Received: 31 October 2023 | Accepted: 28 February 2024

DOI: 10.1111/ene.16275

european journal of neurology
the official journal of the european academy of neurology

CONSENSUS STATEMENT

Management of seizures in patients with primary mitochondrial diseases: consensus statement from the InterERNs Mitochondrial Working Group

Michelangelo Mancuso[1] | Maria T. Papadopoulou[2] | Yi Shiau Ng[3,4] | Anna Ardissone[5] | Marcello Bellusci[6] | Enrico Bertini[7] | Lidia Di Vito[8] | Teresinha Evangelista[9] | Carmen Fons[10] | Omar Hikmat[11] | Rita Horvath[12] | Thomas Klopstock[13,14,15] | Cornelia Kornblum[16] | Costanza Lamperti[5] | Laura Licchetta[8] | Maria Judit Molnar[17] | Kristin N. Varhaug[18] | Mar O'Callaghan[10] | Ronit M. Pressler[19,20] | Manuel Schiff[21,22] | Serenella Servidei[23,24] | Nora Szabo[25] | Gráinne S. Gorman[3,4] | J Helen Cross[19,20] | Shamima Rahman[19,20]

Correspondence
Michelangelo Mancuso, Department of Clinical and Experimental Medicine, Neurological Institute, University of Pisa, Building 13, Via Roma 67, Pisa 56100, Italy.
Email: michelangelo.mancuso@unipi.it

Funding information
This project has received funding from the European Joint Programme on Rare Diseases (EJP RD). The EJP RD initiative has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N°825575

Abstract

Background and purpose: Primary mitochondrial diseases (PMDs) are common inborn errors of energy metabolism, with an estimated prevalence of one in 4300. These disorders typically affect tissues with high energy requirements, including heart, muscle and brain. Epilepsy may be the presenting feature of PMD, can be difficult to treat and often represents a poor prognostic feature. The aim of this study was to develop guidelines and consensus recommendations on safe medication use and seizure management in mitochondrial epilepsy.

Methods: A panel of 24 experts in mitochondrial medicine, pharmacology and epilepsy management of adults and/or children and two patient representatives from seven countries was established. Experts were members of five different European Reference Networks, known as the Mito InterERN Working Group. A Delphi technique was used to allow the panellists to consider draft recommendations on safe medication use and seizure management in mitochondrial epilepsy, using two rounds with predetermined levels of agreement.

Results: A high level of consensus was reached regarding the safety of 14 out of all 25 drugs reviewed, resulting in endorsement of National Institute for Health and Care Excellence guidelines for seizure management, with some modifications. Exceptions including valproic acid in *POLG* disease, vigabatrin in patients with γ-aminobutyric acid transaminase deficiency and topiramate in patients at risk for renal tubular acidosis were highlighted.

For affiliations refer to page 9.

Conclusions: These consensus recommendations describe our intent to improve seizure control and reduce the risk of drug-related adverse events in individuals living with PMD-related epilepsy.

KEYWORDS
consensus, epilepsy, management, mitochondrial diseases, recommendations

INTRODUCTION

Primary mitochondrial diseases (PMDs) are the most prevalent metabolic disorders estimated at 1 in 4300. PMDs may be caused by pathogenic variants in both mitochondrial DNA genes and in more than 400 nuclear DNA genes [1]. Since mitochondria are essential organelles in virtually all human cells, PMDs can affect all organs, with a predilection for high-energy-demanding tissues, such as the central and peripheral nervous systems, skeletal muscle, heart and retina [1].

Epilepsy is one of the most common features of central nervous system involvement in PMDs. During the disease course of PMD, approximately 20%–50% of patients will experience seizures that are notoriously recurrent in nature in 90% of cases [2–4]. Frequently observed seizure semiology includes focal motor, myoclonic and tonic–clonic seizures [5]. Recent evidence suggests that seizures are repeatedly resistant to antiseizure medication (ASM) and may develop into drug-resistant epilepsy advocating for careful characterization of seizures to confirm their diagnosis, select the most appropriate treatments and aid in determining prognosis. Treatment of mitochondrial epilepsy is thought particularly challenging, even for expert epileptologists, principally due to limitations of use of certain ASMs in part due to the increased risk of toxicity, for example sodium valproate (valproic acid, VPA) in *POLG* disease or factors that aggravate seizures (e.g., consideration of the drug's potential to negatively influence mitochondrial function) [5]. Therefore, there is an urgent need to develop consensus standards of care for managing seizures associated with PMD.

Another issue is that in an era of genomic sequencing that has increased the diagnostic rate of genetic epilepsies, including those caused by PMDs, and dramatically shortened diagnostic lag time, there is a growing desire amongst patients and clinicians to have personalized medicines tailored to specific genetic disorders. However, evidence-based guidance for ASM prescribing in genetic epilepsies is currently limited to a small number of conditions for which it has been possible to perform controlled clinical trials and observational studies [6]. None of these conditions is PMD. The extreme clinical and genetic heterogeneity of PMDs, which encompass more than 400 ultra-rare monogenic disorders, means that it has not been possible to generate clinical-trial-based evidence for these disorders. As an alternative, the aim was to generate evidence-based guidelines based on a systematic literature review and Delphi consensus expert opinion; although this is a lower level of evidence than clinical trial generated data, it is a pragmatic option for rare diseases.

In 2017, 24 virtual European Reference Networks (ERNs) were launched involving healthcare providers across Europe. ERNs aim to tackle complex or rare diseases and conditions that require highly specialized treatment and concentration of knowledge and resources. The 24 ERNs involve 25 European Union countries and Norway and more than 300 hospitals with over 900 healthcare units covering all major rare disease groups (https://health.ec.europa.eu/european-reference-networks/networks_en). Although different ERNs cover different disease areas, some disease groups have overlapping features and may be in the remit of several ERNs. Five ERNs interested in PMD—EpiCare (for rare epilepsies), ERN EYE (rare ophthalmological diseases), ERN-RND (for rare neurological diseases), EURO-NMD (for rare neuromuscular diseases) and MetabERN (hereditary metabolic diseases)—came together to constitute an InterERN Working Group that aims to develop common work around care, education and research on PMDs, collectively termed the Mito InterERNs.

