NICE advice

Mitochondrial disorders in children: Co-enzyme Q10

Evidence summary
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www.nice.org.uk/guidance/es11

Key Points

The content of this evidence summary was up-to-date in March 2017. See summaries of product characteristics (SPCs), British national formulary (BNF), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Regulatory status: Co-enzyme Q10 has no licensed indications as a medicine in the UK.

Overview

This evidence summary discusses 3 case reports in a total of 6 children with mitochondrial disorders. Because this evidence is very limited, this evidence summary also discusses the best available evidence on the use of co-enzyme Q10 in adults and young people with mitochondrial disorders.

The symptoms of the children described in the case reports were diverse and included motor/muscle symptoms, neurological symptoms, nephrotic syndrome and hypoparathyroidism. Symptoms of all 6 children were reported to improve with co-enzyme

Q10 treatment. However, as uncontrolled observational studies in individual patients, these case reports are prone to bias and other methodological problems. They also provided very limited data on objective measurable outcomes. In addition, mitochondrial disorders are a heterogeneous group of rare diseases and the children included in these case reports may not represent all types of patients seen in clinical practice.

The best available evidence on the use of co-enzyme Q10 in adults and young people with mitochondrial disorders consists of 2 randomised controlled trials (RCTs) and 1 non-randomised study. These studies showed no statistically significant benefit for co-enzyme Q10 compared with placebo for the majority of outcomes assessed including mitochondrial disease-specific activities of daily living and quality of life assessment scores, handgrip fatigue tests and sustained endurance strength. However, the studies had a number of important methodological limitations, were of short duration and included only small numbers of participants. They may therefore have been insufficiently powered to detect any true differences between placebo and co-enzyme Q10. In the non-randomised study, after 6 months treatment with co-enzyme Q10 there was a statistically significant increase in the global Medical Research Council (MRC) muscle scale score and a statistically significant decrease in post-exercise serum lactate levels from baseline. However, the clinical significance of these changes is unclear.

There is currently no established treatment for mitochondrial disorders and the clinical management is largely supportive. The studies included in this evidence summary provide insufficient evidence to evaluate the place in therapy of co-enzyme Q10 for the treatment of mitochondrial disorders in children. The case reports and the studies in adults and young people used a wide variety of doses and formulations of co-enzyme Q10.

A summary to inform local decision-making is shown in table 1.

Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications

Effectiveness

- No statistically significant difference between co-enzyme Q10 at a dose of 600 mg twice daily and placebo for mitochondrial disease-specific activities of daily living and quality of life assessment scores or mean maximal isometric forearm strength (Glover et al. 2010, RCT in adults; n=30, crossover study 60 days taking both co-enzyme Q10 and placebo).
- No statistically significant difference between co-enzyme Q10 at a dose of 160 mg daily and placebo for fatigability in activities of daily living score or sustained endurance strength (mean time taken in seconds to perform specified activities) [Chen et al. 1997, crossover RCT in adults and young people, n=8, 3 months taking co-enzyme Q10 and 1 month taking placebo].
- Statistically significant increase in the global MRC muscle scale score with co-enzyme Q10 at a dose of 160 mg daily compared with placebo. However, the clinical significance of this increase (from approximately 83% to 87%) is unclear (Chen et al. 1997).
- Statistically significant increase in the global MRC muscle scale score from baseline after 6 months treatment with co-enzyme Q10 at a dose of 2 mg per kg daily (from approximately 89% to 91%) and statistically significant decrease in post-exercise serum lactate levels (from approximately 68 to 52 mg %). The clinical significance of these changes is unclear (Bresolin et al. 1990, study in adults and young people, n=44).
- Case reports in 6 children suggest beneficial effects but the clinical significance of this evidence is hard to assess.

Safety

- Co-enzyme Q10 may reduce insulin requirements in people with diabetes and may enhance or reduce the anticoagulant effect of warfarin (BNFc).
- The European Public Assessment Report (EPAR) for idebenone (EPAR: Raxone) includes blood count abnormalities, abnormal liver function and hepatitis as potential safety concerns (based on studies in Leber's Hereditary Optic Neuropathy and other diseases).
- The studies included in this evidence summary provide no information on the safety of co-enzyme Q10.

Patient factors

- Possible side-effects of co-enzyme Q10 include nausea, diarrhoea, heartburn and rarely headache, irritability, agitation and dizziness (BNFc).
- The studies included in this evidence summary provide no information on the tolerability of co-enzyme Q10.

