retrieval. A FastAPI backend exposed retrieval, health, and version endpoints and was deployed through Render.com, while GitHub was used for version control and reproducible deployment. Customized GPT agents were connected to the retrieval API through an OpenAPI schema and instructed to retrieve evidence from the indexed corpus before generating answers. This architecture was designed to keep clinicians and researchers in full control of the documents, metadata, and information sources used by the system.

Results: The system provided a low-cost, modular, and traceable environment for querying selected headache literature eliminating the so-called hallucinations. In practical use, users can ask focused questions on mechanisms, diagnostic criteria, pharmacological treatments, or methodological issues. The agent retrieves relevant passages from the organized, personal library, summarizes the evidence, reports methodological details when available, and links outputs to local source material. This supports rapid preliminary evidence mapping, paper identification, and hypothesis generation.

Conclusions: A personalized, domain-specific RAG system may provide a practical tool for literature-grounded scientific work in headache medicine. Its main value is not to replace systematic reviews or expert interpretation, but to accelerate targeted retrieval, improve traceability, organize scientific libraries, and reduce unsupported generation. An important direction of ongoing development is the transition toward fully local and free/open-source RAG systems.



GAINER-AI: Predicting Acute Rimegepant Response in Migraine Using Machine Learning in a Multicenter Real-World Cohort

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Background: Rimegepant is the first calcitonin gene-related peptide (CGRP) receptor antagonist approved for both acute and preventive migraine treatment. Despite demonstrated efficacy in randomized trials and real-world studies, predictors of individual response remain poorly understood. Machine learning (ML) approaches may facilitate personalized treatment selection by identifying clinical features associated with treatment outcomes.
Objective: To develop and evaluate an ML-based model to predict pain freedom 2 hours after acute rimegepant treatment and to create a web-based prediction tool using routinely available clinical variables.

Methods: We conducted a post hoc analysis of the prospective, multicenter, real-world GAINER study. Adults with episodic or chronic migraine treated up to four migraine attacks with rimegepant 75 mg orally disintegrating tablets. The primary outcome was pain freedom at 2 hours after treatment during the first treated attack. Multiple ML algorithms were evaluated, and a Random Forest model was selected based on performance. Data were randomly split into training (80%) and test (20%) sets. Feature selection was performed using sequential forward selection. Model explainability was assessed through SHapley Additive exPlanations (SHAP) analysis.

Results: A total of 191 participants (80.1% female; mean age 44.8 years) treated 377 migraine attacks. Overall, 44.6% of attacks achieved pain freedom at 2 hours, with higher response rates in episodic than chronic migraine (50.5% vs. 28.4%, p=0.001). The final Random Forest model retained 11 predictors and achieved a weighted F1-score of 0.671 in the independent test set. Monthly headache days (MHD) emerged as the most influential predictor, followed by concomitant anti-CGRP monoclonal antibody treatment, age, age at migraine onset, medication overuse headache, and monthly acute medication use. Higher MHD and older age were associated with lower probabilities of pain freedom. Based on the final model, a freely accessible web-based prediction tool was developed.

Conclusions: This study represents the first application of ML methods to predict response to any acute migraine treatment. Using readily available clinical variables, the GAINER-AI model demonstrated moderate predictive performance and enabled the development of a user-friendly web application. Although external validation is required, these findings support the potential of ML-based tools to advance personalized acute migraine management.



Sleep macrostructure changes across the migraine cycle: preliminary evidence from prolonged home polysomnographic monitoring

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Background: Predicting migraine attacks by identifying reliable pre-ictal biomarkers remains a paramount clinical goal. Although laboratory studies show distinct neurophysiological sleep changes preceding attacks, real-world evidence is lacking. This pilot study aimed to investigate whether longitudinal, home-based polysomnography can track these phase-related fluctuations, providing a foundation for predictive digital biomarkers.

Methods: Eligible participants fulfilled ICHD-3 criteria for episodic migraine and were free of major sleep disorders or sleep-modifying medications. Continuous, home-based polysomnography was performed using a wearable device, yielding a total of 54 analyzable overnight recordings. Nights were classified as inter-ictal (>24 hours from an attack), pre-ictal (<24 hours before an attack), or ictal (the night following attack onset). Sleep parameters, including sleep latency (SL), wake after sleep onset (WASO), wake duration (WD), total sleep time (TST), sleep efficiency (SE) and sleep stage distribution were extracted from recordings. Owing to the repeated-measures design, analyses focused on within-subject comparisons and linear mixed-effects models, with correction for multiple testing.

Results: Ten patients (eight women, aged 24–54) completed 1–7 consecutive monitoring nights. The dataset included 38 inter-ictal, 5 pre-ictal, and 11 ictal nights. Neither comparisons in the whole population nor within-subject analyses revealed any statistically significant differences among interictal, ictal, and pre-ictal recordings; the largest numerical phase-related change was observed in REM sleep, which showed a higher percentage during pre-ictal than during interictal nights (median 22.6% vs 18.8%; Wilcoxon p=0.125).

Discussion: These preliminary observations suggest that migraine preferentially affects REM sleep regulation rather than global sleep architecture. Although the specific REM alterations observed differ from those reported by previous laboratory-based polysomnographic studies, these support the hypothesis that REM sleep represents the sleep stage most closely involved in the migraine cycle. This biological link aligns with literature highlighting shared aminergic and cholinergic brainstem networks that mutually regulate both REM sleep and migraine pathophysiology.

Conclusions: Although limited by the small sample size, this pilot study identifies preliminary trends in REM sleep alterations that align with established neurophysiological literature. These findings suggest that longitudinal, home-based polysomnography represents a promising approach to track phase-related fluctuations, potentially paving the way for future sleep-based digital biomarkers capable of predicting migraine attacks.