Cognisant of the lack of available evidence, Mito InterERNs sought to develop a consensus statement about safe ASM use and management of seizures in children and adults with PMD. A workshop was supported by the Networking Support Scheme of the European Joint Programme on Rare Diseases.

MATERIALS AND METHODS

The Delphi method was used to develop consensus around seizure management for PMDs. The Delphi method provides a systematic approach for collecting opinions from experts (the 'Delphi Panel') and has been widely applied to obtain consensus recommendations on well-defined topics, including several aspects of PMDs [7–10]. Although described as a 'panel', experts provide their opinions freely, individually and anonymously. Moreover, the recently published supporting tool published by the ERN was followed (available at https://www.erknet.org/fileadmin/files/user_upload/0._Intro_Toolkit__D-B.2_.pdf).

Phase I: Pre-meeting phase

The coordinator of the Mito InterERNs (MM), in collaboration with the coordinators of the five ERNs involved, invited experts from established centres of excellence within the ERNs in Europe. Participants were selected based on their known experience in the field of mitochondrial medicine, pharmacology and epilepsy, with

expertise in management of adults and/or children. To broaden the panel of experts, invitees were also asked to nominate other potential participants to achieve geographical and gender balance in the selection of panellists. Candidate panellists were invited by email outlining the study aims and the Delphi process. Patient representatives from two mitochondrial patient advocacy groups, involved in the Mito InterERNs (MITOCON from Italy and Lily Foundation from UK) were also invited to participate.

The consensus panel finally consisted of 24 participants from seven European countries with two patient representatives. During the first virtual call, the initial discussion was about how to approach seizures in this heterogeneous group of diseases, which often occur as part of complex and specific syndromic phenotypes, and to select the ASMs to explore in the Delphi process. It was agreed that good clinical practice must always be kept in mind when treating these frequently multisystem diseases, and that the approach to seizure treatment needs to be tailored to specific phenotypes and genotypes. Moreover, it was unanimously approved to have general queries (drafted by the facilitator MM) and specific queries for the different ASMs.

The list of drugs and other treatments for the management of epilepsy in both children (>28 days and <18 years) and adults was thus created (see Data S1). It was decided to exclude neonates from these guidelines because neonates very rarely present with seizures (around 1%) [11] and, even if they did, the diagnosis would invariably be made or confirmed outside the neonatal period. In order to avoid delay of treatment it is therefore recommended to follow recently published guidelines for the treatment of neonatal seizures [12].

Five different working groups of experts were each allocated to analyse five to six possible treatments (Data S1). Articles published between database inception and 28 February 2023 were searched for in MEDLINE via PubMed, ClinicalTrials.gov and the European Clinical Trials Register. Only articles published in English were considered. Data from unpublished trial registries, abstracts or conference proceedings were not included. Detailed study inclusion/exclusion criteria and the full search strategy are provided in Data S1.

Whilst one member screened full-text papers for inclusion, appraised study quality and extracted the data, all members double checked by rescreening their allocated ASM/treatment. Finally, each group supplied a list of queries to be voted on, as well as the references used to address the specific treatment (Data S1), which was distributed to all experts. Amongst the possible queries, for each ASM two queries were considered mandatory: (1) it is not contraindicated to use XX in children with PMD and (2) it is not contraindicated to use XX in adults with PMD (where XX refers to the analysed ASM).

The facilitator (MM) created two surveys (Data S2) to gauge the level of consensus amongst experts; responses and votes were collected anonymously through the SurveyMonkey platform (surveymonkey.com) and analysed prior to the face-to-face meeting in a second conference call.

Participants voted using a 5-point Likert scale [13] to indicate their level of agreement on each statement (1, absolutely disagree; 2, disagree; 3, no judgement; 4, more than agree; 5, absolutely agree). A 'strong consensus' was defined if >70% of scores were ≥4 or <2 and the mean score was ≥4 or <2. If either of the conditions were met, the consensus was considered a 'good consensus'. If both parameters were not met, the statement was considered to lack consensus agreement.

Phase II: Delphi panel

The 24 experts met in a face-to-face meeting in Budapest from 29 June to 1 July 2023. The two delegates from the patient advocacy groups took part in the meeting without voting but were actively involved in the planning of the Delphi workshop and in the discussions.

Statements from Phase I without consensus were selected for discussion. The working group experts presented those individual treatments, discussing the results of the first round of the survey and presenting the available data supporting the queries. After discussion, when needed, statements from the first round were changed or removed and participants voted again on the revised statements. New statements were also designed and voted on. All participants engaged in all Delphi phases.

RESULTS

During the first voting round, prior to the workshop meeting, out of 25 drugs and other therapies, consensus on their safe use was agreed for 14 drugs plus the ketogenic diet and vagus nerve stimulation but was not achieved for 11 drugs (Data S1). After the in-person workshop, all 11 selected drugs were considered not contraindicated in the management of seizures in PMD with the sole exception of VPA in *POLG* disease (Table 1). During the face-to-face meeting, it was agreed to reformulate the queries starting with 'it is safe to use' to 'it is not contraindicated to use'. The general conclusion of the Delphi process, based on expert consensus (level 4 evidence), was that all the drugs or treatments studied (except VPA) are not generally contraindicated for patients with PMD, although some specific restrictions were considered for certain molecular defects (i.e., pathogenic *POLG* variants) and particular clinical situations (i.e., co-occurrence of liver impairment or metabolic acidosis).

