Alpha-Lipoic Acid: Safe and Effective

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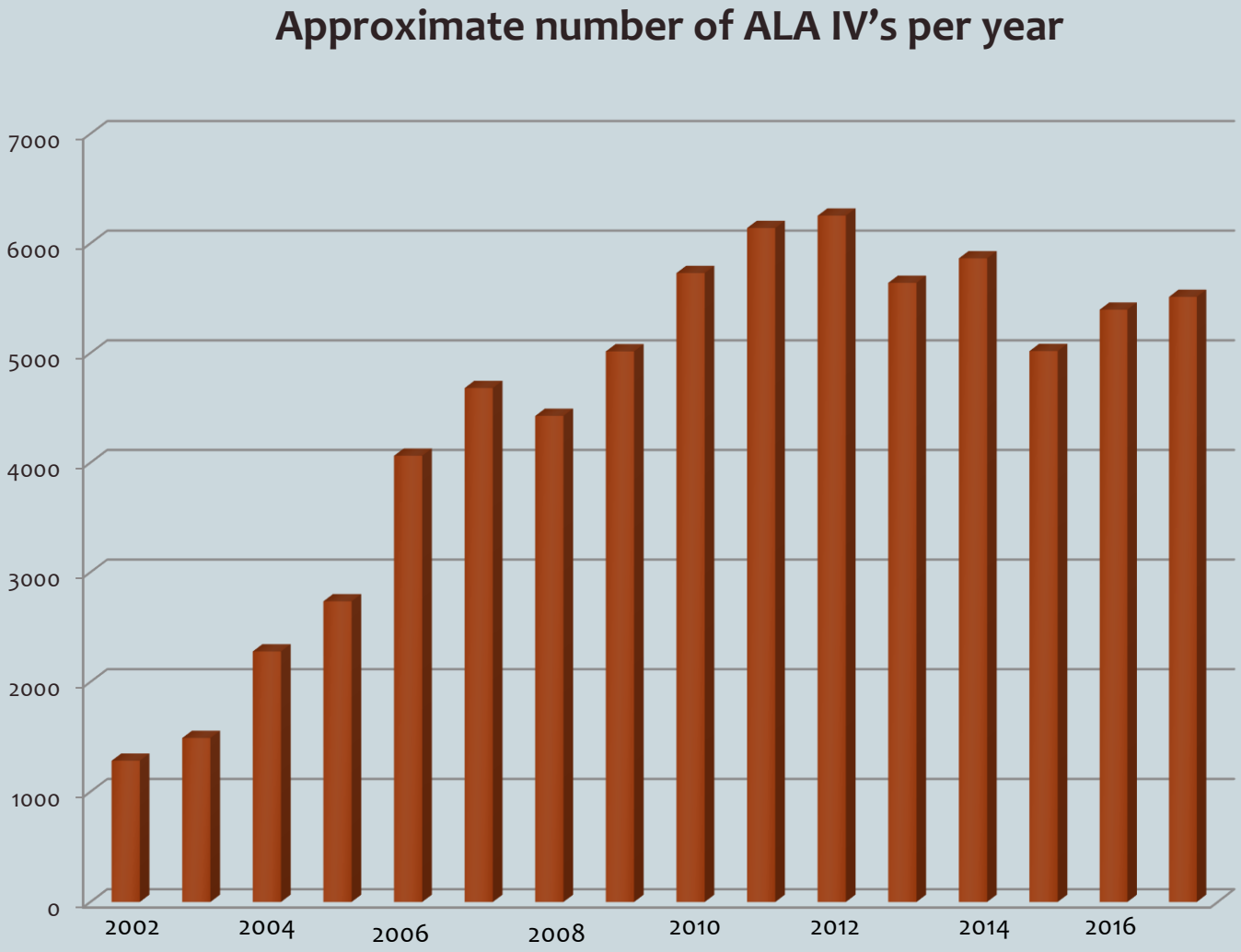
Intravenous Alpha-Lipoic Acid: Essential in the Treatment of Diabetic Neuropathy

- FDA:
  - Safe ("do not appear to be significant adverse effects associated with its use")
  - Effective ("ALA appears to show symptom improvement with treatment for several weeks in the treatment of diabetic neuropathy")
- There really is no available equivalent treatment in terms of safety and efficacy
- There are promising uses that can be subjects of future controlled studies
- IV ALA is safe, effective, and stable
- Case reports

Approximate Number of ALA IV's given at IMCNM



Approximate total number of ALA IV's given since 2002:

75,360

Number of serious adverse events:

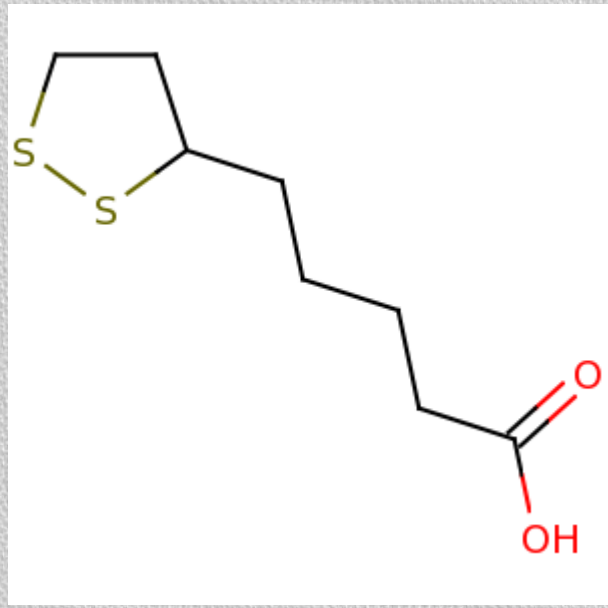
0

We do see episodes of hypoglycemia, headaches, sleepiness

Alpha-Lipoic Acid

Structure and Functions

- Some Functions:
  - Water- and fat-soluble antioxidant[1]
  - Recycles other antioxidants[1]
  - Cofactor in aerobic ATP production in mitochondria[2]
  - Heavy metal chelator[3]
  - Insulin mimetic[2] and reduces insulin resistance[4]
  - Inhibits nf kappa-B activation[5]



1. Moura FA, et al. Lipoic Acid: its antioxidant and anti-inflammatory role and clinical applications. Curr Top Med Chem. 2015;15(5):458-83
2. Rochette L, et al. Alpha-Lipoic Acid: molecular mechanisms and therapeutic potential in diabetes. Can J Physiol Pharmacol. 2015 Dec;93(12):1021-7.
3. Rochette L, et al.Direct and indirect antioxidant properties of alpha-lipoic acid and therapeutic potential. Mol Nutr Food Res.2013 Jan;57(1):114-25.
4. Akbari, et al. The effects of alpha-lipoic acid supplementation on glucose control and lipid profiles among patients with metabolic diseases: A systemic review and meta-analysis of randomized controlled trials. Metabolism. 2018 July 7.
5. Ying, et al. Evidence that alpha-lipoic acid inhibits NF-kB activation independent of its antioxidant function. Inflamm Res. 2011 Mar;60(3):219-25.

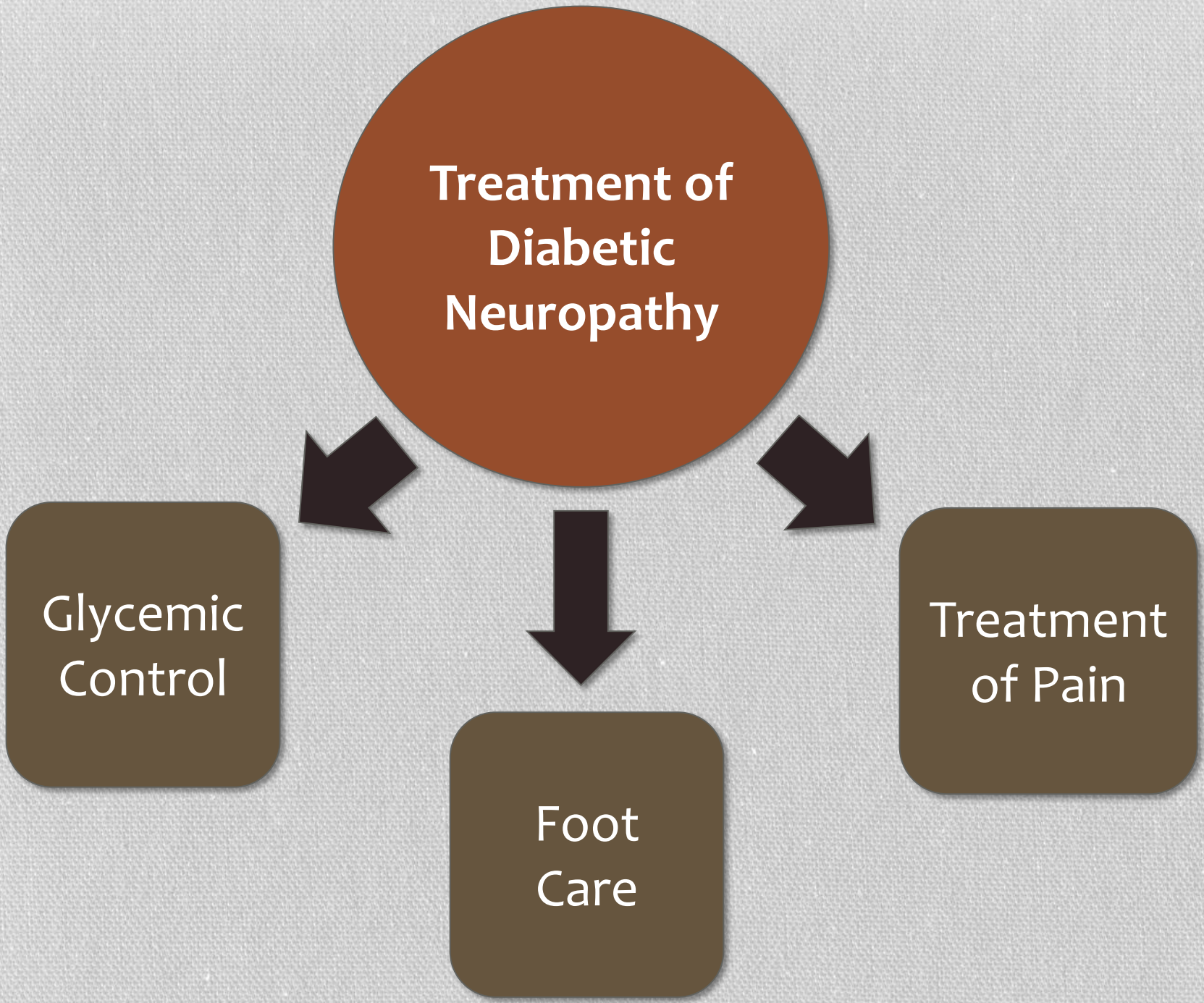
Partial List of Diseases in the Literature

- Metabolic
  - Diabetes Mellitus, Insulin Resistance
  - Weight Loss, Kwashiorkor
  - Osteoporosis, PCOS
- Diabetic Complications
  - Diabetic Peripheral and Autonomic Neuropathy, Nephropathy, and Retinopathy
- Neurological
  - MS, Alzheimer's Disease
  - Migraine Prophylaxis, Sciatica, Burning Mouth Syndrome, CTS
  - Chemotherapy Induced Neuropathy
- Ophthalmological
  - Age-Related Macular Degeneration, Cataract Protection, Glaucoma
- Immune/ID
  - HIV/AIDS
- Hepatology
  - Hepatitis C, Acute Hepatic Necrosis
- Cardiovascular
  - Hypertension, Ischemia Reperfusion Injury
  - Erectile Dysfunction
- Dermatological
  - Wound Healing, Photoaging

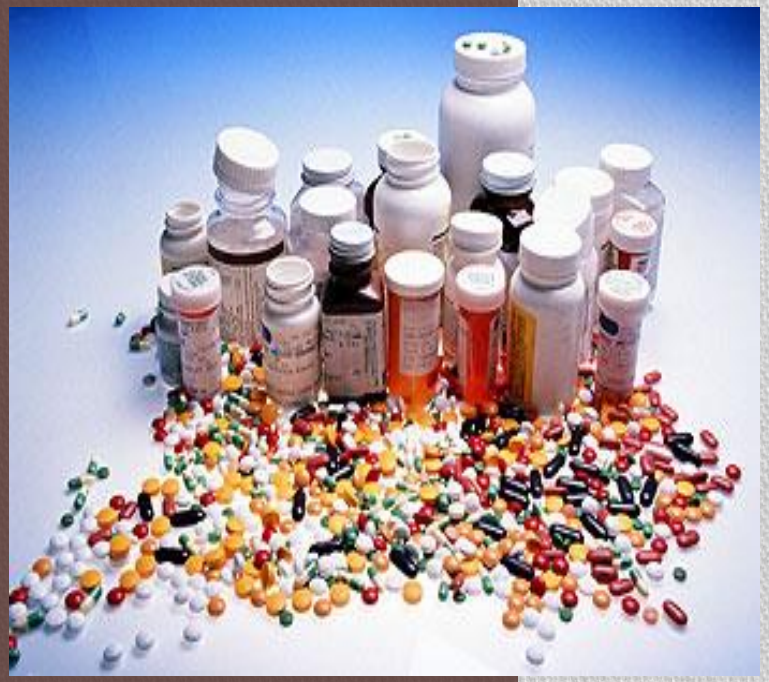
Intravenous Alpha-Lipoic Acid

- **Best evidence**
  - Diabetic Neuropathy[1]

1. Ziegler, D.; Nowak, H.; Kempler, P.; Vargha, P. & Low, P. (2004). Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha lipoic acid: a meta-analysis. *Diabet Med*, vol.24, no.2, (February 2004), pp.114-121, ISSN 1464-5491.


Treatment of Diabetic Neuropathy
Glycemic Control
Foot Care
Treatment of Pain

Treatment Options in Diabetic Neuropathy



- **Strong Evidence:**
  - Pregabalin*
- **Moderate Evidence:**
  - Gabapentin
  - Sodium valproate
  - Amitriptyline
  - Duloxetine*
  - Venlafaxine
  - Dextromethorphan
  - Morphine Sulfate
  - Oxycodone
  - Tramadol
  - Tapentadol**
  - Capsaicin
  - Isosorbide Dinitrate Spray
- **Possibly effective:**
  - Lidocaine

*FDA Approved Treatment
**FDA Approved After Release of Guidelines

Source:
AAN Summary of Evidenced-based Guidelines for CLINICIANS- Treatment of Painful Diabetic Neuropathy, ©2011

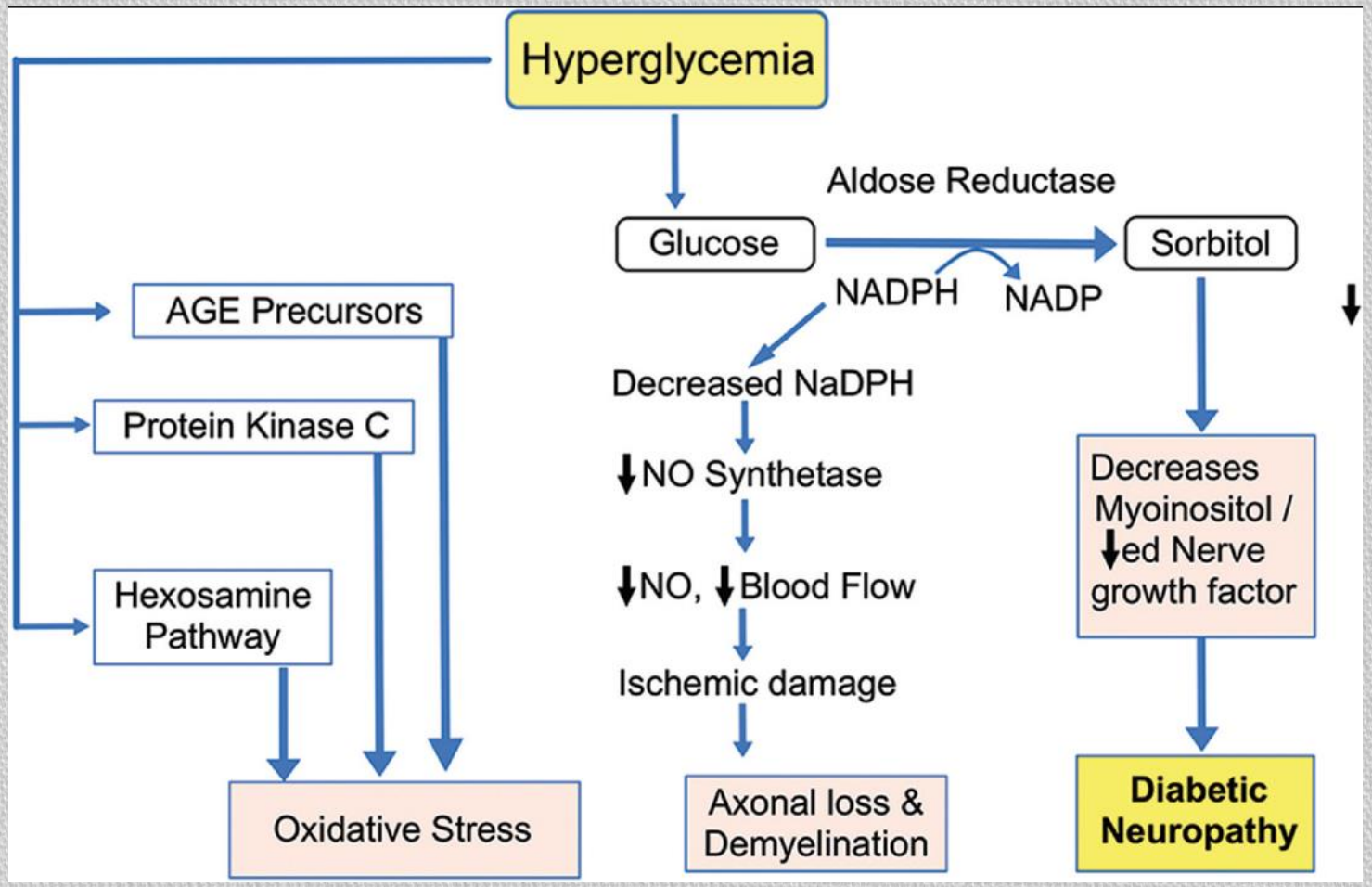
What do all these treatments for diabetic neuropathy have in common?

What do all these treatments for diabetic neuropathy have in common?

They all change perception of pain. They don't treat the underlying cause of the pain.

Why not treat the cause?

Pathophysiology Diabetic Peripheral Neuropathy



Source: Kapoor N, et al. Approach to diabetic neuropathy. *Current Medical Issues*. 2017; 15(3):189-199

Alpha-Lipoic Acid

Structure and Functions

- Some Pertinent Functions:
  - Water- and fat-soluble antioxidant[1]
  - Recycles other antioxidants[1]
  - Cofactor in aerobic ATP production in mitochondria[2]
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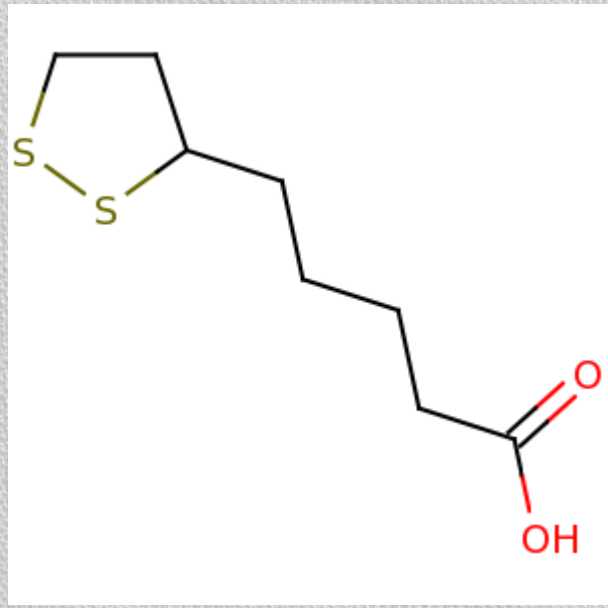

1. Moura FA, et al. Lipoic Acid: its antioxidant and anti-inflammatory role and clinical applications. Curr Top Med Chem. 2015;15(5):458-83
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RCTs of Intravenous ALA in DM Neuropathy

ALADIN I (N=328)

- 3 wk IV ALA v. placebo

- ***Results:***
  - **Total symptom score (TSS)** in feet decreased from baseline to day 19:
    - 58.6% in ALA 1,200 mg (p=0.003 vs. placebo), 63.5% in ALA 600 mg (p<0.0001 vs. placebo)
    - 38.4% in placebo
  - **Response rate** (improvement in TSS≥30%)
    - 70.8% in ALA 1,200 mg , 82.5% in ALA 600 mg (p=0.002 vs. placebo)
    - 57.6% in placebo

"…intravenous treatment with alpha-lipoic acid using a dose of 600mg/day over 3 weeks is superior to placebo in reducing symptoms of diabetic peripheral neuropathy, without causing significant adverse reactions."