Clinical predictors of secondary headache in the Emergency Department: an exploratory model of a four-variable bedside model in the Emergency Department

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Background: Rapid bedside identification of secondary versus primary headache is crucial for Emergency Department (ED) triage. The present study aimed to explore which routinely available variables independently contribute to discriminating secondary from primary headache.

Methods: We retrospectively included consecutive ED headache patients from AOUP Paolo Giaccone of Palermo, Italy (August 2024-September 2025). Demographic, clinical, instrumental, and biochemical data were collected. Headache diagnoses were reviewed and classified as primary or secondary by a headache specialist according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria. From exploratory bivariate analyses, four candidate variables were retained based on consistency with established red-flag literature and clinical interpretability [2]: patient age, systolic blood pressure (SBP), photophobia, and prior headache history. A multivariable logistic regression model was fitted, and internal performance was estimated using Harrell's optimism-corrected bootstrap (500 resamples) to mitigate bias introduced by data-driven variable selection. Adjusted odds ratios were estimated with 1,000 bootstrap percentile 95% confidence intervals (CIs).

Results: A total of 263 patients with complete diagnostic classification were available, of whom 102 had complete data on all four candidate variables (69 primary, 33 secondary). The clinical model showed an apparent AUC of 0.853 and an optimism-corrected AUC of 0.828 (95% bootstrap CI 0.75–0.90), indicating good discrimination with modest optimism (Δ = +0.025). At an optimal Youden threshold, sensitivity was 0.76 and specificity 0.81 for secondary headache. Three of the four candidates retained independent association with secondary headache: SBP per 10-mmHg increment (OR 1.46, 95% CI 1.12–2.15), absence of photophobia (OR for presence 0.17, 95% CI 0.02–0.66), and absence of prior headache history (OR for presence 0.12, 95% CI 0.02–0.35). Age per 10-year increment did not retain independent significance after adjustment (OR 0.83, 95% CI 0.48–1.29), suggesting an interaction with headache history.

Conclusions: in this exploratory analysis, three readily available bedside variables (SBP, photophobia, and prior headache history) together provide good discrimination between primary and secondary headache. Hypertension combined with absence of typical migraine features identifies patients who require further workup. Prospective external validation is warranted to prove the usefulness of this model in clinical practice.



Validation of a Structured Pre-Visit Questionnaire for Headache Specialist Consultations

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Background: In an era of increasing demand for headache specialists, digitally assisted triage may help optimize initial evaluations. However, structured consultations conducted by headache experts may reveal clinical aspects that patient self-report alone cannot. To define the contribution of physician-guided assessment, we conducted a prospective study to evaluate the extent to which information obtained through a structured pre-visit questionnaire, when interpreted by a neurologist, could substitute the traditional visit in guiding diagnostic and therapeutic decisions.

Methods: Fifty consecutive patients attending the tertiary Headache Centre at AOUP Paolo Giaccone, Palermo, for their first evaluation completed a structured pre-visit questionnaire. One neurologist independently reviewed the questionnaire and recorded diagnostic hypotheses and treatment decisions without seeing the patient (questionnaire condition). A second neurologist, blinded to questionnaire data, conducted the standard clinical encounter and recorded post-visit decisions (visit condition). Agreement between the two conditions was assessed across four domains: ICHD-3 diagnostic category, indication for additional investigations, acute medication class, and preventive treatment decision (initiation, confirmation, modification, or no preventive therapy). Drug-level concordance was additionally evaluated for five preventive treatment classes (amitriptyline, beta-blockers, anti-CGRP monoclonal antibodies, topiramate, and flunarizine). The primary agreement metric was the Prevalence- and Bias-Adjusted Kappa (PABAK), with 95% confidence intervals. McNemar's test was used to assess directional bias in decisions regarding neuroimaging.

Results: Preventive treatment decisions showed near-perfect agreement (PABAK = 0.91; 95% CI 0.55–1.00; p_o = 94%), indicating that headache frequency and disability measures captured by the questionnaire were sufficient to guide prophylactic decisions in most cases. Agreement on diagnostic category was substantial (PABAK = 0.81; 95% CI 0.55–1.00; p_o = 69%), with some discrepancies attributable to less common diagnoses (e.g., new daily persistent headache or secondary headache disorders), identified only during the traditional clinical consultation, as well as medication-overuse headache, which requires a more detailed assessment of drug-use patterns. Agreement on acute medication class was moderate (PABAK = 0.58; 95% CI −0.41–1.00; p_o = 67%). Concordance regarding additional investigations was moderate (PABAK = 0.38; 95% CI 0.22–1.00; p_o = 67%), with no evidence of systematic over- or under-prescription (McNemar $\chi^2 = 0.80$; p = 0.37). At the drug level, anti-CGRP monoclonal antibodies and flunarizine showed the highest agreement (PABAK = 0.88 for both; p_o = 94%), whereas amitriptyline and topiramate showed lower concordance (PABAK = 0.33; p_o = 50%), likely reflecting differences in the evaluation of comorbidities and contraindications.

Conclusions: When interpreted by a trained neurologist, a structured pre-visit headache questionnaire achieves substantial agreement with standard specialist assessment for diagnostic categorization and preventive treatment decisions, and moderate agreement for acute treatment selection. These findings supports an approach in which questionnaire-guided pre-structuring allows specialist time to be focused on domains that genuinely require specific evaluation, such as diagnostic refinement, assessment of comorbidities, and optimization of acute treatment strategies.



Sequential machine learning models for predicting onabotulinumtoxinA response in chronic migraine: a cohort study

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Background: Chronic migraine (CM) is associated with high disability and heterogeneous response to onabotulinumtoxinA (BoNT-A). Baseline clinical predictors of response remain inconsistent, limiting individualized treatment decisions. Machine learning may improve prediction by integrating longitudinal treatment data. This study aimed to develop sequential machine-learning models to predict BoNT-A response in CM after successive treatment cycles under real-world conditions.