General considerations

There was strong consensus that good clinical practice including general indications, contraindications, clinical monitoring and side effects for all ASMs must always be considered, and that robust protocols are imperative for good management of seizures. The experts strongly endorsed the previous study on safety of drug use in patients with a PMD [8], pertaining to ASMs, and suggested that, for

TABLE 1 Queries for which a consensus was reached.

Queries	Consensus
General queries	
Good clinical practice including general indications, contraindications, clinical monitoring and side effects for all antiseizure medications must always be kept in mind (with or without mitochondrial genetic defect)	Strong
This consensus covers children older than 28 days	Strong
Children with PMD who develop seizures should be referred to a specialist in paediatric epilepsy for advice about epilepsy management	Strong
Protocols in place are imperative for good management of seizures	Strong
I agree with the content of the consensus study PMID: 32030781 (Safety of drug use in patients with a PMD: an international Delphi-based consensus) regarding the safety and toxicity results for the explored ASMs	Strong
For all drugs where clear evidence in vivo of mitochondrial toxicity is absent or poor, they can be used with careful monitoring in the first few days of treatment for potential side effects and measurement of blood lactate	Strong
I endorse the NICE guidelines (NG217, published in April 2022) also for the treatment of PMDs in adults and children	Strong
If the patient develops generalized, convulsive status epilepticus, management and when needed escalation to intensive care setting should follow the local status epilepticus guidelines (e.g., NICE Clinical Guidelines, SIGN guidelines, EFNS guidelines), except sodium valproate which is contraindicated in *POLG* patients	Strong
Specific drugs	
It is not contraindicated to use topiramate in adults and children with PMDs	Strong
Topiramate inhibits isoenzymes of carbonic anhydrase, which may contribute to the drug side effects, including its propensity to cause renal tubular acidosis and calcium phosphate kidney stones. Therefore, caution is recommended in the use of topiramate in patients with PMDs, e.g. those at risk for renal tubular acidosis	Strong
It is not contraindicated to use levetiracetam in adults and children with PMDs	Strong
It is not contraindicated to use perampanel in adults and children with PMDs	Strong
It is not contraindicated to use vigabatrin in adults and children with PMDs	Strong
It is not contraindicated to use pregabalin in adults and children with PMDs	Strong
It is not contraindicated to use pregabalin in children and adults with PMD and myoclonus	Consensus
It is not contraindicated to use phenytoin in adults with PMDs	Strong
It is not contraindicated to use phenytoin in children with PMDs	Consensus
Valproic acid is contraindicated in patients with pathogenic variants in *POLG*	Strong
In non-POLG patients with mitochondrial disease and without liver impairment, valproic acid could be used to manage refractory epilepsy as well as refractory mood disorders	Consensus
It is not contraindicated to use carbamazepine in adults and children with PMDs	Strong
It is not contraindicated to use benzodiazepines, including midazolam, in adults and children with PMDs	Strong
It is not contraindicated to use oxcarbazepine in adults with PMDs	Strong
It is not contraindicated to use oxcarbazepine in children with PMDs	Consensus
It is not contraindicated to use brivaracetam in adults and children with PMDs	Strong
It is not contraindicated to use ethosuximide in adults and children with PMDs	Consensus
It is not contraindicated to use vagus nerve stimulation in adults and children with PMDs	Strong
It is not contraindicated to use gapabentin in adults and children with PMDs	Strong
It is not contraindicated to use felbamate in children with PMDs	Consensus
It is not contraindicated to use lacosamide in adults and children with PMDs	Strong
It is not contraindicated to use lamotrigine in adults and children with PMDs	Strong
It is not contraindicated to use cannabidiol in adults and children with PMDs	Strong
It is not contraindicated to use zonisamide in adults and children with PMDs	Consensus
It is not contraindicated to use cenobamate in adults and children with PMDs	Strong
It is not contraindicated to use ketogenic diet in adults and children with PMDs	Strong
Vigabatrin is contraindicated in patients with γ-aminobutyric acid transaminase deficiency	Strong
It is not contraindicated to use ketamine in adults and children with PMDs	Strong

TABLE 1 (Continued)

Queries	Consensus
It is not contraindicated to use propofol in adults and children with PMDs	Strong
Propofol should be closely monitored for prolonged use in the context of refractory status epilepticus due to the risk of propofol infusion syndrome	Strong
It is not contraindicated to use thiopentone, phenobarbital, phenobarbitone (barbiturates) in adults and children with PMDs	Strong
It is not contraindicated to use desflurane, isoflurane and sevoflurane in adults and children with PMDs	Strong

Note: Consensus: the statement reached only one of the two conditions mentioned above. Strong: the statement reached both more than 70% of scores ≥4 and the mean score was ≥4 agreement. For details see Data S1–S3.

Abbreviations: ASMs, anti-seizure medications; EFNS, European Federation of Neurological Societies; NICE, National Institute for Health and Care Excellence; PMD, primary mitochondrial disease; SIGN, Scottish Intercollegiate Guidelines Network.

all ASMs where clear evidence of in vivo mitochondrial toxicity is absent or poor, they may be used cautiously with careful monitoring for potential side effects.

In terms of personalized medicine tailored to specific monogenic disorders, it was agreed that specific metabolic therapies are indicated in certain PMDs associated with seizures: biotin for biotinidase deficiency, biotin and thiamine for disorders of the SLC19A3 thiamine transporter, thiamine for thiamine pyrophosphokinase-1 (TPK1) deficiency, high dose coenzyme Q_{10} supplementation for disorders of coenzyme Q_{10} biosynthesis, and ketogenic diet for pyruvate dehydrogenase complex deficiency. Topiramate should be used with caution in patients with PMD who are at particular risk for renal tubular acidosis. As there was no robust evidence to support the use of carnitine supplementation in PMD or epilepsy, including in the setting of VPA toxicity, this was not explored by the Mito InterERNs.

