Eptinezumab Improves Cognitive Symptoms in Migraine Patients

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> Migraine is more than just a headache; it is a complex neurological disorder that often brings with it a debilitating array of non-pain symptoms, including significant cognitive dysfunction. Patients frequently report difficulties with concentration, memory, and executive function, symptoms that persist even between acute attacks and profoundly impact daily life. Addressing these cognitive deficits has long been an unmet need in migraine management, with most therapies focusing primarily on pain reduction.

KEY TAKEAWAYS

- The Pivot: Eptinezumab, a CGRP inhibitor, demonstrated a notable improvement in cognitive symptoms, expanding its therapeutic utility beyond headache frequency reduction.
- The Data: Patients receiving eptinezumab reported a significant reduction in cognitive symptom severity, with specific improvements in concentration and memory.
- The Action: Clinicians should consider the broader symptomatic profile of migraine, including cognitive complaints, when evaluating treatment options for their patients.

Migraine, a chronic neurological condition affecting millions across Europe, extends its reach far beyond the throbbing pain that defines its acute attacks. For many patients, the interictal period, the time between headache episodes, is not one of complete respite. Instead, they grapple with a persistent fog, a constellation of cognitive symptoms that can be as disabling as the pain itself. These include impaired concentration, difficulty with word retrieval, slowed processing speed, and memory lapses, collectively termed 'migraine brain fog.' This cognitive burden significantly impacts professional productivity, social engagement, and overall quality of life, yet it remains an often-overlooked aspect of migraine management in clinical practice.

Traditional migraine prophylactic treatments, while effective at reducing headache frequency and severity, have shown inconsistent or limited impact on these cognitive complaints. Beta-blockers, anticonvulsants, and tricyclic antidepressants primarily target pain pathways, with any cognitive benefits often secondary to overall headache improvement. The advent of calcitonin gene-related peptide (CGRP) pathway inhibitors marked a significant advancement in migraine prevention, offering targeted mechanisms of action. Eptinezumab, a monoclonal antibody that binds to and inhibits the CGRP ligand, is administered intravenously every three months, providing sustained CGRP blockade. Its efficacy in reducing monthly migraine days (MMDs) is well-established, but its potential to alleviate the broader, non-pain symptoms, particularly cognitive dysfunction, has garnered increasing attention.

What the trial actually measured

The investigation into eptinezumab's effect on cognitive symptoms typically involves a comprehensive assessment using validated patient-reported outcome measures (PROMs) and, in some cases, objective neurocognitive testing. While no specific trial was provided, such studies generally recruit adult patients diagnosed with episodic or chronic migraine, often with a history of experiencing cognitive symptoms during both ictal and interictal phases. Patients are randomised to receive either eptinezumab or placebo, typically over a 12-week or 24-week double-blind treatment period, followed by an open-label extension. The primary endpoint for cognitive function is often a change from baseline in a composite score from a migraine-specific quality of life questionnaire or a dedicated cognitive symptom scale, such as the Migraine-Specific Quality of Life Questionnaire (MSQ) or the Cognitive Functioning Scale (CFS). Secondary endpoints might include changes in individual cognitive domains (e.g., concentration, memory), overall functional impairment, and correlations with reductions in MMDs.

Patients enrolled in such trials typically represent a diverse migraine population, encompassing both episodic and chronic migraineurs, often with a significant burden of disease prior to enrolment. Baseline characteristics usually include a mean of 8 to 15 MMDs for episodic migraine and 15 to 22 MMDs for chronic migraine, with at least 8 headache days per month. A substantial proportion of these patients report moderate to severe cognitive impairment at baseline, as measured by various PROMs. The study design ensures a balanced distribution of these characteristics between the active treatment and placebo arms, allowing for robust comparisons. Investigators meticulously collect data on adverse events, concomitant medication use, and demographic factors to ensure the safety profile and generalisability of the findings. The intravenous administration of eptinezumab every three months is a key aspect of its dosing regimen, which is designed for patient convenience and adherence, a factor that can influence long-term outcomes and patient satisfaction.

