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Mitochondrial Medicine Therapies: Rationale, Evidence, and Dosing Guidelines

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Abstract

Purpose of review—Primary mitochondrial disease is highly heterogeneous but collectively common inherited metabolic disorder, affecting at least 1 in 4,300 individuals. **Therapeutic management of mitochondrial disease typically involves empiric prescription of enzymatic co-factors, antioxidants, and amino acid as well as other nutrient supplements**, based on biochemical reasoning, historical experience and consensus expert opinion. As the field continues to rapidly advance, we review here the pre-clinical and clinical evidence, and specific dosing guidelines, for common mitochondrial medicine therapies to guide practitioners in their prescribing practices.

Recent findings—Since publication of Mitochondrial Medicine Society guidelines for mitochondrial medicine therapies management in 2009, data has emerged to support consideration for using additional therapeutic agents and discontinuation of several previously used agents. **Pre-clinical animal modeling data have indicated a lack of efficacy for vitamin C as an antioxidant for primary mitochondrial disease, but provided strong evidence for vitamin E and N-acetylcysteine. Clinical data has suggested L-carnitine may accelerate atherosclerotic disease.** Long-term follow up on L-arginine use as prophylaxis against metabolic strokes has provided more data supporting

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Conflicts of interest:

Marni J. Falk, MD (MJF) is co-inventor on International Patent Application No. PCT/US19/39631 based on U.S. Serial No. 62/690,718 filed on 6/27/2018 and U.S. Serial No. 62/830,850 filed on 4/8/2019 Entitled, "Compositions and Methods for Treatment of Mitochondrial Respiratory Chain Dysfunction and Other Mitochondrial Disorders and Methods for Identifying Efficacious Agents for the Alleviating Symptoms of the Same," filed in the Name of The Children's Hospital of Philadelphia on 6/27/2019. MJF is a co-founder of MitoCUREia, Inc, scientific advisory board member with equity interest in RiboNova, Inc., and scientific board member as paid consultant with Khondrion. MJF has previously been or is currently engaged with several companies involved in mitochondrial disease therapeutic pre-clinical and/or clinical stage development as a paid consultant (Astellas (formerly Mitobridge) Pharma Inc, Cycleron Therapeutics, Imel Therapeutics, NeuroVive, Reneo Therapeutics, Stealth BioTherapeutics) and/or a sponsored research collaborator (AADI Therapeutics, Cardero Therapeutics, Cycleron Therapeutics, Minovia Therapeutics Inc, Mission Therapeutics, NeuroVive, Raptor Therapeutics, REATA Inc., RiboNova Inc, Standigm Therapeutics, Stealth BioTherapeutics). The other authors have no relevant financial conflicts of interest to declare.

its clinical use in individuals with MELAS and Leigh syndrome. Further, several precision therapies have been developed for specific molecular etiologies and/or shared clinical phenotypes of primary mitochondrial disease.

Summary—We provide a comprehensive update on mitochondrial medicine therapies based on current evidence and our single-center clinical experience to support or refute their use, and provide detailed dosing guidelines, for the clinical management of mitochondrial disease. The overarching goal of empiric mitochondrial medicines is to utilize therapies with favorable benefit-to-risk profiles that may stabilize and enhance residual metabolic function to improve cellular resiliency and slow clinical disease progression and/or prevent acute decompensation.

Keywords

Primary mitochondrial disease; mitochondrial cocktail; nutrient therapies; antioxidants; cofactors; dose guidelines

INTRODUCTION

Primary mitochondrial disease (PMD) are a heterogeneous group of inherited genetic disorders, caused by several hundred different pathogenic variants in both nuclear and mitochondrial DNA genes[1,2]. PMD is highly clinically heterogeneous, presenting with a myriad of signs and symptoms that may variably affect every organ in the body[3]. Although each individual genetic cause of mitochondrial disease is itself rare, mitochondrial disease collectively affects at least 1 in 4300 individuals[4]. Unfortunately, there exist no evidence-based treatments or cures that have been proven effective in randomized, controlled, double-blind clinical trials[5]. This extensive locus, allelic, and phenotypic heterogeneity, rapid pace of novel genetic etiologies, lack of validated outcome measures that are responsive to change, lack of generalizable biomarkers with high sensitivity and specificity for all PMD cases, and poorly defined natural histories that often involve long periods of relative stability punctuated by episodic acute decline have made performing randomized controlled trials to demonstrate or refute the safety and efficacy of candidate therapies especially difficult in this population[6].