Considering the lack of clinical trial evidence for any interventional treatment to manage seizures in PMD, and considering that all analysed treatments (except VPA in *POLG* disease and vigabatrin in patients with γ-aminobutyric acid transaminase deficiency) are not contraindicated in PMDs, the experts strongly endorsed adoption of the National Institute for Health and Care Excellence (NICE) guidelines [14] for the management of seizures and status epilepticus in adults and children (above 28 days) diagnosed with a PMD.

Finally, there was an extensive debate in relation to the use of VPA in PMDs other than *POLG*-related disease, particularly in those PMDs where hepatopathy could be part of the clinical phenotype. This aspect could not be explored thoroughly during the face-to-face meeting owing to time constraints, but all experts agreed to produce a table with all mitochondrial genes anecdotally associated with liver dysfunction/failure after exposure to VPA (Table S1). The decision to prescribe VPA should be tailored to the specific needs and risks of each individual patient with a PMD. In addition to avoidance of VPA in patients of child-bearing potential, consideration of the substantial risk of liver failure associated with VPA use is needed to support decision-making. Caution is therefore recommended in using VPA in patients with variants in the genes listed in Table S1, as well as in any individual with variants in a gene known to cause mitochondrial liver disease.

Management of seizures and status epilepticus

Figures 1–3 present the consensus results for the management of focal, generalized, myoclonic seizures and infantile epileptic spasms, respectively, in both adults and children >28 days. The suggested treatments follow the NICE guideline recommendations (https://www.nice.org.uk/guidance/ng217) with few exceptions, mostly related to VPA use or liver impairment, and are thus presented with the same form, proposing first-line, second-line and third-line ASMs.

Figure 4 presents the consensus results for the management of convulsive status epilepticus in children (>28 days) and adults with PMDs, including frequently used doses for first-intention ASMs. The suggested treatments also follow the NICE guideline recommendations, as well as the Italian guidelines [15], with few exceptions, mostly related to VPA use or liver impairment.

DISCUSSION

In this study, 24 experts from seven European countries plus two patient representatives met to discuss the optimal management of seizures in patients with PMD to assist clinicians and patients in decision-making and agreed on following the general NICE guidelines for seizure management, with some minor modifications. It is important to underline that consensus-based information is useful to provide guidance, but that decisions related to treatment of seizures, in both children and adults, should always be tailored to the specific needs and risks of each patient.

It is conceded that these recommendations are not evidence-based due, in part, to the inherent challenges of conducting clinical trials in rare diseases. Our search in both ClinicalTrials.gov and the European Clinical Trials Register revealed no ongoing or planned clinical trials focusing on specific ASMs and PMDs. Although consensus methods are widely used to inform clinical practice in the absence of empirical data, expert judgement ranks low in the hierarchy of evidence. Our recommendations are derived from the consensus approach, based on clinical experience from leading mitochondrial clinical services and epileptic services belonging to the EpiCare ERN of several European countries and the appraisal of current literature.