Methods: We performed a post-hoc analysis of a prospectively collected cohort of adults with CM treated with BoNT-A according to the PREEMPT protocol at a tertiary headache center. Response was defined as a ≥30% reduction in monthly headache days (MHDs) from baseline. Four sequential supervised classification models were trained to predict response after cycles 1-4. Model 1 used baseline demographic and clinical variables only; models 2-4 progressively incorporated post-treatment MHDs and acute medication use after preceding cycles. Multiple algorithms were compared using stratified 5-fold cross-validation, with balanced accuracy as the primary performance metric. Model performance was assessed using accuracy, sensitivity, specificity, positive and negative predictive values, macro-F1 score, and AUC-ROC. Feature importance was evaluated using SHapley Additive exPlanations.

Results: The baseline cohort included 385 patients with CM; mean age was 48.1±13.1 years, 82.9% were female, baseline MHDs were 25.4±5.9, and medication overuse was present in 326/383 patients (85.1%). The number of patients included decreased across models with 385 in model 1 and 161 in model 4. Baseline-only prediction showed limited performance, with balanced accuracy of 0.60±0.03 and AUC-ROC of 0.62±0.04. Incorporating early post-treatment data markedly improved discrimination. Model 2 achieved balanced accuracy of 0.82±0.04 and AUC-ROC of 0.88±0.01, while model 3 showed the highest balanced accuracy, 0.84±0.04, and AUC-ROC of 0.87±0.03. Across longitudinal models, on-treatment MHDs were the dominant predictors of response.

Conclusions: Sequential machine-learning models incorporating early post-treatment headache-frequency data outperformed baseline-only prediction of BoNT-A response in CM. These findings support dynamic, monitoring-informed prediction models and require prospective external validation before clinical implementation.



REHABILITATION AND PHYSICAL ACTIVITY IN THE PREVENTION AND TREATMENT OF CHRONIC CONDITIONS

Physiotherapy interventions for migraine: effect on frequency, duration, pain intensity, use of medication and disability. A systematic review with meta-analysis

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Background: To assess the effects of non-instrumental physiotherapy (PT) interventions targeting the cranio-cervical-thoracic region on headache frequency, pain intensity, episode duration, medication use, and disability in individuals with migraine (M), compared with no intervention, sham intervention, or other active interventions (any other PT intervention, pharmacological treatment, or other non-PT, non-pharmacological interventions).

Methods: This systematic review included randomized controlled trials (RCTs) enrolling adult patients diagnosed with migraine. Eligible studies evaluated PT interventions involving manual therapy and/or exercise targeting the cranio-cervical-thoracic region, compared with no intervention, sham intervention, or other active interventions. MEDLINE (PubMed), Web of Science, Scopus, and CENTRAL were searched from inception to November 2025. Risk of bias was assessed for each outcome using the Cochrane Risk of Bias 2.0 tool. Random-effect meta-analyses were conducted for each outcome within each headache type and comparator (PT vs no intervention; PT vs sham intervention; PT vs other active interventions) when at least three comparisons were available. Certainty of evidence was evaluated using the GRADE approach.

Results: A total of 16 studies were included, comprising 833 participants. Most studies were judged at high risk of bias across outcomes.
Low-certainty evidence suggests that PT may reduce headache frequency post-treatment compared to no intervention; may reduce headache intensity and disability post-treatment, and disability at follow-up, compared to sham intervention; and may reduce the use of symptomatic medication at follow-up compared to other active interventions.
Low-certainty evidence also suggests that PT may not reduce disability either post-treatment or at follow-up compared to other active interventions.
Evidence for all other outcomes is very uncertain across all comparators (no intervention, sham intervention, and other active intervention).

Conclusions: This systematic review suggests that manual therapy techniques and specific exercises targeting the cranio-cervical-thoracic region may provide clinically relevant benefits for individuals with migraine. Low-certainty evidence supports reductions in headache frequency, intensity, disability, and the use of symptomatic medication. However, substantial methodological limitations and the risk of bias in the included studies warrant cautious interpretation.



Physiotherapy interventions for tension-type headache: effect on frequency, duration, pain intensity, use of medication and disability. A systematic review with meta-analysis

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Background: To assess the effects of non-instrumental physiotherapy (PT) interventions targeting the cranio-cervical-thoracic region on headache frequency, pain intensity, episode duration, medication use, and disability in individuals with tension-type headache (TTH) compared with no intervention, sham intervention, or other active interventions (any other PT intervention, pharmacological treatment, or other non-PT, non-pharmacological interventions).

Methods: This systematic review included randomized controlled trials (RCTs) enrolling adult patients diagnosed with TTH. Eligible studies evaluated PT interventions involving manual therapy and/or exercise targeting the cranio-cervical-thoracic region, compared with no intervention, sham intervention, or other active interventions. MEDLINE (PubMed), Web of Science, Scopus, and CENTRAL were searched from inception to November 2025. Risk of bias was assessed for each outcome using the Cochrane Risk of Bias 2.0 tool. Random-effect meta-analyses were conducted for each outcome within each headache type and comparator (PT vs no intervention; PT vs sham intervention; PT vs other active interventions) when at least three comparisons were available. Certainty of evidence was evaluated using the GRADE approach.

Results: A total of 18 studies were included, comprising 1092 participants with TTH. Most studies were judged at high risk of bias across outcomes.
Low-certainty evidence suggests that PT may reduce headache intensity post-treatment compared to sham intervention and may reduce headache frequency at follow-up and headache disability post-treatment compared to other active interventions.
Moderate-certainty evidence indicates that PT probably reduces headache frequency both post-treatment and at follow-up compared to sham intervention.
High-certainty evidence indicates that PT reduces headache disability post-treatment compared to sham intervention.
Evidence for all other outcomes is very uncertain across all comparators (no intervention, sham intervention, and other active intervention).