1. Ziegler D, et al. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial. Diabetologia. 1995 Dec; 38(12):1425-33.

RCTs of Intravenous ALA in DM Neuropathy

ALADIN III (N=509)

Cross over ALA IVx3wk + POx6mo vs. IV + PO placebo vs. placebo IV + placebo oral

Key results:

- **Total Symptom Score:**
  - No significant difference vs. placebo
- **Neuropathy Improvement Score at day 19:**
  - Decreased by 4.34 in ALA vs. 3.49 in placebo (p=0.016)
  - Decreased in lower extremities by 3.32 in ALA vs. 2.79 in placebo (p=0.055)

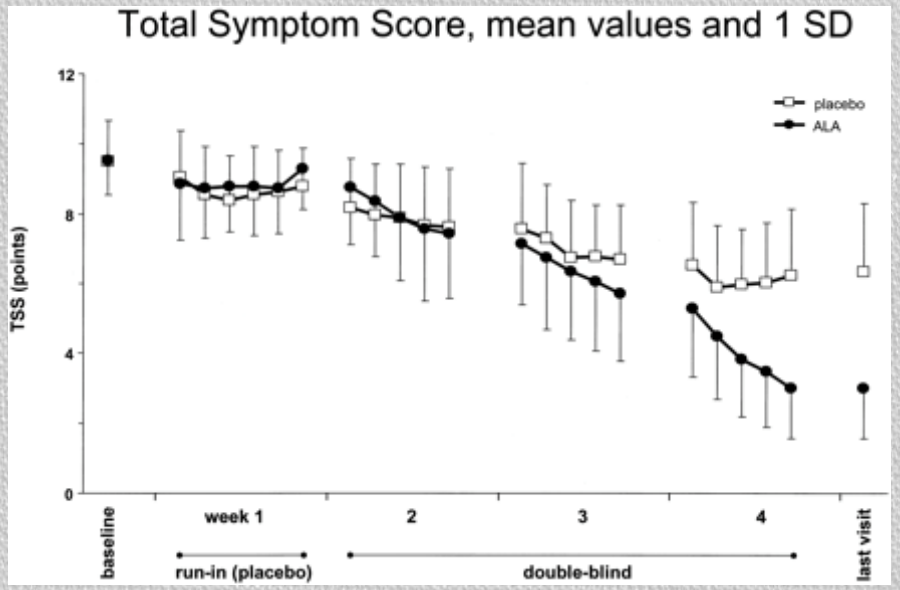
"…this treatment was associated with a favorable effect on neuropathic deficits without causing significant adverse reactions."

Ziegler D, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). Diabetes Care 1999 Aug; 22(8):1296-1301.

RCTs of Intravenous ALA in DM Neuropathy

SYDNEY3 (N=120)

3 wk IV x14 over 3 wk vs. placebo



Key Results:

- **Total Symptom Score** (14.64 max score)
  - Decreased by 5.7 points in ALA group vs. 1.8 points in placebo (p=<0.001)
- **Neuropathy Improvement Score**
  - Improved by 2.7 points in ALA group vs. 1.2 points in placebo (p<0.001)

"Intravenous racemic ALA, a potent antioxidant, rapidly and to a significant and meaningful degree, improved such positive neuropathic sensory symptoms as pain and several other neuropathic endpoints. This improvement of symptoms was attributed to improved nerve pathology…"

- Ametov, et al. The Sensory Symptoms of Diabetic Polyneuropathy Are Improved With Alpha-Lipoic Acid. Diabetes Care. 2003 Mar;26(3):770-6.

Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis

Ziegler, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. *Diabetic Medicine*. 2004 Feb;21(2):114-21.

Study:

- Randomized, double-blind, placebo-controlled trials
- 600 mg IV ALA/d x 3 wk (15 treatments)
- 4 trials
- n=1258
- **Evaluated:**
  - Total Symptom Score
  - Neuropathy Impairment Score

Results:

- 24.1% decrease in TSS compared to placebo ($p<0.05$)
- 16% decrease in NIS (didn't meet significance)
- Responder rate for ALA 52.7% vs. 36.9% placebo ($p<0.05$)
- No difference in adverse event rate

Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis

Ziegler, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. *Diabetic Medicine*. 2004 Feb;21(2):114-21.

"The results of this meta-analysis (n=1258) provide evidence that treatment with alpha-lipoic acid (600 mg/day i.v.) over 3 weeks is safe and significantly improves both positive neuropathic symptoms and neuropathic deficits to a clinically meaningful degree in diabetic patients with symptomatic polyneuropathy."

Alpha-lipoic acid in the treatment of autonomic diabetic neuropathy

Rom J Intern Med. 2004;42(2):457-64.

Alpha-lipoic acid in the treatment of autonomic diabetic neuropathy (controlled, randomized, open-label study).

Tankova T[1], Koev D, Dakovska L.

⊕ **Author information**

Abstract

AIM: to evaluate the effect of alpha-lipoic acid in autonomic diabetic neuropathy in a controlled, randomized, open-label study.

MATERIAL AND METHODS: 46 patients with type 1 diabetes and different forms of autonomic neuropathy, of mean age 38.1 +/- 12.5 years and mean duration of diabetes 16.8 +/- 8.9 years were treated with alpha-lipoic acid for 10 days 600mg daily iv, thereafter one film tablet of 600mg daily for 50 days. 29 type 1 diabetic patients with autonomic diabetic neuropathy, of mean age 40.2 +/- 9.3 years and mean duration of diabetes 15.4 +/- 7.9 years served as a control group. We have followed-up patients' complaints, Ewing's tests, laboratory parameters of oxidative stress.

RESULTS: There was a significant improvement after treatment in the score for severity of cardiovascular autonomic neuropathy--from 6.43 +/- 0.9 to 4.24 +/- 1.8 ($p<0.001$), while in the control group it worsened from 6.18 +/- 1.3 to 6.52 +/- 0.9 ($p>0.1$). We found improvement in the Valsalva manoeuvre after treatment - from 1.05 +/- 0.04 to 1.13 +/- 0.08 ($p<0.001$); in the deep-breathing test -from 3.4 +/- 2.8 to 10.4 +/- 5.7 ($p<0.001$); and in the lying-to-standing test--from 0.99 +/- 0.01 to 1.01 +/- 0.02 ($p>0.1$), while in the control group there was no improvement. There was a beneficial effect of treatment on the change of systolic blood pressure at the lying-to-standing test--from 22.7 +/- 11.5 to 9.8 +/- 7.9 ($p<0.001$), while in the control group the change was 20.5 +/- 11.1 mmHg and 19.7 +/- 12.9 mmHg ($p>0.1$), respectively. We found improvement in diabetic enteropathy in six patients; in the complaints of dizziness, instability upon standing in six patients; in neuropathic edema of the lower extremities in four patients and in erectile dysfunction in four patients after treatment, while in the control group no change was reported in the symptoms and signs of autonomic neuropathy by the end of the follow-up period. There were changes in the laboratory parameters of oxidative stress after therapy--total serum antioxidant capacity increased from 20.42 +/- 1.8 to 22.96 +/- 2.3 microgH2O2/ml/min ($p<0.05$), serum SOD activity - from 269.8 +/- 31.1 to 319.8 +/- 29.IU/l ($p=0.02$) and erythrocyte SOD--from 0.89 +/- 0.10 to 1.11 +/- 0.09 U/gHb ($p=0.04$).

CONCLUSION: Our results demonstrate that alpha-lipoic acid (Thiogamma) appears to be an effective drug in the treatment of the different forms of autonomic diabetic neuropathy.

"… alpha-lipoic acid (Thiogamma) appears to be an effective drug in the treatment of different forms of autonomic neuropathy."

How does oral ALA affect diabetic neuropathy in the real world?

- J Diabetes Complications. 2009 May-Jun;23(3):174-7. doi: 10.1016/j.jdiacomp.2008.02.002. Epub 2008 Apr 9.

  Switching from pathogenetic treatment with alpha-lipoic acid to gabapentin and other analgesics in painful diabetic neuropathy: a real-world study in outpatients.

- Ruessmann HJ German Society of outpatient diabetes centres AND (Arbeitsgemeinschaft niedergelassener diabetologisch tätiger Arzte e.V.)

Study results:

- 293 patients switched from oral ALA to gabapentin or no treatment
- Untreated group developed symptoms within 2 wks
- Gabapentin group: 45% stopped treatment due to side effects
  - 55% nonresponders to gabapentin and changed to another drug
- Daily cost lower for ALA
- Outpatient visits doubled when switched off ALA

How does oral ALA affect diabetic neuropathy in the real world?

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  Ruessmann HJ German Society of outpatient diabetes centres AND (Arbeitsgemeinschaft niedergelassener diabetologisch tätiger Arzte e.V.)

"In conclusion, switching from long-term treatment with alpha-lipoic acid to central analgesic drugs such as gabapentin in painful diabetic neuropathy was associated with considerably higher rates of side effects, frequencies of outpatient visits, and daily costs of treatment."

FDA Report: Response

Don't take my word, look at the FDA report…

Safety:

- "There has been extensive literature reporting clinical evaluation of ALA, and there do not appear to be significant adverse effects associated with its use."

Efficacy:

- "ALA appears to show symptom improvement with treatment for several weeks in the treatment of diabetic neuropathy."
- "No trial has shown ALA to improve diabetic autonomic neuropathy."

  See 2004 Tankova study

FDA Report: Response

Concerns:

- "A search of the British Pharmacopoeia, the European Pharmacopoeia, and the Japanese Pharmacopoea did not show any monograph listings for alpha-lipoic acid."
  - Intravenous ALA is a known pharmaceutical drug in Germany
  - Intravenous ALA is a recently approved pharmaceutical drug in Colombia

Stability of ALA in Aqueous Solution

1) Studies of IV ALA

- Experience with IV ALA in studies since the 1970's
- Multiple studies of ALA as an IV preparation (acknowledged in FDA report)
- Presence of IV ALA as a prescription drug in Germany and Colombia

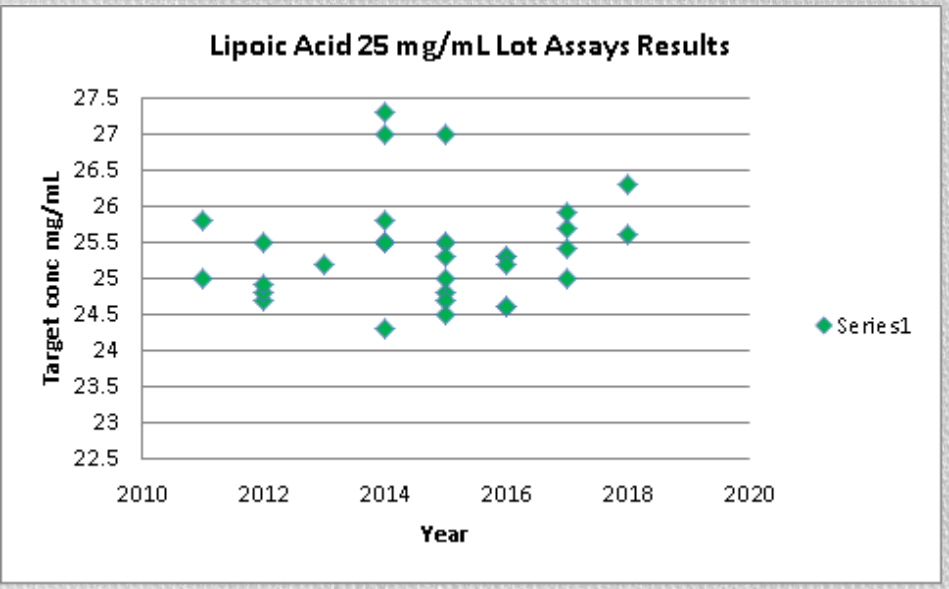
2) Data

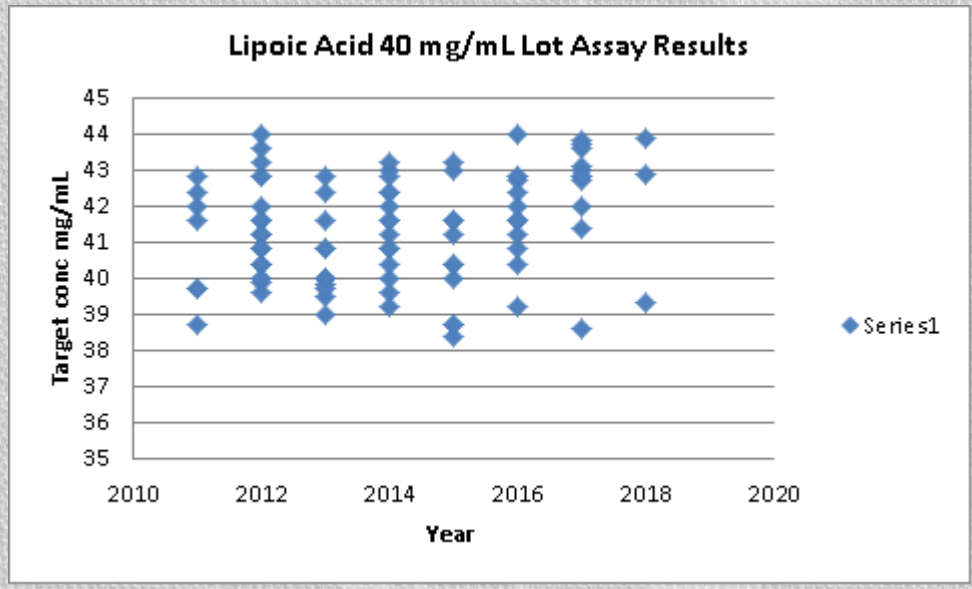
- Extensive testing for appearance, particulate matter, pH, potency, sterility, integrity, and preservative effectiveness and concentration in multidose vials
- Response by pharmacists

3) FDA Statement

- "The aqueous formulations are likely to be much more unstable than the solid dosage forms."
- "Due to lack of precise stability information supporting solution forms of ALA, the stability of the solution cannot be determined. Therefore, the stability of the liquid formulations of the drug substance is still of concern."
- No citation

Historical Potency Assay Data from McGuff





MCPS's formulations of 25 mg/mL and 40 mg/mL have been verified by numerous HPLC potency assays.

McGuff CPS's Lipoic Acid Injection Stability Study

Data / Results Table for Stability Study			
Characteristic	Test Method	Result at T_o	Result at T_{BUD}
Date of study initiation / conclusion		March 16, 2015	September 3, 2015
Study drug Lot Number		15B3101:082615	
Number of samples placed into inverted storage [Room temperature]			27
Appearance, Seal	Visual	Passed	Passed
Appearance, Vial	Visual	Passed	Passed
Appearance, Product	Visual	Yellow	Yellow
Foreign Matter, Visible Particulate	Per Pharmacy Procedure or Current USP <790>	No visible ppt	No visible ppt
pH	Per Pharmacy Procedure	7.1	7.5
Assay	[USP <621> HPLC, USP<851> Spectrophotometry]	38.4 mg/mL	38.7 mg/mL
Sterility	Current USP Chapter <71>	Sterile	Sterile
Or, in lieu of Sterility Container/Closure Integrity	BTS Method # CM413 (dye ingress)	NA	CCI post BUD for Lot 17H5611 – Passed -
Sterility test Method Suitability Test	Current USP Chapter <71>	Lot 14G4311 - Passed -	NA
Preservative Effectiveness (for Multi Dose Vials)	Antimicrobial Effectiveness current USP <51>	Meets USP	NA
Preservative concentration (for Multi Dose Vials)	Current USP Chapter <341>	Benzyl alcohol 1.03 %	Benzyl alcohol 1.2 %

At the Integrative Medical Center of New Mexico, we treat diabetic neuropathies (and other conditions) with IV ALA every day.

We need to be on our patients' team

Where do we stand?

Alpha-Lipoic Acid

- FDA:
  - Safe ("do not appear to be significant adverse effects associated with its use")
  - Effective ("ALA appears to show symptom improvement with treatment for several weeks in the treatment of diabetic neuropathy")
- There really is no available equivalent treatment in terms of safety and efficacy
- There are promising uses that can be subjects of future controlled studies
- IV ALA is safe, effective, and stable

- Stand up for our patients, our friends, our families, ourselves
- Follow the science
- Continue to allow for the compounding of ALA in the oral and IV forms

Questions?

COENZYME Q_{10}

Pharmacy Compounding Advisory Committee
September 12th, 2018

A.J. Day, PharmD
Director of Pharmacy Consulting
PCCA

FDA Briefing – Recommendation

1. Physiochemical characteristics

CoQ_{10} is a well characterized substance that is likely to be stable under ordinary storage conditions for oral dosage forms. Due to solubility concerns, it is not appropriate for compounding for IV administration.

2. Safety – no concerns

Available safety data for CoQ_{10} suggest that the substance is primarily associated with non-serious gastrointestinal adverse events; however, there is a minimal amount of information to assess the safety profile of CoQ_{10} in patients with mitochondrial disorders.

3. Historical use in compounding

CoQ_{10} has been compounded in oral and other dosage forms, including for injection, for the treatment of various disorders, including mitochondrial disease since at least 1999. It is also found in the British and European Pharmacopoeia.

FDA Briefing – Recommendation

4. Effectiveness

There are no compelling data establishing the effectiveness of CoQ_{10} for the treatment of mitochondrial diseases. Mitochondrial diseases encompass a wide variety of conditions related to genetic mutations in nDNA and mtDNA, with different phenotypic presentations. Based on a small amount of clinical data, clinical guidelines that recommend the use of ubiquinone in the treatment of primary CoQ_{10} deficiency and, in the absence of FDA approved therapies, therapeutic experts recommend CoQ_{10} for the treatment of other mitochondrial disorders. The results of CoQ_{10} therapy have been described in numerous publications, but do not appear to definitively support effectiveness for particular uses other than primary CoQ_{10} deficiency or in particular doses.

Based on this information the Agency has considered, a balancing of the four evaluation criteria ***weighs in favor of*** ubiquinone for oral administration being added to the 503A Bulks List.

Problems in achieving Level I evidence in mitochondrial disorders

1. Rare disease. No treatments which are dramatically effective in small-scale trials exist.
2. Small number of patients available for study. With variable genotypes and clinical phenotypes, thus matching the control and study populations is very difficult. Crossover trial design can help alleviate inter-patient phenotypic variability.
3. Defining outcome measures in treatment trials of mitochondrial diseases is difficult.
4. First phase 3 of a large-scale, double-blind, randomized clinical trial evaluating CoQ10 in children with primary mitochondrial disorders has been completed. Results haven't been published (Stacpoole 2012).
5. Case series and case reports are commonly used.

Level I – RCT with p<=0.05 and b<=0.2, or meta-analysis
Level II – randomized, p>0.05 or b >0.2 with trend
Level III – uncontrolled, non-randomized with historical control group
Level IV – case series w/o control
Level V – case reports

Stacpoole et al. (2012) Mitochondrion 12: 623-629.

Haas et al. (2007) Pediatrics 120: 1326-1333

FDA Assessment – Primary CoQ10 Deficiency

Distinct from the general recommendations, CoQ_{10} is considered a standard, effective treatment for one mitochondrial disorder, primary CoQ_{10} deficiency (Parikh et al. 2015), which will be discussed in the next section.

Trial	Design	Size	CoQ10 dose	Genotype	Phenotypes	Onset of effectiveness	Measurements	Outcome	Evidence Level
Ogasahara 1989	OL	2	150mg/d	Unknown	Myopathy Extremely low CoQ10 in muscle (~4%), normal in serum	3 months in muscle function	Muscle function	+	IV
Sobreira 1997	OL	1	150mg/d	unknown	Muscle CoQ10 8% Encephalomyopathy	Not mentioned	Exercise tolerance	+	IV
Boitier 1998	OL	1	60-250mg/d	unknown	Muscle CoQ10 16% Encephalomyopathy	6 months in subjective feeling	1. Muscle function 2. Neurological tests	1. + 2. No change	IV
Di Giovanni 2001	OL	2	200-300mg/d	unknown	Muscle CoQ ~37%, normal in serum Myopathy	2 months (CK and lactic acid levels)	CK Lactic level	1. + Back to normal 2. + Back to normal	IV
Musumeci 2001	OL	6	600mg-3000mg/d	Unknown	Cerebella ataxia Muscle weakness Low muscle CoQ10	6 months in muscle strength	1. Muscle strength 2. Ataxia	1. + 2. No change	IV
Lamperti 2003	OL	13	200-900mg/d	unknown	Cerebella ataxia Development delay Low muscle CoQ10	Not mentioned	Enzymatic activities and Symptoms of ataxia	No change in 3/13 (3 patients with oldest age, 27-35yo)	IV
Artuch 2006	OL	1	2500mg/d tapered down to 1000mg/d during 12m	Unknown	Cerebella ataxia Low muscle CoQ10	3 months in ICARS evaluation	1. ICARS 2. Muscle function	+	IV
Montini 2008 Salviati 2005	OL	2	30mg/kg/d	**COQ2 mutation**	Infantile Encephalomyopathy, CR-nephropathy	11 months	1. Muscle function 2. Brain MRI and 3. Seizures 4. Renal function	1. + 2. + 3. + 4. No change	IV
						20 days, 80 days to reach normal protein level in urine	1. Renal function 2. Neurologic examination	1. + Back to normal 2. + Back to normal	
Horvath 2006	OL	3	150-500mg/d	unknown	Low muscle CoQ10 Myopathy	3-6 months	CK and muscle function	+	IV
Gempel 2007	OL	3	200-500mg/d	**ETFDH mutation**	myopathy	3 weeks to 3 months	CK, muscle biopsy and subjective feeling	+	IV

While primary CoQ_{10} deficiencies are very rare, secondary forms are much more frequent. Patients present with CoQ_{10} deficiency (usually documented in skeletal muscle or cultured skin fibroblasts) but harbor defects in genes unrelated to CoQ_{10} biosynthesis.

Examples of secondary CoQ_{10} deficiency include mitochondrial myopathies (Sacconi et al 2010), and mitochondrial DNA depletion syndrome (Montero et al 2013), ataxia and oculomotor apraxia type I caused by mutations in aprataxin (*APTX*) (Quinzii et al 2005), glutaric aciduria type II or multiple acyl-CoA dehydrogenase deficiency (MADD), caused by mutations in *ETFDH* (Gempel et al 2007), cardiofaciocutaneous syndrome caused by mutations in *BRAF* (Aeby et al 2007), and methylmalonic aciduria (Haas et al 2009). CoQ_{10} deficiency has been reported also in non-genetic conditions such as fibromyalgia (Cordero et al 2009). The exact mechanisms by which these genetic defects cause CoQ_{10} deficiency are still unknown. Several hypotheses have been proposed, including interference with the signaling pathways regulating CoQ_{10} biosynthesis, alteration of the mitochondrial inner membrane milieu, interference with the formation of the CoQ_{10} biosynthetic complex, increased degradation of CoQ_{10} or a general impairment of mitochondrial function. In the case of MADD it has been shown that the mutant protein binds CoQ_{10} less tightly than the wild-type, suggesting oxygen can get access to the electrons in the misfolded mutant protein and generate superoxide and oxidative stress, which affect the CoQ_{10} pool (Cornelius et al 2013).

