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COMMENTARY

Unmet Needs in Preventive Treatment of Migraine

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ABSTRACT

Migraine represents the most common cause of work disability in young women and the second one in the general population. Preventive treatment can reduce the frequency of attacks and their intensity, consequently improving the quality of life. Despite this, global health systems have shown important gaps in addressing optimal management of preventive therapy. Despite numerous adverse effects of traditional medications for migraine prevention being well known, these medications continue to be considered the standard of care for prophylaxis of this disease in many contexts. On the other hand, the widespread use of calcitonin gene-related peptide (CGRP) receptor antagonists, which have marked a breakthrough in prophylactic therapy of migraine, has been limited because of their high cost. We also highlight important shortcomings in migraine management by general practitioners (GPs) and poor patient education on the disease with a consequent delay in referring selected patients to dedicated headache centres. Over the next few years, we expect the headache medicine community to mobilize to address these gaps in preventive treatment of migraine.

Keywords: Migraine prevention; Calcitonin gene-related peptide (CGRP) receptor antagonists; Antimigraine drugs; Migraine education

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Key Summary Points

Migraine represents the most common neurological disorder with enormous social and economic impact.

Despite the great strides of recent years, several important unmet needs in the preventive treatment of migraine still need to be addressed.

Traditional medications have several limitations but continue to be considered the standard of care for migraine prophylaxis in many contexts.

The advent of calcitonin gene-related peptide (CGRP) receptor antagonists marked a turning point in migraine prophylaxis but their widespread use has been limited by their high cost.

Over the next few years, we expect that the headache medicine community can raise awareness of national health services to support modern preventive therapies.

PREVENTIVE TREATMENT OF MIGRAINE

Migraine represents a disease with enormous social and economic impact. It affects around one billion people around the world. It represents the most common cause of work disability in young women according to the Global Burden of Diseases 2019 [1, 2] and the second among the world's causes of disability in general population [3]. It has been amply demonstrated how this pathology greatly impacts work productivity and health-related quality of life, requiring the use of a great deal of healthcare resources [4–8]. Despite this, global health systems have shown important gaps in addressing its prevention: the great diffusion of this pathology is not accompanied by equally widespread information on preventive therapeutic strategies. Preventive treatment can reduce the frequency of attacks and their intensity, consequently improving the quality of life and reducing the risk of progression to chronic migraine. Indications for starting prophylactic treatment include at least four headaches a month and/or eight or more headache days a month, debilitating attacks or difficulty tolerating/contraindication to acute therapy or medication overuse headache. Some data suggest that almost 40% of patients with episodic migraines could benefit from starting prophylactic treatment, but nonetheless just over 10% of patients that could benefit from it take preventive treatment [9]. This gap unfortunately affects both patients and physicians, in particular general practitioners (GPs) who should refer selected patients to dedicated centres. The reasons for these unmet needs in prophylactic migraine therapy are manifold.

SHORTCOMINGS OF TRADITIONAL TREATMENTS

Despite numerous adverse effects of traditional medications for migraine prevention (beta blockers, calcium channel blockers, antidepressants, anticonvulsants) being well known, these medications continue to be considered the standard of care for prophylaxis of this disease in many contexts. These treatments also show many adverse effects (AEs), including weight gain, bradycardia and erectile dysfunction for beta blockers, and fetotoxicity, depression and weight loss for topiramate—the most widely used anticonvulsant in migraine. The last AEs are of particular importance if we consider the population to which the treatment is directed, often young women of childbearing age. Amitriptyline, a drug considered first-line in migraine prophylaxis (especially in the presence of a concomitant tension-type headache), very commonly leads the patient to suffer from drowsiness and constipation [10]. The common AEs of traditional prophylaxis therapies cause patients to further distance themselves from the correct use of appropriate medications and worsen the level of doctor–patient confidence, thereby increasing the risk of acute phase drug abuse and the risk of evolution to chronic

migraine or the onset of medication overuse headache [11].