Conclusions: This systematic review suggests that manual therapy techniques and specific exercises targeting the cranio-cervical-thoracic region may provide clinically relevant benefits for individuals with TTH. Moderate- to high-certainty evidence supports reductions in headache frequency and disability. However, substantial methodological limitations and risk of bias in included studies warrant cautious interpretation.



Atogepant Demonstrates Greater Improvement in Function Using the Activity Impairment in Migraine-Diary (AIM-D) During Interictal Days: Post-Hoc Analysis From the PROGRESS Chronic Migraine Trial

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**This individual has been added to this publication author by-line, with the permission of the original authors, for the express purpose of conducting the presentation at a local congress or in a local language. He did not contribute to the content of the publication.*

Background: Atogepant is approved for the preventive treatment of migraine in adults and has recently demonstrated its efficacy and safety for the acute treatment of migraine. This analysis evaluated the impact of atogepant 60mg administered as needed (PRN) for acute treatment of migraine on cognitive function assessed by the ability to think clearly.

Methods: ECLIPSE was a double-blind (DB), placebo-controlled, multiple-attack, crossover trial evaluating atogepant's efficacy, safety, and tolerability for acute migraine treatment. Adults with 2-8 monthly moderate-to-severe attacks were randomised to receive atogepant for three qualifying attacks and placebo for one attack during the up to 16-week DB period. Cognitive function scale is a single-item, patient-reported questionnaire measuring participants' difficulty in ability to think clearly, rated from 0 (not difficult at all) to 3 (very difficult). The proportion of participants achieving the ability to think clearly at 2-, 4-, and 8-hours postdose across attacks 1-4 was an additional (exploratory) efficacy endpoint. Data for atogepant and placebo are presented with nominal P-values.

Results: Atogepant treatment resulted in a nominally significant higher proportion of participants achieving the ability to think clearly compared with placebo as early as 2-hours postdose in the first treated attack (OR: 1.78); this effect increased over time through 4- and 8-hours postdose (OR: 3.39, 3.73, respectively). A similar reliable response was observed across attacks 2-4 ().

Conclusions: A greater proportion of participants treated with atogepant achieved the ability to think clearly compared to placebo as early as 2-hours and up to 8-hours postdose across multiple attacks.



Chronic Migraine and Residual Symptoms: Physiotherapy as an Ally of Preventive Therapies in Patients with Central Sensitization, Cervicalgia, and Sleep Disturbances

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Background: Chronic migraine is one of the leading causes of neurological disability, significantly affecting quality of life and daily functioning. Despite the availability of conventional and advanced preventive treatments, including anti-CGRP monoclonal antibodies and botulinum toxin type A, many patients continue to experience residual symptoms such as tension-type headache, neck pain, sleep disturbances, and, in some cases, bruxism. These factors may contribute to the persistence of peripheral and central sensitization, negatively influencing treatment response. This study aims to evaluate the role of physiotherapy as a complementary intervention to preventive pharmacological treatments in chronic migraine.

Methods: An ongoing prospective observational study is enrolling adult patients diagnosed with chronic migraine according to ICHD-3 criteria and receiving stable preventive therapy, either conventional or advanced. To date, 12 patients have been enrolled and are undergoing scheduled quarterly follow-up assessments. Eligible participants present residual tension-type headache associated with cervicalgia, with or without bruxism, and varying degrees of sleep impairment. Baseline assessment includes headache characteristics, headache frequency, neck pain severity, sleep quality, central sensitization, pain-related cognitive-emotional factors, and migraine-related disability. Participants undergo an individualized physiotherapy program including manual therapy, therapeutic exercise, movement education, and treatment of cervico-cranio-mandibular dysfunctions.

Results: Preliminary baseline data indicate a population with a high disease burden. The mean MIDAS score was 28 (SD ±10), indicating severe migraine-related disability. Seventy percent of participants showed poor sleep quality, defined as a PSQI score >5, with a mean score of 9 (SD ±2). A marked degree of central sensitization was observed, with a mean CSI score of 54. Assessment using the Pain Catastrophizing Scale revealed a mean score of 26.5 (SD ±14), suggesting substantial pain-related distress and maladaptive coping patterns. The study is ongoing, and quarterly reassessments will evaluate the effects of physiotherapy on these clinical and functional parameters.

Conclusions: Preliminary findings describe a cohort characterized by high disability, poor sleep quality, significant central sensitization, and elevated pain catastrophizing despite ongoing preventive pharmacological treatment. Integrating physiotherapy within a multidisciplinary care pathway may represent an effective strategy to address musculoskeletal and biopsychosocial factors contributing to persistent symptoms, with the potential to optimize clinical outcomes in chronic migraine.



HEADACHES AND GENDER-BASED MEDICINE

Information needs for migraine treatment across the reproductive journey: insights from a five-year Teratology Information Service experience

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Background: Migraine is highly prevalent among women of reproductive age, and pharmacological management throughout pregnancy planning, pregnancy and breastfeeding remains a common clinical challenge. Characterizing women's information needs may help identify potential unmet needs and optimize counselling strategies.

Methods: We retrospectively analyzed requests received by the Teratology Information Service of Careggi University Hospital between 2021 and 2025 from women with migraine seeking information on acute or preventive migraine treatments during preconception, pregnancy or breastfeeding. Requests were classified according to reproductive stage, treatment type, and timing relative to drug exposure (pre-exposure vs post-exposure).