PMDs share a common cellular pathophysiology involving reduced energy production in the form of adenosine triphosphate (ATP), together with increased oxidative stress due to imbalance between oxidant production and scavenging within both mitochondria and the broader cell[7,8]. Therefore, commonly used mitochondrial medicines are generally empirically based to support and enhance the residual oxidative phosphorylation capacity of the mitochondrial respiratory chain as well as to reduce oxidative stress. While no cure has been identified, the clinical goal of available therapies is to enhance maximal enzymatic and cellular functioning and provide resiliency to support cellular needs during times of metabolic stress sufficient to prevent acute clinical decompensation. Therapeutic management of mitochondrial disease typically involves empiric prescription of enzymatic co-factors, antioxidants, and amino acid as well as other nutrient supplements[9], based on biochemical reasoning, historical experience and consensus expert opinion[10–12].

Clinical goals of mitochondrial medicine therapies are to mitigate symptoms and prevent disease progression. Given the phenotypic heterogeneity of PMD, goals for each patient may vary based depending on their current symptoms or in anticipation of the eventual development of symptoms given natural histories available for specific genetic conditions. Acute treatment and prevention of metabolic stroke are therapeutic goals when treating patients with arginine, citrulline and, more recently, taurine[13–16]. Therapies to improve vision or prevent further vision loss for pigmentary retinopathy include lutein and n-acetylcysteine[17–19]. N-acetylcysteine also has some evidence supporting its use for neurobehavioral symptoms and hepatopathy[20–24]. A thorough review of specific phenotypic indications for individual mitochondrial medicine therapy components is presented in Table 1. Unfortunately, randomized controlled clinical trials that provide the gold-standard of evidence for therapeutic effect are currently lacking for most of these agents.

In the absence of safety and efficacy evidence from gold-standard randomized clinical trials, clinical care for the growing cadre of definite PMDs has been guided by consensus expert opinion, including from the Mitochondrial Medicine Society (MMS)[11,12]. These guidelines offer rationale considerations to approach PMD based upon what is known about the underlying pathophysiology and biochemistry of PMD, animal and cellular experimental studies, and expert clinical experience of what has been deemed generally low-risk and tolerable. Since the 2009 publication of therapeutic dosing guidelines for “mitochondrial cocktail” therapies[12], a number of advances have been made in the field of mitochondrial medicine. Here, we update and discuss current rationale, evidence, and dosing guidelines for mitochondrial medicine therapies in patients with PMD including practical considerations as to which therapies may be administered parenterally and which genetic etiologies and/or phenotypes might be particularly responsive to specific therapies[25].

MITOCHONDRIAL MEDICINES

Within the literature and clinical practice, mitochondrial medicine regimens (colloquially referred to as ‘mitochondrial cocktails’) encompass a highly diverse selection of nutrients with extensive variability in their combinations and dosages. Indeed, the specific therapeutic agents used have been shown to vary widely between clinical practitioners[26], although a typical combination often is comprised of B vitamins, other mitochondrial enzyme cofactors, antioxidants, and nutrient supplements. Here, we have systematically catalogued the specific individual therapies standardly utilized, current rationale and existing evidence to support the safety and/or potential efficacy for each medication, and additional considerations to support dose selection in children or adults, including whether there are monitoring tests available useful for monitoring therapeutic dosing, parenterally available formulations, FDA approved formulations, or specific genetic and/or phenotypic defined PMD subpopulations for whom a specific therapy might be particularly useful to consider (Table 1). Indeed, while we anticipate some of these therapies may be broadly useful to any individual with a definite PMD, we recognize that in the growing era of precision medicine a personalized approach to tailor the precise therapeutic selection to each patient’s broader genomic or metabolic profile and specific molecular diagnosis (Table 2).

Ultimately, the goal of empiric mitochondrial medication regimens is to support alternative energy production pathways, reduce oxidative stress, remove toxic metabolites when relevant, and stabilize and/or optimize residual mitochondrial respiratory complexes. The extensive heterogeneity and episodic nature of mitochondrial diseases, along with a lack of real-time biomarkers to evaluate disease severity, makes it difficult to measure day-to-day clinical response. However, as most of the empiric therapeutic agents that are commonly used are typically tolerable at even very high doses, it is reasonable to start a combination of agents that have complementary mechanisms of action rather than initiating them individually and attempting to gauge their individual response. Indeed, mitochondrial medicine starting regimens and dosing have been standardized across all practitioners at our clinical site (Table 1), with recommendation to obtain compounded regimens to standardize medication source, stability, and dosing adherence; tailored adjustments are then made based on tolerability concerns or additional patient-specific genetic and/or clinical features. Relevant considerations to temper this approach is that reliable sources or formulations may not be readily available, cost may be prohibitive, and insurance coverage may be limiting. To minimize costs, a minimal general mitochondrial medicine regimen may include a multivitamin, a B50 vitamin (as opposed to a B100 compound that is often too large for many individuals to safely swallow), one or more antioxidant(s), and coenzyme Q10, with additional agents selected based on the individual patient's genotype and phenotype (Table 1). Indeed, as the volume or quantity of pills may be highly challenging for patients with mitochondrial disease, many of whom have dysphagia, use of a compounding pharmacy may be of benefit to provide a minimal volume for the selected therapies. We anticipate multiple other precision therapies will be developed in the coming years, as dozens of additional pharmaceutical companies are now working to develop a wide range of additional therapeutic agents for PMD to be tested in randomized clinical trials (see [ClinicalTrials.Gov](https://clinicaltrials.gov) for updated search of completed and active trials enrolling PMD patients).

