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Perspective

The botox paradox: beyond episodic and chronic migraine and the need for a new nomenclature for treatment-induced remission

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Abstract

The International Classification of Headache Disorders, 3rd edition (ICHD-3), distinguishes episodic from chronic migraine mainly by headache frequency. However, increasingly effective preventive therapies have exposed a limitation of this framework: patients with chronic migraine who respond to treatment may fall below the diagnostic threshold for chronic migraine and subsequently be classified as having episodic migraine, despite requiring continued therapy to maintain this clinical state. This issue is particularly evident with onabotulinumtoxinA, whose efficacy is established in chronic but not episodic migraine. Successful treatment may therefore reclassify a patient into a diagnostic category for which the same therapy is not generally indicated—a phenomenon we term the "Botox paradox". Similar transitions occur with calcitonin gene-related peptide-targeted preventive therapies and may become increasingly relevant as migraine treatment advances. We argue that primary episodic migraine and treatment-induced remission of chronic migraine represent clinically distinct states that should not be conflated by nomenclature. We propose that future headache classifications consider terminology such as "chronic migraine in remission" to preserve information about the underlying disease trajectory, improve clinical and research communication, and better reflect the dynamic nature of migraine under effective preventive treatment.

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The purpose of a medical classification extends far beyond assigning diagnostic labels. A robust classification should distinguish entities that differ in pathophysiology, prognosis, therapeutic response, and biological behavior. As medical knowledge evolves, classifications require periodic revision to incorporate new concepts and avoid oversimplification. The International Classification of Headache Disorders 3 (ICHD-3) has been extraordinarily successful in standardizing headache diagnosis worldwide (1). Nevertheless, advances in preventive migraine therapy have exposed a conceptual limitation that deserves reconsideration (1,2).

Under the current ICHD-3 criteria, migraine is categorized as episodic or chronic according to the number of headache days per month. This distinction has proven clinically useful and has guided therapeutic development for more than two decades. However, the classification assumes that disease status is static. It does not distinguish patients whose phenotype is naturally episodic from those whose episodic phenotype is the direct consequence of successful preventive treatment (1,2).

This distinction is not merely semantic. It reflects different biological states.

Consider two patients who both fulfill ICHD-3 criteria for episodic migraine during today's consultation. The first has always had four migraine days per month and has never required preventive therapy. The second previously experienced twenty-five headache days per month, fulfilled criteria for chronic migraine, and after one year of treatment with onabotulinumtoxinA now has only five migraine days per month. According to the current classification, both patients are simply classified as having episodic migraine. Yet they clearly are not the same disease state.

The first patient has primary episodic migraine. The second has chronic migraine successfully controlled by preventive therapy. Their underlying biology, prognosis, risk of relapse, treatment requirements, and response to preventive therapies are fundamentally different.

This limitation becomes particularly evident with onabotulinumtoxinA. Randomized controlled trials established its efficacy exclusively in chronic migraine, leading to its approval only for this population. Patients with primary episodic migraine did not demonstrate comparable benefit and therefore the treatment is generally not indicated in this setting. However, after several treatment cycles, many chronic migraine patients improve sufficiently to fall below the diagnostic threshold of fifteen headache days per month. They are subsequently classified as having episodic migraine, despite continuing the same treatment that produced the remission (3,4).

This creates an apparent paradox, which we propose to call the "Botox paradox": onabotulinumtoxinA has demonstrated efficacy only in chronic migraine, yet successful treatment converts many patients into the episodic migraine category while the therapy remains effective and often indispensable. The paradox therefore lies not in the pharmacological action of onabotulinumtoxinA, but in the current classification system, which fails to distinguish primary episodic migraine from treatment-induced remission of chronic migraine (3–5).

If onabotulinumtoxinA is ineffective for episodic migraine, why does it remain effective in patients who are now classified as episodic migraine?

The answer is straightforward. These patients do not have primary episodic migraine. They have chronic migraine in therapeutic remission. The paradox therefore lies not in the biology of the disease or in the pharmacology of the treatment, but in the limitations of the current nomenclature.

The same phenomenon is increasingly observed with monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or its receptor. Large proportions of patients initially diagnosed with chronic migraine revert to episodic migraine after months of treatment. Nevertheless, discontinuation frequently results in recurrence of chronic migraine. Their episodic phenotype exists only while effective preventive therapy is maintained (6–11).