Specific symptoms in these patients depend on the underlying condition. However, most reports focus on skeletal muscle and the central nervous system (CNS). Muscular manifestations consist of weakness, hypotonia, exercise intolerance, myoglobinuria, while the main CNS manifestations include ataxia and general CNS impairment. Although in these situations CoQ_{10} deficiency is a secondary phenomenon, it probably exacerbates the symptoms caused by the primary molecular defect, and these patients often benefit from oral CoQ_{10} supplementation (Quinzii et al 2005), even though the response is not as dramatic as in those with the primary forms.

Desbats et al. (2015) Journal of Inherited Metabolic Disease 38: 145-156.

Short-term studies in other mitochondrial disorders (< 6 months)

A RANDOMIZED TRIAL OF COENZYME Q_{10} IN MITOCHONDRIAL DISORDERS

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ABSTRACT: Case reports and open-label studies suggest that coenzyme Q_{10} (CoQ_{10}) treatment may have beneficial effects in mitochondrial disease patients; however, controlled trials are warranted to clinically prove its effectiveness. Thirty patients with mitochondrial cytopathy received 1200 mg/day CoQ_{10} for 60 days in a randomized, double-blind, cross-over trial. Blood lactate, urinary markers of oxidative stress, body composition, activities of daily living, quality of life, forearm handgrip strength and oxygen desaturation, cycle exercise cardiorespiratory variables, and brain metabolites were measured. CoQ_{10} treatment attenuated the rise in lactate after cycle ergometry, increased (∽1.93 ml) Vo_2/kg lean mass after 5 minutes of cycling ($P < 0.005$), and decreased gray matter choline-containing compounds ($P < 0.05$). Sixty days of moderate- to high-dose CoQ_{10} treatment had minor effects on cycle exercise aerobic capacity and post-exercise lactate but did not affect other clinically relevant variables such as strength or resting lactate.

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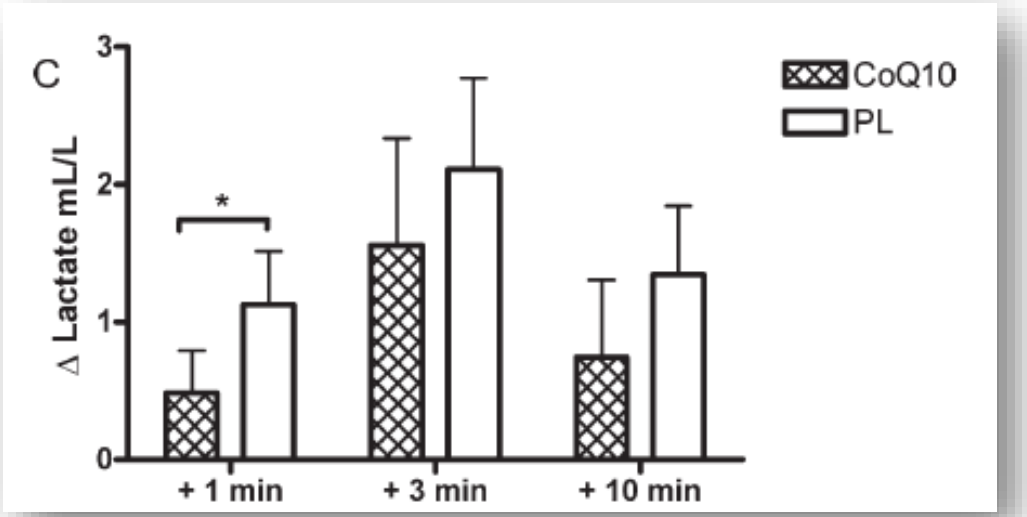

Glover et al. (2010) Muscle & Nerve 42: 739-748

Short-term studies in other mitochondrial disorders (< 6 months)

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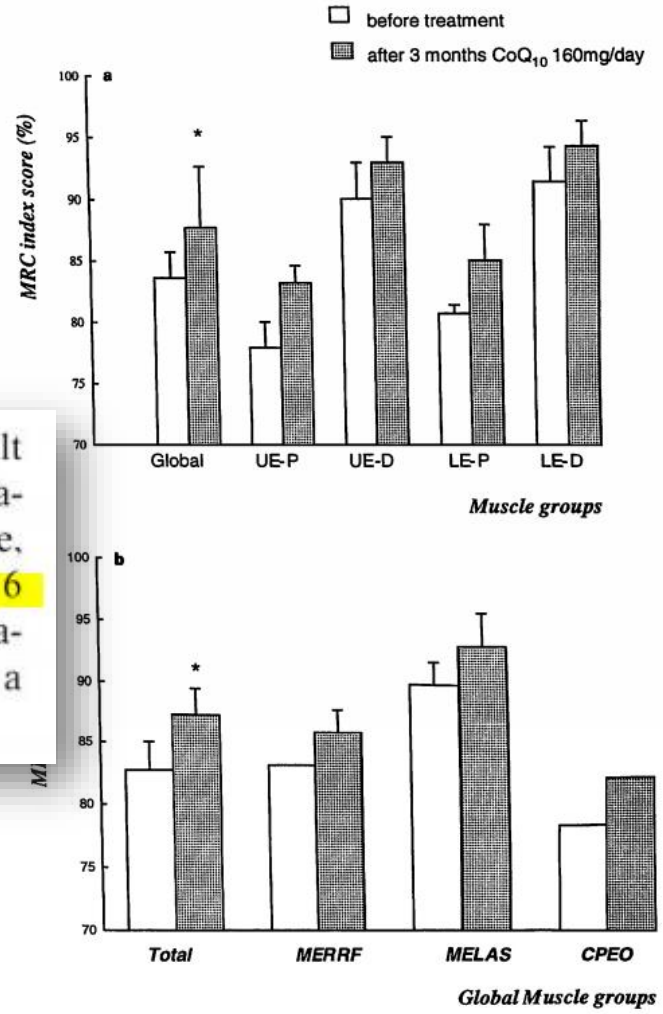
Coenzyme Q_{10} Treatment in Mitochondrial Encephalomyopathies

Short-Term Double-Blind, Crossover Study

patients felt subjectively exhausted (fig. 1, 3). It is difficult to express subjective effectiveness in chronically ill patients except for a dramatic improvement. Furthermore, it was suggested that the improvement might be noted 6 months after CoQ_{10} therapy [16]. Therefore, CoQ_{10} therapy may require a longer duration (>3 months) before a response can be seen.



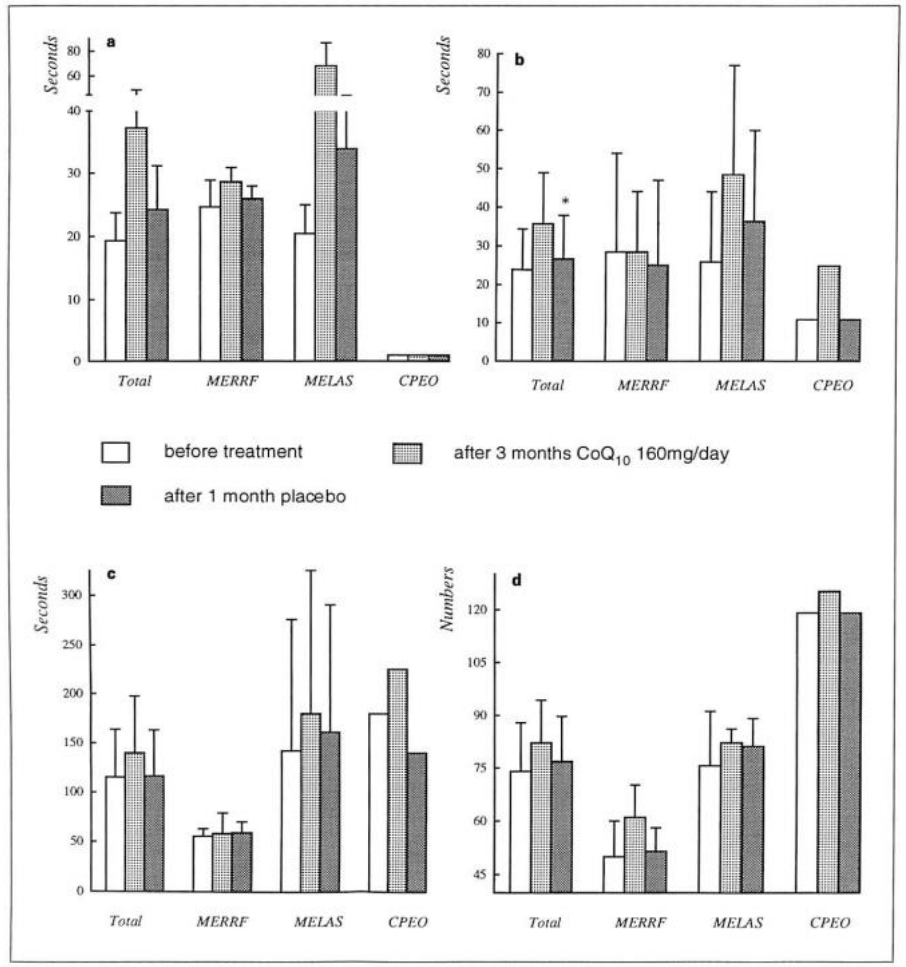


Fig. 3. Mean duration of performing sustained activities in different maneuvers. **a** Raising head. **b** Lifting legs. **c** Stretching out arms. **d** Rapid thumb tapping for 30 s. * $p < 0.05$.

Chen et al. (1997) European Neurology 37: 212-218.

Studies in Other Mitochondrial Disorders

- < 6 months duration

Trial	Design	Size	Dosage	Phenotypes	Baseline CoQ10	Measurements	Outcome	Conclusion	Evidence Level	Limitations
Glover 2010	DBX	30	1200mg/d x 60d	15 MELAS 11 CPEO 1 MM, 1 NARP, 1 LHON	not measured	1. Biochemical 2. ADL and QOL questionairs 3. NIRS 4. Muscle fatigue 5. Exercise lactate (15min)	1. No change 2. No change 3. No change 4. No change 5. +	Very high dose of CoQ10 would be unlikely to show additional benefit and in fact may be deleterious when taken for prolonged periods	II	Very high dose Short duration
Chen 1997	DBX	8	160mg/d x 3 m	4 MERRF 3 MELAS 1 CPEO	Low	1. Subjective ADL score 2. Objective MRC index score 3. Sustained endurance strength 4. Exercise lactate (8.7min)	1. + (NS) 2. + 3. + (NS) 4. No change (may due to short duration and low intensity)	MRC index score could be modified by short-term supplement	II	Short duration (3 months)

A Two-phase study
(6 months + 3 months)

Ubidecarenone in the treatment of mitochondrial myopathies: a multi-center double-blind trial

N. Bresolin [1], C. Doriguzzi [2], C. Ponzetto [4], C. Angelini [3], I. Moroni [1], E. Castelli [1], E. Cossutta [1], A. Binda [8], A. Gallanti [1], S. Gabellini [5], G. Piccolo [6], A. Martinuzzi [3], E. Ciafaloni [1], E. Arnaudo [2], L. Liciardello [7], A. Carenzi [7] and G. Scarlato [1]

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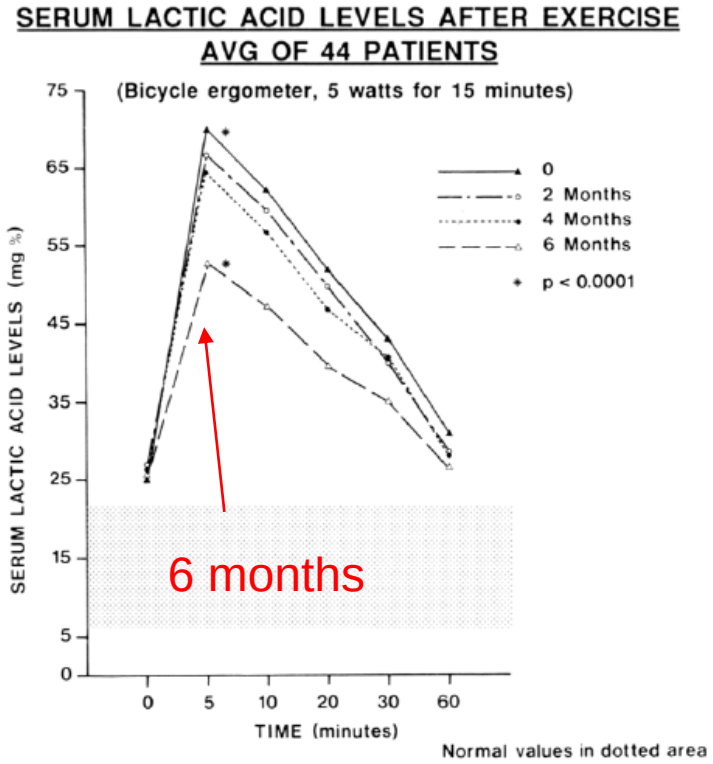

Fig. 2. Lactic acid level before and after exercise (bicycle ergometer, 5 W for 15 min), before and after 6 months of CoQ10 therapy.

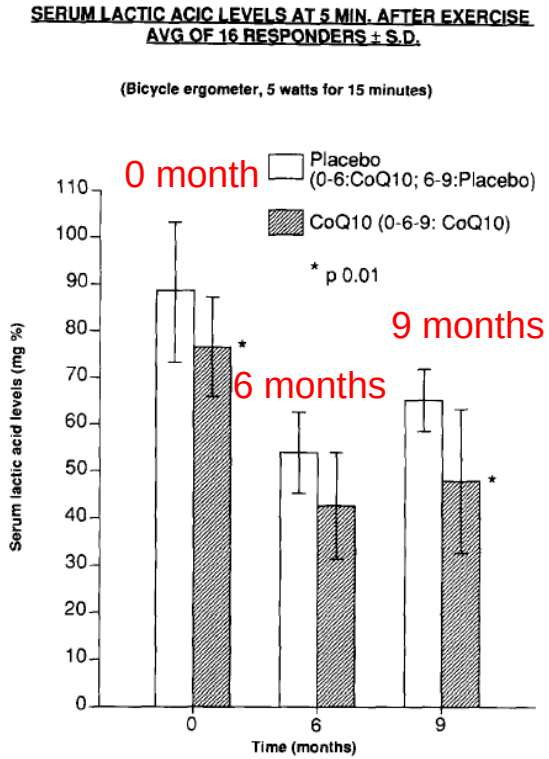

Fig. 5. Lactic acid levels obtained 5 min after exercise (bicycle ergometer, 5 W for 15 min) in 16 responders during the double-blind part of the trial, compared with values obtained at time 0 and 6 months (paired *t*-test).

Altogether the results of the blind part of the trial indicate that: (1) any improvement brought about by CoQ10 therapy is probably maximal after 6 months; (2) 3 months is possibly too short a time to show a difference between responders treated with placebo or with CoQ10. On the

Bresolin et al. (1990) Journal of the Neurological Sciences 100: 70-78.

Studies in Mitochondrial Disorders (continued)

- ≥ 6 months duration

Trial	Design	Size	Dosage	Phenotypes	Baseline CoQ10	Measurements	Outcome	Conclusion	Evidence Level	Limitations
Bresolin 1990	OL	59	2mg/kg/d x 6m	41 CPEO 9 KSS 6 MM 3 MERRF	normal	1. Exercise lactate (5w, 15min) 2. MRC score	1. + 2. +	Improved exercise tolerance and muscle strength after 6 months treatment	III	1. Therapeutic effects may be maximized after 6 months. 2. A reversed effects after switching from CoQ10 to placebo 3. 3 months is too short to differentiate effects between 2 groups 4. No washout period for placebo group 5. Failed to identify candidate responders before treatment
	DB	16	2mg/kg/d x 3m	13 CPEO 1 KSS 1MERRF 1 MM		1. Exercise lactate (5w, 15min) 2. MRC score	1. No change 2. No change	Further 3 months treatment failed to further increase exercise tolerance and muscle strength	II	

Long-term studies in other mitochondrial disorders (≥ 6 months)

The effects of coenzyme Q_{10} treatment on maternally inherited diabetes mellitus and deafness, and mitochondrial DNA 3243 (A to G) mutation

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Lactate after exercise

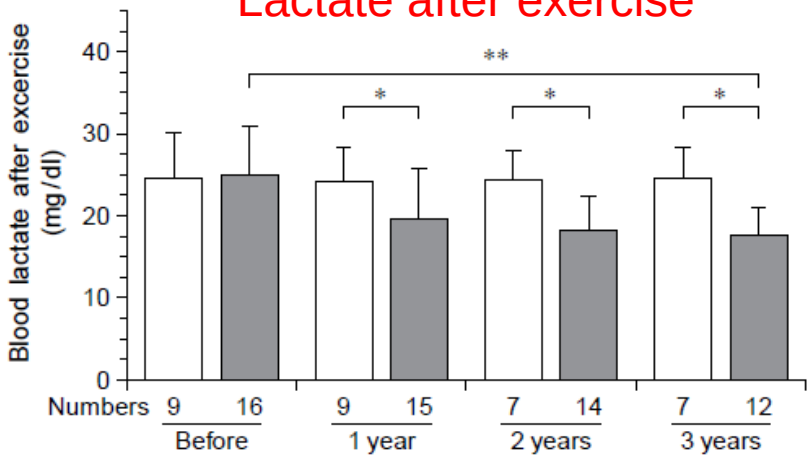

Fig. 3. The effects of long-term CoQ_{10} treatment on plasma lactate after exercise in the MIDD patients. Open bars are shown as the control-DM group, closed bars are the CoQ_{10}-DM group. Results are mean ± S.D. $^{*}p < 0.05$, $^{**}p < 0.01$

Insulin secretory

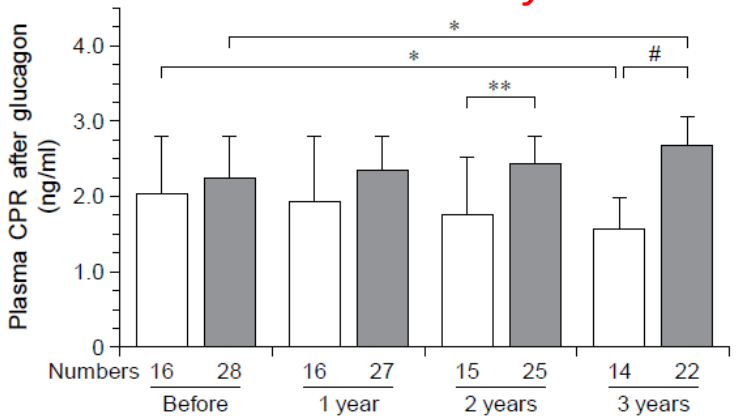

Fig. 1. The effects of long-term CoQ_{10} treatment on plasma C-peptide concentration 6 min after glucagon injection in MIDD patients. Open bars are shown as the control-DM group, closed bars are the CoQ_{10}-DM group. All measurements are presented as mean ± SD. $^{*}p < 0.02$, $^{**}p < 0.001$, $^{\#}p < 0.0001$

Hearing loss

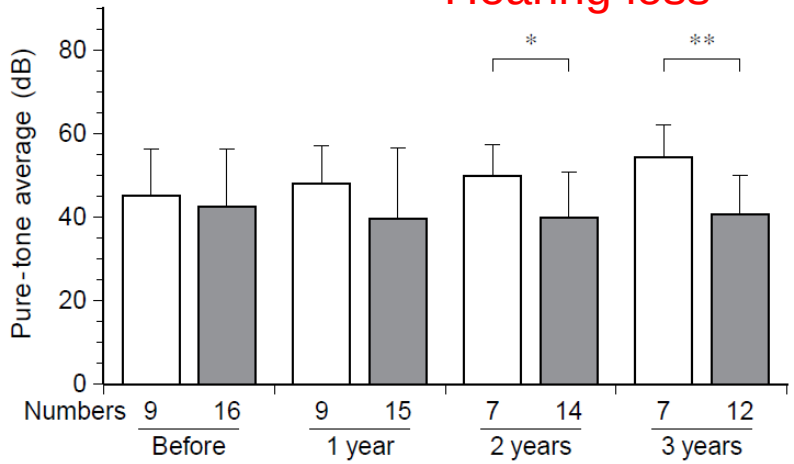

Fig. 4. The effects of long-term CoQ_{10} treatment on pure-tone average in MIDD patients. Open bars are shown as the control-DM group, closed bars are the CoQ_{10}-DM group. Results are mean ± S.D. $^{*}p < 0.05$, $^{**}p < 0.02$

Suzuki et al. (1998) Diabetologia 41: 584-588.

Long-term studies in other mitochondrial disorders (≥ 6 months)

Acta Oto-Laryngologica, 2005; 125: 510–512

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Coenzyme Q-10 treatment of patients with a 7445A→G mitochondrial DNA mutation stops the progression of hearing loss

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CoQ10-treated patients did not show any additional deterioration of their SNHL after 12 (familial case) and 13 months (sporadic case). The progression rate of SNHL was 6 dB/year in the 2 years prior to initiation of treatment in the familial case who received CoQ10 treatment. One year after being diagnosed with mitochondrial hearing loss, the patient who refused CoQ10 treatment exhibited an 11-dB deterioration of his hearing thresholds. There were no side-effects related to treatment of the two patients with CoQ10.

