Int. j. adv. multidisc. res. stud. 2026; 6(4):1529-1530

Received: 02-08-2026
Accepted: 12-08-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

Are Idebenone, Taurine, Doxecitine/Doxribtimine, and Elamipretide Actually Beneficial for Mitochondrial Disorders in Real World Experience

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DOI: https://doi.org/10.62225/2583049X.2026.6.4.6775
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Letter to the Editor

We read with interest the article by Wang *et al*., which provides a comprehensive overview of experimental as well as approved invasive and non-invasive therapies for mitochondrial diseases (MIDs) [1]. It highlighted that four agents are approved for the treatment of MIDs: idebenone for Leber's hereditary optic neuropathy (LHON) in the EU, taurine for MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) in Japan, doxecitabine and doxuridine for thymidine kinase 2 deficiency (TK2D) in the USA, and elamipretide for Barth syndrome in the USA [1]. While this review is forward-looking, certain aspects warrant discussion.

Idebenone is an antioxidant that, while capable of enhancing mitochondrial antioxidant capacity, may not be effective against other pathophysiological changes in the mitochondria. Furthermore, spontaneous recovery is known to occur in some LHON patients [2]. Consequently, it is often difficult to determine conclusively whether an improvement is attributable to idebenone itself or to the spontaneous course of the disease. Moreover, the efficacy of idebenone can depend heavily on the mutated gene, the mutation type, the distinction between pure LHON and LHON-plus, concomitant medications, and comorbidities unrelated to mtDNA. As no cohorts homogeneous with respect to these confounding factors have been studied to date, it is difficult to draw general conclusions regarding its benefits or to assess whether any potential effect extends to all LHON subtypes. Overall, the possibility cannot be ruled out that the therapeutic effect of idebenone in LHON is limited to specific subtypes and remains uncertain for others.

As for taurine, it is—much like idebenone—an antioxidant that likely influences only those pathophysiological mechanisms associated with oxidative stress. However, antioxidants presumably have no impact on the genetic defect itself, on mtDNA replication, maintenance, or repair, or on mitochondrial physiological functions. Although it has been concluded that taurine prevents stroke-like episodes (SLEs) [1], the baseline incidence of SLEs in MELAS, the factors predicting them, the risk and triggering factors involved in their development, their recurrence rate, and their clinical course remain unknown. Given that genotypes and phenotypes can differ significantly among MELAS patients—due to the diverse factors influencing the phenotypic expression of the mutation [3]—therapeutic efficacy can vary widely from patient to patient. It depends, among other things, on the specific characteristics of the underlying genetic defect and the factors governing phenotypic expression. Furthermore, it should be noted that taurine is not free of side effects, particularly at the dosages used (9–12 g/day). Common side effects at recommended doses include nausea, vomiting, diarrhea, and abdominal pain [4]. Headache, dizziness, and fatigue may also occur. Since taurine is generally effective only at high doses, such side effects are highly likely to occur during administration. Overall, despite its approval, taurine is not widely used in clinical practice; moreover, there is limited post-marketing data and scant real-world data regarding this substance.

Regarding Doxecitin, it should be noted that while it does not cure or reverse all manifestations of TK2-D, it halts disease progression and can lead to significant functional recovery. Minor side effects to consider include diarrhea, nausea, vomiting, abdominal pain, elevated liver enzyme levels, and skin rash. More serious side effects may include jaundice, dark amber urine, pale clay-colored stools, loss of appetite, fatigue, and vomiting. A limitation associated with its approval is the absence of placebo-controlled trials to confirm its efficacy.

Regarding elamipretide, the study results underpinning the drug's approval have not yet been published. Furthermore, the 6-minute walk test served as the primary endpoint, an approach associated with several drawbacks [5]. It does not reveal whether a reduced score stems from pulmonary, cardiac, or musculoskeletal issues; moreover, the result depends heavily on patient motivation, the physical exertion involved may be excessive for individuals with sedentary lifestyles or joint pain, and there is

a lack of robust reference values [5]. Additionally, adverse effects such as severe allergic reactions or respiratory insufficiency may occur.

Overall, a drug's approval by the relevant authority does not necessarily mean it provides actual clinical benefit to patients in routine care. A common issue with most studies leading to drug approval is insufficient statistical power and flawed study design (often lacking a double-blind, placebo-controlled setup), which limits the validity of the findings. Even when proposed therapeutic concepts work at a theoretical or experimental level, their clinical applicability remains limited, as a drug's efficacy depends heavily on the choice of biomarkers used as endpoints. The more specific these biomarkers are, the more precisely they reflect the therapeutic effect.

Acknowledgements

Funding: No funding was received.

Data Access Statement: All data are available from the corresponding author.

Ethics Statement: Not applicable.

Author Contribution: JF: design, literature search, discussion, first draft, critical comments, final approval.

Disclosures: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Access Statement: Not applicable.

Compliance with Ethics Guidelines: This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Keywords: Mitochondrial Disorders, Treatment, Idebenone, Taurine, Doxecitine, Elamipretide

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