CO-FACTORS

B vitamin serve as co-factors for many cellular reactions. Thiamine (Vitamin B1) is a cofactor of alpha-ketoacid dehydrogenases, including the pyruvate dehydrogenase complex (PDHC). Riboflavin (Vitamin B2) is a precursor both of flavin mononucleotide (FMN), a necessary prosthetic component in the biosynthesis of respiratory chain complex I and flavin adenine dinucleotide (FADH), the reducing equivalent consumed by respiratory chain complex II. Thus, vitamin B2 helps to promote the assembly of respiratory chain complex I[27,28]. Niacin (Vitamin B3) is a precursor of nicotinamide adenine dinucleotide (NADH), which is the primary electron donor for respiratory chain complex I, whose enzymatic name is NADH dehydrogenase and converts NADH to NAD⁺. NAD⁺ precursor therapies include a suite of different formulations involved in either its synthesis or recycling (niacin, niacinamide, nicotinamide mononucleotide, nicotinamide riboside, etc), the optimal of which for mitochondrial disease is not currently known. However, it has been shown that vitamin B3 supplementation in the form of niacin helps to restore cellular NADH/NAD⁺ balance and encourages mitochondrial biogenesis in human fibroblasts from a complex I disease patient[29], and has been shown to improve survival in a respiratory chain complex I disease *C. elegans* animal model[30]. Biotin (Vitamin B7) is the cofactor for the

mitochondrial carboxylases, including pyruvate carboxylase[31]; secondary biotin deficiency, although rare, is theoretically possible in individuals treated with lipoic acid[32,33], based on which biotin is often supplemented in individuals on lipoic acid therapy. Folic acid (Vitamin B9) is necessary for one-carbon transfer reactions; the active form, folinic acid (5-formyltetrahydrofolate) is able to cross the blood brain barrier[34] and is especially important in mitochondrial diseases associated with cerebral folate deficiency[35] (e.g. Polymerase Gamma (*POLG*) deficiency[36], mtDNA deletion disorders[37], Kearns Sayre Syndrome[38,39]), which may present with white matter changes that may be reversible upon folinic acid (leucovorin) supplementation[40].

ANTIOXIDANTS

A range of different cellular antioxidants exist that have different mechanisms of action and levels of efficacy. In PMD, antioxidants are empirically used to reduce oxidative stress in attempt to mitigate DNA, lipid, and protein damage within mitochondria and the broader cell. Commonly used antioxidants that have generally high tolerability include vitamin E (alpha tocopherol), alpha lipoic acid, and coenzyme Q10 (CoQ10) specifically in its reduced form, ubiquinol[8,41]. Vitamin E is a potent lipophilic antioxidant, which primarily acts at the mitochondrial and plasma membrane to scavenge free radicals and prevent oxidative damage to polyunsaturated fatty acids in the membranes[42]. Oxidized vitamin E is a stable free radical, which can itself be reduced again by ascorbate to continue the antioxidant cycle. Additional vitamin E effects include transcriptional inhibition of protein kinase C, which reduces the downstream activity of oxidative pathways including NADPH oxidase[43,44]. In pre-clinical animal models, vitamin E led to complete rescue of *C. elegans* short lifespan in a genetic-based chronic mitochondrial complex I disease, and provided significant protection from brain death in zebrafish exposed to a toxin that acutely inhibits mitochondrial respiratory chain complex I function[8]. Alpha lipoic acid is a prominent intra-mitochondrial antioxidant and cofactor of PDHC, which is water soluble and generally well-tolerated[45–47]. Ubiquinol is the reduced and more bioavailable form of CoQ10, which plays a central role in mitochondrial biochemistry through its role in shuttling electrons from respiratory chain complexes I or II and the electron transport flavoprotein to respiratory chain complex III. Ubiquinol also serves as a lipophilic and vitamin E-sparing antioxidant, with similar *in vitro* efficacy[41,48]. The oxidized form of CoQ10, ubiquinone, does not itself have antioxidant potential, although in some model systems it may decrease oxidative stress, perhaps by its endogenous conversion to ubiquinol[41]. The recycling pathway of ubiquinol is distinct, as it is not reduced by ascorbate, but rather by glutathione or directly by the electron transport system [48]. Secondary CoQ10 deficiency, while uncommon, may also occur in mitochondrial diseases[49]. Leukocyte CoQ10 levels are used by many clinicians to adjust ubiquinol dosing, with a common therapeutic goal to keep levels at, or up to twice, the upper normal range limit as a proxy for tissue CoQ10 levels. Although plasma CoQ10 levels can also be measured, this is very sensitive to lipoprotein content of the blood, and therefore is not reflective of tissue CoQ10 levels[49]. Idebenone, a synthetic version of CoQ10, is not approved for the treatment of mitochondrial disease by the Food and Drug Administration (FDA) in the United States, as trials have not shown clinical efficacy[50], although it has

received provisional approval by the European Medical Agency (EMA) for Leber's Hereditary Optic Neuropathy, pending completion of a pivotal clinical trial[51].