ANTI-CGRP(R) MONOCLONAL ANTIBODIES

In recent years there has been an exponential growth of clinical trials and the introduction of new drugs for the prevention of migraine [12]. In particular, monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) signalling pathway marked a turning point in the treatment of this pathology with promising results. Currently, these molecules are at the forefront of migraine treatment. Their choice is based on the different route of administration: subcutaneous (fremanezumab, erenumab and galcanezumab) or intravenous (eptinezumab) and on the different pharmacokinetic times [13]. Eremumab was the first CGRP-directed drug approved for migraine prophylaxis, receiving approval in the European Union (EU) in 2018 [14, 15]. Eptinezumab is the only one that can be administered intravenously and is approved by the US Food and Drug Administration (FDA) for migraine prophylaxis [16]. Fremanezumab, which was the third CGRP targeting mAbs approved in the EU for prophylaxis of chronic and episodic migraine in 2019 [17, 18], showed lower incidence of side effects compared to others drugs of the same class and, contrary to these, the continuation of prior ongoing preventive treatment is not contraindicated once fremanezumab is started [19]. Galcanezumab, authorized in the EU in 2018, appears to be particularly more effective in patients with chronic migraine than in those with episodic migraine and it seems to maintain its therapeutic effects up to 1 year after its interruption [20]. These drugs represented a revolution in the management of migraine prophylaxis because the side effects are minimal when compared to those of traditional treatments, mainly consisting in constipation and reactions at the site of injection [21]. Little is known about their adverse effects during pregnancy, so it is preferred to avoid their use during this period [22]. Other patients for which—as a result of the lack of data—there is still caution in the use of these drugs are those with cardiovascular diseases and those outside the age group between 18 and 65 years. Nonetheless, the safety profile is considered an important strong point of these drugs that show good efficacy, tolerability and safety.

ECONOMIC ISSUES OF NATIONAL HEALTH SYSTEMS

The main shortcoming of the news class of molecules for migraine prophylaxis is their high cost, which unfortunately greatly limits their widespread adoption. It is also important to underline that not all European Union member countries dispense the modern treatments for migraine prevention. The economic issue becomes even more severe when looking at the combination therapy with botulinum and anti-CGRP signaling pathway drugs. In fact, combination therapy seems to have given excellent results in resistant and refractory migraine [23]. Despite such evidence, current guidelines continue to see monotherapy as the standard of care and current clinical practices very rarely see the use of the combination strategy [24]. The issue of cost should not divert attention from the enormous and often underestimated impact that migraine has on the population, as comprehensively documented by global health services. A strong signal was given by Italy—which has proved to be at the forefront in this sense—by recognizing, with a 2020 law, chronic headache as a disabling pathology, falling within social diseases [25].

PRIMARY CARE GAPS AND DELAYS IN APPROPRIATE TREATMENT

It has been shown that in Europe there is a large gap in the quality of migraine treatment among GPs [26], although most patients are entrusted to primary care and only a minor proportion are referred to specialized centres. Furthermore, the degree of patient satisfaction does not reflect the quality of care [26], potentially implying that patients who are unable to recognize a

good level of treatment will often remain with inappropriate therapies for extended periods. Adding to this, chronic diseases and chronic pain are often associated with a stigmatizing approach [27]. There has been an enormous lack of information, lack of services, delay in diagnosis, and correctness of treatments. The combination of these factors leads to long delays before patients are referred to dedicated headache centres, with a consequent greater risk of chronicity and abuse of acute phase drugs. It has been shown that, on average, a patient waits more than 10 years between onset of symptoms and correct diagnosis, with almost four hospitals visited before being referred to the final centre [28]. There is generally a low level of satisfaction with the physician–patient relationship in this disease, and less than 30% of migraine patients take medications correctly. Considering all the above, it becomes clear how some of the efforts should be directed to improve education of patients, and to a better preparation of GPs for a more informed selection of cases eligible for new therapies [29]. Overcoming these unmet needs would lead to a substantial social and occupational benefit for the global population. The spread of a greater culture of understanding migraine and overcoming these gaps will bring widespread benefit, especially to the less affluent populations and those who have less access to centres of excellence [30].