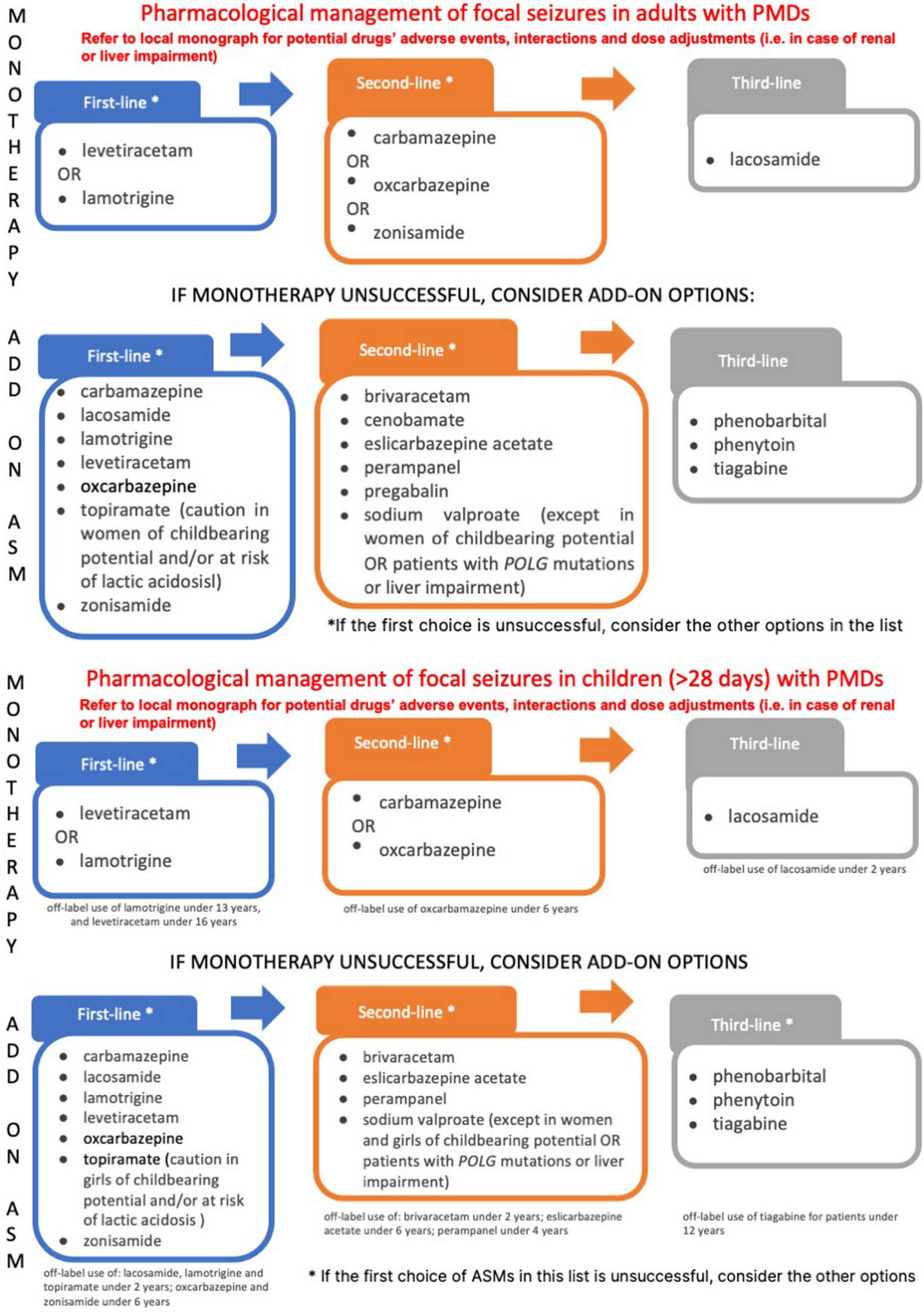

FIGURE 1 (A) Consensus results for the management of focal seizures in adults with PMDs. (B) Consensus results for the management of focal seizures in children (>28 days) with PMDs. ASMs, antiseizure medications; PMDs, primary mitochondrial diseases.

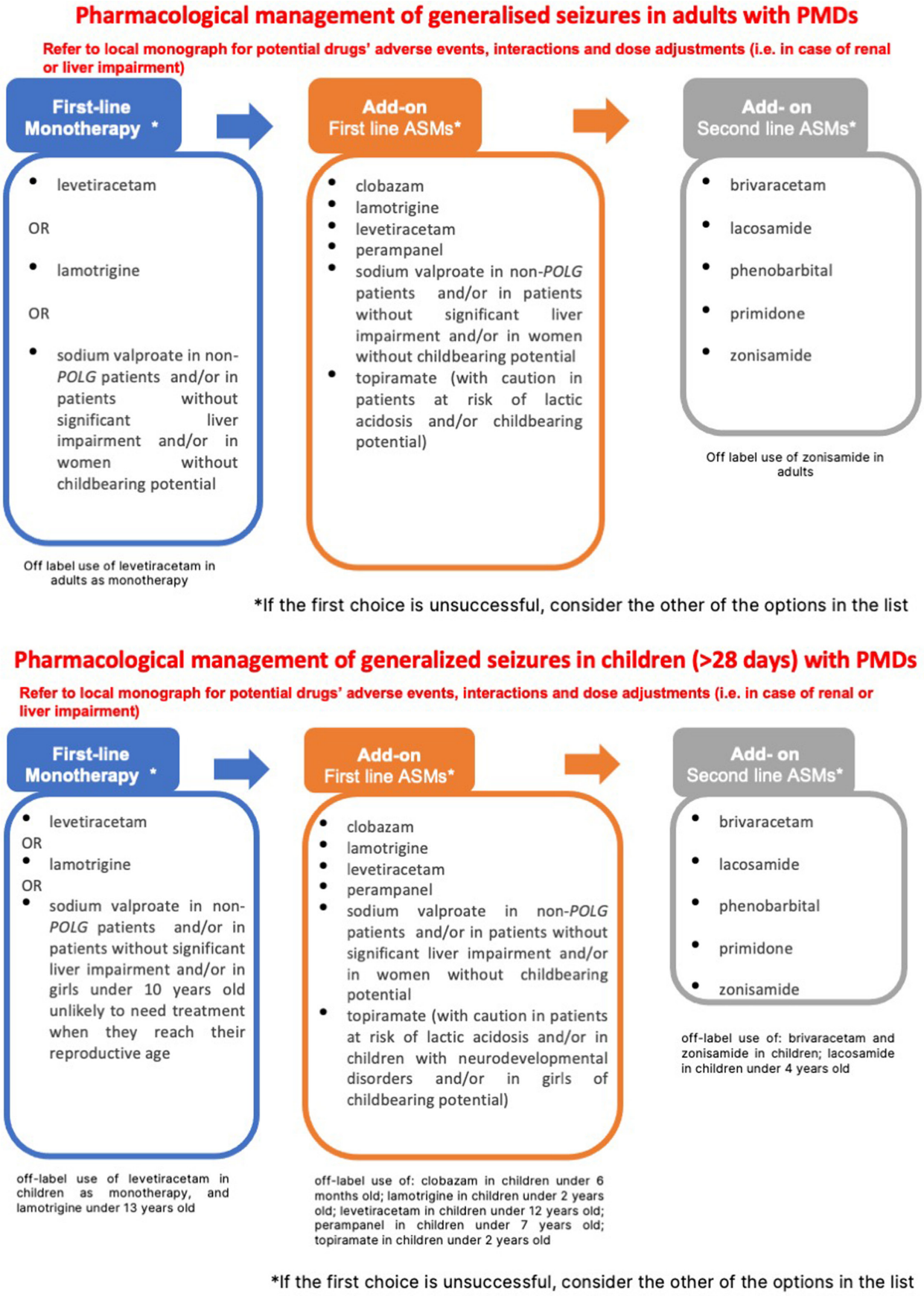

FIGURE 2 (A) Consensus results for the management of generalized seizures in adults with PMDs. (B) Consensus results for the management of generalized seizures in children (>28 days) with PMDs. ASMs, antiseizure medications; PMDs, primary mitochondrial diseases.