Consistent with Suzuki 1998 study on prevention of hearing loss

Long-term studies in other mitochondrial disorders (≥ 6 months)

Trial	Design	Size	Dosage	Phenotypes	Baseline CoQ10	Measurements	Outcome	Conclusion	Evidence Level	Limitations
Suzuki 1998	OL, placebo-controlled	44	150mg/d x 3 years	A3243G mutation with MIDD	normal	1. Insulin secretory capacity 2. Exercise tolerance (blood lactate) (5w, 15min) 3. Hearing test	1. + (after 2 years) 2. + (after 1 year) 3. + (after 2 years)	Long term treatment prevents progressive insulin secretory defect, exercise intolerance and hearing loss in MIDD patients	II	• Short term (3 months) showed no effects. • No effects in mutant IGT and NGT subjects. • Mainly affect insulin secretory capacity.
Angeli 2005	OL	3	150mg/d x 1 year	3 A7445G mutation with SNHL	Not measured	Hearing test	+	No additional deterioration of hearing loss during the year of treatment	IV	Consistent with Suzuki 1998 (2.2-3.1dB/year vs. no progression after 3 years, n=38)
Papadimitriou 1996	OL	2	100mg/d x 11m or 28m	2 KSS with hypoparathyroidism	Not measured	Total serum calcium concentration	+	Maintain normal total serum calcium concentration and improve tremor and other cerebellar symptoms	IV	Only 2 patients were studied, very small sample size
Remes 2002	OL	5	3mg/kg/d x 6m	5 MELAS (A3243G)	not measured	1. L/P 2. CIBIC	1. + (NS) 2. No change	Showed favorable trend of biochemical effects but no change in CIBIC	IV	Five patients died during and after the trial due to severity of disease unrelated to treatment . Meaning severely affected patients were selected for the trial

Ubiquinone and nicotinamide treatment of patients with the 3243A→G mtDNA mutation

A.M. Remes, MD, PhD; E.V. Liimatta, MD; S. Winqvist, Psych Lic; U. Tolonen, MD, PhD; J.A. Ranua, MD; K. Reinikainen, MD, PhD; I.E. Hassinen, MD, PhD; and K. Majamaa, MD, PhD

trations showed a decreasing trend. Indeed, favorable biochemical effects on mitochondrial function appear within a few days of the initiation of drug treatment.[5] Physiologic changes, such as changes in muscle ^{31}P-NMR, somatosensory evoked potentials, and nerve conduction velocity, become apparent only after several months of treatment.[2,6] The potential clinical benefits may appear even later. The progression rate of mitochondrial diseases is slow[10]; the clinical efficacy of treatment requires trials lasting much longer than 6 months.

The two patients who died during the present trial had been evaluated clinically 1 to 3 weeks previously, and no predictive symptoms or signs could be detected in either case. Autopsy revealed fibrotic changes in the myocardium, and both patients had had EKG abnormalities, suggesting a cardiac cause for their sudden death that was considered unrelated to the drugs studied here. Both patients had a multiorgan disease, however, suggesting the intriguing possibility that these drugs may be harmful in patients with severely disturbed mitochondrial function. The two deaths occurred during 74 person-months of followup during the trial, suggesting a mortality rate of 0.32/year. Three of the subjects (Patients 4, 6, and 7) have died since the completion of the trial, during 158 person-months of followup, giving a mortality rate of 0.22/year. This high mortality may thus only indicate the fact that severely affected patients were selected for the trial.

Remes et al. (2002) Neurology 50: 1275-1277.

Studies in Mitochondrial Disorders (continued)

Trial	Design	Size	CoQ10 dose	Phenotypes	Baseline CoQ10	Measurements	Outcome	Evidence Level
Barbiroli 1997	OL	6	150mg/d x 6m	MC	unknown	Muscle and brain 31P-MRS	+	III
Abe 1999	OL	2	200mg/d x 2 weeks	MELAS	unknown	Tissue oxygenation	+	IV
Chan 1998	OL	9	150mg/d x 6m	MEM	unknown	Exercise L/P ratio	+ in 6/9	IV
Gold 1996	OL	8	150mg/d x 6m	MEM	unknown	Muscle 31P-MRS	+ in 1/8	IV
Bendahan 1992	OL	2	150mg/d x 10m	MEM	unknown	Exercise and muscle 31P-MRS	+	IV
Desnuelle 1989	OL	2	150mg/d	KSS	Unknown, with Complex I & IV deficiency	Muscle strength and fatigue, ADL, weight	+	IV
Bresolin 1988	OL	7	120mg/d x 1 year	1 KSS, 2 CPEO	Low in serum	Exercise L+P	+	IV
Ogasahara 1986	OL	5	120-150mg/d x 1.2 years	KSS	Low in muscle	Exercise L/P, CSF protein and L/P, ECG, Neuro exam, ADL	+	IV
Sacconi 2010	OL	8 vs. 15	300mg/d x 12m	CPEO, MM	Low in muscle vs. normal	Muscle fatigue, exercise tolerance	+ 7/8 vs 1/15	IV

A Patient Survey

1. First and last initials of the patient:

GH

2. Patient's age:

6

3. Patient's sex:

Male

4. How long has the patient been on compounded CoQ10?

1.7 years

5. What condition is the compounded CoQ10 being used to address?

Mitochondrial disorders

6. What dosage form? (Check all that apply.)

Oral (capsules, troches, liquid, gel)

7. Please describe the patient's experience with CoQ10. Does it impact the patient's health? If so, what results have you seen? Also, does the patient experience any side effects? If so, please describe these side effects below.

CoQ10 has made a huge difference in our son's quality of life. He is less tired and can focus much better. We tried to use over the counter CoQ10, but it just made him hyper and then he would crash. Once we started using the compounded CoQ10 he was like a different child...attentive and needed less naps during the day. Gavin has a g-tube and needs his supplements compounded to go in the g-tube since he has severe acid reflux and sometimes vomits after meds if given by mouth.

Conclusions

- Effects seen in studies ≥ 6 months
- Effective in increasing exercise tolerance by reducing serum lactate
- Showed benefits in preventing hearing loss and maintaining serum calcium level in patients with mitochondrial disorders.

Guidelines and Expert Opinions

Natural Medicines Comprehensive Database

Effectiveness

See detailed evidence summary

LIKELY EFFECTIVE

Coenzyme Q-10 deficiency. Taking coenzyme Q-10 orally seems to improve symptoms of coenzyme Q-10 deficiency (8160, 8161). Rare cases of documented coenzyme Q-10 deficiency with symptoms of weakness, fatigue, and seizures have been reported.

Mitochondrial encephalomyopathies. Taking coenzyme Q-10 orally seems to reduce symptoms in some patients with genetic and acquired disorders of mitochondrial dysfunction (8159, 8162, 8163, 8912, 11050, 44240). The onset of effect is slow, with maximal effect at 6 months (8163). A specific coenzyme Q-10 formulation (UbiQGel) has US Food and Drug Administration (FDA) Orphan Drug Status for mitochondrial encephalomyopathies, including MELAS (myoclonic epilepsy with lactic acidosis and stroke-like episodes) syndrome, Kearns-Sayre syndrome, and MERRF (myoclonus epilepsy with ragged red fibers).

Safety

LIKELY SAFE ...when used orally and appropriately. Coenzyme Q-10 has been safely used in studies lasting up to 30 months (2134, 6037, 6038, 6407, 8163, 8938, 8939, 8940, 15395, 17413, 17716). ...when used topically on the gums (2107).

2017

Original Article

A Guideline for the Diagnosis of Pediatric Mitochondrial Disease: The Value of Muscle and Skin Biopsies in the Genetics Era

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Neuropediatrics

Abstract

Mitochondrial diseases are highly heterogeneous on the clinical, biochemical, and genetic level. In the traditional diagnostic approach ("biopsy first") the evaluation of the affected individual and his body fluids, combined with the analysis of the respiratory chain enzymes in muscle based the subsequent Sanger sequencing of single candidate genes ("from function to gene"). Within the past few years, next-generation sequencing techniques of leucocyte-derived DNA (e.g., exome sequencing), with a diagnostic yield of more than 40%, have become the first line routine technology. This implicates that the invasive muscle biopsy is performed less often, especially in children. Furthermore, in this "genetics-first" approach the detection of new candidate genes precedes functional evaluations ("from gene to function") leading to reverse phenotyping of affected individuals. Here, we line out the value of muscle and other tissue biopsies in this "genetics-first" era. We describe when and why it is still needed. We create awareness of pitfalls in the genetic diagnostics of mitochondrial diseases still necessitating tissue biopsies. Finally, we discuss why tissue biopsies are required for confirmatory diagnostics, or for getting a biochemical diagnosis in patients with hidden variants not detectable by standard genetics.

Keywords

- exome sequencing
- genome sequencing
- next-generation sequencing
- mitochondrial disease
- mitochondrial DNA

Introduction

Mitochondrial diseases (MD) are a rapidly growing group of inborn errors affecting the energy metabolism, with an estimated incidence of at least 1: 5,000.[1–3] The majority of children with MD presents at least with one or more neurological signs or symptoms (e.g., muscle weakness, peripheral neuropathy, ophthalmoplegia, movement disorder, epilepsy or migraine), which illustrates why the neuropediatrician is one of the key physician involved in diagnosis and management of childhood MD.[4]

Here, we use the term MD to describe diseases with a primary disorder in the entire route of the pyruvate oxidation process (OXPHOS), including the pyruvate dehydrogenase complex (PDHc), the citrate cycle and the respiratory chain including adenosine triphosphate synthase (complex I–V). In this regard, the requisite "support machinery" of mitochondrial DNA (mtDNA)-related protein synthesis (including mtDNA replication, mitochondrial RNA metabolism, mitochondrial translation), the metabolism of mitochondrial cofactors and their metabolism and finally mitochondrial homeostasis (including protein import into mitochondria, lipid metabolism,

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Here, we use the term MD to describe diseases with a primary disorder in the entire route of the pyruvate oxidation process (OXPHOS), including the pyruvate dehydrogenase complex (PDHc), the citrate cycle and the respiratory chain including adenosine triphosphate synthase (complex I–V). In

If the patient is severely and progressively ill (e.g., neonatal lactic acidosis), a more rapid diagnostic procedure is important (exome sequencing including data interpretation takes several weeks to 3 months) and a muscle biopsy with functional investigations is necessitated in parallel with starting genetic testing (see ►**Supplementary data** [online only] for practical details of the muscle biopsy). This holds true especially if the suspected diagnosis influences the disease management (e.g., PDHc deficiency: initiation of ketogenic diet) or if it can guide the end of life decisions (e.g., Leigh syndrome).

In this regard, empirical therapy with thiamine (20 mg/kg/d), biotin (5 mg/kg/d), riboflavin (20 mg/kg/d), and coenzyme Q_{10} (15 mg/kg/d) might be considered in patients with rapidly progressive or potential life-threatening course of disease.[23] Another indication is the individual with single organ involvement suggesting tissue specificity of genetic findings (e.g., pure myopathy [mtDNA mosaicism with mtDNA variants only detectable in DNA extracted from muscle]). In this context, one should also take into account that the level of heteroplasmy of mtDNA mutations tends to decrease during life in leukocytes, whereas it can increase in postmitotic tissues (e.g., muscle). For practical reasons, it is also advisable to follow this parallel diagnostic approach in affected individuals living far away from the diagnostic center.

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Conference Proceedings

Nutritional interventions in primary mitochondrial disorders: Developing an evidence base☆

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4.3. The MMS North American Mitochondrial Disease Survey (2012) and Consensus Project (2013)

The results of this survey call into question the appropriateness and efficacy of one approach over another, and spurred an effort by the MMS to develop consensus diagnostic criteria and treatment recommendations based on the existing evidence base [80]. Using the Delphi consensus methodology, agreement was reached on the use of nutritional interventions which is summarized here:

- CoQ_{10} should be administered to most patients with a diagnosis of mitochondrial disease, and not exclusively for primary CoQ_{10} deficiency. Reduced CoQ_{10} (ubiquinol) is the most bioavailable form, and when used, dosing should be modified relative to other forms. Leukocyte CoQ_{10} levels are helpful to monitor absorption and adherence to treatment whereas plasma levels are more variable and less reflective of tissue levels.

4.4. North American Mitochondrial Disease Consortium patient survey on dietary supplement use

constipation. Among all the patients who are or were taking dietary supplements, 64% indicated taking four or more dietary supplements at once. The five most frequently used supplements were CoQ_{10} (28%), L-carnitine (25%), vitamin D (19%), riboflavin (16%), and vitamin C (12%). The reported doses taken for each supplement varied greatly

All participants who were taking CoQ_{10} believed that this supplement was the most beneficial in improving their (or their child's) symptoms. Seventy-eight percent taking L-carnitine, 39% taking riboflavin, 28% taking creatine, and 26% taking vitamin B_{12} believed that these supplements caused the most improvement in their symptoms. Approxi-

Camp et al. (2016) Molecular Genetics and Metabolism 119: 187-206.

2017

REVIEW | Genetics inMedicine

Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society

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Myopathy

Myopathy is a common manifestation of some mitochondrial diseases and may include ophthalmoplegia and ptosis. Early-onset myopathy may present with profound hypotonia in infancy. Patients are at risk of associated dysphagia, respiratory insufficiency, cardiomyopathy, exercise intolerance, myalgia, fatigue, and infrequently rhabdomyolysis. Mitochondrial myopathies do not typically lead to marked baseline elevations in creatine kinase (CK) (with the exception of the myopathic form of *TK2*-related mitochondrial disease).

Recommendations.

1. An initial evaluation of muscle function is routinely needed including assessment of strength, CK measurement, and consideration of an electromyogram.
2. Annual CK levels should be considered in patients with a myopathy, especially with symptom worsening or a decline in function.
3. Secondary causes of a myopathy should be considered and assessed for, especially if CK levels are above 1,000 (other than in *TK2*-related disease) and include at least a complete blood count, thyroid-stimulating hormone, and toxicology screen when appropriate.
4. Management for recurrent rhabdomyolysis and myoglobinuria, at times triggered by exercise or illness, should follow general treatment recommendations; acylcarnitine and urine organic acid analysis may be needed to exclude fatty acid oxidation defects in new cases.
5. Exercise may benefit patients with mitochondrial myopathies (see prior exercise recommendations).[3]
6. Agents such as statins, corticosteroids, metformin, and antiretrovirals should be used with caution since they may exacerbate the underlying myopathy.
7. Riboflavin should be considered for myopathy associated with *ACAD9* deficiency; a combination of coenzyme Q_{10} and riboflavin should be considered for *ETFDH*-related myopathy.

Parikh et al. (2017) Genetics in Medicine19(12). doi: 10.1038/gim.2017.107.

The Journal of Rare DISORDERS

CURRENT UNDERSTANDING OF DIAGNOSIS AND TREATMENT OF RARE MITOCHONDRIAL DISORDERS

L.V.K.S. Bhaskar[1]*, Hrishikesh Mishra[1] and P.K. Patra[1,2]
[1]Sickle Cell Institute Chhattisgarh, Raipur, India, [2]Department of Biochemistry, Pt. JNM Medical College, Raipur, India

S.No.	Disorder	Age of Onset	Key Clinical Features	Gene Implicated/ Inheritance Pattern	Diagnosis	Treatment	Reference
15	Kearns-Sayre Syndrome	Before 20 years age	Chronic progressive external ophthalmoplegia, pigmentary retinopathy, cardiac conduction defects.	mtDNA deletions/ Maternal	Muscle biopsy to visualize "ragged red fibers", DNA analysis and Lactic and pyruvic acid levels	Coenzyme Q10, insulin, cardiac drugs and surgical intervention for drooping eyelids.	106
19	Leigh Syndrome	Infants or childhood	Seizures, hypotonia, poor motor function, ataxia. Visible necrotizing lesions on the brain MRI scan	BCS1L, COX10, NDUF gene family/ Autosomal recessive/X-linked recessive	DNA analysis, lactic acidosis or acidemia and hyperalanin emia	Thiamine, coenzyme Q10, riboflavin, biotin, creatine, succinate, and idebenone. Dichloroacetate is being used in some clinics.	111

Bhaskar et al. (2016) Journal of Rare Disorders 4: 44-58.

20	Luft Disease or Nonthyroidal hypermetabolism	Childhood	Hypermetabolism, hyperthermia, polyphagia, polydipsia, and resting tachycardia.	Unknown inheritance	Muscle biopsies showed ragged red fibers	Vitamins C, E, K and Coenzyme Q10, high calorie diet.	112
21	Glutaric aciduria type 2 or Multiple Acyl -CoA Dehydrogenase Deficiency (MADD)	Neonates and childhood to adulthood	Respiratory distress, muscular hypotonia, hepatomegaly, hypoglycemia, encephalopathy, seizures and heart failure.	ETFDH, ETFA, ETFB/ Autosomal recessive	Enzyme assay for short chain dicarboxylic acids in urine	Low fat and low protein diet. Coenzyme Q10 and Riboflavin	113, 114
22	Medium-Chain Acyl-CoA Dehydrongenase Deficiency (MCAD)	Infants and young children	episodes of encephalopathy, enlarged and fatty degeneration of the liver, and low carnitine in the blood.	*ACADM* / Autosomal recessive	Enzyme assay for plasma acylcarnitin, urine organic acid and acylglycine analysis	High carbohydrate-low fat diet, medium-chain fatty acids. Carnitine or riboflavin supplementation.	115
23	Mitochondrial Encephalomyopathy Lactic Acidosis and Strokelike Episodes (MELAS)	between the ages of 2 and 15	Seizures, stroke-like episodes with focused neurological deficits, recurrent headaches and cognitive regression.	mtDNA point mutations/ Maternal	Elevated serum lactate during acute episodes. Respiratory enzyme defects in skeletal muscle	CoQ10, creatine, phylloquinone, other vitamins and anticonvulsants.	116
24	Myoclonic Epilepsy and Ragged-Red Fiber Disease (MERRF)	in childhood	Myoclonus, epilepsy, progressive ataxia, muscle weakness and degeneration, deafness, and dementia	mtDNA point mutations/ Maternal	Histopathology for ragged red fibers, strong reaction for SDH and COX deficiency.	CoQ10, creatine, phylloquinone, other vitamins and anticonvulsants.	117
29	Pearson Syndrome	Infants	sideroblastic anemia, exocrine pancreas dysfunction, steatorrhea, pancreatic fibrosis and insulin-dependent diabetes.	mtDNA deletions/ maternal inheritance	Ring sideroblasts are erythroblasts with iron-loaded mitochondria visualized by Prussian blue staining.	Administration of coenzyme Q_{10} and L -carnitine, physical and occupational therapy.	124

Bhaskar et al. (2016) Journal of Rare Disorders 4: 44-58.

Search Orphan Drug Designations and Approvals

FDA Home › Developing Products for Rare Diseases & Conditions

Generic Name:	Ubiquinone
Trade Name:	Ubi-Q-Gel
Date Designated:	12/14/1999
Orphan Designation:	Treatment of mitochondrial cytopathies.
Orphan Designation Status:	Designated
FDA Orphan Approval Status:	Not FDA Approved for Orphan Indication
Marketing Approval Date:	N/A
Approved Labeled Indication:	
Exclusivity End Date:	N/A
Sponsor:	Gel-Tec, Division of Tishcon Corp. 30 New York Avenue P. O. Box 331 Westbury, New York 11590 USA *The sponsor address listed is the last reported by the sponsor to OOPD.*

Conclusion

- CoQ10 demonstrated some beneficial effects in mitochondrial disease regardless of endogenous CoQ10 level
- Patients with an underlying deficit in CoQ10 status may be more responsive to therapy
- Factors such as disease severity, dosage and duration of CoQ10 therapy may influence the efficacy of treatment
- Responders are difficult to be predicted.
- Used in compounding since at least 1993
- Treatment guidelines consistently recommend CoQ10 therapy for patients with mitochondrial diseases

THANK YOU

Questions from the Committee?

CREATINE MONOHYDRATE

Pharmacy Compounding Advisory Committee
September 12, 2018

A.J. Day, PharmD
Director of Pharmacy Consulting
PCCA

FDA Briefing – Recommendation

1. Physiochemical characteristics – stability issue

Creatine monohydrate is easily characterized, and its preparation has been well developed. It is likely to be stable under ordinary storage conditions in its solid form and in solid oral dosage forms when kept away from moisture. However, aqueous formulations, including aqueous oral formulations, are unlikely to be stable.

2. Safety – no concerns

Creatine monohydrate is generally associated with non-serious adverse events, and safe doses have been identified for healthy adults. We did not find adequately designed safety evaluations to provide data with which to identify safe doses for mitochondrial disease patients or other patients having, or at risk of having, renal impairment. Some data support the potential for creatine to be associated with renal toxicity, particularly in patients who have, or are at risk of, renal impairment. One case of urinary creatine crystals was reported in an AGAT patient using 800 mg/kg/day, which resolved with dose reduction. Safety data were not identified in the reviewed literature regarding GAMT deficiency.

FDA Briefing – Recommendation

3. Effectiveness

Mitochondrial disorders encompass a wide variety of conditions, genetic mutations, and phenotypic presentations. There are no compelling data that establish the effectiveness of creatine monohydrate in the treatment of mitochondrial diseases. Recommendations for creatine supplementation do not appear in treatment guidelines, no well-designed clinical trials have demonstrated creatine monohydrate's efficacy, and there are no trials which appear to support definitive uses or dosing.

4. Historical use in compounding

It appears that creatine monohydrate is/has been compounded along with various other ingredients into a cocktail for treatment of patients with mitochondrial disease. There is insufficient information available to determine how long creatine had been used in pharmacy compounding.

Based on this information the Agency has considered, a balancing of the four evaluation criteria ***weighs in favor of*** creatine monohydrate solid oral dosage forms being added to the 503A Bulks List.

Problems in achieving Level I evidence in mitochondrial disorders

1. Rare disease. No treatments which are dramatically effective in small-scale trials exist.
2. Small number of patients available for study. With variable genotypes and clinical phenotypes, thus matching the control and study populations is very difficult. Crossover trial design can help alleviate inter-patient phenotypic variability.
3. Defining outcome measures in treatment trials of mitochondrial diseases is difficult.
4. First phase 3 of a large-scale, double-blind, randomized clinical trial evaluating CoQ10 in children with primary mitochondrial disorders has been completed. Results haven't been published (Stacpoole 2012).
5. Case series and case reports are commonly used.