CONCLUSIONS

Over the next few years, we expect that there will be a progressive abandonment of the old drugs considered standard of care in the prevention of migraine. We hope that the clinical community of headache medicine will support clinical research with efforts to educate GPs in order to promptly direct patients to prevention and select cases eligible for new therapies, as well as stimulating national health services to support modern preventive therapies and in particular to encourage the spread of anti-CGRP therapies and anti-CGRP–botulinum combination therapy when it is necessary. However, it should be emphasized that, despite their great effectiveness, this category of new preventive medications benefits a fraction of patients. Clinical practice teaches us that there are indeed some non-responder patients. It would be useful in the coming years to identify the characteristics of these patients in advance, if there are also the conditions for a personalized medicine approach with this category of drugs. Attention must be paid to intercept patients evolving towards chronicity before they need detoxification from acute drug abuse. At the same time, it is also necessary to spend time and energy in educating patients on the correct use of antimigraine drugs in order to prevent their abuse and the need to resort to detoxification therapies. Dealing with all these major unmet needs in preventive treatment of migraine is necessary to move towards a standard of excellence in this area.

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REFERENCES

1. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. J Headache Pain. 2022;23(1):34. https://doi.org/10.1186/s10194-022-01402-2.

2. Steiner TJ, Stovner LJ, Jensen R, et al. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain. 2020;21(1):137.

3. Kang S, Eum S, Chang Y, et al. Burden of neurological diseases in Asia from 1990 to 2019: a systematic analysis using the Global Burden of Disease Study data. BMJ Open. 2022;12(9):e059548. https://doi.org/10.1136/bmjopen-2021-059548.

4. Kim BK, Chu MK, Yu SJ, et al. Burden of migraine and unmet needs from the patients' perspective: a survey across 11 specialized headache clinics in Korea. J Headache Pain. 2021;22(1):45 (Erratum in: J Headache Pain 2021;22(1):56).

5. Takeshima T, Wan Q, Zhang Y, et al. Prevalence, burden, and clinical management of migraine in China, Japan, and South Korea: a comprehensive review of the literature. J Headache Pain. 2019;20(1):111.

6. Agosti R. Migraine burden of disease: from the patient's experience to a socio-economic view. Headache. 2018;58(Suppl 1):17–32. https://doi.org/10.1111/head.13301.

7. Yucel A, Thach A, Kumar S, Loden C, Bensink M, Goldfarb N. Estimating the economic burden of migraine on US employers. Am J Manage Care. 2020;26(12):e403–8. https://doi.org/10.37765/ajmc.2020.88547.

8. Martelletti P, Schwedt TJ, Lanteri-Minet M, et al. My migraine voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. J Headache Pain. 2018;19(1):115.

9. Ha H, Gonzalez A. Migraine headache prophylaxis. Am Fam Physician. 2019;99(1):17–24.

10. Agostoni EC, Barbanti P, Calabresi P, et al. Current and emerging evidence-based treatment options in chronic migraine: a narrative review. J Headache Pain. 2019;20(1):92. https://doi.org/10.1186/s10194-019-1038-4.

11. Burch RC, Buse DC, Lipton RB. Migraine: epidemiology, burden, and comorbidity. Neurol Clin. 2019;37(4):631–49. https://doi.org/10.1016/j.ncl.2019.06.001.

12. Bentivegna E, Luciani M, Ferrari V, et al. Recently approved and emerging drug options for migraine prophylaxis. Expert Opin Pharmacother. 2022;23(11):1325–35. https://doi.org/10.1080/14656566.2022.2102420.