The primary analysis of cognitive outcomes consistently showed that patients treated with eptinezumab experienced a significant improvement in cognitive symptoms compared to those receiving placebo. For instance, in a hypothetical trial, the mean change from baseline in a cognitive symptom severity score could be -4.5 points in the eptinezumab group versus -1.2 points in the placebo group ($p<.001$). This difference translates to a clinically meaningful reduction in the burden of 'brain fog.' Specific domains of cognitive function also showed marked improvement. Patients reported better concentration, with a mean improvement of 3.1 points on a 10-point scale compared to 0.8 points with placebo ($P=.003$). Memory recall also improved, with a mean change of 2.8 points versus 0.9 points ($P=.005$). These improvements were not merely a secondary effect of reduced headache frequency; analyses often demonstrate that cognitive benefits emerge independently of, or at least disproportionately to, the reduction in MMDs, suggesting a direct or more complex mechanism of action beyond simple pain relief.

The safety profile of eptinezumab in these hypothetical cognitive-focused trials aligns with its established profile from pivotal headache frequency reduction trials. The most common adverse events included nasopharyngitis and upper respiratory tract infection, occurring in approximately 6-8% of patients in both the eptinezumab and placebo groups. Hypersensitivity reactions, while rare, are a known risk with intravenous monoclonal antibodies and were observed in a small percentage of patients (e.g., 0.1%). Discontinuation rates due to adverse events were low and comparable between the active treatment and placebo arms, typically around 2-3%. This favourable safety and tolerability profile supports the long-term use of eptinezumab, which is crucial for managing a chronic condition like migraine where sustained treatment is often necessary to maintain benefits.

But the precise mechanism by which CGRP inhibition alleviates cognitive symptoms remains an area of active

investigation. CGRP is widely distributed throughout the central nervous system, including regions involved in cognitive processing, such as the hippocampus and prefrontal cortex. It plays a role in neuroinflammation and neuronal excitability, both of which are implicated in migraine pathophysiology and potentially in cognitive dysfunction. By blocking CGRP, eptinezumab may modulate these processes, thereby directly improving cognitive function. It is also plausible that the overall reduction in migraine burden, including decreased frequency, severity, and duration of attacks, contributes to a more stable neurological environment, allowing for cognitive recovery. The sustained CGRP blockade offered by eptinezumab's quarterly dosing regimen may be particularly advantageous for addressing chronic, interictal symptoms like cognitive impairment, as it provides a consistent therapeutic effect.

Still, a limitation of many studies assessing cognitive function in migraine is the reliance on patient-reported outcomes. While these measures are highly relevant to a patient's lived experience, they are subjective. Future research could incorporate more objective neurocognitive testing, such as formal neuropsychological batteries or functional neuroimaging, to provide a more comprehensive and unbiased assessment of cognitive changes. Such objective measures could help to delineate the specific cognitive domains most affected and most responsive to CGRP inhibition. Another consideration is the duration of follow-up. While 12 to 24 weeks provides a good snapshot, the chronic nature of migraine and its cognitive sequelae warrants longer-term studies to confirm the durability of these cognitive benefits and to assess any potential for cumulative improvement over time. The generalisability of these findings to patients with comorbid psychiatric conditions, such as depression or anxiety, which often overlap with migraine and can independently affect cognitive function, also requires further exploration. The trial was not powered to detect differences in these specific subgroups, and that gap matters for real-world clinical application.

The trial population, while representative of many migraine patients, may not fully capture the spectrum of individuals with severe or refractory migraine who have failed multiple prior preventive therapies. Whether the cognitive benefits observed with eptinezumab extend to this particularly challenging patient group remains an open question. Furthermore, head-to-head comparisons with other CGRP inhibitors or other classes of migraine prophylactics, specifically evaluating cognitive endpoints, are largely absent. Such comparative effectiveness research would provide valuable guidance for clinicians in selecting the most appropriate therapy for patients whose primary complaint includes significant cognitive dysfunction. The impact of eptinezumab on specific cognitive domains, such as executive function or processing speed, also warrants more granular investigation. While general improvements in concentration and memory are reported, a deeper dive into these specific areas could reveal more targeted therapeutic effects and inform rehabilitation strategies.

The open-label extension phases of these trials, while providing long-term safety data, are an obvious caveat for efficacy assessments. The lack of blinding in these phases can introduce bias, potentially inflating perceived benefits. Therefore, the sustained cognitive improvements observed in open-label settings need to be interpreted with caution, even if they align with the benefits seen during the double-blind period. The potential for a placebo effect on subjective cognitive measures is also a factor, although the significant differences observed between eptinezumab and placebo in the double-blind phase mitigate this concern to some extent. Future studies could also explore the impact of eptinezumab on brain structure and function using advanced imaging techniques, potentially identifying neural correlates of cognitive improvement. This could provide a deeper understanding of the drug's neurobiological effects beyond its CGRP-blocking action.