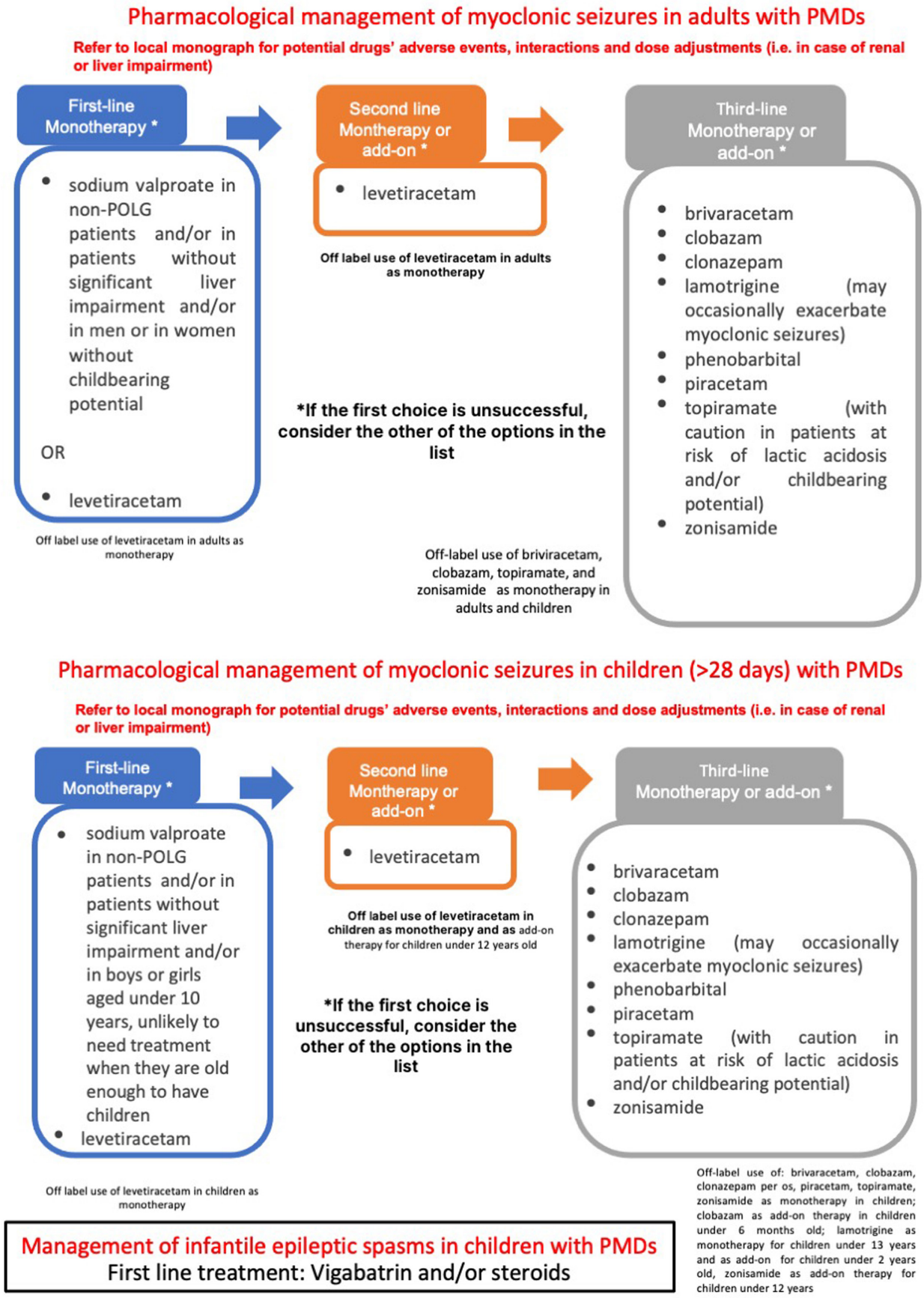

FIGURE 3 (A) Consensus results for the management of myoclonic seizures in adults with PMDs. (B) Consensus results for the management of myoclonic seizures and infantile spasms in children (>28 days) with PMDs. PMDs, primary mitochondrial diseases.