Resource implications

- Co-enzyme Q10 formulations for prescription are available from 'special-order' manufacturers or specialist importing companies. Costs will vary depending on the brand or manufacturer.
- Idebenone is a synthetic analogue of co-enzyme Q10. It is licensed for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (SPC: Raxone). It costs £6364.00 for 30 days' treatment (MIMs, March 2017).

Introduction and current guidance

Mitochondria are responsible for converting food into energy within human cells. Mitochondrial disorders are a diverse group of conditions that often involve the nervous system, are usually progressive, and often cause significant disability and premature death. The term 'mitochondrial disorders' usually refers to primary disorders of the mitochondrial respiratory chain (Pfeffer et al. 2012). Secondary mitochondrial disorders

such as Friedreich's ataxia will not be discussed in this evidence summary.

Mitochondrial disorders mainly affect tissues dependent upon oxidative metabolism, including the central nervous system, peripheral nerves, the eye, skeletal and endocrine muscle, and endocrine organs. Many people with mitochondrial disease have a multi-system disorder that often involves skeletal muscle and the central nervous system, although some people may have a disorder that only affects 1 organ system. Specific mitochondrial disease conditions include Alpers disease, Leigh syndrome, Leber's hereditary optic neuropathy (LHON), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibres (MERRF), neurogenic weakness with ataxia and retinitis pigmentosa (NARP) and mitochondrial neuro-gastrointestinal encephalopathy (MNGIE) (Pfeffer et al. 2012).

There is currently no established treatment for mitochondrial disorders and the clinical management is largely supportive. Interventions used to modify the disease process include dietary modification, pharmacological agents and a variety of nutritional supplements such as co-enzyme Q10, thiamine, vitamin C and vitamin E and exercise therapy (Pfeffer et al. 2012).

Product overview

Mode of action

Co-enzyme Q10 (also known as ubiquinone or ubidecarenone) is a fat-soluble compound primarily synthesised by the body and also consumed in the diet. It is involved in the process of energy production by mitochondria and functions as an antioxidant in cell membranes and lipoproteins.

Regulatory status

Co-enzyme Q10 has no licensed indications as a medicine in the UK.

In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the patient and whether using co-enzyme Q10 is suitable. Supporting information and advice is also available from the GMC.

Dosing information

The BNF for children (BNFc) provides dosing information on the use of co-enzyme Q10 for mitochondrial disorders. The BNFc recommends an initial dose of 5 mg once or twice daily for both neonates and children aged 1 month to 18 years. The dose should be adjusted according to response. The BNFc recommends that up to 200 mg daily may be required for neonates and up to 300 mg daily may be required for children aged 1 month to 18 years.

Cost

Co-enzyme Q10 is available from 'special-order' manufacturers or specialist importing companies. Costs will vary depending on the brand or manufacturer.

Evidence review

A literature search was conducted to identify studies on the use of co-enzyme Q10 for mitochondrial disorders in children. This identified 125 references (see search strategy for full details). These references were screened using their titles and abstracts and 18 references plus a further 13 studies and case reports referenced in a Cochrane review on treatment for mitochondrial disorders (Pfeffer et al. 2012) were obtained and assessed for relevance.

Of these references 3 case reports in children (Montini et al. 2008, Papadimitriou et al. 1996 and Rotig et al. 2000) are briefly discussed in this evidence summary. No randomised controlled trials (RCTs) or higher quality observational data in children were found. Because the evidence found relating to children was very limited, the best available evidence (in this case, RCTs or the best comparative studies) on the use of co-enzyme Q10 for mitochondrial disorders in adults and young people identified from the search has also been included in this evidence summary. This comprised 2 RCTs (Chen et al. 1997 and Glover et al. 2010) and a non-randomised study (Bresolin et al. 1990).

The literature search was repeated without the children limit to identify any additional RCTs on the use of co-enzyme Q10 for mitochondrial disorders in adults. Any studies that had already been identified during the search in children were excluded. This literature search identified 262 references (see search strategy for full details). These references were also screened using their titles and abstracts and 4 were obtained and assessed for

relevance. None of these 4 references were included in the evidence summary (see excluded studies).

Summaries of Bresolin et al. (1990), Chen et al. (1997) and Glover et al. (2010) are shown in table 2 (see evidence tables for full details). The 3 case reports in children (Montini et al. 2008, Papadimitriou et al. 1996 and Rotig et al. 2000) are briefly discussed in the clinical effectiveness section.