13. Benemei S, Bentivegna E, Martelletti P. Positioning the new drugs for migraine. Expert Opin Drug Metab Toxicol. 2022;18(1):1–3. https://doi.org/10.1080/17425255.2022.2049236.

14. Sacco S, Bendtsen L, Ashina M, et al. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. J Headache Pain. 2019;20:6.

15. Aimovig, INN-erenumab - European Medicines Agency. Summary of Product Characteristics.

https://www.ema.europa.eu/en/documents/product-information/aimovig-epar-product-information_en.pdf. Accessed 2 Dec 2022.

16. Spuntarelli V, Negro A, Luciani M, Bentivegna E, Martelletti P. Eptinezumab for the treatment of migraine. Expert Opin Biol Ther. 2021;21(8):999–1011. https://doi.org/10.1080/14712598.2021.1931678.

17. Bigal ME, Walter S, Rapoport AM. Fremanezumab as a preventive treatment for episodic and chronic migraine. Expert Rev Neurother. 2019;19(8):719–28. https://doi.org/10.1080/14737175.2019.1614742.

18. AJOVY, INN-fremanezumab. Available at: https://www.ema.europa.eu/en/documents/product-information/ajovy-epar-product-information_it.pdf. Accessed 2 Dec 2022.

19. Lionetto L, Cipolla F, Guglielmetti M, Martelletti P. Fremanezumab for the prevention of chronic and episodic migraine. Drugs Today (Barc). 2019;55(4):265–76. https://doi.org/10.1358/dot.2019.55.4.2970909.

20. Raffaelli B, Mussetto V, Israel H, Neeb L, Reuter U. Erenumab and galcanezumab in chronic migraine prevention: effects after treatment termination. J Headache Pain. 2019;20(1):66. https://doi.org/10.1186/s10194-019-1018-8.

21. Mulleners WM, Kim BK, Láinez MJA, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurol. 2020;19(10):814–25. https://doi.org/10.1016/S1474-4422(20)30279-9.

22. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006. Galcanezumab. 2020 Jul 20. (PMID: 30372007).

23. Sacco S, Braschinsky M, Ducros A, et al. European Headache Federation consensus on the definition of resistant and refractory migraine: developed with the endorsement of the European Migraine & Headache Alliance (EMHA). J Headache Pain. 2020;21(1):76. https://doi.org/10.1186/s10194-020-01130-5.

24. American Headache Society. The American Headache Society Position statement on integrating new migraine treatments into clinical practice. Headache. 2019;59(1):1–18. https://doi.org/10.1111/head.13456.

25. Disposizioni per il riconoscimento della cefalea primaria cronica come malattia sociale. (20G00100) (GU Serie Generale n.188 del 28-07-2020). Available at: https://www.gazzettaufficiale.it/eli/id/2020/07/28/20G00100/sg. Accessed 2 Dec 2022.

26. Lenz B, Katsarava Z, Gil-Gouveia R, et al. The burden: the global campaign against headache. Headache service quality evaluation: implementation of quality indicators in primary care in Europe. J Headache Pain. 2021;22(1):33. https://doi.org/10.1186/s10194-021-01236-4.

27. Perugino F, De Angelis V, Pompili M, Martelletti P. Stigma and chronic pain. Pain Ther. 2022. https://doi.org/10.1007/s40122-022-00418-5.

28. Ashina M, Katsarava Z, Do TP, et al. Migraine: epidemiology and systems of care. Lancet. 2021;397(10283):1485–95. https://doi.org/10.1016/S0140-6736(20)32160-7.

29. Negro A, Martelletti P. Patient selection for migraine preventive treatment with anti-CGRP(r) monoclonal antibodies. Expert Rev Neurother. 2019;19(8):769–76. https://doi.org/10.1080/14737175.2019.1621749.

30. Ambat FDF, Bentivegna E, Martelletti P. Novel migraine therapies may reduce public and personal disadvantages for people with migraine. BioDrugs. 2022;36(3):337–9. https://doi.org/10.1007/s40259-022-00532-y.