Level I – RCT with p<=0.05 and b<=0.2, or meta-analysis
Level II – randomized, p>0.05 or b >0.2 with trend
Level III – uncontrolled, non-randomized with historical control group
Level IV – case series w/o control
Level V – case reports

Stacpoole et al. (2012) Mitochondrion 12: 623-629.

Haas et al. (2007) Pediatrics 120: 1326-1333

Stability of Creatine

Creatine is likely to be stable at room temperature in its solid form. However, it is known that this substance is unstable in aqueous solutions. Intramolecular cyclization of creatine will occur to give inactive creatinine as the product. This reaction is accelerated under acidic conditions (pH < 4) (Edgar and Shiver 1925; Cannan and Shore 1928). One study on the aqueous formulations of creatine reported that, at room temperature, 5 – 20% of creatine degraded after 4 days and 15 – 55% degradation was observed after one week. The pH value also increased from 3.6 to 4.5 (Ganguly et al. 2003). Therefore, creatine is unlikely to be stable when compounded as aqueous formulations, including those intended for oral administration.

Table 1. Change in Creatine Concentration in the Solution With Time at Different Storage Conditions and Over a Period of 45 Days*

Days	Room Temperature % Creatine Remaining in Solution (wt/vol)				Refrigerated Conditions % Creatine Remaining in Solution (wt/vol)				
	pH†	CC	CC	CE	CE	pH†	CC	CC	CE	CE
Day 1	3.6 ± 0.0	100	100	100	100	3.6 ± 0.0	100	100	100	100
Day 2	3.6 ± 0.1	99.4	99.3	98.8	98.8	3.6 ± 0.1	98.2	100	74.4	100
Day 4	3.7 ± 0.1	59.9	85.1	96.4	94.1	3.5 ± 0.1	98.2	97.9	72.4	100
Day 7	3.9 ± 0.1	44.3	49.4	94.1	85.3	3.5 ± 0.1	96.3	93.6	66.8	98.1
Day 10	3.9 ± 0.1	32.9	38.3	40.1	36.5	3.5 ± 0.0	38.8	49.2	36.2	47.5
Day 21	4.2 ± 0.1	24.0	29.2	38.3	31.8	3.5 ± 0.0	29.4	37.9	26.6	37.7
Day 45	4.5 ± 0.0	10.2	13.2	12.5	12.9	3.7 ± 0.1	27.5	28.8	18.1	24.7

*CC indicates Creatine Clear; CE, Creatine Edge.
†Mean ± SD; n = 4.

RESULTS AND DISCUSSION

Stability of Creatine in Solutions Prepared from Effervescent Formulations

CC and CE are the 2 effervescent formulations used in this study. As per the manufacturer's specification, these formulations contain only di-creatine citrate as the creatine source. Most of the creatine supplements in the market usually contain creatine monohydrate salt as the creatine source. Creatine monohydrate has a poor aqueous solubility and palatability. The use of di-creatine citrate salt on the other hand eliminates these problems and enhances consumer compliance. Solu-

Ganguly et al. (2003) AAPS PharmSciTech 4: E25

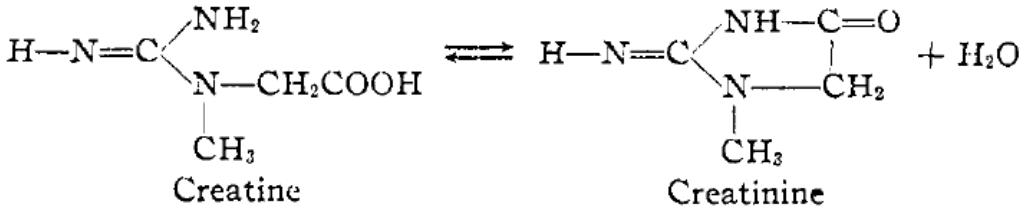
THE EQUILIBRIUM BETWEEN CREATINE AND CREATININE, IN AQUEOUS SOLUTION. THE EFFECT OF HYDROGEN ION

By Graham Edgar and H. E. Shiver

Received February 4, 1925 Published April 4, 1925

I. In Aqueous Solution

Introduction.—The reversible reaction



(1)

is of interest not only from its importance in biochemistry, but also because of the ease with which it is adapted to physicochemical study. The

Discussion of Data

It is clear from the data (a) that the effect of changing hydrogen-ion concentration on the creatine-creatinine equilibrium is very marked, the equilibrium shifting towards the creatinine side with decreasing P_H; (b) the nature of the buffer solution is unimportant; (c) the effect is particularly marked between P_H 1.5 and P_H 3.0; (d) the *rate* at which equilibrium is reached increases with increasing hydrogen-ion concentration.

Edgar and Shiver. (1925) Journal of the American Chemical Society 47: 1179-1188.

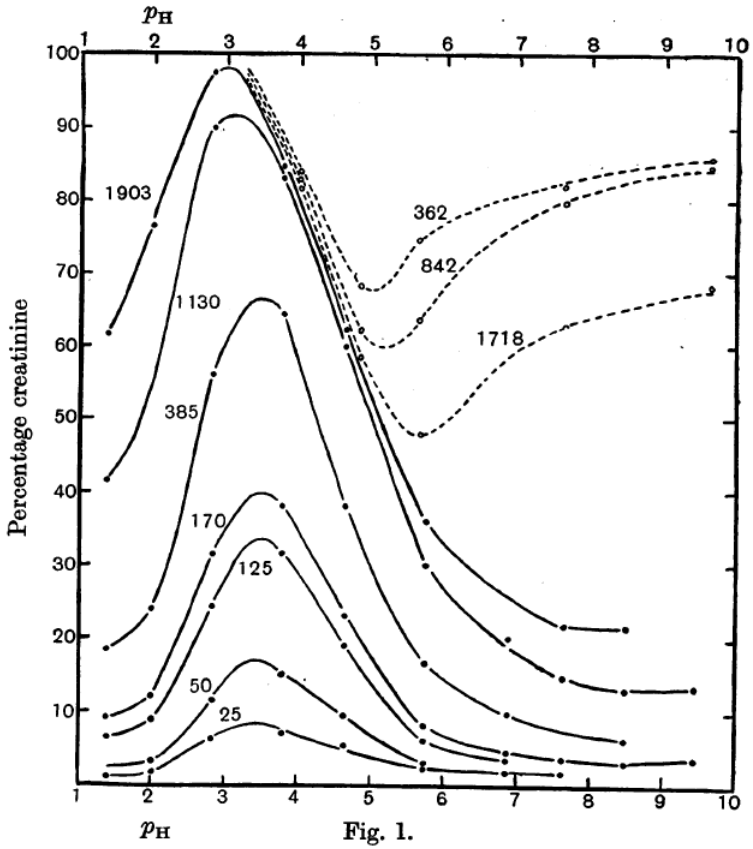


Fig. 1.

● Percentage creatinine formed in solutions of creatine at times (hours) indicated.
o Percentage creatinine remaining in solutions of creatine.

Summary.

1. Determination has been made of the apparent dissociation constant (uncorrected for activity) of creatinine at 15°, 25° and 30° and of the first dissociation constant (uncorrected) of creatine at 17°, 25° and 30°.

2. The velocity constants of the reversible system creatine-creatinine have been determined at 30° over the p_H range 2 to 10, and have been related to $[H^+]$, the dissociation constants of the reactants and certain empirical constants.

The creatine was prepared from a good commercial sample by repeated recrystallisation from water. After drying to constant weight over calcium chloride, a typical preparation gave

Nitrogen (Kjeldahl)	...	28·19 %	Water 12·18 %
Theory for $C_4H_9O_2N_3.H_2O$		28·19	12·08

Cannan and Shore. (1928) The Biochemical Journal 22: 920-929.

Creatine Monohydrate Aqueous Suspension

- Independent testing from FDA-registered analytical lab
- pH 4.9-5.3, stored at refrigerated temperature

Chemical Tests:	Date	Reported	Measured	Potency
Creatine Monohydrate	3/7/2014	200 mg/mL	192 mg/mL	96.0 %
xExtended Analysis 1	3/27/2014	200 mg/mL	187 mg/mL	93.4 %
xExtended Analysis 2	4/16/2014	200 mg/mL	194 mg/mL	97.0 %

PCCA stability data

- 1% aqueous solution of creatine monohydrate in water
  - pH 7.51-7.68
  - pH has not changed in 18 days at room temperature

Stability of Creatine in aqueous solution at 25°C

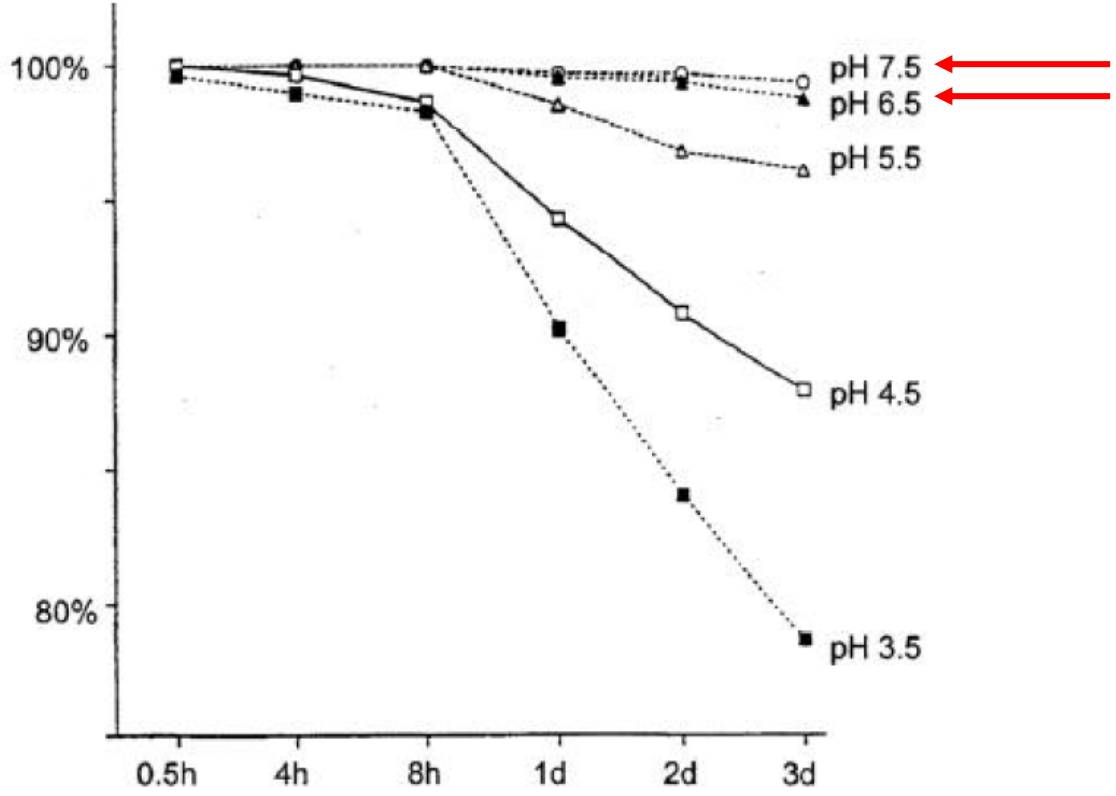


Figure 1. Degradation of Creatine at 25°C, after 0.5h, 4h, 8h, 1d, 2d, 3d at different pH values (7.5, 6.5, 5.5, 4.5, 3.5). The pH of the samples was adjusted to the desired values using 50% acetic acid or 5N KOH. The pH of the samples was also tested to ensure that pH did not alter during the experiment (cf. A.N. Howard, R.C. Harris, US 5,968,544).

CREAPURE Fact Sheet. BioActives, Degussa Health & Nutrition, Freising, Germany

Stability of Creatine in aqueous solution at 4°C

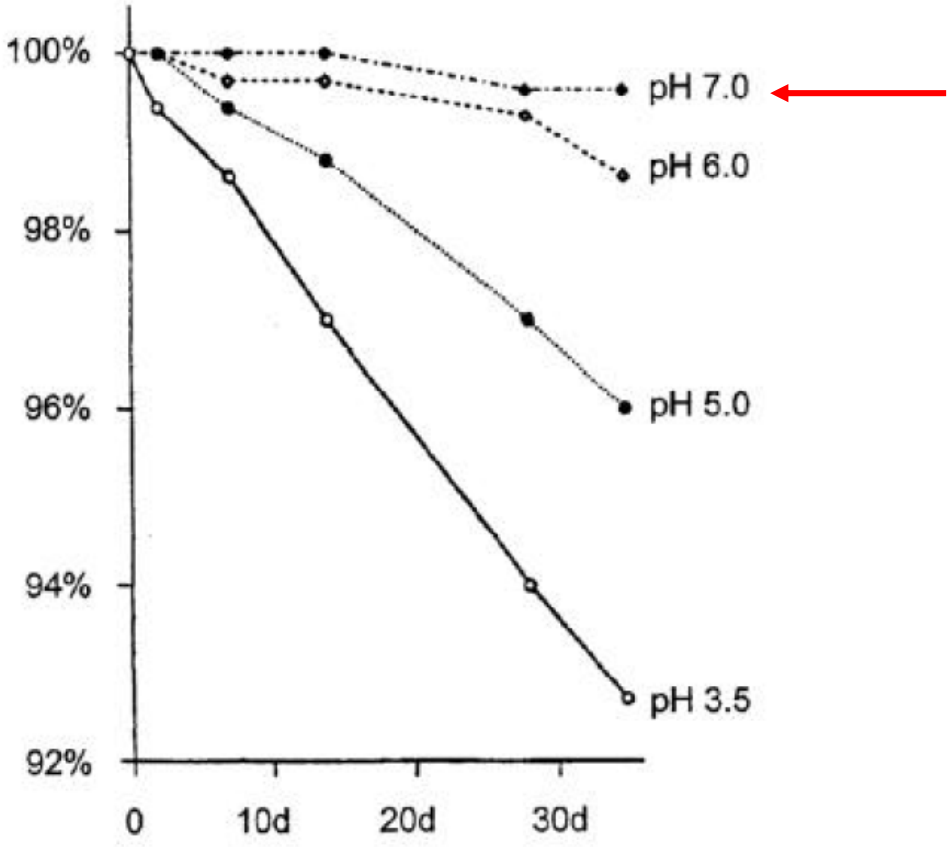


Figure 2. Degradation of Creatine at 4°C, after 2d, 7d, 14d, 28d, 35d at different pH values (7.0, 6.0, 5.0, 3.5). The pH of the samples was also tested to ensure that pH did not alter during the course of experiment (cf. A.N. Howard, R.C. Harris, US 5,968,544).

CREAPURE Fact Sheet. BioActives, Degussa Health & Nutrition, Freising, Germany

[redacted] Analytical Laboratory

[redacted]

Shelf Life Analysis

Company: [redacted]
Date: 08-21-18

Product Name:	Lot Number:	P.O. Number:
Liquid[redacted]	[redacted]	**Verbal**

pH > 7

Test	Length	Results	Comments
Accelerated Shelf life testing	36 months	>99.00%	Stable Product
Real Time Testing	48 months	>99.00%	Stable Product
Purity		>99.00%	Stable Product
Packaging			Plastic
Micro	Total Plate Count	0 cfu/g	Stable Product.

Compound Identification	Positive

Shelf Life: If stored under cool, dry conditions a shelf life of 36 months can be awarded

Test Points:

Accelerated:
- Test 1: Initial Test of product before entering stability chamber
- Test 2: 30 days
- Test 3: 60 days
- Test 4: 90 days

Real Time:
- Test 1: Initial Test of product at time of manufacturing
- Test 2: 1 year
- Test 3: 2 years
- Test 4: 3 years
- Test 5: 4 years

FDA Briefing – Effectiveness of Creatine in Mitochondrial Diseases

Conclusions: There are no compelling data that establish effectiveness in the support the treatment of mitochondrial diseases with creatine. Mitochondrial diseases encompass a wide variety of conditions related to genetic mutation in nDNA and mtDNA with different phenotypic presentations. Recommendations for creatine supplementation do not appear in treatment guidelines. The theoretical action for creatine in the treatment of mitochondrial disorders, to help support alternative ATP synthesis mechanisms in the context of dysfunctional oxidative phosphorylation, suggest a mechanism of action, and there is some indication that creatine may improve aspects of exercise performance. However, well-designed clinical trials have not demonstrated creatine's efficacy, and there are no trials which appear to support definitive indications or dosing.

FDA Assessment – Creatine Effectiveness in MELAS

- Tarnopolsky (1997)

included. In a study by Tarnopolsky et al. (1997) seven patients with MELAS or mitochondrial myopathy were randomized to receive 5 g creatine monohydrate orally twice a day for 2 weeks followed by 2 g creatine monohydrate orally twice a day for 1 week, or placebo for 3 weeks. Patients were crossed over to receive the alternate treatment after a 5 week washout. Evaluations were made at the end of each 3 week treatment period including:

- a visual analog scale assessment of the physical demand of activities of daily living
- blood sampling for lactate levels following a 2 minute walk test and subsequent 75 minutes of rest
- ischemic isometric handgrip strength (1 minute)
- evoked and voluntary contraction strength of the dorsiflexors
- nonischemic, isometric, dorsiflexion torque (NIDFT) (2 minutes)
- aerobic cycle ergonometry with pre- and post-lactate levels.

Creatine treatment was associated with significantly increased handgrip strength, NIDFT, and postexercise lactate after both isometric grip and cycle ergonometry. No effects of treatment were observed with other assessments. The authors concluded that creatine's effects were limited to high-intensity aerobic and anaerobic activities and there was no effect on lower intensity aerobic activities. It is noted that Tarnopolsky and Martin (1999) later reported on

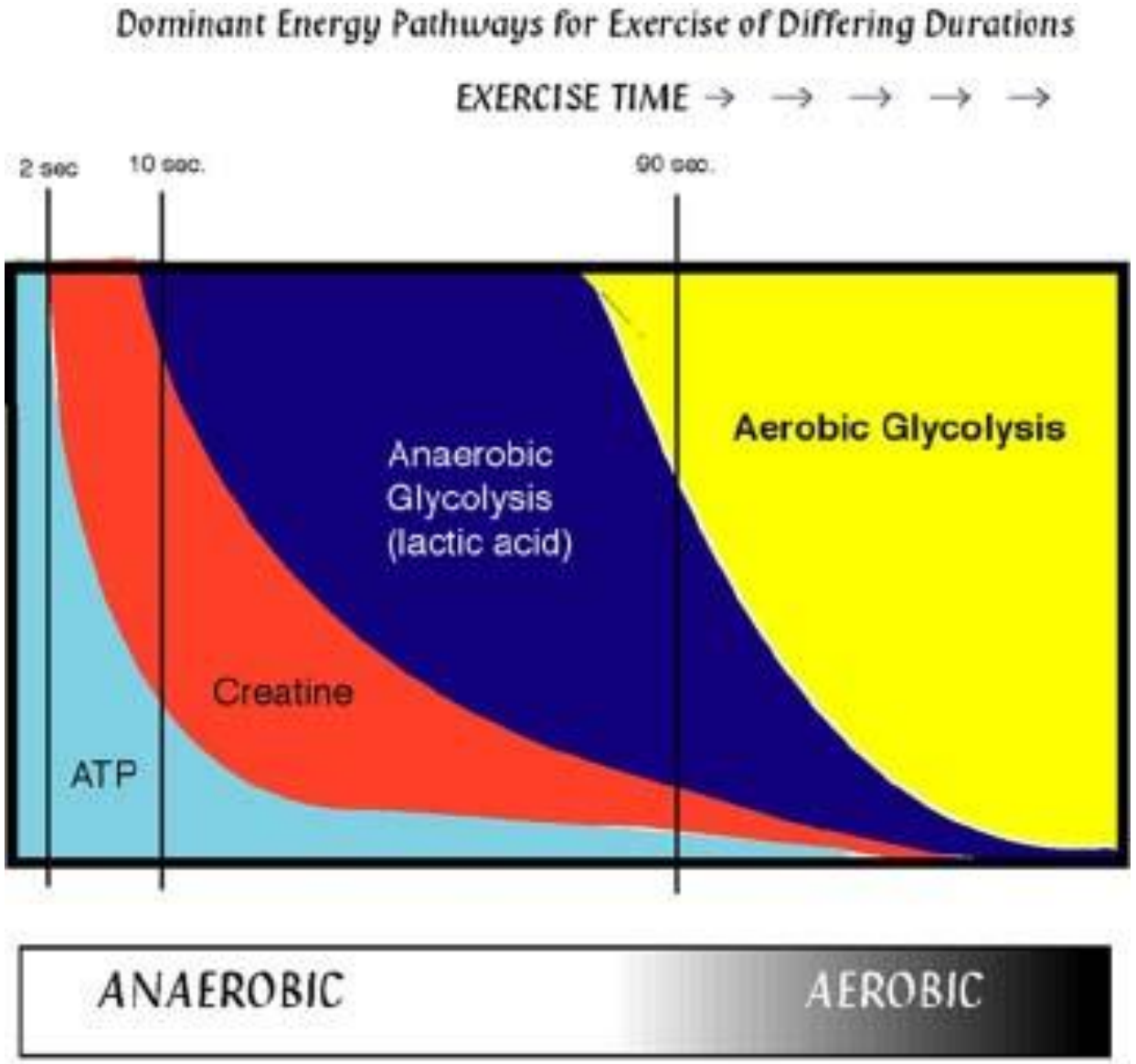
Creatine Effectiveness in MELAS

Table 1. Subject characteristics.