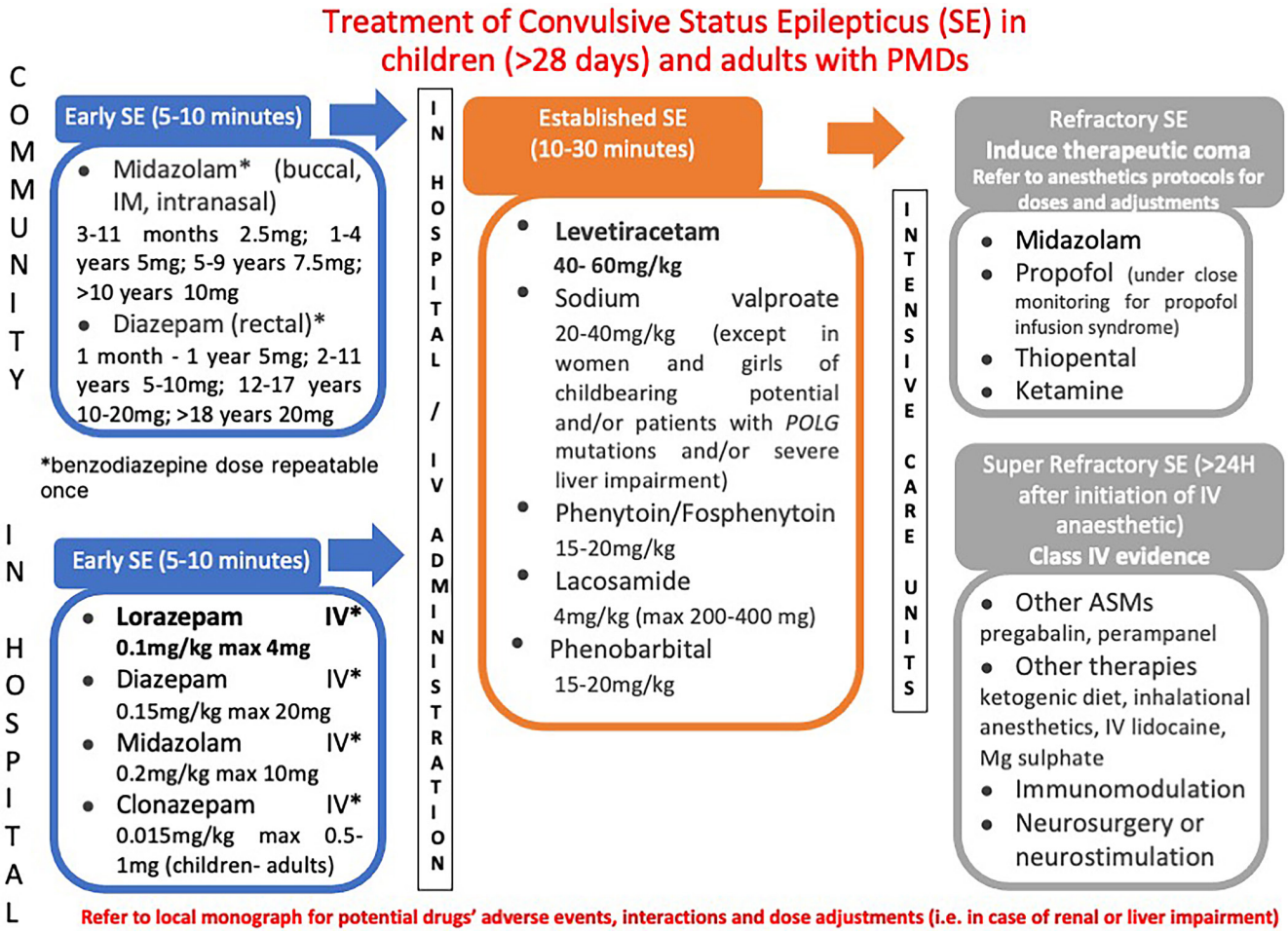

FIGURE 4 Consensus results for the management of convulsive status epilepticus in children (>28 days) and adults. ASMs, antiseizure medications; IM, intramuscular; IV, intravenous; Mg, magnesium; PMDs, primary mitochondrial diseases.

The aim was to provide transparent opinions based on the available studies and clinical evidence, and to prevent unnecessary withholding of effective ASMs from patients with PMDs. It was agreed by everyone that the NICE guidelines should be applied to PMD with the only exception of VPA which is absolutely contraindicated in patients with pathogenic *POLG* variants and in those with known liver disease and/or a mitochondrial genotype where liver dysfunction is expected to manifest during the disease course. There was agreement for the application of the NICE guidelines only for children >28 days. Another important limitation was that the NICE guidelines were last reviewed in 2022. Newer drugs may not be included if no approval for specific seizure type was available at the time of the guidelines release and other drugs included may not be available/approved for specific populations in some countries. The choice of the drugs listed and of other drugs not included in the list should be made by experts in the field on a case-by-case basis.

In conclusion, the consensus statements developed in this Delphi process seek to address an unmet need for providing recommendations on the safe use of ASMs to improve seizure management in patients with mitochondrial epilepsy. The experts strongly agreed on treating seizures and status epilepticus mainly following the NICE guideline recommendations, with few exceptions. In case a new treatment is initiated in a PMD patient, careful monitoring is suggested for potential side effects, including measurement of blood lactate and other laboratory parameters.

AUTHOR CONTRIBUTIONS

All authors contributed to the acquisition of data, preparation and critical revision of the paper. MM contributed to the study conception and design, and analysis and interpretation of data and drafting the manuscript. The supplementary table 'Sodium valproate in primary mitochondrial disease' was created by SR, revised by GG, MS, EB, MB and YN, and approved by the entire group. All authors except TE contributed to workshop participation.

AFFILIATIONS

[1]Department of Clinical and Experimental Medicine, Neurological Institute, University of Pisa, Pisa, Italy
[2]Department of Pediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, University Hospital of Lyon, Member of the ERN EpiCARE, Lyon, France

[3]Wellcome Centre for Mitochondrial Research, Translational and Clinical Research Institute AND National Institute for Health and Care Research (NIHR) Newcastle Biomedical Research Centre (BRC), Newcastle University, Newcastle upon Tyne, UK
[4]NHS Highly Specialised Service for Rare Mitochondrial Disorders, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[5]Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
[6]Reference Center for Inherited Metabolic Disorders MetabERN, Mitochondrial Disorders Research Group (imas12), '12 de Octubre' University Hospital, Madrid, Spain
[7]Research Unit of Neuromuscular Disease, Translational Pediatrics and Clinical Genetics, Bambino Gesu' Children's Research Hospital, IRCCS, Rome, Italy
[8]IRCCS Istituto delle Scienze Neurologiche di Bologna, Full Member of the European Reference Network for Rare and Complex Epilepsies (EpiCARE), Bologna, Italy
[9]Department of Neuropathology, Functional Unit of Neuromuscular pathology and Department of Neuromyology, Institute of Myology, EURO-NMD coordination, Pitié-Salpêtrière Hospital, APHP Sorbonne University, Paris, France
[10]Epilepsy and Neurometabolics Units, Pediatric Neurology Department, Hospital Sant Joan de Déu, Institut de Recerca Sant Joan de Déu, Barcelona, Spain
[11]Department of Paediatrics and Adolescent Medicine, Haukeland University Hospital, Bergen and Department of Clinical Medicine (K1), University of Bergen, Bergen, Norway
[12]Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
[13]Department of Neurology, Friedrich-Baur-Institute, LMU University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany
[14]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany
[15]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
[16]Department of Neurology, Section of Neuromuscular Diseases, University Hospital Bonn, Bonn, Germany
[17]Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary
[18]Department of Neurology, Haukeland University Hospital, Bergen, Norway
[19]UCL Great Ormond Street Institute of Child Health, London, UK
[20]Great Ormond Street Hospital for Children, London, UK
[21]Reference Center for Mitochondrial Disorders (CARAMMEL) and Reference Center for Inborn Errors of Metabolism, Department of Pediatrics, Necker-Enfants-Malades Hospital, Assistance Publique-Hôpitaux de Paris, University of Paris-Cité, MetabERN, Paris, France
[22]INSERM UMRS_1163, Imagine Institute, Paris, France
[23]Dipartimento di Neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[24]Dipartimento Di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy
[25]Saint John's Hospital, Child Epilepsy Centre, Budapest, Hungary