Other antioxidant agents empirically used in mitochondrial disease have changed over time. Vitamin C (ascorbic acid) is used to boost immune function and has been suggested to have antioxidant function. However, the latter has not been demonstrated in mitochondrial disease models and, in contrast, lack of benefit with potential for toxicity at high doses was seen when vitamin C was evaluated in a PMD complex I disease *C. elegans* animal model [8]. N-acetylcysteine has been recognized as a central nervous system penetrant antioxidant that may enhance the endogenous synthesis of glutathione, the major endogenous antioxidant scavenging system[52] that is often deficient in mitochondrial disease patient tissues[53]. Brain magnetic resonance spectroscopy analysis demonstrated efficacy of N-acetylcysteine supplementation to increase brain glutathione levels [54]. In addition, benefits of N-acetylcysteine on animal viability, lifespan, health span, and systemic resiliency were demonstrated in *C. elegans*, human cell, and zebrafish models of mitochondrial complex I disease[8]. Plasma glutathione level analyses (total level, reduced glutathione, and oxidized glutathione) have become clinically available in several US labs, which may be used to determine which PMD patients have glutathione deficiency as an indicator of chronic oxidative stress as well as to adjust N-acetylcysteine dosing to keep glutathione levels in the normal range.

OTHER NUTRIENTS

Several additional nutrients may be variably used as mitochondrial medicines. L-arginine is a substrate of nitric oxide synthase in the vascular endothelium that may be administered to increase nitric oxide levels and relax vascular smooth muscle[55]. L-arginine is used to treat and prevent metabolic stroke in mitochondrial disease, with recent long-term data suggesting improved survival and reduced debility when compared to the natural history of mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)[13,14] and clinical benefit when administered acutely to pediatric Leigh syndrome patients for metabolic stroke[13]. L-citrulline is a precursor of L-arginine that leads to even greater nitric oxide synthesis[15,56], and is empirically used in individuals with recurrent stroke-like episodes despite prophylaxis with L-arginine[57]. Finally, L-creatine, when phosphorylated, provides a cellular energy store that has particular clinical utility as a therapy for individuals with mitochondrial myopathy presenting with exercise intolerance and muscle fatigue.

While L-carnitine was historically used widely to promote the shuttling of long-chain fatty acids and other organic acids into the mitochondria while removing toxic metabolites, it is no longer routinely used due to the association of its chronic use in the general population with atherosclerosis[58,59]. Pyruvate and taurine recently been evaluated in PMD trial trials. Pyruvate has been suggested to rebalance NADH/NAD⁺ levels with short-term benefit in a small clinical cohort[60], but is not currently broadly used for this purpose in PMD patients. Recent clinical studies in Japan of high-dose taurine demonstrated efficacy in reducing the frequency of metabolic strokes in MELAS**[16,61], an indication for which it gained regulatory approval in Japan but has not been approved by the FDA. Additional information for health professionals about these and other dietary supplements are maintained on the

NIH Office of Dietary Supplements Fact Sheet, “Dietary Supplements for Primary Mitochondrial Disorders (<https://ods.od.nih.gov/factsheets/PrimaryMitochondrialDisorders-HealthProfessional/>).

CONCLUSION

Despite the absence of randomized controlled trials evaluating mitochondrial medicine empiric therapies to stabilize and/or improve health mitochondrial disease, progress has been made to identify potentially beneficial compounds with a high benefit-to-risk ratio that are generally well-tolerated for patients with inherited PMDs. Compounded regimens of empiric therapies that have complementary mechanism of action, such as a multivitamin, B50 complex, one or more antioxidants (vitamin E and/or lipoic acid, as well N-acetylcysteine when plasma glutathione deficiency is present), and coenzyme Q are generally well-tolerated when started together. Precision mitochondrial medicine further supports the use of specific therapies that have particular benefit for some genetic etiologies and/or shared phenotypes, such as arginine for metabolic strokes, folinic acid for white matter disorders, creatine for metabolic myopathy, high-dose N-acetylcysteine for ethylmalonic encephalopathy, biotin and thiamine for biotin/thiamine-responsive basal ganglia disease, and high-dose ubiquinol for primary CoQ10 deficiencies (Figure 1). The future of mitochondrial medicine will increasingly require therapeutic personalization based on molecular diagnosis and clinical phenotype.