Subject	Gender	Age (years)	Weight (kg)	Height (cm)	Diagnosis
1. LA	F	25	62.5	170	MELAS-3271
2. KL	F	27	88.0	165	MELAS-3271
3. CW	M	33	69.0	169	MELAS-3243
4. BD	M	48	78.7	180	MELAS-3271
5. SA	F	49	56.7	168	MELAS-3271
6. GD	M	49	61.3	180	MELAS
7. KD	F	64	60.0	170	M-MYOP

In summary, we have demonstrated that short-term creatine monohydrate supplementation can increase high-intensity, isometric, anaerobic and aerobic power in patients with mitochondrial cytopathies. This study and others have demonstrated the lack of side effects from this regimen.[4,12,14,15,18,19] Thus, creatine supplementation in mitochondrial cytopathy patients may be of potential benefit in situations such as high-intensity activity (i.e., sports, manual labor, etc.) or possibly in weaning from a ventilator in an already fatigued patient. This positive effect in our patients was demonstrated with a

Tarnopolsky et al. (1997) Muscle & Nerve 20: 1502-1509.



https://www.rice.edu/~jenky/sports/creatine.html

Creatine Effectiveness in MELAS

CREATINE TREATMENT IN MELAS

Lars Hagenfeldt, MD, PhD
Ulrika von Döbeln, MD, PhD
Göran Solders, MD, PhD
Lennart Kaijser, MD, PhD
Departments of Clinical Chemistry, Neurology, and Clinical Physiology
Huddinge University Hospital
S-141 86 Huddinge, Sweden

MELAS is a maternally inherited disease characterized by mitochondrial myopathy, stroke-like episodes, encephalopathy with seizures, and/or dementia and lactic acidosis.[2] Recurrent headache and vomiting are also common symptoms. Most of the MELAS patients carry mtDNA mutations at bp 3243 or 3271. A deficiency of complex I or multiple defects of respiratory chain enzymes are common biochemical defects observed in muscle tissue from these patients.[2] Different treatments have been suggested including a high carbohydrate intake;

1. Balsom PD, Ekblom B, Söderlund K, Sjödin B, Hultman H: Creatine supplementation and dynamic high-intensity intermittent exercise. *Scand J Med Sci Sports* 1993;3:143–149.
2. Ciafaloni E, Ricci E, Shanske S, et al.: MELAS: clinical features, biochemistry, and molecular genetics. *Ann Neurol* 1992;31:391–398.
3. Harris RC, Söderlund K, Hultman E: Elevation of creatine

We have tried creatine treatment in a 25-year-old man with MELAS and a heteroplasmic mutation at bp 3243. His symptoms started at 5 years of age and have included a chronic lactic acidosis, exercise-induced muscle pain, headache, generalized seizures, and episodes of cortical blindness, visual hallucinations, dysphasia, and arm paresis. He has a moderate mental retardation and subnormal height and weight. Brain MRI shows atrophic changes, the EEG is pathological with epileptic activity, and he has a moderate polyneuropathy. A muscle biopsy has revealed ragged-red fibers and a defect in the respiratory electron transport chain. His present treatment includes carbamazepine, ASA, dipyridamol, carnitine, coenzyme Q10, thiamine, and vitamins K1 and C.

Creatine was given orally at 5 g twice daily for 2 weeks and 2 g twice daily thereafter. The patient and his family reported reduced headache, less weakness, better appetite, and an improved general well-being during treatment. In a graded exercise test starting at 10 W and with 10-W increments every 4 min, the patient stopped because of leg tiredness after 15 s at 20 W before treatment. After 3 months on creatine, he exercised for the full 4 min at 30 W. Venous blood lactate at rest was 2.6 mmol/L before and 2.7 mmol/L during treatment. A negative T-wave in the resting ECG became less abnormal during creatine treatment.

Hagenfeldt et al. (1994) Muscle & Nerve 17: 1236-1237.

Creatine Effectiveness in MELAS

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Effects of Oral Creatine Supplementation in a Patient with MELAS Phenotype and Associated Nephropathy

Short Communication

Abstract

An 18-year-old male patient with MELAS phenotype and 2 previous episodes of cerebral stroke, recurrent seizures and nephropathy, was treated with creatine monohydrate after the acute onset of psychomental regression and changing states of somnolence and aggressive and agitated behaviour. These symptoms disappeared completely after 4 weeks of treatment with creatine after which the patient regained all his previous mental abilites.

Abbreviations

MELAS	mitochondrial encephalopathy
Lac	lactic acid
Cr	creatine
Cho	choline-containing compounds
NAA	N-acetylaspartic acid
2 D CSI	2 dimensional chemical shift imaging

Results

After 7 days of creatine supplementation, the symptoms of psychomental regression and aggressive behaviour improved significantly and they had disappeared completely after 4 weeks of treatment when the patient had regained all his previous mental abilites. He was able to work with textiles in a special workshop for handicapped persons and to support himself in everyday life activities as before. Neuropsychologic testing (visual organisation and visual motor integration test) at 6 weeks after the psychotic crisis revealed an IQ of < 65. 6 months later there was a clear improvement of his vocabulary, his concentration and alertness, while his IQ remained unchanged. EEG improved after 4 weeks of creatine treatment. The patient remained without seizures during the 28 month period of treatment.

In vivo proton magnetic resonance spectroscopy (MRS) of the brain, performed after 6 months of treatment, showed increased Cr as related to Cho and high Lac levels in most brain voxels studied. Levels of N-acetyl-aspartate (NAA) as a neuronal marker are low in most voxels (Fig. **1**). Similar results were obtained at a second measurement 12 months later. Plasma lactate levels remained in the usual range of mild elevation during the creatine treatment period.

Various parameters characteristic for creatine metabolism and renal function are shown in Table **1.** Plasma creatine was determined by an HPLC method as described. Creatinine was determined by a dry chemistry method (Kodak Ektachem). Determination of plasma and urinary creatinine in single samples obtained during the supplementation period both by dry chemistry and HPLC method did not show significant differences between the values obtained with both methods, thus excluding coreaction of plasma creatine and artificially high creatinine values on dry chemistry during creatine supplementation.

Barisic N et al. Effects of Oral ... Neuropediatrics 2002; 33: 157–16

Barisic et al. (2002) Neuropediatrics 33: 157-161.

FDA Assessment – Komura (2003)

In an uncontrolled study of five patients between the ages of 7 and 19 years with mitochondrial encephalopathy from Kearns-Sayre syndrome, NARP (neuropathy, ataxia, retinitis pigmentosa syndrome) or MELAS, the effects on exercise performance were assessed following creatine monohydrate supplementation with doses between 0.08 g/kg and 0.35 g/kg per day (Komura et al. 2003). This retrospective study compared exercise performance prior to treatment and after variable periods of dosing (between 9 months and nearly 5 years). A skeletal muscle power analysis based on cycle ergonometer performance showed an increase in performance compared to baseline of between 4 and 30%. Design considerations of this study, such as lack of a control group, and the variability of patients, doses and treatment duration, limit the ability to generalize from these findings.

Effectiveness of Creatine Monohydrate in Mitochondrial Encephalomyopathies

Kiyomi Komura, MD*, Elke Hobbiebrunken, MD†, Ekkehard K. G. Wilichowski, MD†, and Folker A. Hanefeld, MD†

Five children with genetically proven mitochondrial disorders were orally treated with pure creatine monohydrate. To evaluate the effectiveness, maximum of muscle performance, functional muscle speed, and vital capacity of the lung were measured according to standardized protocol prior and during the treatment.

All patients reported herein demonstrated an improvement of maximal muscle performance with an increase of 4-30% (mean, 12.1%). In one patient an "on/off" study was performed, which demonstrated a decrease of maximal performance to the baseline during the "off" phase. In this patient the second "on" phase was performed with a threefold dose of creatine, which resulted in a twofold increase in performance. This dose dependancy was also demonstrated in the second patient. Studies from athletes have demonstrated that there is an increase of muscle strength with rising creatine dosages [18]. Although the bicycle ergometry reflects the long-holding muscle power, the functional muscle tests were designed to test the short-acting muscle strength.

Komura et al. (2003) Pediatric Neurology 28: 53-58.

Creatine Effectiveness in dose-independent manner in KSS

Table 1. Patient data

Patient No.	1	2	3	4	5
Diagnosis	KSS	KSS	NARP	MELAS	MELAS
Sex	F	M	F	F	F

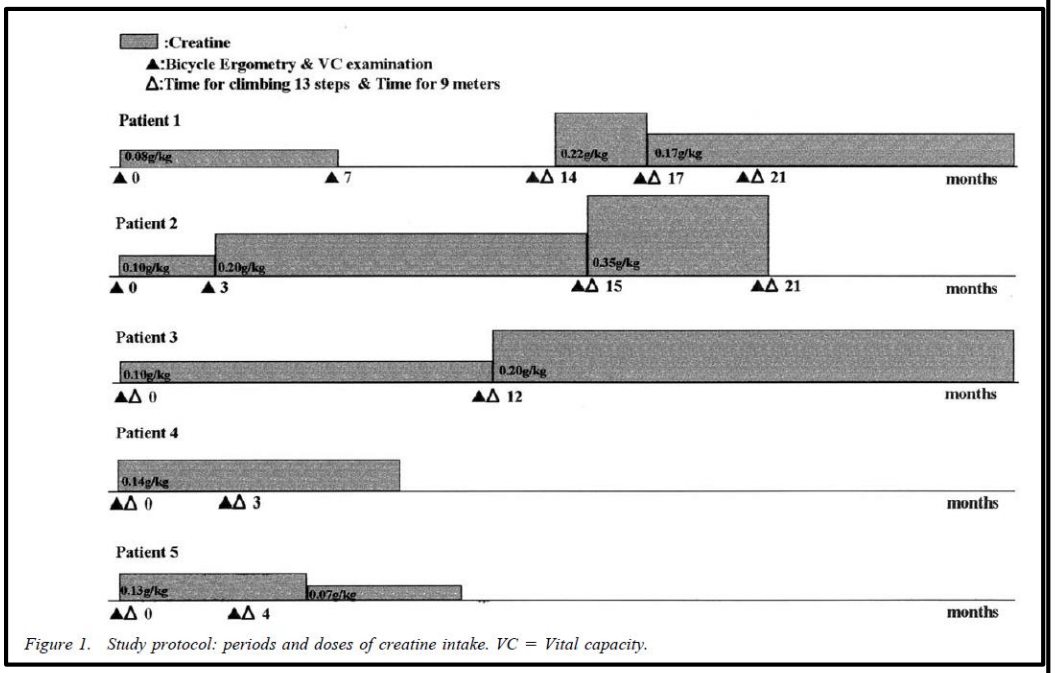

Figure 1. Study protocol: periods and doses of creatine intake. VC = Vital capacity.

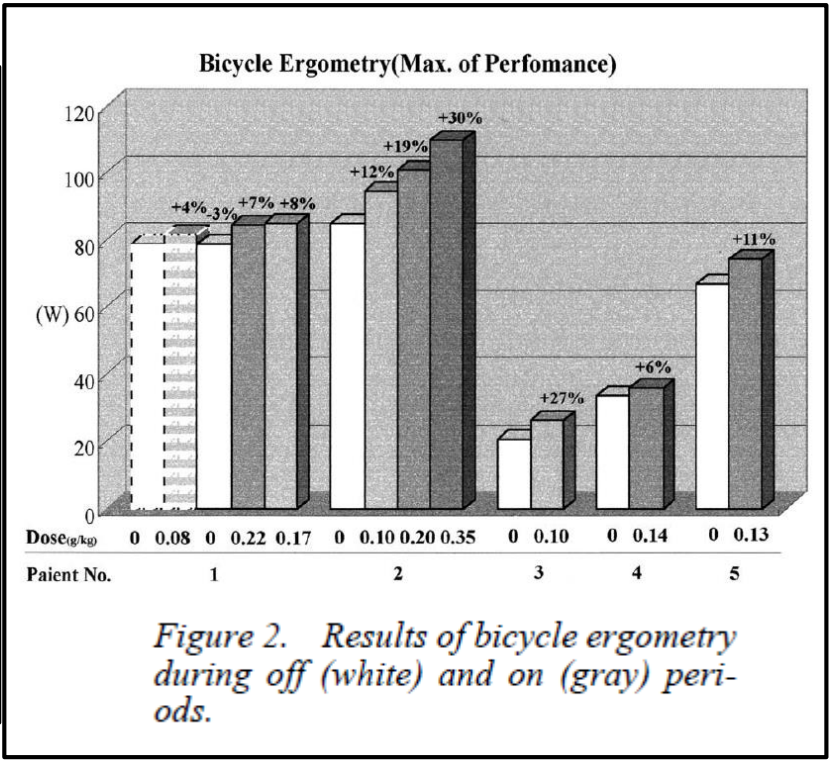

Figure 2. Results of bicycle ergometry during off (white) and on (gray) periods.

Komura et al. (2003) Pediatric Neurology 28: 53-58.

Creatine effectiveness in Leigh Syndrome

Patient Report

Creatine monohydrate therapy in a Leigh syndrome patient with A8344G mutation

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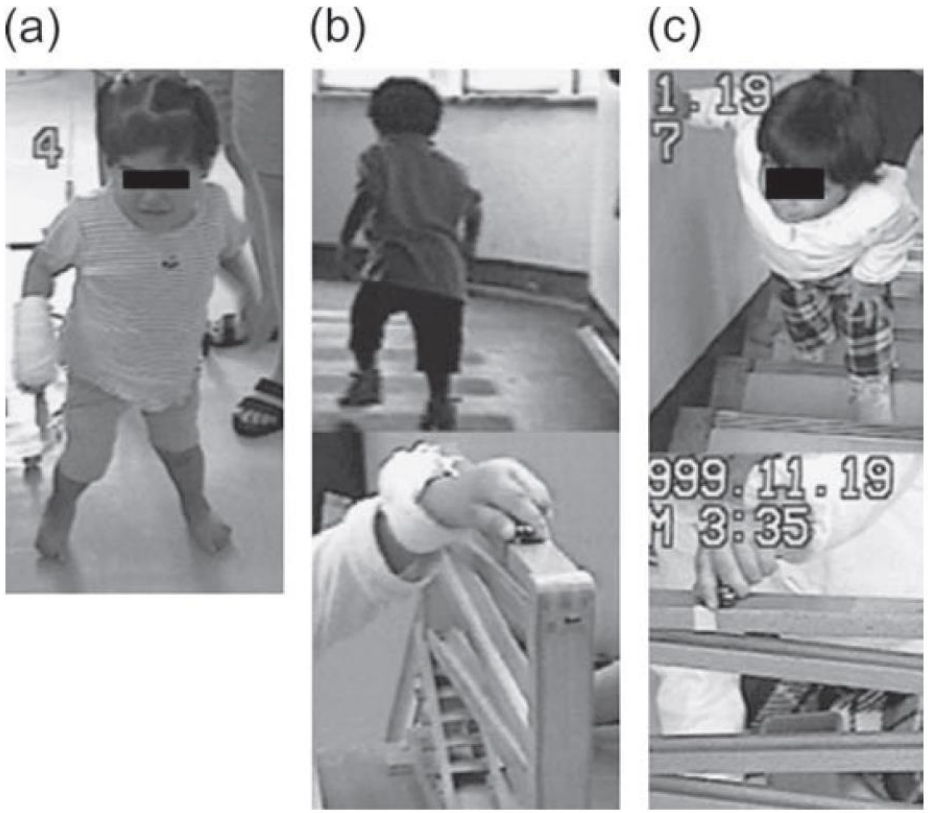
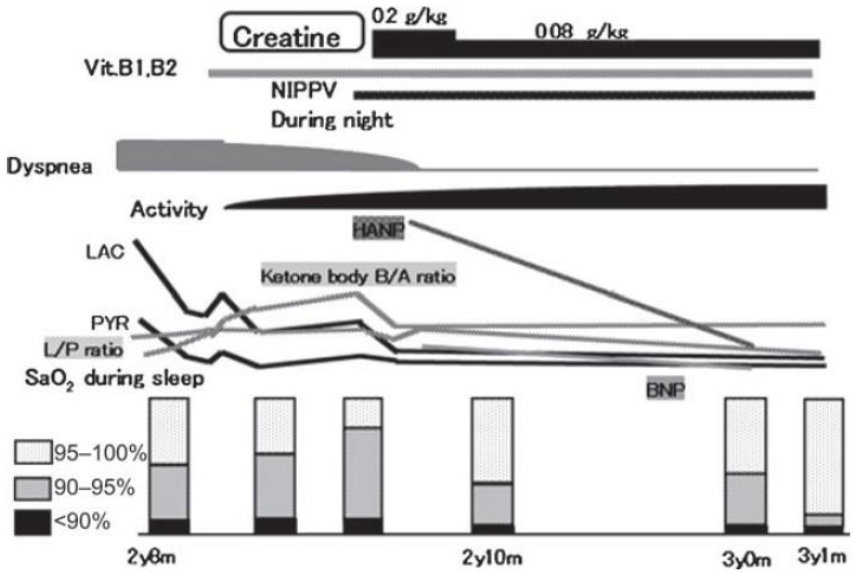


Fig. 2 Improvements in gross and fine motor function. Gross motor function: (a) before treatment, the patient was unable to walk and could stand only with her feet wide apart. (b) Soon after the initiation of vitamin B_1–B_2 therapy, she was able to walk up and down a slope. (c) Three months after starting creatine therapy, she was able to climb up and down stairs. Fine motor function: (b) she was initially only able to put a small ball into a hole if her wrist was fixed, so as to prevent involuntary movements. (c) After 3 months of creatine therapy, she could put two balls into the hole without needing to have her wrist fixed.

Komura et al. (2006) Pediatrics International 48: 409-412.

Komura (2006) continued



In conclusion, creatine monohydrate supplementation improved gross and fine motor skills and respiratory and cardiac function in the present Leigh syndrome patient. These results suggest that creatine monohydrate supplementation is a potential strategy for managing mitochondrial encephalomyopathy.

Komura et al. (2006) Pediatrics International 48: 409-412.

FDA Assessment – Creatine Effectiveness in CPEO

- Klopstock (2000)

Sixteen patients with CPEO (chronic progressive external ophthalmoplegia) or myocardial myopathy were randomized in a double-blind, crossover study by Klopstock et al. (2000) to receive 20 g creatine (given as 5 g 4 times a day) or placebo daily for 4 weeks separated by a washout period of approximately 29 days. No significant differences were observed between treatments for exercise performance (including a variety of assessments of strength, torque, aerobic cycle ergonometry, plasma lactate, ataxia, and symptom scores), eye movements or activities of daily life.

- Kornblum (2005)

Kornblum et al. (2005) conducted a randomized double-blind crossover study in 15 patients with CPEO or Kearns-Sayre syndrome (patients experience retinitis pigmentosa at an early age, ataxia, heart block and other conduction defects, sensorineural deafness, elevated protein in cerebral spinal fluid, and seizures) comparing 6-week treatments with 150 mg/kg per day of creatine monohydrate and placebo. The authors found that based on ^{31}P magnetic resonance spectroscopy, creatine treatment showed no effects (e.g., on phosphocreatine or ATP status). In addition, creatine treatment showed no effects on clinical scores or laboratory tests, with the exception that creatine plasma levels were increased during creatine treatment.

Klopstock (2000)

Table 1 *Patient characteristics and results of muscle biopsy and mtDNA analysis*

No.	Diagnosis	Sex	Age, y	Age at onset, y	mtDNA
1	CPEO	M	43	31	
2	CPEO	F	63	<46	Deletion
3	CPEO	M	43	17	Deletion
4	CPEO	F	35	29	
5	CPEO	F	29	13	Deletion
6	CPEO	F	62	<40	
7	CPEO	M	26	10	
8	CPEO	M	76	60	
9	CPEO	M	32	<25	
10	CPEO	M	30	<21	
11	CPEO	F	36	<30	
12	CPEO+	M	24	15	Deletion
13	CPEO+	F	74	55	
14	MM	F	59	44	
15	MM	F	52	42	
16	MM	M	58	47	Deletion

How can we explain the inefficacy of Cr in this study? In the trials of Tarnopolsky et al., mitochondrial diseases encompassed mainly MELAS and Leber hereditary optic neuropathy (LHON).[6,9] CPEO and MM may respond differently to Cr, because they are chronic and long-standing conditions, and muscle weakness is often more pronounced than in MELAS and LHON. Moreover, Cr supplementation is most effective in subjects with low endogenous muscle Cr concentrations.[1,2] As these concentrations are normal in CPEO,[10] these patients may benefit less than patients with other mitochondrial diseases. Thus, Cr may be effective in certain but not all mitochondrial

ergometry. As in our study most variables measured low-intensity exercise, which may be more relevant for daily life, we cannot exclude an effect of Cr in high-intensity exercise.

Klopstock et al. (2000) Neurology 55: 1748-1751.

Kornblum (2005)

Patient no.	Age (year)/sex/diagnosis
Group 1 (placebo in phase A)	
2	37/f/KSS
3	51/f/CPEO
4	33/f/CPEO
7	41/f/CPEO
9	47/m/KSS
11	56/f/CPEO
13	48/m/CPEO
Group 2 (creatine in phase A)	
1	60/m/CPEO
5[a]	36/f/CPEO
6	60/m/CPEO
8	49/f/CPEO
10	50/m/CPEO
12	60/m/CPEO
14[b]	59/f/CPEO
15[c]	48/f/CPEO

To address this controversy on the biochemical level, we investigated *in vivo* effects of Cr on skeletal muscle by means of ^{31}P-MRS. Although our CPEO/KSS patients showed low endogenous PCr/ATP ratios prior to therapy, intramuscular PCr contents did not change with high-dose Cr supplementation. This is in contrast to several studies showing an improvement of muscle performance associated with higher PCr concentrations under Cr supplementation in trained healthy subjects, where low endogenous muscle Cr levels seem to facilitate muscle Cr accumulation during Cr loading (Harris *et al.*, 1992; Casey *et al.*, 1996; Hultman *et al.*, 1996; Smith *et al.*, 1999).