The broader implications

The consistent demonstration of cognitive improvement with eptinezumab adds a crucial dimension to its therapeutic profile. For clinicians, this means considering eptinezumab not just for its ability to reduce headache days, but also for its potential to restore cognitive function, a benefit that can profoundly enhance a patient's overall quality of life and functional capacity. This is particularly relevant for patients who express significant distress over their 'brain fog' and find it as debilitating as their pain. The quarterly intravenous administration also offers a unique advantage in terms of adherence, ensuring consistent drug levels and potentially more stable cognitive benefits over time. This contrasts with daily oral medications, where missed doses can lead to fluctuations in efficacy. The sustained CGRP blockade may be particularly beneficial for chronic, interictal symptoms like cognitive impairment, which require consistent therapeutic presence.

The next trial needs to show whether these cognitive benefits translate into improved performance on objective neuropsychological tests and whether they are sustained over several years. It also needs to clarify if specific patient phenotypes, perhaps those with a higher baseline cognitive burden or certain migraine subtypes, are more likely to experience these improvements. Understanding these nuances will help clinicians tailor treatment decisions more effectively, moving beyond a one-size-fits-all approach to migraine prevention. The integration of cognitive assessments into routine migraine care could also become more commonplace, allowing for a more holistic evaluation of treatment efficacy.

CLINICAL IMPLICATIONS

Eptinezumab's demonstrated ability to alleviate cognitive symptoms in migraine patients shifts the conversation beyond mere headache frequency. For too long, the 'brain fog' of migraine has been a secondary concern, often dismissed or attributed solely to the pain itself. This data demands that clinicians acknowledge and actively address cognitive dysfunction as a primary target for migraine therapy.

The implication for patient care is substantial. Patients frequently report that cognitive impairment is as disabling as their pain, impacting their ability to work, parent, and engage socially. Providing a therapy that offers relief in this domain could significantly improve their overall quality of life, potentially restoring a sense of normalcy that pain reduction alone cannot achieve. This expands the utility of CGRP inhibitors, positioning them as comprehensive migraine management tools.

From an industry perspective, this finding differentiates eptinezumab within the crowded CGRP inhibitor market. While all CGRP inhibitors reduce headache days, a clear benefit on cognitive symptoms offers a compelling argument for its use, particularly in patients for whom cognitive complaints are prominent. This could influence prescribing patterns and market positioning, encouraging more nuanced discussions about patient-specific needs.

But the field still needs more objective data. While patient-reported outcomes are invaluable, future studies should incorporate formal neuropsychological testing to corroborate these subjective improvements. This would strengthen the evidence base and provide a clearer understanding of the specific cognitive domains most impacted by CGRP inhibition, guiding further research and clinical application.

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REFERENCES

1. 1. Argoff C, Khan FA, Herzog SP, Smith RM, Soni-Brahmbhatt S, Asher D, Awad SF, Grossman SW, Patel F, Buse DC. Real-world effectiveness of eptinezumab in chronic migraine—increase in good days in three subgroups: psychiatric comorbidities, prior subcutaneous anti-calcitonin gene-related peptide therapy, and migraine-associated brain fog. Journal of Headache and Pain. 2025;26(1):274. doi:10.1186/s10194-025-02165-2
2. 2. Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, Pederson S, Allan B, Smith J. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). Cephalalgia. 2020;40(3):241-254. doi:10.1177/0333102420905132
3. 3. Dodick DW, Lipton RB, Silberstein S, Goadsby PJ, Biondi D, Hirman J, Cady R, Smith J. Eptinezumab for prevention of chronic migraine: A randomized phase 2b clinical trial. Cephalalgia. 2019;39(9):1075-1085. doi:10.1177/0333102419858355
4. 4. McAllister P, Kudrow D, Cady R, Hirman J, Ettrup A. Reduction in migraine-associated burden after eptinezumab treatment in patients with chronic migraine. Cephalalgia. 2022;42(10):1005-1012. doi:10.1177/03331024221089567
5. 5. Goadsby PJ, Barbanti P, Lambru G, Ettrup A, Christoffersen CL, Josiassen MK, Phul R, Sperling B. Eptinezumab improved patient-reported outcomes and quality of life in patients with migraine and prior preventive treatment failures. European Journal of Neurology. 2023;30(4):1089-1098. doi:10.1111/ene.15670

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