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KEY POINTS

- While randomized controlled trial data is lacking, supporting pre-clinical evidence and favorable benefit-to-risk ratios justify empiric use of mitochondrial medicine regimens to manage PMDs.
- The overarching goal of mitochondrial medicines is to stabilize and enhance residual metabolic function to improve cellular resiliency to slow clinical disease progression and/or prevent acute decompensation.
- Mitochondrial medicine empiric therapies commonly include a combinatorial regimen of vitamins, antioxidants, and co-factors, with further modification based on genetic etiology, clinical phenotype(s), and biochemical findings.

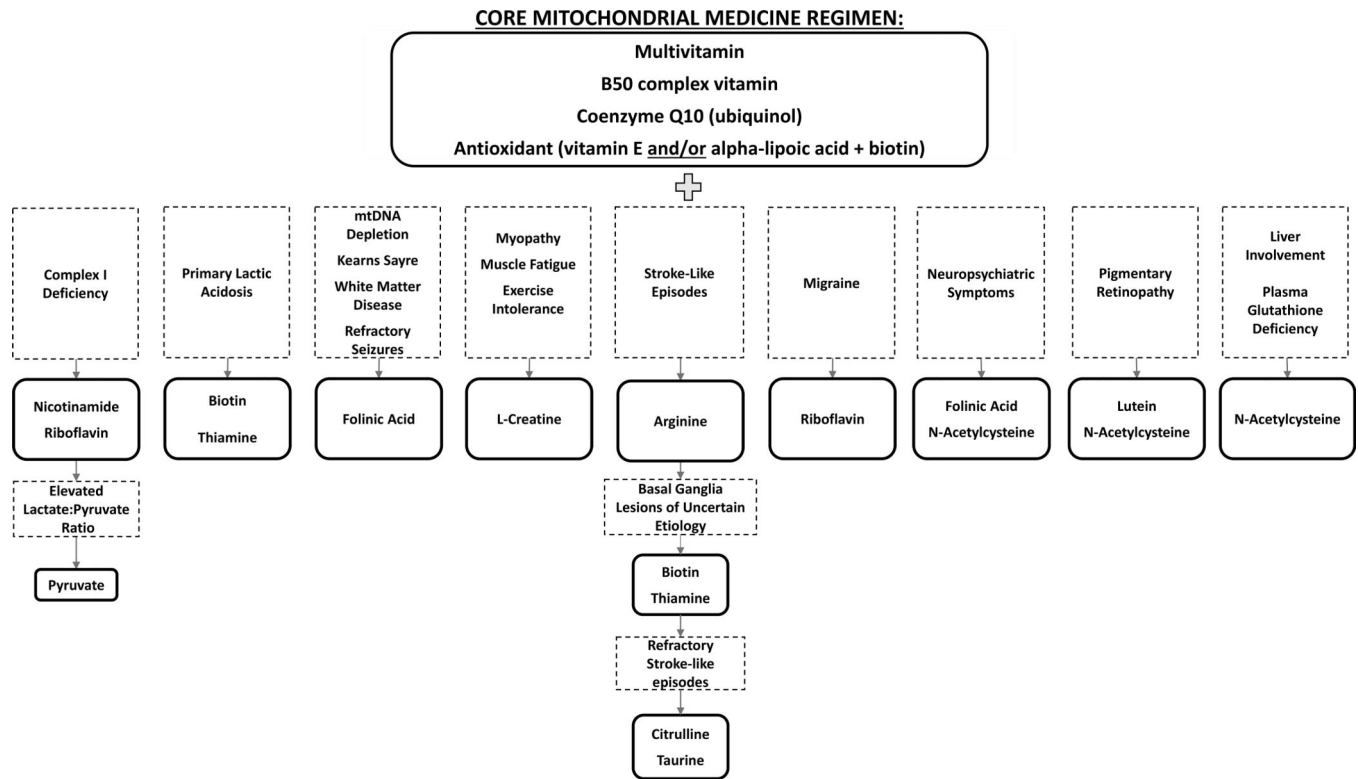


Figure 1: Personalized prescribing of mitochondrial supplements.

This figure represents the recommended approach to prescribing mitochondrial medicines.
 (Elevated lactate:pyruvate ratio indicates elevated NADH/NAD⁺ ratio.)

Table 1.