The failure to improve muscle energy metabolism in our patients with mitochondrial disorders may therefore be attributed to the inefficacy of Cr supplementation to increase intramuscular PCr contents. This finding is in agreement with recently published results in patients with myotonic dystrophy type 1, muscular dystrophy and McArdle disease (Vorgerd *et al.*, 2000a, 2002; Zange *et al.*, 2002; Louis *et al.*, 2003; Tarnopolsky *et al.*, 2004). The reasons for the failure of the supplementation to increase muscle PCr/ATP ratios remain elusive. As blood concentrations of Cr significantly increased under oral Cr treatment, disturbances of Cr uptake into muscle cells should be considered. Cr is transported into the cells via specific Cr transporters that are regulated by plasma Cr levels, insulin, vitamin E, high-carbohydrates and exercise (Wyss and Walli-

Regarding the evaluation of intracellular Cr contents, it is important to note that intramuscular total Cr stores cannot be assessed by ^{31}P-MRS. Although Cr supplementation may result in a greater increase in muscle total Cr than PCr (Hultman *et al.*, 1996; Brose *et al.*, 2003), no study has examined muscle total Cr stores

Kornblum et al. (2005) European Journal of Neurology 12: 300-309.

FDA Assessment – Rodriguez (2007)

- Combination: Creatine, CoQ10, Alpha Lipoic Acid

Creatine has been studied in combination with other agents for the treatment of mitochondrial diseases. The contribution of creatine to the effects seen cannot be discerned. Rodriguez et al. (2007) assessed the combination of creatine, CoQ_{10}, and lipoic acid in the treatment of 16 patients with various mutations and/or mitochondrial disease diagnoses. The authors conclude that combination therapies may target multiple common pathways of mitochondrial dysfunction, but larger studies of combination therapies in homogeneous populations are needed.

Rodriguez (2007)

- Combination: Creatine, CoQ10, Alpha Lipoic Acid

BENEFICIAL EFFECTS OF CREATINE, CoQ_{10}, AND LIPOIC ACID IN MITOCHONDRIAL DISORDERS

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Mitochondrial diseases represent a group ders affecting mitochondrial energy trans and are characterized by clinical, biochemi genetic heterogeneity.[18] In spite of great va in phenotypic expression, most patients have bination of lactic acidosis, stroke or seizur aches, retinitis pigmentosa, ptosis, exercise

Table 1. Patient characteristics.

Subject	Sex	Age (y)	Height (cm)	Weight (kg)	Diagnosis	Mutation	Main symptoms
1	F	54	164	62.8	MELAS	T3271C	Exercise intolerance, hearing loss
2	F	31	164	85.1	MELAS	T3271C	Exercise intolerance, hearing loss
3	M	51	135	74.5	MELAS	T3271C	Stroke-like episodes, hearing loss
4	M	40	178	111.8	CPEO	Deletion	CPEO, Exercise intolerance
5	M	45	170	90.4	CPEO	Deletion	CPEO, Exercise intolerance
6	F	58	161	76.3	CPEO	Deletion	CPEO, Exercise intolerance
7	F	42	160	75.2	KSS	Deletion	CPEO, Exercise intolerance
8	F	30	157	76.6	Cytopathy	Unknown	Exercise intolerance, hearing loss
9	F	35	150	46.5	Cytopathy	Unknown	Exercise intolerance
10	F	23	167	78.2	Cytopathy	T9035C	Ataxia, neuropathy
11	F	40	150	71.8	Cytopathy	T4452C	Ataxia
12	M	45	175	85.4	Cytopathy	T9035C	Ataxia, neuropathy
13	F	43	141	100.5	Cytopathy	Unknown	Exercise intolerance
14	M	12	154	43.9	LHON	G3460A	Visual loss
15	F	47	150	77.4	LHON	G3460A	Asymptomatic
16	M	16	162	42.6	MNGIE	Analysis pending	Gastrointestinal pain, neuropathy

CPEO, chronic progressive external ophthalmoplegia; Cytopathy, mitochondrial cytopathy; KSS, Kearns–Sayre syndrome; LHON, Leber's hereditary optic neuropathy; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MNGIE, mitochondrial neurogastrointestinal encephalopathy (absent thymidine phosphorylase activity, high thymidine levels).

Abbreviations: 8-IsoP, 8-isoprostane; 8-OHdG, 8-hydro yguanosine; %BF, percent body fat; CoQ_{10}, coenzyme Q_{10}; CP progressive external ophthalmoplegia; CrM, creatine monohy electron transport chain; FFM, fat-free mass; HPLC high-perfor chromatography; KSS, Kearns–Sayre syndrome; MELAS, mitoc cephalopathy, lactic acidosis, and stroke-like episodes; mtDNA drial DNA; PCr, phosphocreatine; ROS, reactive oxygen species; body water

Key words: coenzyme Q_{10}; creatine; lipoic acid; mitochondrial randomized trial

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Rodriguez et al. (2007) Muscle & Nerve 35: 235-242.

#	Trial	Design	Size	Creatine dose	Phenotypes	Measurements	Safety	Efficacy
1	Hagenfeldt 1994	Case report	1	5g bid x 2w, then 2g bid x 3 months	MELAS	1. Aerobic exercise tolerance 2. Self-report feeling	Well tolerated	Increased exercise tolerance, reduced headache, improved general well-being
2	Tarnopolsky 1997	randomized, double-blind, placebo controlled, crossover	7	5g bid x 14d then 2g bid x 7d	6 MELAS 1 MM	1. Anaerobic and aerobic short-acting muscle strength test 2. Low intensity aerobic activities such as ADL and 2-minute walk	Well tolerated	Increased muscle strength of high-intensity anaerobic and aerobic activities, but not on lower intensity aerobic activities.
3	Tarnopolsky 1999	Open trial	81 (17 MITO)	10 qd x 5d, then 5g qd x 5d	8 MELAS, 5 LHON, 1 MNGIE, 2 CMPX-I, 1 CARDIO+RRF	Muscle strength	Well tolerated	Increased muscle strength
4	Klopstock 2000	Randomized, double-blind, place-controlled, crossover	16	5g qid x 4 weeks	13 CPEO 3 MM	1. Aerobic exercise 2. ADL 3. Muscle strength test 4. Eye movements	• Well tolerated • Muscle cramps in 2/16	No significant benefits
5	Barisic 2002	Case report	1	5g qid x 12d then 5g qd x 28 months	MELAS	1. Psychotic symptoms 2. Renal function	Slow progression of pre-existing renal insufficiency	Improved psychotic symptoms, aggressive behavior, and mental deterioration.
6	Komura 2003	Retrospective, Open-label	5	0.08g-0.35g/kg/day x 9 months – 4 years, 10 months	2 KSS 1 NARP 2 MELAS	1. Aerobic exercise (long-acting) 2. aerobic muscle strength (short-acting)	Well tolerated	Increased muscle performance and power, but more pronounced in long-acting exercises (aerobic activities).
7	Kornblum 2005	Randomized, double-blind, placebo-controlled crossover	15	0.15g/kg/day x 6 weeks	13 CPEO 2 KSS	1. Intramuscular level of P-creatine and other metabolites. 2. Muscle function	• Well tolerated • Flatulence in 3/15	No significant benefits
8	Komura 2006	Case report	1	0.2g/kg/day x 2 weeks, then 0.08g/kg x 4 months	Leigh Syndrome (mitochondrial encephalopathy)	1. Gross and fine motor functions 2. Respiratory function 3. Cardiac function markers	• No adverse reactions reported	Improved gross and fine motor skills and respiratory and cardiac function
9	Rodriguez 2007	Randomized, double-blind, placebo-controlled, crossover	16	3g creatine + 300mg a-lipoic acid + 120mg CoQ10 bid x 2 months	3 MELAS, 3 CPEO, 1 KSS, 6 Cytopathy, 2 LHON, 1 MNGIE	1. Pulmonary function 2. Muscle strength	Well tolerated	Combination treatment showed improvement in muscle strength. Greater benefits were showed in MELAS than CPEO/KSS.

Guidelines and Expert Opinions

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A Modern Approach to the Treatment of Mitochondrial Disease

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Opinion statement

The treatment of mitochondrial disease varies considerably. Most experts use a combination of vitamins, optimize patients' nutrition and general health, and prevent worsening of symptoms during times of illness and physiologic stress. We agree with this approach, and we agree that therapies using vitamins and cofactors have value, though there is debate about the choice of these agents and the doses prescribed. Despite the paucity of high-quality scientific evidence, these therapies are relatively harmless, may alleviate select clinical symptoms, and theoretically may offer a means of staving off disease progression. Like many other mitochondrial medicine physicians, we have observed significant (and at times life-altering) clinical responses to such pharmacologic interventions. However, it is not yet proven that these therapies truly alter the course of the disease, and some experts may choose not to use these medications at all. At present, the evidence of their effectiveness does not rise to the level required for universal use.

Based on our clinical experience and judgment, however, we agree that a therapeutic trial of coenzyme Q10, along with other antioxidants, should be attempted. Although individual specialists differ as to the exact drug cocktail, a common approach involves combinations of antioxidants that may have a synergistic effect. Because almost all relevant therapies are classified as medical foods or over-the-counter supplements, most physicians also attempt to balance the apparent clinical benefit of mitochondrial cocktails with the cost burden that these supplements pose for the family.

Table 2. Mitochondrial medications and supplements*

Medication	Dosage (pediatric)	Dosage (adult)	Monitoring	Adverse effects	Comments
CoQ10 as ubiquinol (preferred)	2–8 mg/kg po daily divided in two doses	50–600 mg po daily	May obtain pretherapy level and monitor CoQ10 level in leukocytes or plasma	Wakefulness, sleep disruption; may reduce warfarin concentration	Solubilized bioavailable formulation preferred. Absorption may be improved when taken with meals
CoQ10 as ubiquinone	10–30 mg/kg po daily divided in 2 doses	300–2400 mg po daily divided 2–3 times a day	May obtain pretherapy level and monitor CoQ10 level in leukocytes or plasma	Wakefulness, sleep disruption; may reduce warfarin concentration	Less potent than ubiquinol and less well absorbed; solubilized bioavailable formulation preferred. Absorption may be improved when taken with meals
Riboflavin (B_2)	50–400 mg po daily	50–400 mg po daily	Not usually done	High doses may cause anorexia and nausea	Changes urine color and smell; effects may be minimized by giving at bedtime
L-Creatine	0.1 g/kg po daily; maximum 10 g/d	5 g po daily, given 1–2 times per day	Renal function	GI upset	Primarily used in myopathy patients, though evidence exists for routine use in all mitochondrial disease patients; converted to creatinine in the gut
L-Arginine	*Acute stroke:* 500 mg/kg IV per day for 1–3 days; *Maintenance:* 150–300 mg/kg po or IV daily divided 2–3 times a day	*Acute stroke:* 500 mg/kg IV per day for 1–3 days; *Maintenance:* 150–300 mg/kg po or IV daily divided 2–3 times a day	Plasma arginine in amino acid profile	Hypotension (with IV loading), hyponatremia, headache, nausea, diarrhea. Myelinolysis reported with high dose in single case	Used with metabolic strokes, especially in MELAS or in those with low-normal plasma arginine; citrulline is used in urea cycle defects as an alternative to arginine
L-Carnitine	10–100 mg/kg per day IV or po divided 3 times a day	100–1000 mg per dose, given IV or po 2–3 times a day	Pretherapy free and total plasma carnitine levels	GI upset, fishy odor (due to bacterial degradation; may be improved with antibiotic). Reports of cardiac rhythm disturbances in long-chain fatty acid oxidation defects	FDA-approved for metabolic diseases; available as prescription generic and brand. Only 10%–20% absorbed. Acetyl-carnitine is an alternative
B50 or B100 (B vitamin complexes)	1 tab po given 1–2 times a day	1 tab po given 1–2 times a day	Not usually done	Toxic neuropathy may occur with chronic use of larger doses than recommended	Poorly palatable
Vitamin E	1–2 IU/kg po daily	100–200 IU po daily	Not usually done	Possible adverse cardiac risks at doses > 400 IU/d	Absorption may be improved when taken with meals
Vitamin C	5 mg/kg po daily	50–200 mg po daily	Not usually done	Increases iron absorption; high doses may cause renal insufficiency (single case report)	Easily absorbed water-soluble vitamin

*CoQ10 and a B vitamin are the most commonly used medications in a starting "mitochondrial treatment cocktail."
CoQ10—coenzyme Q10; FDA—US Food and Drug Administration; GI—gastrointestinal; IV—intravenous; MELAS—mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; po—by mouth.

Standard dosage	*Adult*: 10 g/d, divided into two doses. *Pediatric*: 0.1 g/kg per day, divided into two doses.
Contraindications	None known.
Main drug interactions	None known.
Main side effects	Gastrointestinal distress.
Special points	L-Creatine supplementation may produce elevation of serum creatinine and should be used with caution in patients with renal or hepatic disease. Crystals may form in the urine with high doses (single case report).
Cost	$20 for a 1000-g container (powder).

Parikh et al. (2009) Curr Treat Options Neurol 11: 414-430.

Parikh (2015)

Treatment with vitamins and xenobiotics

Multiple vitamins and cofactors are used in the treatment of mitochondrial disease, although such therapies are not standardized and multiple variations of treatments exist.[138–144] Despite empiric rationale for the use of such vitamins or xenobiotics, few trials have explored the clinical effects of these treatments.[145] There is a general lack of consensus regarding which agents should be used, although most physicians prescribe CoQ_{10}, L-carnitine, creatine, α-lipoic acid (ALA), and certain B-vitamins.[146] A Cochrane review of

Genet Med. Author manuscript; available in PMC 2016 September 01.

mitochondrial therapies has found little evidence supporting the use of any vitamin or cofactor intervention.[147]

Parikh et al. (2015) Genetics in Medicine 17: 689-701.

Parikh (2013)

Table 1
Pattern of vitamin and xenobiotic use among providers.

	N out of 32 unless stated	%
Compounds used most often		
L-Arginine for metabolic strokes	32	100%
CoQ10 as ubiquinol or ubiquinone	32	100%
Levo-Carnitine	30	94%
Creatine	24	75%

Parikh et al. (2013) Mitochondrion 13: 681-687.

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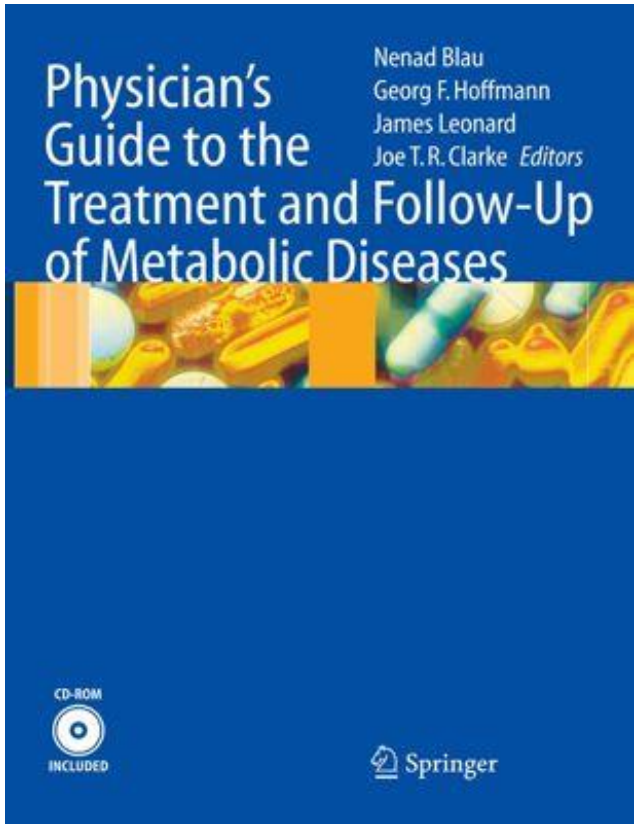


Despite great progress in the understanding of the metabolic and genetic bases of mitochondrial disorders in the last decade, various therapeutic approaches have had limited success over the years. The clinical management of patients with mitochondrial disease depends on the clinical phenotype, the biochemical and morphological results in muscle and/or fibroblasts, and mutational analysis. There are clear differences in clinical management of young children with encephalomyopathies or multiorgan failure, and older children that often have a more chronic disease course similar to adult patients. Mitochondrial DNA (mtDNA) mutations are uncommon in affected children, whereas most of the adults have pathogenic mtDNA mutations (Smeitink et al. 2001; DiMauro and Schon 2003).

The various treatment strategies can be divided into different categories (DiMauro et al. 2000; Gillis and Kaye 2002):

1. Supportive care
2. Removal of noxious metabolites, i. e., dichloroacetate
3. Administration of artificial electron acceptors, i. e., menadione (vitamin K_3), ascorbate (vitamin C), and ubiquinone (coenzyme Q_{10})
4. Administration metabolites and cofactors, i. e., riboflavin (vitamin B_2), ubiquinone, carnitine, and creatine
5. Administration of oxygen radical scavengers, i. e., tocopherol (vitamin E), ubiquinone, idebenone, selenium, copper, and glutathione peroxidase
6. Dietary interventions
7. Gene therapy

10. Starting dose of creatine monophosphate 2×5 g/day for 5–14 days, followed by maintenance of 2×2 g/day. Stop every 4^{th} month to avoid cytotoxic effect of formaldehyde, eventually formed by conversion of methylamine, a metabolite of creatine metabolism (Persky and Brazeau 2001).

Conclusion

- Aqueous formulation of creatine monohydrate in amber bottle and keep refrigerated can be stable for at least 40 days at pH ≥ 4.9, and for 36 months at pH > 7.
- Creatine monohydrate has shown more effectiveness in certain phenotypes of mitochondrial disorders (MELAS and KSS) than other phenotypes, such as CPEO, due to intrinsic differences among phenotypes.
- Creatine monohydrate may benefit more in high-intensity activities than in low-intensity activities.

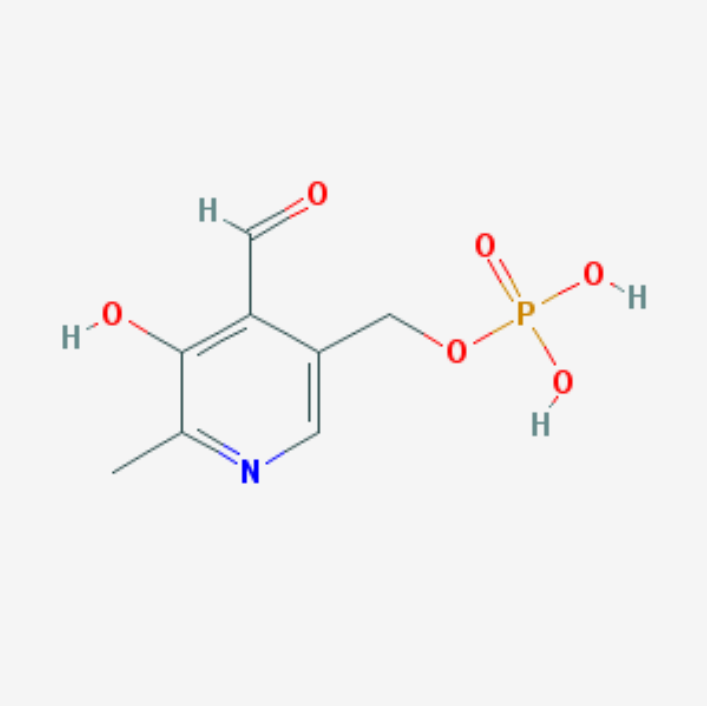
THANK YOU

Questions from the Committee?

Fagron North America, IACP, NCPA: Nominators

Pharmacy Compounding Advisory Committee
review: Pyridoxal 5 Phosphate

- Pyridoxal Phosphate (P5P) is considered the most important member of the Vitamin B6 group.
- It is an active coenzyme for more than 100 enzymes, including glutamic acid decarboxylase and enzyme involved in gamma-amino butyric acid synthesis.



Wang H-S, Kuo M-F, Chou M-L, et al. Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. *Arch Dis Child*. 2005;90(5):512-515. doi:10.1136/adc.2003.045963.

Glutamic Acid Decarboxylase

- Glutamic acid decarboxylase(GAD) synthesizes gamma-aminobutyric acid (GABA)
- (GABA), the principal inhibitory neurotransmitter in the cerebral cortex, maintains the inhibitory tone that counterbalances neuronal excitation.
- P5P is needed by GAD as a coenzyme for the synthesis of GABA

Gospe Jr SM, Olin KL, Keen CL. Reduced GABA synthesis in pyridoxine-dependent seizures. Lancet 1994;343:1133–4.

Pyridoxine dependent seizures

- Pyridoxine dependent seizure (PDS) is a condition caused by autosomal recessive inborn error of metabolism, and affected patients are dependent upon regular pharmacologic doses of pyridoxine.
- Untreated, the disorder results in death from status epilepticus
- In most instances, the institution of either parenteral or oral pyridoxine rapidly results in seizure control and improvement in the encephalopathy.
- The diagnosis of PDS is made by clinical observation, where an infant with anticonvulsant-resistant seizures is offered a trial of pyridoxine that results in an often dramatic cessation of these events.

Gospe SM. Neonatal vitamin-responsive epileptic encephalopathies. *Chang Gung Med J*. 2009;33(1):1-12. http://www.ncbi.nlm.nih.gov/pubmed/20184790.

Positive Outcome following Early Diagnosis and Treatment of Pyridoxal-5′-Phosphate Oxidase Deficiency: A Case Report

Stephanie Porri1 Joel Fluss1 Barbara Plecko2 Eduard Paschke3 Christian M. Korff1 Ilse Kern4

Introduction

Pyridoxal-5′-phosphate oxidase (PNPO) deficiency is a rare autosomal recessive, vitamin responsive metabolic disorder causing refractory neonatal seizures that respond to the administration of pyridoxal-5′-phosphate (PLP). There are currently few case studies that have documented the functional outcome in PNPO deficiency, which remains poor in the majority of cases. We present the case of **a male infant born at 35 weeks gestation who promptly responded to oral administration of PLP**, following resistance to common anticonvulsive therapy and to a pyridoxine trial. **Neurological outcome at 21 months is favorable and illustrates the importance of standardized vitamin trials in the acute setting of "therapy-resistant" neonatal seizures.** Early recognition of PNPO deficiency and appropriate intervention might be associated with a more favorable outcome than initially considered

Positive Outcome following Early Diagnosis and Treatment of Pyridoxal-5′-Phosphate Oxidase Deficiency: A Case Report

- Within the first 12 hours, irritability and erratic myoclonic jerks involving all four extremities were noted. The first EEG recorded two hours after the onset of symptoms showed a suppression-burst pattern with synchronized bursts of bilateral moderate-amplitude spike-and-waves.
- These seizures were resistant to phenobarbital, phenytoin, and vigabatrin.
- Profound lethargy and hypotonia were noticed over the following 3 weeks. PLP was administered every 6 hours at 35mg/kg/day and anticonvulsive therapy withdrawn. After 5 weeks the infant was discharged with mild hypotonia and adequate bottle feeding.