Current terminology fails to acknowledge this distinction.

Interestingly, this issue has already emerged in the migraine literature, although without formal incorporation into headache classification. Lipton and colleagues introduced the concept of "remission from chronic migraine to episodic migraine," recognizing that chronic migraine may revert to an episodic pattern. Their terminology appropriately described the clinical observation but did not propose a new diagnostic category. Similarly,

An important distinction should be made between reversion and remission. Reversion from chronic migraine to episodic migraine has generally been used to describe an observed reduction in headache frequency below the diagnostic threshold for chronic migraine. However, this frequency-based transition does not necessarily imply resolution of the underlying susceptibility to chronic migraine, particularly when the episodic-frequency phenotype is maintained by ongoing preventive treatment. In this context, remission may be a more informative term because it preserves the patient's history of chronic migraine while acknowledging the current controlled disease state (6,12).

European Headache Federation recommendations regarding onabotulinumtoxinA recognize that many patients become episodic during treatment while simultaneously discussing the uncertainty surrounding treatment discontinuation because relapse remains common (5,6,13,14). Thus, the concept of remission already exists. What remains absent is terminology capable of distinguishing re-

mission induced by treatment from naturally occurring episodic migraine.

Medicine already employs this concept in many chronic disorders. Patients with rheumatoid arthritis who respond to biologic therapy are described as being "in clinical remission." Patients with inflammatory bowel disease may achieve "endoscopic remission." Oncology routinely distinguishes active disease from complete remission. Epilepsy recognizes patients as being seizure-free on treatment. Hypertension controlled by medication is not considered cured merely because blood pressure has normalized. Migraine should adopt similar language.

A patient whose chronic migraine has become episodic through preventive therapy should not simply be reclassified as episodic migraine. Such terminology obscures the patient's clinical history and biological vulnerability.

We therefore propose that future classifications consider introducing terminology capable of identifying treatment-induced remission.

Several expressions may be appropriate, including: (1) Chronic migraine in remission; (2) Chronic migraine in treatment-associated remission; (3) Treatment-induced episodic migraine; or Chronic migraine controlled with preventive therapy.

Among these, "chronic migraine in remission" appears to be the simplest, most intuitive, and most consistent with terminology already used across medicine. Such terminology offers several advantages. First, it preserves information regarding the patient's original disease biology. Second, it better explains why preventive therapy remains necessary despite apparent conversion to episodic migraine. Third, it facilitates interpretation of clinical trials, observational studies, and real-world evidence by distinguishing patients with primary episodic migraine from those with treatment-induced remission. Fourth, it improves communication between physicians, researchers, regulatory agencies, and patients.

Finally, it better reflects contemporary understanding that migraine is a dynamic disorder whose phenotype may change over time, either spontaneously or through effective intervention (13).

This discussion extends well beyond onabotulinumtoxinA. It equally applies to CGRP monoclonal antibodies, oral CGRP receptor antagonists used preventively, and perhaps future disease-modifying therapies capable of inducing prolonged remission. As preventive treatments become increasingly effective, larger numbers of patients will no longer satisfy the diagnostic threshold for chronic migraine while continuing to require treatment to prevent relapse (14–16).

Without an appropriate nomenclature, the discrepancy between diagnosis and disease biology will continue to grow. The ICHD has always evolved alongside advances in headache science. The introduction of chronic migraine itself represented an important conceptual advance. Today, effective preventive therapies challenge us once again to refine our terminology. Classification should describe not only the number of headache days observed during a clinic visit but also the biological state that produced that phenotype.

Recognizing "chronic migraine in remission" would not replace existing diagnostic criteria. Rather, it would complement them by acknowledging that identical phenotypes may arise from different biological pathways and therefore require different clinical management.

As migraine treatment enters an era increasingly focused on disease modification rather than simple symptom reduction, our nomenclature should evolve accordingly. Accurate terminology is not merely an academic exercise. It shapes clinical reasoning, influences therapeutic decisions, guides research, and ultimately improves patient care (11,15,16).

The "Botox paradox" is therefore not a paradox of therapy, but a paradox of nomenclature. Resolving it requires not new treatments, but a more accurate classification capable of distinguishing primary episodic migraine from chronic migraine in treatment-induced remission.