Standard components of nutrient therapy for mitochondrial disease, and recommended dosage range, side-effects, and specific considerations. Core Supplements commonly used in PMD include a B50 complex, antioxidant(s) including vitamin E or alpha lipoic acid), and coenzyme Q10 (ubiquinol). Additional components are considered based on patient genetic etiology and phenotype. Enteral, by oral or gastrostomy feeds. IV, intravenous. FDA, Food and Drug Administration. BID, twice daily dosing. TID, three times daily dosing. mcg, microgram. mg, milligram. kg, kilogram. IU, international unit. PMD, primary mitochondrial disease. CNS, central nervous system. GI, gastrointestinal. CoQ10, coenzyme Q10. CK, creatine kinase. MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome. PMD, primary mitochondrial disease.

Medicine	Enteral Total Dose (per day, divided BID or TID)	Enteral Maximal Dose (per day)*	Parenteral (IV) Formulation Available?	Known Adverse Effects	FDA Approved Formulation Available?	Diagnostic Indication	Clinical Indication	Monitoring Guidelines and Other Notes
B Vitamin Complex	B50 (one daily)		No		No	PMD		B vitamin complexes may vary in composition among brands. B100 pills may be difficult to swallow. Check brand-specific information for specific content, and be aware of high-dose B6 content that may cause peripheral neuropathy.
Ubiquinol (CoQ10) [7,12,49,62–64]	Pediatric: 2–8 mg/kg Adult: 50–600 mg	1,200 mg	No	Difficulty sleeping, Nausea	No	PMD		Can follow Leukocyte CoQ10 levels and dose adjust to maintain therapeutic goal of at least the upper limit of normal Ubiquinol is preferred formulation to ubiquinone due to improved tissue bioavailability and lower dosing requirements[12] Maximal daily dose of ubiquinone is 2,400 mg/day due to renal clearance threshold[12]
Vitamin E[8,12,65–69]	Pediatric: 1–2 IU/kg Adult: 100–200 IU	5,500 IU	No	Decreased HDL of unknown clinical significance, Vitamin K deficiency reported	No	PMD		
Alpha-Lipoic Acid[7,12,33,46,70–79]	50–600 mg	1,800 mg	No	Hypersensitivity reactions reported	No	PMD		Follow glucose levels if on hypoglycemic agents May interfere with other

Medicine	Enteral Total Dose (per day, divided BID or TID)	Enteral Maximal Dose (per day)*	Parenteral (IV) Formulation Available?	Known Adverse Effects	FDA Approved Formulation Available?	Diagnostic Indication	Clinical Indication	Monitoring Guidelines and Other Notes
								water-soluble vitamin absorption
Biotin (B7) [7,80–83]	2–10 mg	200 mg	No		No	Profound biotinidase deficiency, Holocarboxylase synthetase deficiency, Biotin-thiamine-responsive basal ganglia disease	Undiagnosed patients with basal ganglia lesions or primary lactic acidosis	May need to hold for 2–3 days week before obtaining some lab tests where biotin may interfere with assay (such as for thyroid screen in some labs) Commonly used to prevent secondary biotin deficiency in individuals taking alpha lipoic acid therapy
Folinic Acid (B9) [7,12,38,84–88]	1.5–5 mg/kg	100 mg	Yes	Rare Tics/ Agitation, rare reports of hypersensitivity	Yes: Leucovorin	mtDNA depletion disorders (including <i>POLG</i>), Keams Sayre Syndrome	Refractory seizures, Mood disturbances	Preferred over folic acid because of central nervous system (CNS) penetration. May want to discontinue folate to prevent competition for CNS uptake
L-Arginine[7,12–14,57]	150–300 mg/kg	Unknown	Yes: 500 mg/kg/day in bolus repeated q24 hours for 3–5 days depending on continued response[13]	Chemical burn at IV site if leak, Hypotension with IV loading, Electrolyte abnormalities, Headache, GI upset, Lysine deficiency due to competition for renal reabsorption Metabolic acidosis with intravenous bolus (if given as arginine hydrochloride)	Yes: R-Gene 10	Mitochondrial Encephalopathy, Lactic acidosis, and Stroke-like episodes (MELAS) syndrome; Leigh syndrome	Acute or past history of metabolic stroke	Chronic therapy goal: maintain plasma arginine of > 168 micromol/L[89]
L-Citrulline[57,90–94]	Pediatric: 150 mg/kg Adult: 3g	15 g	No	GI upset	No		Breakthrough metabolic strokes despite chronic arginine therapy	
L-Creatine[7,12,62,73,95,96]	Pediatric: 0.1 g/kg Adult: 5g	10 g	No	Unknown	No		Muscle Fatigue, Exercise Intolerance, Myalgia	Stop 1–2 days prior to checking creatine kinase or chemistry panel as may interfere with assay