Results: The analysis included 642 women with migraine and 1,256 drug-related consultations during preconception, pregnancy, and breastfeeding. Most consultations concerned acute migraine treatments (979/1,256, 77.9%), whereas preventive therapies accounted for 277/1,256 consultations (22.1%). Triptans accounted for the largest proportion of information requests (413/1,256, 32.9%), and amitriptyline was the most frequently requested preventive therapy (144/277, 52.0%).
The distribution of consultations varied according to treatment type. The first trimester was the most frequent period for both acute (450/979, 46.0%) and preventive therapies (130/277, 46.9%). Preconception consultations were more common among preventive therapy requests (34.3% vs 14.0%), whereas breastfeeding consultations were more common among acute treatment requests (26.7% vs 12.6%).
Overall, 76.6% of consultations occurred after drug exposure. Post-exposure consultations accounted for 82.4% of first-trimester requests, whereas this proportion decreased to 53.8% during breastfeeding, with a corresponding increase in pre-exposure consultations.

Conclusions: Information needs of women with migraine across the reproductive journey predominantly concern acute migraine treatment. The marked concentration of consultations during the first trimester, together with a second peak during breastfeeding, identifies two key time points for structured counselling.



Alexithymia increases the risk of migraine chronification in women without depression

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Background: Alexithymia is a psychological construct, characterized by a deficit in identifying and communicating feelings. Emerging data suggest a role for alexithymia in migraine, within a complex interplay with psychiatric comorbidities. This study was aimed to investigate the relationship between alexithymia and migraine chronification in females.

Methods: This was an observational, multicenter study, enrolling female patients with migraine. Each patient underwent a psychological assessment for alexithymia (TAS-20 scale), anxiety and mood comorbidities (STAI-Y1/STAI-Y2, BDI-II) and apathy (Starksteln's Apathy scale, SAS-I). Data on headache frequency, intensity and medication use were recorded.
A multivariable logistic regression model was fitted to evaluate the association between alexithymia (TAS-20 score) and the probability of chronic migraine. The model included BDI-II categories, the TAS-20 × BDI-II interaction term, STAI-Y2 and SAS-I score, age and education as covariates.

Results: The study included 507 participants. In the overall sample, 384 (75.74%) had episodic migraine, 31 (6.11%) had chronic migraine (CM), 43 (8.48%) CM with medication overuse headache (MOH), and 48 (9.47%) could not be classified (missing data).
Alexithymia was identified in 207 patients (40.83%), depression in 206 (40.63%). Both variables had 34 missing observations (6.7%).
In the logistic regression analysis performed on complete cases (n= 366), the association between alexithymia and chronic migraine was modified by depression severity. In patients with no or minimal depression, higher TAS-20 scores were associated with a higher probability of chronic migraine. The average marginal effect of TAS-20 was 1.74 percentage points for each one-point increase in TAS-20 among patients with BDI-II score 0–4, and 0.70 percentage points among subjects with BDI-II score 5–9. Conversely, the marginal effect of TAS-20 was not statistically significant among patients with a BDI-II score >10.
These findings indicate a significant interaction between alexithymia and depression, with the association between TAS-20 and chronic migraine progressively attenuating as depression severity increases. Multiple imputation analysis on the whole sample confirmed this finding, with a milder modifier effect of depression.
Conclusion: These results indicate a role of alexithymia in increasing the risk of migraine chronification in women without clinically relevant depression. Moreover, a modifier effect for depression is suggested.



Sex differences in the impact of targeted migraine treatments on associated obsessive-compulsive traits

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Background: Psychiatric comorbidities associated with migraine differ between men and women. While sex differences in anxiety and depression have been extensively investigated, obsessive–compulsive (OC) traits remain poorly explored. Although targeted therapies, including anti-calcitonin gene-related peptide monoclonal antibodies (anti-CGRP mAbs) and Onabotulinumtoxin-A (OBT-A), effectively reduce migraine burden, their impact on OC traits and potential sex-specific differences remains unclear.
Aims: To evaluate the effect of targeted migraine therapies on OC traits and investigate sex differences in treatment-related changes.

Methods: Consecutive patients attending the tertiary Headache Center of the Neurological Clinic, AOU delle Marche, who initiated anti-CGRP mAbs or OBT-A were prospectively enrolled. Participants completed the Obsessive–Compulsive Inventory-Revised (OCI-R) at baseline (T0) and after one year (T1). OCI-R categories at T1 were analysed using a full-factorial multinomial logistic regression model including baseline OCI-R, sex, and their interaction.

Results: Ninety patients were included. Overall, targeted therapy was associated with a shift toward lower OCI-R severity categories at T1. Multinomial logistic regression identified significant sex-by-baseline OCI-R interactions for Class 3 versus Class 1 (β =13.33, $p<0.001$) and Class 4 versus Class 1 (β =−7.77, $p<0.001$), whereas no interaction was observed for Class 2 versus Class 1 ($p = 0.981$). At low baseline OCI-R values (mean −1SD), the probability of remaining in the lowest OCI-R class was similar in men (95.0%) and women (94.2%). At higher baseline OCI-R values (mean +1SD), this probability declined to 77.5% in men and 64.8% in women. Concurrently, women showed a progressive increase in the probability of belonging to the most severe OCI-R class (13.3%), whereas men mainly transitioned to Class 2 (22.5%), with the probability of the most severe class increasing only at the highest OCI-R levels.

Conclusions: Targeted migraine therapies were associated with an overall improvement in obsessive–compulsive symptoms. However, sex significantly moderated the relationship between baseline OC symptom severity and longitudinal symptom trajectories, revealing distinct patterns of symptom evolution in men and women. These findings underscore the importance of considering sex-specific psychiatric phenotypes in migraine and support the integration of neuropsychiatric profiling into personalised therapeutic strategies.