ACKNOWLEDGEMENTS

This project has received funding from the European Joint Programme on Rare Diseases (EJP RD). The EJP RD initiative has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N°825575. The authors are grateful for the support of Mrs Heike Pascal, Project Manager of ERN EURO-NMD. MM and CL were partially supported by Telethon-MITOCON grant GSP16001, RF-2016-02361495, the EJPRD2019 project GENOMIT and the Italian Ministry of University and Research (2022B9WY4A). This work was generated within the European Reference Network for Rare Hereditary Metabolic Disorders (MetabERN) PM-MD (mitochondrial) subnetwork coordinated by SR, EB and MS. MB is also a member of this subnetwork. SR acknowledges grant funding from Great Ormond Street Hospital Children's Charity, the Lily Foundation and the National Institute of Health Research (NIHR) Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. RH is a Wellcome Trust Investigator (109915/Z/15/Z), who receives support from the Medical Research Council (UK) (MR/V009346/1), the Addenbrookes Charitable Trust (G100142), the Evelyn Trust, the Stoneygate Trust, the Lily Foundation, Action for AT and an MRC strategic award to establish an International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) MR/S005021/1. This research was supported by the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. OH was supported by grants from the Western Norway Regional Health Authority (Helse-Vest, grants no. F-12135). JHC has received grants from Vitaflo (International) Ltd, Marinius, GW Pharma/Jazz, Zogenix/UCB, Stoke Therapeutics, Ultragenyx for clinical trials to her department as well as NIHR, LifeARC and GOSHCC. Her research is supported by the NIHR Great Ormond Street Biomedical Research Centre. JHC also reports honoraria to her department from Nutricia, GW Pharma, Zogenix and Biocodex. JHC has a patent Nutritional product (WO2013186570) and a patent Anticonvulsant compound (WO2016038379A1) issued.

CONFLICT OF INTEREST STATEMENT

The authors declare no financial or other conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

ORCID

Michelangelo Mancuso https://orcid.org/0000-0003-2738-8562
Anna Ardissone https://orcid.org/0000-0003-1969-0147
Rita Horvath https://orcid.org/0000-0002-9841-170X
Thomas Klopstock https://orcid.org/0000-0003-2805-4652
J Helen Cross https://orcid.org/0000-0001-7345-4829
Shamima Rahman https://orcid.org/0000-0003-2088-730X

REFERENCES

1. Ng YS, Bindoff LA, Gorman GS, et al. Mitochondrial disease in adults: recent advances and future promise. *Lancet Neurol*. 2021;20:573-584.
2. Rahman S. Mitochondrial diseases and status epilepticus. *Epilepsia*. 2018;59(Suppl 2):70-77.
3. Lopriore P, Gomes F, Montano V, Siciliano G, Mancuso M. Mitochondrial epilepsy, a challenge for neurologists. *Int J Mol Sci*. 2022;23:13216.
4. Bindoff LA, Engelsen BA. Mitochondrial diseases and epilepsy. *Epilepsia*. 2012;53(Suppl 4):92-97.
5. Whittaker RG, Devine HE, Gorman GS, et al. Epilepsy in adults with mitochondrial disease: a cohort study. *Ann Neurol*. 2015;78:949-957.
6. Guerrini R, Balestrini S, Wirrell EC, Walker MC. Monogenic epilepsies: disease mechanisms, clinical phenotypes, and targeted therapies. *Neurology*. 2021;97:817-831.

7. Mancuso M, McFarland R, Klopstock T, Hirano M, consortium on Trial Readiness in Mitochondrial Myopathies. International workshop: outcome measures and clinical trial readiness in primary mitochondrial myopathies in children and adults. Consensus recommendations. 16–18 November 2016, Rome, Italy. *Neuromuscul Disord*. 2017;27:1126-1137.
8. De Vries MC, Brown DA, Allen ME, et al. Safety of drug use in patients with a primary mitochondrial disease: an international Delphi-based consensus. *J Inherit Metab Dis*. 2020;43:800-818. doi:10.1002/jimd.12196
9. Koene S, van Bon L, Bertini E, et al. Outcome measures for children with mitochondrial disease: consensus recommendations for future studies from a Delphi-based international workshop. *J Inherit Metab Dis*. 2018;41:1267-1273.
10. Ng YS, Bindoff LA, Gorman GS, et al. Consensus-based statements for the management of mitochondrial stroke-like episodes. *Wellcome Open Res*. 2019;4:201.
11. Ebihara T, Nagatomo T, Sugiyama Y, et al. Neonatal-onset mitochondrial disease: clinical features, molecular diagnosis and prognosis. *Arch Dis Child Fetal Neonatal Ed*. 2022;107:329-334.
12. Pressler RM, Abend NS, Auvin S, et al. Treatment of seizures in the neonate: guidelines and consensus-based recommendations—special report from the ILAE task force on neonatal seizures. *Epilepsia*. 2023;64:2550-2570.
13. de Winter JCF, Dodou D. Five-point Likert items: *t* test versus Mann–Whitney–Wilcoxon. *Pract Assess Res Eval*. 2010;15:1-10.
14. Overview | Epilepsies in children, young people and adults | Guidance | NICE. 2022. https://www.nice.org.uk/guidance/ng217.
15. Minicucci F, Ferlisi M, Brigo F, et al. Management of status epilepticus in adults. Position paper of the Italian League Against Epilepsy. *Epilepsy Behav EB*. 2020;102:106675.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Mancuso M, Papadopoulou MT, Ng YS, et al. Management of seizures in patients with primary mitochondrial diseases: consensus statement from the InterERNs Mitochondrial Working Group. *Eur J Neurol*. 2024;31:e16275. doi:10.1111/ene.16275