Medicine	Enteral Total Dose (per day, divided BID or TID)	Enteral Maximal Dose (per day)*	Parenteral (IV) Formulation Available?	Known Adverse Effects	FDA Approved Formulation Available?	Diagnostic Indication	Clinical Indication	Monitoring Guidelines and Other Notes
Lutein[17,18,97–99]	6–12 mg	20 mg	No	Case report of crystalline maculopathy	No		Pigmentary retinopathy	
N-acetylcysteine[8,19–21,54,100–102]	Low dose (use in standard mitochondrial regimens): 10 mg/kg High dose (liver disease; precision therapy, see Table 2): 150 mg/kg	8g	Yes	GI upset, Headache, Paresthesia, Neutropenia documented in 2 cases at high dose (6g/day)	Yes; Cetyl, Acetate	<i>ECHS1, ETHE, HIBCH, TRMU</i> , Complex I deficiency	PMD with low blood glutathione level; Liver disease; Pigmentary retinopathy; Psychiatric symptoms[22–24]	Can follow total glutathione levels or oxidized/reduced glutathione ratio to dose adjust
Nicotinic acid (niacin) (B3) [7,81,103,104]	10mg/kg	3,000 mg	No	Flushing (with nicotinic acid, not common with other formulations in class including nicotinamide); Rare reports of hepatotoxicity at > 3 g/d	No	Complex I deficiency, <i>DGUK</i>	Hypertriglyceridemia	Follow blood glucose level (if diabetic), CK, potassium (if on statin), platelets and Coag screen (if on anticoagulants), uric acid (if prone to gout), and Phosphate (if predisposed to hypophosphatemia)
Sodium Pyruvate[60,105–107]	Pediatric: 0.5–1 g/kg Adults: 3–6 g	25 g	No	GI upset	No	Complex I deficiency with elevated lactate:pyruvate ratio		Monitor serum lactate, pyruvate, and plasma amino acids Is commonly used in Japan
Riboflavin (B2) [12,27,28,81,108–118]	50–400 mg	1,200 mg	No	GI upset; Changes in urine color smell; infrequently hepatotoxicity	No	<i>ACAD9, AIFM1, DGUK, FLAD1, DLD</i> , Complex I disease, Riboflavin transporter defects	Migraines[119,120]	May start with low dose and increase as tolerated over time.
Taurine[16,61,121]	Pediatric: < 15 kg – 3 g 15–24 kg – 6 g Adults: 25–39 kg – 9 g 40+ kg – 12 g	12 g	No	GI Upset, Insomnia, GGT elevation Contraindicated in Renal Failure	No		MELAS	Functions as a buffer to maintain mitochondrial pH gradient. In MELAS patients with m.3243A>G pathogenic variant, taurine is hypothesized to improve a modification defect of the tRNA-Leucine[16]
Thiamine (B1) [7,65,73,81,122–127]	< 3y: 150 mg > 3y: 300 mg	900 mg	Yes	Nausea reported at > 7,000 mg/d; Rare Anaphylaxis with IV use	Yes	PDHC deficiency, Thiamine pyrophosphokinase deficiency		No guidelines exist for monitoring plasma B1 levels

Table 2.
Specific molecular entities and phenotypes of PMD for which individualized mitochondrial medicine therapies are recommended.

g, gram. IU, international unit kg, kilogram. mcg, microgram. mg, milligram. SC, subcutaneous. TID, three times a day. μ mol, micromole.