THE EMPATHIC RELATIONSHIP IN THE CARE PROCESS

Patient depressive symptoms and reciprocity influence Distress in the Caregiver of patients with migraine: insights from the MIDEAR observational cohort study.

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Background: As awareness of migraine disability is becoming higher, the recognition of the pivotal role of caregivers of people with migraine and their burden is still scarce. We aimed to investigate the factors influencing the distress of informal caregivers of patients affected by high-frequency or chronic migraine with depressive symptoms.
Methods: All consecutive adult patients with high-frequency or chronic migraine and depressive symptoms were considered, along with their caregivers. Sociodemographic characteristics and the average number of weekly hours spent together were assessed in patients and their caregivers (dyads). In patients, we evaluated monthly migraine days, monthly acute medications, pain intensity, migraine-related disability, the composite 4D score on migraine burden, and depressive symptoms (Patient Health Questionnaire-9-PHQ-9). Caregivers filled in the Relative Stress Scale (RSS). The mutuality scale (MS) was also collected in the dyads.
Results: 154 dyads (308 participants) were enrolled (patients aged 42.6 years, SD 12.7; 80.5% female; and their caregivers aged 48.1 years, SD 12.2; 36.4% female). The mean shared reported time was 89.7, SD 29.7 hours per week. In patients, PHQ-9 scores were higher among females ($p=0.017$) and in those with higher disability scores (MIDAS $p<0.001$; HIT-6 $p=0.025$; 4D scale $p=0.043$), while MMDs were not directly related ($p=0.356$). The RSS score in caregivers was 20.6 (SD 10.9). Among caregivers' features, the reciprocity subdomain of the MS was inversely related ($p=0.009$) to the perceived stress (RSS).
The MS total scores and subdomains (p consistently <0.05) were highly related in the dyad. A positive relation was observed between caregiver RSS and patient PHQ-9 ($r=0.197$; $p=0.014$), 4D ($r=0.234$; $p=0.004$), and MIDAS ($r=0.207$; $p=0.010$) scores, while a non-significant trend was observed for MMDs ($r=0.157$; $p=0.052$). Finally, when both caregiver and patient characteristics were included, the caregiver reciprocity MS subdomain ($p < 0.001$) and PHQ scores ($p = 0.004$) were the only factors associated with RSS scores.
Conclusions: The MIDEAR study highlighted the elevated perceived stress of caregivers of patients with migraine. Among its possible determinants, low reciprocity, a higher multidimensional migraine burden, and more severe depressive symptoms in patients worsen the caregivers' psychological health.



Assessment of Personality Traits in Patients with Chronic Migraine and Analgesic Overuse According to the Alternative DSM-5-TR Model: An Observational Study

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Background: Chronic migraine associated with medication overuse (MOH) is a highly disabling neurological condition (1,2). The present study aims to explore personality traits and affective comorbidities in this population using the dimensional model of DSM-5-TR.

Methods: Seventy patients (82.9% women; mean age 47.8 years) diagnosed with chronic migraine and MOH according to ICHD-3 criteria were recruited at the Regional Headache Centre of Catanzaro. The assessment was conducted by a senior clinical psychologist and psychotherapist through a clinical interview and the administration of the Personality Inventory for DSM-5 (PID-5) and the Hospital Anxiety and Depression Scale (HADS).

Results: Analysis of PID-5 domains showed elevated scores in Disinhibition (M = 67.8) and Detachment (M = 66.8). Among the facets, Risk Taking (M = 82.6) and Suspiciousness (M = 78.3) were the most pronounced traits. The HADS revealed significant levels of anxiety (M = 9.20), which correlated positively with Disinhibition (r = .615) and Detachment (r = .599). Antagonism showed no significant associations with affective symptomatology.

Conclusions: The findings suggest that the psychological profile of patients with MOH is characterized by anxiety vulnerability, impaired impulse regulation, and social withdrawal (53,54). These personality traits appear to sustain medication overuse behaviours. A multidisciplinary approach integrating neurological management with psychotherapeutic interventions aimed at emotional regulation is therefore essential to improve long-term clinical outcomes.



HEADACHES, PRIMARY CARE, AND CARE PATHWAYS: COMPARING EXPERIENCES

Differences in clinical characteristics across low-frequency episodic migraine, high-frequency episodic migraine, and chronic migraine: a cross-sectional observational study

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Background: The aim of this study was to investigate differences in demographic characteristics, healthcare utilization, headache management and medication use, and headache-related disability among patients with low-frequency episodic migraine (LFEM), high-frequency episodic migraine (HFEM), and chronic migraine (CM).

Methods: This cross-sectional observational study, carried between May and July 2025, included patients with migraine attending first visit at one of the nine tertiary headache centres in the Liguria region. No exclusion criteria were applied. Patients were classified as having LFEM (<8 monthly migraine days), HFEM (8–14 monthly migraine days), or CM (≥15 headache days per month, of which at least 8 had migraine features). The presence of aura was also recorded. All patients completed a standardized questionnaire assessing demographic characteristics, healthcare utilization, headache management and medication use, and completed the Migraine Disability Assessment (MIDAS).

Results: A total of 170 patients were included: 117 (59%) had LFEM, 51 (26%) had HFEM, and 30 (15%) had CM. A higher proportion of CM patients had previously attended another headache centre compared with LFEM patients (12 [43%] vs 16 [14%], p=0.001), with no differences between CM and HFEM or between LFEM and HFEM (HFEM: 12 [24%]).
A higher proportion of CM patients had previously consulted a healthcare professional outside a headache centre compared with LFEM patients (14 [47%] vs 25 [21%], p=0.015), with no differences between CM and HFEM or between LFEM and HFEM (HFEM: 13 [26%]).
The three groups also differed in MIDAS score and previous use of preventive treatments. CM patients had higher MIDAS scores than LFEM patients (40 [32–79] vs 8 [2–15], p<0.001) and HFEM patients (40 [32–79] vs 20 [11–42], p=0.003), while HFEM patients had higher MIDAS scores than LFEM patients (p<0.001).
Compared with LFEM patients (26 [22%]), a higher proportion of CM patients (15 [50%] (p=0.006) and HFEM patients (22 [43%]) (p=0.018) had previously used preventive treatments, with no difference between CM and HFEM patients (p=1.000).
No other differences were found across LFEM, HFEM, and CM

Conclusions: CM was associated with greater disability and healthcare utilization than LFEM, while HFEM showed an intermediate burden.