References

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211. Doi:10.1177/0333102417738202.
2. Chalmer MA, Hansen TF, Lebedeva ER, Dodick DW, Lipton RB, Olesen J. Proposed new diagnostic criteria for chronic migraine. Cephalalgia 2020;40:399–406. Doi:10.1177/0333102419877171.
3. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Results From the Double-Blind, Randomized, Placebo-Controlled Phases of the PREEMPT Clinical Program. Headache: The Journal of Head and Face Pain 2010;50:921–36. Doi:10.1111/j.1526-4610.2010.01678.x.
4. Aurora SK, Gawel M, Brandes JL, Pokta S, VanDenburgh AM. Botulinum Toxin Type A Prophylactic Treatment of Episodic Migraine: A Randomized, Double-Blind, Placebo-Controlled Exploratory Study. Headache: The Journal of Head and Face Pain 2007;47:486–99. Doi:10.1111/j.1526-4610.2006.00624.x.
5. Bendtsen L, Sacco S, Ashina M, Mitsikostas D, Ahmed F, Pozo-Rosich P, et al. Guideline on the use of onabotulinumtoxinA

in chronic migraine: a consensus statement from the European Headache Federation. J Headache Pain 2018;19. Doi:10.1186/s10194-018-0921-8.
6. Lipton RB, Tepper SJ, Silberstein SD, Kudrow D, Ashina M, Reuter U, et al. Reversion from chronic migraine to episodic migraine following treatment with erenumab: Results of a post-hoc analysis of a randomized, 12-week, double-blind study and a 52-week, open-label extension. Cephalalgia 2021;41:6–16. Doi:10.1177/0333102420973994.
7. Lipton RB, Cohen JM, Bibeau K, Galic M, Seminerio MJ, Ramirez Campos V, et al. Reversion From Chronic Migraine to Episodic Migraine in Patients Treated With Fremanezumab: Post Hoc Analysis From HALO CM Study. Headache 2020;60:2444–53. Doi:10.1111/head.13997.
8. Wang S-J, Kim B-K, Wang H, Zhou J, Wan Q, Yu T, et al. Effect of erenumab on the reversion from chronic migraine to episodic migraine in an Asian population: A post hoc analysis of the DRAGON study. Headache 2025;65:143–52. Doi:10.1111/head.14733.
9. Raffaelli B, Terhart M, Overeem LH, Mecklenburg J, Neeb L, Steinicke M, et al. Migraine evolution after the cessation of CGRP(-receptor) antibody prophylaxis: a prospective, longitudinal cohort study. Cephalalgia 2022;42:326–34. Doi:10.1177/03331024211046617.
10. Gantenbein AR, Agosti R, Gobbi C, Flügel D, Schankin CJ, Viceic D, et al. Impact on monthly migraine days of discontinuing anti-CGRP antibodies after one year of treatment - a real-life cohort study. Cephalalgia 2021;41:1181–6. Doi:10.1177/03331024211014616.
11. Makita LM, Fagundes TP, Reginato PH, Carpinelli LP, de Freitas Morais G, Montanarin RT, et al. Estimating Changes in Clinical Outcomes after Discontinuation of Anti-CGRP Targeting Therapy for Migraine Prophylaxis: A Systematic Review and Meta-analysis. CNS Drugs 2026;40:71–82. Doi:10.1007/s40263-025-01233-0.
12. Lipton RB, Penzien DB, Turner DP, Smitherman TA, Houle TT. Methodological Issues in Studying Rates and Predictors of Migraine Progression and Remission. Headache: The Journal of Head and Face Pain 2013;53:930–4. Doi:10.1111/head.12128.
13. Manack A, Buse DC, Serrano D, Turkel CC, Lipton RB. Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. Neurology 2011;76:711–8. Doi:10.1212/WNL.0b013e31820d8af2.
14. Sacco S, Amin FM, Ashina M, Bendtsen L, Deligianni CI, Gil-Gouveia R, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update. J Headache Pain 2022;23. Doi:10.1186/s10194-022-01431-x.
15. Puledda F, Sacco S, Diener H-C, Ashina M, Al-Khazali HM, Ashina S, et al. International Headache Society Global Practice Recommendations for Preventive Pharmacological Treatment of Migraine. Cephalalgia 2024;44. Doi:10.1177/03331024241269735.
16. Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. Headache: The Journal of Head and Face Pain 2024;64:333–41. Doi:10.1111/head.14692.

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