PMD Disease Name	Causal Gene(s) Disorder	Specific Therapy Recommendation
Acyl-CoA Dehydrogenase 9 Deficiency[111]	<i>ACAD9</i>	Riboflavin: 10–20 mg/kg/day *[111]
Combined Oxidative Phosphorylation Deficiency [108]	<i>AIFM1</i>	Riboflavin: 100 – 200 mg/day *[108]
Mitochondrial tRNA synthetase deficiency[1,128]	<i>AARS2, CARS2, DARS, DARS2, EARS2, FARS2, GARS, HARS2, IARS, IARS2, KARS, LARS, LARS2, MARS2, NARS2, PARS2, QARS, SARS2, SARS2, TARS2, VARS2, WARS2, YARS2</i>	Supplementation with cognate amino acids shows <i>in vitro</i> efficacy in some cases[128]; <i>in vivo</i> treatment guidelines do not exist
Biotin-Thiamine-Responsive Basal ganglia disease[25,123]	<i>SLC19A3</i>	Biotin: 5 –20 mg/kg/day Thiamine: 10–40 mg/kg/day
Profound Biotinidase Deficiency[129]	<i>BTID</i>	Biotin: 10 mg/day
Riboflavin transporter deficiency (Brown-Vialetto-Van Laere and Fazio-Londe syndrome[25,114,117,130])	<i>SLC52A2, SLC52A3</i>	Riboflavin: 10 mg/kg/day (divided TID)[130]; can titrate up to 50 mg/kg/day in unresponsive patients *
Primary CoQ10 deficiency[25,49,131]	<i>COQ2, COQ4, COQ6, COQ7, COQ8A, COQ8B, COQ9, PDSS1, PDSS2</i>	CoQ10 (doses were originally established for ubiquinone[25,131]. Ubiquinol is now preferred based on greater bioavailability, but specific dosage guidelines do not exist – see Table 1 for general ubiquinol dosing guidelines) Pediatric: 10–30 mg/kg/d Adult: 1,200–3,000 mg/d
SCO Cytochrome c oxidase assembly protein 2 deficiency[25,132,133]	<i>SCO2</i>	Bezafibrate, Copper Copper–histidine 500 mcg/day SC
Deoxyguanine Kinase Deficiency	<i>DGUOK</i>	Nicotinamide shows <i>in vitro</i> efficacy in cell models [134]; <i>in vivo</i> treatment guidelines do not yet exist
Short Chain Enoyl-CoA Hydratase deficiency[135–137] and 3-hydroxyisobutyryl-CoA Hydrolase deficiency[25,138,139]	<i>ECHS1, HIBCH</i>	Valine restricted diet (goal of <45 mg/kg/day; target valine level of 83 μ mol/L)) N-acetylcysteine: 150 mg/kg/day
Ethylmalonic encephalopathy[25,140–142]	<i>ETHE1</i>	Metronidazole: 30 mg/kg/day (divided BID) N-acetylcysteine: 105 mg/kg/day (divided TID); (100 mg/kg/day IV if comatose) Methionine: 20–30 mg/kg/day Restricted cysteine
Flavin adenine dinucleotide synthetase deficiency[113]	<i>FLAD1</i>	Riboflavin 100–200 mg/day[113,143]
<i>GOT2</i> -related Epileptic encephalopathy[144]	<i>GOT2</i>	Serine: 200 – 500 mg/kg/day
Holocarboxylase synthetase deficiency[25,80,145]	<i>HLC5</i>	Biotin: 10–20 mg/kg/d (divided BID)
Multiple acyl CoA dehydrogenase deficiency[25,113,116,146]	<i>ETFA, ETFB, ETFDH</i>	Riboflavin: 10 mg/kg/d *

PMD Disease Name	Causal Gene(s) Disorder	Specific Therapy Recommendation
Mitochondrial Encephalopathy, Lactic acidosis, and Stroke-like episodes ^{8,15,**16,122}	<i>MT-TL1, MT-ND5, MT-TC, MT-TF, MT-TL, MT-TK, MT-TL2, MT-TQ, MT-TV, MT-TW, MT-TS1, MT-TS2, MT-ND1, MT-ND6, MT-CO2, MT-CO3, MT-CYB</i>	Arginine: 150–300 mg/kg (divided BID) *In acute metabolic stroke, IV arginine dose is 500 mg/kg given over 60 minutes and repeated in 2 hours if no effect. Can be given q24 hours up to 5 days
mtDNA depletion syndromes ^{54, 120,123}	<i>ABAT, AGK, DGUOK, DNA2, FBXL4, MFN2, MGME1, MPV17, OPA1, POLG, POLG2, RNASEH1, RRM2B, SLC25A4, TFAM, TK2, TWNK, TYMP</i>	Folinic acid
Pyruvate Dehydrogenase Deficiency[25,124,149]	<i>DLAT, PDHA1, PDHB, PDHX, PDP1</i>	Ketogenic diet Thiamine: 30–40 mg/kg/d (Max: 900 mg/d)
Dihydropyrimidine Dehydrogenase Deficiency	<i>DLD</i>	Riboflavin 200–400mg/day[150]
Thiamine Pyrophosphokinase Deficiency[25,125,127]	<i>TPK1</i>	Thiamine: 20 mg/kg/d (Max: 900 mg/d) Biotin: 15 mg/d (divided TID) (Max: 100 mg/d) Niacin: 10 mg/kg (divided TID) α-lipoic acid: 5 mg/kg (divided TID)
Thioredoxin 2 deficiency[25]	<i>TXN2</i>	Idebenone up to 20 mg/kg/d
tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase[151]	<i>TRMU</i>	L-cysteine: 300 mg/kg/d N-acetylcysteine: 70–105 mg/kg/d
Encephalopathy due to defective mitochondrial and peroxisomal fission I[152]	<i>DNM1L</i>	Bezafibrate is of particular efficacy in <i>in vitro</i> models; clinical data do not yet exist
Retinitis pigmentosa ^{69, 75}		Lutein 12 mg/day, Vitamin A palmitate 15,000 IU/d N-acetylcysteine 600 – 1,800 mg/d

* Published riboflavin doses for individual conditions described in case reports are highly variable. In general, doses up to 200–400 mg/day are well-tolerated. Some patients experience nausea/vomiting with higher doses and require a slow up-titration to fully tolerate. Higher doses of riboflavin up to 50 mg/kg/day are indicated in patients with a confirmed riboflavin transporter defect.