Characteristic of patients attending tertiary headache centres in Liguria: a cross-sectional observational study

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Background: The aim of this study was to characterize the demographic characteristics, healthcare access, referral pathways, and healthcare utilization of patients attending tertiary headache centres in Liguria
Methods: This cross-sectional observational study included patients attending nine tertiary headache centres in the Liguria region. No exclusion criteria were applied. All patients attending first visit completed a standardized questionnaire assessing demographic characteristics, healthcare access, referral pathways, and healthcare utilization.
Results: A total of 244 patients were included from May to July 2025. The headache centre with the highest number of patients was the University Neurology Department of the IRCCS Azienda Ospedaliera Metropolitana (n=73, 30% of the total sample).
Among all patients, 191 (78%) were female. The mean age was 39.7 years (SD 17.1). Most patients had completed either upper secondary education (123, 51%) or university education (59, 24%).
The most common referral source was the general practitioner (128, 53%), followed by other medical specialists (67, 28%), self-referral (25, 10%), the emergency department (16, 7%), other sources (10, 4%), pharmacists (5, 2%), and other healthcare professionals (2, 1%).
The most frequent diagnosis was migraine alone (170, 70%), followed by tension-type headache (TTH) alone (19, 8%), while 27 patients (11%) had both migraine and TTH. Four patients (1.5%) were diagnosed with secondary headache disorders.
Among patients diagnosed with migraine, 117 (59%) had low-frequency episodic migraine, 51 (26%) had high-frequency episodic migraine, and 30 (15%) had chronic migraine. A total of 42 patients (22%) also experienced aura. Among patients diagnosed with TTH, 33 (72%) had episodic TTH and 13 (28%) had chronic TTH.
Overall, 49 patients (20%) had previously attended another headache centre. In addition, 64 patients (26%) had previously consulted healthcare professionals outside a headache centre. Ninety-two patients (39%) had previously attended an emergency department for headache. A total of 148 patients (64%) had previously undergone at least one diagnostic investigation.
Conclusions: Most patients attending tertiary headache centres in Liguria had migraine and were referred by general practitioners. Despite the majority of patients were diagnosed with low-frequency episodic migraine, previous healthcare utilization was common, particularly emergency department attendances and diagnostic investigations.



The Role of Neuroticism and Depressive Symptoms in Modulating Migraine Burden: A Cross-Sectional Study

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Background: Migraine is one of the most prevalent and disabling neurological disorders worldwide, carrying a substantial clinical, social, and economic burden. Beyond its biological underpinnings, psychological and personality factors are increasingly recognized as modulators of disease severity and chronification. The primary aim was to investigate the role of psychological and personality variables in modulating migraine severity within a biopsychosocial framework, focusing on an integrated migraine–depression–neuroticism model to assess the joint and independent contributions of these factors as predictors of headache burden and quality-of-life impairment.

Methods: This cross-sectional, observational, single-center study enrolled 402 patients (aged 18–70 years) attending the Headache Outpatient Clinic of Policlinico Umberto I, Rome, with diagnoses of migraine without aura (n=222), migraine with aura (n=98), or chronic migraine (n=82) according to ICHD-3 criteria. The sample was predominantly female (n=318; 79.1%). Exclusion criteria included neurological comorbidities, uncontrolled systemic conditions, and language barriers. Data collected between 2022 and 2026 via structured interviews and validated questionnaires (HIT-6, PHQ-9, MDQ, PVQ, Big Five Inventory) were analyzed using descriptive statistics, One-Way ANOVA, Spearman correlations, multiple linear regression, and General Linear Model (GLM).

Results: Migraine severity (HIT-6) correlated significantly with depressive symptomatology (rho=0.293; $p<0.001$) and with neuroticism (rho=0.124; p=0.016). Neuroticism also correlated positively with PHQ total score (rho=0.371; $p<0.001$), suggesting a role of emotional vulnerability in perceived headache burden. Multiple linear regression identified neuroticism as an independent predictor of HIT-6 score (B=1.306; p=0.032). In the multivariate GLM, pain intensity, conscientiousness, and agency were significantly associated with HIT-6, while extraversion was significantly associated with PHQ total score.

Conclusions: Depression and neuroticism were both associated with migraine severity through distinct mechanisms. While depression showed a significant positive correlation with headache burden, neuroticism emerged as the primary independent contributor in multivariate models, with the depression–severity association attenuating after controlling for personality variables. This suggests that part of the depressive burden in migraineurs may be mediated by stable personality traits—particularly emotional vulnerability inherent to neuroticism. These findings support a multidimensional approach to migraine assessment and highlight the need for integrated therapeutic strategies addressing emotional, depressive, and personality-related aspects alongside neurological treatment.



Impact of the North-East Italian chronic headache project on workplace disability and work productivity in patients treated with atogepant

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Background: Italy has recognized primary chronic headache as a social disease, prompting the development of innovative projects for the management of patients with chronic headache. In 2025, the Headache Centre of the University of Trieste launched a pilot project dedicated to chronic headache, including an ad hoc network, training activities for general practitioners, information initiatives for the general population, and a new Chronic Headache Outpatient Clinic staffed by a neurologist and a nurse specialized in headache disorders, aimed at ensuring priority access and management for patients with chronic headache.