Porri S, Fluss J, Plecko B, Paschke E, Korff C, Kern I. Positive Outcome following Early Diagnosis and Treatment of Pyridoxal-5′-Phosphate Oxidase Deficiency: A Case Report. *Neuropediatrics*. 2013;45(1):064-068. doi:10.1055/s-0033-1353489.

Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy

H-S Wang, M-F Kuo, M-L Chou, P-C Hung, K-L Lin, M-Y Hsieh, M-Y Chang

Aim: To study the difference between pyridoxine (PN) and its active form, pyridoxal phosphate (PLP), in control of idiopathic intractable epilepsy in children.
Methods: **Among 574 children with active epilepsy, 94 (aged 8 months to 15 years) were diagnosed with idiopathic intractable epilepsy for more than six months**. All received intravenous PLP 10 mg/kg, then 10 mg/kg/day in four divided doses. If seizures recurred within 24 hours, another dose of 40 mg/kg was given, followed by 50 mg/kg/day in four divided doses. For those patients whose seizures were totally controlled, PLP was replaced by the same dose of oral PN. If the seizure recurred, intravenous PLP was infused followed by oral PLP 50 mg/kg/day.
Results: Fifty seven patients had generalized seizures (of whom 13 had infantile spasms) and 37 had focal seizure. Eleven had dramatic and sustained responses to PLP; of these, five also responded to PN. Within six months of treatment with PLP or PN, five of the 11 patients were seizure free and had their previous antiepileptic medicine tapered off gradually. Two were controlled with pyridoxine and the other three needed PLP to maintain seizure freedom. The remaining six responders needed PLP exclusively for seizure control. Six of the 11 responders to PLP had infantile spasms (46%); four of them needed PLP exclusively. The other five responders were in the remaining 81 patients with other seizure type.
Conclusions: PLP could replace PN in the treatment of intractable childhood epilepsy, particularly in the treatment of infantile spasms.

Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy

- After the first attempt to treat West syndrome with high dose vitamin B_6 (that is, PN), PN has been recognized as a treatment of choice in West syndrome
- 574 children with active epilepsy were referred to our Pediatric Neurology Department. After appropriate management, 219 patients had medically intractable epilepsy. 94 children (59 boys and 35 girls), aged between 8 months and 15 years, were defined as having idiopathic intractable epilepsy and were enrolled in this study.
- Eleven of the 94 patients responded dramatically to intravenous infusion of PLP, achieving a seizure-free status Three of the 11 patients responded to a dose of 10 mg/kg/day (cases 7, 8, 11). The other eight patients needed a dose of 50mg/kg/day.
- Our present study showed that PLP was effective in controlling up to 46% of the patients with intractable infantile spasms. In conclusion, our data suggest that PLP is more effective than PN in some children with idiopathic intractable epilepsy, particularly children with infantile spasms.

Wang HS, Kuo MF, Chou ML, et al. Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. *Arch Dis Child*. 2005;90(5):512-515. doi:10.1136/adc.2003.045963.

Pyridox(am)ine-5-Phosphate Oxidase Deficiency Treatable Cause of Neonatal Epileptic Encephalopathy With Burst Suppression: Case Report and Review of the Literature

Andrea Guerin, MD1, Aly S. Aziz, MD2, Carly Mutch, OT3, Jillian Lewis, MD4, Cristina Y. Go, MD2, and Saadet Mercimek-Mahmutoglu, MD, PhD1,5

Abstract

Pyridox(am)ine-5-phosphate oxidase deficiency is an autosomal recessive disorder of pyridoxine metabolism. Intractable neonatal epileptic encephalopathy is the classical presentation. Pyridoxal-5-phosphate or pyridoxine supplementation improves symptoms. We report a patient with myoclonic and tonic seizures at the age of 1 hour. Pyridoxal-5-phosphate was started on the first day of life and seizures stopped at the age of 3 days, but encephalopathy persisted for 4 weeks. She had normal neurodevelopmental outcome at the age of 12 months on pyridoxal-5-phosphate monotherapy. She had novel homozygous pathogenic frameshift mutation (c.448_451del;p.Pro150Argfs*27) in the PNPO gene. Long-lasting encephalopathy despite well-controlled clinical seizures does neither confirm nor exclude pyridox(am)ine-5-phosphate oxidase deficiency. Normal neurodevelopmental outcome of our patient emphasizes the importance of pyridoxal-5-phosphate treatment. Pyridox(am)ine-5-phosphate oxidase deficiency should be included in the differential diagnosis of Ohtahara syndrome and neonatal myoclonic encephalopathy as a treatable underlying cause. In addition, we reviewed the literature for pyridox(am)ine-5-phosphate oxidase deficiency and summarized herein all confirmed cases.

Pyridox(am)ine-5-Phosphate Oxidase Deficiency Treatable Cause of Neonatal Epileptic Encephalopathy With Burst Suppression: Case Report and Review of literature

- Forty-one percent of the patients with pyridox(am)ine-5-phosphate oxidase deficiency were treated with pyridoxine supplementation (up to 30 mg/kg/d). Of those patients, 71% were seizure free and 42% had normal neurodevelopmental outcome on pyridoxine monotherapy.
- Pyridoxal-5-phosphate and pyridoxine supplementation therapies are the only treatments, and untreated pyridox(am)ine-5-phosphate oxidase deficiency results in early death.
- Dosing ranged from 30mg/kg/day to 100mg/kg/day per neogastric tube.

Guerin A, Aziz AS, Mutch C, Lewis J, Go CY, Mercimek-Mahmutoglu S. Pyridox(am)ine-5-Phosphate Oxidase Deficiency Treatable Cause of Neonatal Epileptic Encephalopathy With Burst Suppression. *J Child Neurol*. 2015;30(9):1218-1225. doi:10.1177/0883073814550829.

Stability of water-soluble vitamins and coenzymes. Hydrolysis of pyridoxal-5-phosphate in acidic, neutral, and weakly alkaline solutions

- Tested the use of sodium metabisulfite to stabilize pyridoxal 5 phosphate in solution.
- pH range was 3-6.4.
- Solutions were made and protected from light.
- The formation of a pyrodoxal 5 phosphate and bisulfite complex was detected using a spectrometer.

Kozlov EI, L'vova MS. Stability of water-soluble vitamins and coenzymes. Hydrolysis of pyridoxal-5-phosphate in acidic, neutral, and weakly alkaline solutions. *Pharm Chem J*. 1977;11(11):1543-1549. doi:10.1007/BF00778244.

Clinical Safety

- Review of cases and literature showed no safety issues with Pyridoxal 5 Phosphate supplementation.
- Seizure breakthrough was only issue listed.

Guerin A, Aziz AS, Mutch C, Lewis J, Go CY, Mercimek-Mahmutoglu S. Pyridox(am)ine-5-Phosphate Oxidase Deficiency Treatable Cause of Neonatal Epileptic Encephalopathy With Burst Suppression. *J Child Neurol*. 2015;30(9):1218-1225. doi:10.1177/0883073814550829

Main points for Pyridoxal 5 Phosphate

- The other commercially available options have limited if any effect on infantile spasms.
- Pyridoxal 5 phosphate has shown to be superior to pyridoxine.
- No severe adverse effects reported.
- Infantile spasms, if not treated, will result in early death.

Quercetin Dihydrate

Inclusion in the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act

Dr. Paul S. Anderson

Seattle, WA

Presented to the Food and Drug Administration September 2018

Nominated Indications / Outline

- Asthma
- Allergy
- Cancer prevention and treatment
- Hypertension
- Forms of administration

A note about references:

- Quercetin currently has 16,423 references on PubMed

- For the purposes of this presentation I have included the most recent or germane papers based on the indications nominated.

Asthma and Allergy:

Askari G, et.al. The effect of quercetin supplementation on selected markers of inflammation and oxidative stress. J Res Med Sci. 2012 Jul; 17(7): 637–641. PMID: 23798923

(Human trial)

Supporting the common use of quercetin with other antioxidants as synergist in inflammatory conditions:

“however, our finding showed significant differences in F2-isoprostanes – a reliable index of in vivo free radical generation and oxidative damage of lipids – between pre- and postsupplementation in the group taking quercetin + vitamin C.”

David AVA, Arulmoli R, and Parasuraman S. Overviews of Biological Importance of Quercetin: A Bioactive Flavonoid. Pharmacogn Rev. 2016 Jul-Dec; 10(20): 84–89. doi: 10.4103/0973-7847.194044. PMID: 28082789

"Quercetin is a **flavonoid with antioxidant properties**. The ability of quercetin is claimed to exert many beneficial effects on health, including protection against various diseases such as osteoporosis, lung cancer, and cardiovascular disease. The studies showed that there has been a reduction in the risk of cardiovascular disease in subjects, who had a high intake of flavonoids. Flavonols is the most prominent flavonoids in fruits and vegetables and of these, **quercetin is the most commonly consumed in the human diet.**"

Yao Li, et.al. Quercetin, Inflammation and Immunity (Review). Nutrients 2016, 8, 167; doi:10.3390/nu8030167

(Review)

This review focuses on the physicochemical properties, dietary sources, absorption, bioavailability and metabolism of quercetin, especially main effects of quercetin on inflammation and immune function. **According to the results obtained both in vitro and in vivo, good perspectives have been opened for quercetin.** Nevertheless, further studies are needed to better characterize the mechanisms of action underlying the beneficial effects of quercetin on inflammation and immunity.

Mlcek J, et.al. Quercetin and Its Anti-Allergic Immune Response (Review). Molecules 2016, 21, 623; doi:10.3390/molecules21050623

(Review)

"All mentioned mechanisms of action contribute to the **anti-inflammatory and immunomodulating properties of quercetin that can be effectively utilized in treatment of late-phase, and late-late-phase bronchial asthma responses, allergic rhinitis and restricted peanut-induced anaphylactic reactions.** Plant extract of quercetin is the main ingredient of many potential anti-allergic drugs, supplements and enriched products, which is **more competent in inhibiting of IL-8 than cromolyn (anti-allergic drug disodium cromoglycate) and suppresses IL-6 and cytosolic calcium level increase**."

Oncology:

Ferry DR, et.al. Phase I Clinical Trial of the Flavonoid Quercetin: Pharmacokinetics and Evidence for in Vivo Tyrosine Kinase Inhibition. Clin Cancer Res. Vol. 2, 659-668, April 1996

(Phase-1 Trial)

Mechanism evidence and Phase-1 safety data.

Discussed later in the safety assessment.

Jeong JH, et.al. Effects of low dose quercetin: Cancer cell-specific inhibition of cell cycle progression. J Cell Biochem. 2009 January 1; 106(1): 73–82. doi:10.1002/jcb.21977.

(In vitro mechanism at low dose trial)

Due to its anti-oxidant, anti-tumor and anti-inflammatory activity, quercetin has been studied extensively as a chemoprevention agent in several cancer models. Since most of these studies used higher doses of quercetin than clinically achievable, we focused on the **effectiveness of physiologically relevant doses of quercetin.** ... **This study proved that the chemopreventive efficacy of a physiologically relevant dose of quercetin can be achievable through the inhibition of cell cycle progression.**

Yang F, et.al. Quercetin in prostate cancer: Chemotherapeutic and chemopreventive effects, mechanisms and clinical application potential (Review). Oncol Rep. 2015 Jun;33(6):2659-68. doi: 10.3892/or.2015.3886. Epub 2015 Mar 31. PMID: 25845380

(Review)

Quercetin is a natural flavonoid compound that has attracted increased interest and attention due to its anticancer activity. In vitro and in vivo studies have verified that quercetin effectively inhibits prostate cancer via various mechanisms. **Clinical trails concerning the pharmacokinetics and application of quercetin in humans have also obtained promising results. Meanwhile, epidemiologic studies have demonstrated a negative association between quercetin intake and prostate cancer incidence and have suggested a chemopreventive effect of quercetin on prostate cancer that has been exhibited in animal experiments.**

Men K, et.al. Nanoparticle-delivered quercetin for cancer therapy. Anticancer Agents Med Chem. 2014;14(6):826-32. PMID: 24851877

(Review)

Quercetin, a natural protective bioflavonoid, possesses diverse pharmacologic effects, such as antioxidant, anti-inflammatory, anti-proliferative, and anti-angiogenic activities. **Recently, quercetin's effect in cancer prevention and treatment was recognized.** However, the poor water solubility and low-bioavailability of quercetin limit its clinical use in cancer therapy. Nanotechnology provides a method to create novel formulations for hydrophobic drug. **Nanoparticles-delivered quercetin has attracted many attentions for its enhanced anticancer potential and promising clinical application.**

Brito AF, et.al. Quercetin in Cancer Treatment, Alone or in Combination with Conventional Therapeutics? Curr Med Chem. 2015;22(26):3025-39. PMID: 26264923

(Review)

"In the last decades, several anticancer properties of quercetin have been described, such as cell signaling, pro-apoptotic, anti-proliferative and anti-oxidant effects, growth suppression. **In fact, it is now well known that quercetin has diverse biological effects, inhibiting multiple enzymes involved in cell proliferation, as well as, in signal transduction pathways. On the other hand, there are also studies reporting potential synergistic effects when combined quercetin with chemotherapeutic agents or radiotherapy.** In fact, several studies which aim to explore the anticancer potential of these combined treatments have already been published, the majority with promising results. Actually it is well known that quercetin can act on the chemosensitization and radiosensitization but also as chemoprotective and radioprotective, protecting normal cells of the side effects that results from chemotherapy and radiotherapy, which obviously provides notable advantages in their use in anticancer treatment. **Thus, all these data indicate that quercetin may have a key role in anticancer treatment.**

Hypertension:

Serban M, Sahebkar A, Zanchetti A, et al. Effects of Quercetin on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease. 2016;5(7):e002713. doi:10.1161/JAHA.115.002713.

(Review of Placebo controlled randomized controlled trials investigating the effect of quercetin on BP.)

The results of the meta-analysis **showed a statistically significant effect of quercetin supplementation in the reduction of BP**, possibly limited to, or greater with dosages of >500 mg/day. Further studies are necessary to investigate the clinical relevance of these results and the possibility of quercetin application as an add-on to antihypertensive therapy.

Administration:

Quote from page 323 https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM617333.pdf

"It should be noted that the safety of intravenous quercetin is quite different from oral quercetin. **Ferry et al. 1996** reported multiple, serious adverse events that occurred after administration of high dose intravenous quercetin to patients with cancer no longer responding to standard treatments. Fifty-one patients with cancer no longer amenable to standard therapies were treated with escalating intravenous doses of quercetin administered at three-week or one week intervals.

The dose range was 60 mg/m2 to 2000 mg/m2. Pain at the site of injection was noted at all dose levels and was worse at higher doses. Dyspnea was noted starting at 1400 mg/m2 and was severe at 2000 mg/m2. Vomiting occurred at 1700 mg/m2 and was grade 4. Significant renal toxicity was noted at doses as low as 630 mg/ m2 and became dose limiting at 1700 mg/m2 (grade 1 to grade 4) with some patients having residual renal toxicity after treatment was stopped (Ferry et al. 1996)."

Page 323 references “Ferry, et.al 1996”
Ferry DR, et.al. Phase I Clinical Trial of the Flavonoid Quercetin: Pharmacokinetics and Evidence for in Vivo Tyrosine Kinase Inhibition. Clin Cancer Res. Vol. 2, 659-668, April 1996

- Issues in extrapolating “IV Safety” from the Ferry 1996 study given modern compounding and use:
  - Compounded formulation:
    - 50 mL of RIMSO (DMSO) 50% in which the quercetin was diluted
  - Administration type:
    - IV Push

Page 323 references “Ferry, et.al 1996”
Ferry DR, et.al. Phase I Clinical Trial of the Flavonoid Quercetin: Pharmacokinetics and Evidence for in Vivo Tyrosine Kinase Inhibition. Clin Cancer Res. Vol. 2, 659-668, April 1996

- Conclusion quotations from the Ferry 1996 Phase-1 study:
  - “No clinically significant toxicities were seen until the 10h dose level (1700 mg/m2) when renal toxicity, manifesting as elevation of serum creatinine, occurred. In one patient, this was grade 4 reaching 2145 um but **without dialysis, serum creatinine normalized within 34 days**.”
  - “it became clear that **simple i.v. prehydration** could at least partially abrogate the nephrotoxicity of quercetin. With this in mind, the emesis and the pain on injection, we believe that 1400 mg/m2 given weekly or every 3 weeks can be recommended for Phase II trials.”

Recent IV use of Quercetin Experience:

- In the past six years a group of over five compounding pharmacies have made parenteral quercetin available at different times.
- Preparation of the admixture was either as an emulsion or in cyclodextrin.
  - (Not DMSO)
- Dose escalation averaged 1 mg/kg to 50 mg/kg
- IV dilution of the sterile product is accomplished in 500 – 1500 mL NS or D5W (per pharmacy recommendations and based on dose.)
  - (Not pushed).
- Administration times ranged between 5 to 15 mg / minute

Recent IV use of Quercetin Experience:

- Multiple clinics administered over 2500 doses with no high grade adverse events. Transient nausea and flushing were self limited and experienced in 10% or less infusions – and – were relieved by slower infusion rate and or higher dilution.

Recent references supporting stability and safety of parenteral quercetin:

- Curcio M, et.al. Quercetin-Imprinted Nanospheres as Novel Drug delivery devices. J. Funct. Biomater. 2012, 3, 269-282; doi:10.3390/jfb3020269, ISSN 2079-4983. www.mdpi.com/journal/jfb/
- Zhu Y, Teng T, Wang H, Guo H, Du L, Yang B, Yin X, Sun Y. Quercetin inhibits renal cyst growth in vitro and via parenteral injection in a polycystic kidney disease mouse model. Food Funct. 2018 Jan 24;9(1):389-396. doi: 10.1039/c7fo01253e.
- Ahire Eknath, etal. Parenteral nanosuspensions: a brief review from solubility enhancement to more novel and specific applications. Acta Pharmaceutica Sinica B (2018), https://doi.org/10.1016/j.apsb.2018.07.011
- Mok SW, et.al. Intra-Articular Delivery of Quercetin Using Thermosensitive Hydrogel Attenuate Cartilage Degradation in an Osteoarthritis Rat Model. Cartilage. 2018 Aug 30:1947603518796550. doi: 10.1177/1947603518796550. PMID: 30160166

Summary:

Quercetin is safe:

CFSAN Adverse Event Reporting System (CAERS).

A search of CAERS was conducted for adverse events associated with quercetin dihydrate in June 2018 based on the term “quercetin”. Twenty cases were spontaneously reported from April 2009 to January 2018 with quercetin listed as the suspected product in 11 reports and as a concomitant product in 9 reports.

None of the seven cases that involved hospitalization appeared directly related to taking quercetin (i.e., hospitalized for peri-tonsillar abscess, exacerbation of asthma, headache and dizziness (“all tests normal”), faint (observed overnight), “mini stroke” (consumer told to discontinue her 12+ dietary supplements), “allergic reaction to shrimp” and 75 year old “falling down a pyramid.” The **majority of cases were 16 confounded by multiple medications and/or underlying disease or there was insufficient information for assessment.**

FDA Adverse Event Reporting System (FAERS) for reports of adverse events for quercetin/quercetin dihydrate from January 1, 2000 to January 30, 2018. Seven (six US) nonduplicated cases were identified that reported both exposure to quercetin/quercetin dihydrate and at least one adverse event. These reports were submitted to the FDA because they listed a co-suspect drug that was approved by the FDA. **It should be noted that three of the seven reports were coded with a serious outcome.**

FAERS Case #13251227, Expedited, Foreign

A 72-year old male … **it is considered unlikely that the quercetin was the cause of his hospital admission.**

FAERS Case #14170737, Expedited, US

A 10-year old male … **it is considered unlikely that the quercetin was the cause of his hospital admission because of his history of anxiety and multiple other medications.**

FAERS Case #977288 Expedited, US

A 55-year old male ... **Because such minimal information was provided regarding the reaction of this patient to quercetin, no clinical assessment is possible.**

Harwood M, Danielewska-Nikiel B, Borzelleca JF et al. **A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties.** Food Chem Toxicol. 2007 Nov;45(11):2179-205.

Quercetin is a naturally-occurring flavonol (a member of the flavonoid family of compounds) that has a long history of consumption as part of the normal human diet. Because a number of biological properties of quercetin may be beneficial to human health, interest in the addition of this flavonol to various traditional food products has been increasing. Prior to the use of quercetin in food applications that would increase intake beyond that from naturally-occurring levels of the flavonol in the typical Western diet, its safety needs to be established or confirmed. This review provides a critical examination of the scientific literature associated with the safety of quercetin. Results of numerous genotoxicity and mutagenicity, short- and long-term animal, and human studies are reviewed in the context of quercetin exposure in vivo. **To reconcile results of in vitro studies, which consistently demonstrated quercetin-related mutagenicity to the absence of carcinogenicity in vivo, the mechanisms that lead to the apparent in vitro mutagenicity, and those that ensure absence of quercetin toxicity in vivo are discussed. The weight of the available evidence supports the safety of quercetin for addition to food.**

Due to its safety:

Nominators Statement

(Contained in PharmacyCompoundingAdvisoryCommittee/UCM617333.pdf)

"(We) intend to preserve for its nomination all routes until adequate time is allowed to prepare a response, including but not limited to oral, intravenous, intramuscular and sublingual uses."

Thank you.