Methods: We performed a four-month retrospective analysis of employed patients with high-frequency or chronic migraine treated with atogepant at the Chronic Headache Outpatient Clinic of Headache Centre of the University of Trieste. Patients were either treatment-naïve for preventive therapy or receiving stable preventive treatment for more than 3 months. Demographic data, waiting time, defined as the number of days from booking to treatment initiation, absenteeism, defined as workdays missed due to headache, presenteeism, defined as workdays with less than 50% work productivity, disability assessed by the MIDAS score, impairment in work productivity and activity assessed by the WPAI questionnaire, and monthly headache days were collected at baseline (T0) and after three months of atogepant treatment (T1). Data were analysed using SPSS 22.0.

Results: Twenty-one patients were included (mean age 48±11 years old; 17 females), 71.4% had chronic migraine and 76.2% were not receiving preventive treatment at baseline. Mean waiting time was 15±4 days. After three months of atogepant treatment, we observed a significant reduction in absenteeism (T0: 2 [0–8] vs T1: 0 [0–1] days; $p=0.006$), presenteeism (T0: 21±17 vs T1: 2 [0–7] days; $p<0.005$), disability (MIDAS score, T0: 81±33 vs T1: 15±8; $p<0.005$), impairment in work productivity (T0: 5.5±3 vs T1: 2±1.8; $p=0.012$), and monthly headache days (T0: 16.3±7.8 vs T1: 5.5±4.7; $p<0.005$).

Conclusions: Workplace disability and work productivity rapidly improved in patients treated with atogepant within a dedicated care setting designed to provide rapid access and management for patients with chronic headache.



The Ligurian Headache Network: a survey of nine headache centres, resources and challenges

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Background: Chronic migraine represents a major cause of disability as well as a significant and growing burden for the National healthcare systems. Structured and integrated models of headache care have been proposed to optimize headache management. New targeted therapies for migraine highlight the need for integrated healthcare service models capable of ensuring equity and sustainability. This study aimed to assess the organisational characteristics, clinical workload, and unmet healthcare needs of the regional headache network in Liguria.

Methods: In April 2025, all nine headache centres operating in Liguria completed a structured survey, investigating organisational models, clinical workload, available resources, waiting times and pathways for patient access. Monthly outpatient clinical resources available werw mapped across headache centres by exploring scheduled consultation slots.

Results: Overall, during a representative month 543 consultation were reported by the centres, including 119 first visits (21.9%), 376 follow-up visits (69.2%), and 46 urgent consultations (8.5%), with a predominance of follow-up consultations. Three centres accounted for 55.6% of the overall workload. The overall no-show rate was 6.3%, with a relevant inter-centre variability (2.0 - 13.8%). Mean consultation duration was 27 minutes. Informal clinical activity (i.e., telephone and email consultations) not captured within administrative records represented considerable workload. First consultations waiting times ranged from 6 to 12 months in most centres, whereas patient-reported data were shorter but highly heterogeneous; suggesting coexistence of informal access pathways. Organisational heterogeneity emerged regarding referral systems, urgent-access pathways, availability of anti-CGRP therapies and botulinumtoxin administration, as well as for integration between secondary and tertiary care. Only three centres reported structured integration between different levels of headache care. Limited availability of multidisciplinary professionals and restricted access to diagnostic resources were also observed.

Conclusions: The predominance of follow-up activity suggests progressive overload of tertiary headache centres in the absence of structured referral-back pathways toward community-based care.
The main critical issue within the Ligurian headache network is the limited integration between hospital- and community-based care rather than the absolute volume of clinical activity. Strengthening shared clinical pathways, telemedicine, technological integration, and coordinated multilevel care models may improve sustainability, accessibility, and management of chronic headache disorders.



How much do you know about migraine? Unmet challenges in headache education

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Background: Headache disorders are among the leading causes of disability worldwide, affecting 2.9 billion people in 2023. Instead of this substantial burden, medical education on headache remains limited: on average, only 4 hours of undergraduate curricula are dedicated to the topic, and knowledge of the ICHD-3 criteria is often inadequate. This study aims to assess the interest, training methods, and level of education on headache disorders among Italian specialists, non-specialists, and residents.

Methods: An anonymous survey was conducted in 2025 via Google Forms and disseminated through university channels and word of mouth. Participants were stratified by age, gender, university, geographic region, specialty, and graduation year. The questionnaire explored: presence and number of university lectures on headache, attendance, reasons for non-attendance, perceived usefulness of training, interest in further education, and the ability to provide a free-text definition of chronic migraine according to ICHD-3 criteria.

Results: A total of 114 participants completed the survey (61.4% women), representing 26 Italian universities; 50.8% were neurologists or neurology residents. While 79.9% reported having headache lectures during their degree program, about 8% did not attend due to scheduling conflicts rather than lack of interest. Over 75% considered the lectures useful or very useful for clinical practice. All participants who had not received any training stated they would have liked to. Overall, 58.8% believed that education on headache disorders is relevant to their professional activity. When asked to define chronic migraine, only 17 of 83 respondents (20.4%) provided a correct definition; among 71 neurologists, only 14 gave a complete answer.

Conclusions: The survey reveals substantial gaps in headache education within Italian medical training, even among neurologists, indicating that the mere presence of lectures does not ensure adequate learning. The strong interest in more structured training highlights an unmet educational need. Implementing innovative educational strategies—such as digital modules, flipped-classroom approaches, expert-led sessions, and stratified care pathways—may improve diagnostic accuracy, management skills, and referral appropriateness. Strengthening headache education should be considered a priority to enhance care quality and reduce the burden of one of the most prevalent and disabling neurological conditions.



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