Table 2 Summary of included comparative studies in adults and young people

Study	Population	Intervention and comparison	Primary outcome
Bresolin et al. (1990) 2 part study: part 1 non-comparative part 2 comparative non-randomised vs. placebo	Mitochondrial myopathies (n=59 part 1 and n=16 part 2)	Co-enzyme Q10 2 mg per kg daily vs. placebo	Primary outcome not specified. See evidence table for full details of study outcomes.
Chen et al. (1997) RCT	Mitochondrial encephalomyopathies (n=8)	Co-enzyme Q10 160 mg daily vs. placebo	Primary outcome not specified. See evidence table for full details of study outcomes.
Glover et al. (2010) RCT	Mitochondrial disorders (n=30)	Co-enzyme Q10 600 mg twice daily vs. placebo	Primary outcome not specified. See evidence table for full details of study outcomes.
Abbreviations: RCT, randomised controlled trial.			

The remaining 29 references from the 35 that were obtained and assessed for relevance were excluded. These are listed in excluded studies with reasons for their exclusion.

Clinical effectiveness

Very limited evidence was found on the use of co-enzyme Q10 for treating mitochondrial

disorders in children. Three case reports in a total of 6 children (Montini et al. 2008, Papadimitriou et al. 1996 and Rotig et al. 2000) were identified, no RCTs or higher quality observational data in children were found.

Montini et al. (2008) updated a previous case report by Salviati et al. (2005) of a brother and sister with co-enzyme Q10 deficiency caused by a homozygous missense mutation in the COQ2 gene. The boy developed corticosteroid-resistant nephrotic syndrome at 12 months of age, and progressive encephalomyopathy with stroke-like episodes developed at 18 months of age. Treatment with co-enzyme Q10 (30 mg per kg daily) was started when he was 22 months of age and his neurological signs and symptoms improved. Over the following 11 months, muscle tone and strength returned to normal, myoclonus disappeared, dysphagia improved and he gradually regained lost developmental milestones. However, at the age of 7 years he still had severe neurological symptoms including cognitive impairment, seizures and hemiplegia. His sister was diagnosed with co-enzyme Q10 deficiency at 12 months of age, before any symptoms developed. Immediately after diagnosis she developed nephrotic syndrome. It was reported that treatment with co-enzyme Q10 (30 mg per kg daily) was associated with a resolution of nephrotic syndrome. Treatment with diuretics and continuous haemofiltration were also given. After 50 months' treatment her renal function and neurological status were normal.

Rotig et al. (2000) reported on a brother and sister with multiple respiratory-chain dysfunction attributed to widespread deficiency of co-enzyme Q10. The boy developed nephrotic syndrome at age 3 years and he required renal transplantation at age 9 years. He also developed visual and hearing loss and cardiomyopathy. Progressive ataxia, dystonia and muscle atrophy meant that by age 12 years he could no longer walk unaided or ride his bike. His 1-year-older sister had a milder form of the disease: she also had myopia and hearing loss and nephrotic syndrome that necessitated renal transplantation at age 8 years. However, she did not require wheelchair or motor assistance. Co-enzyme Q10 at a dose of 90 mg daily was given to both siblings, although it is unclear at what age this was started. After 2 months' treatment the boy could stand, walk unaided and ride his bicycle. His bodyweight, muscle bulk, head control and precise movements also improved. His sister's skills and general condition greatly improved; she could pronounce an increasing number of words, became able to write her name, catch a ball and interact better with her environment.

Papadimitriou et al. (1996) reported their observations on 2 children (a 12 year old boy and a 10 year old girl) with Kearns-Sayre Syndrome and hypoparathyroidism who were already

being treated with alfacalcidol. Hypercalcaemia developed in both children after 2 months of concomitant treatment with co-enzyme Q10 (100mg daily). Discontinuation of both alfacalcidol and co-enzyme Q10 led to hypocalcaemia. Treatment with co-enzyme Q10 alone was reported to maintain serum calcium levels within the normal range. During treatment with co-enzyme Q10, both patients experienced a slight clinical improvement of tremor and other cerebellar symptoms, but not their muscle strength, ophthalmoplegia or cardiac abnormalities.

Three comparative studies on the use of co-enzyme Q10 for treating mitochondrial disorders in adults and young people (Bresolin et al. 1990, Chen et al. 1997 and Glover et al. 2010) were found, all of which have a number of serious limitations (see evidence strengths and limitations).

An overview of the study results for clinical effectiveness for Bresolin et al. (1990), Chen et al. (1997) and Glover et al. (2010) can be found in results tables.

Glover et al. (2010) reported a randomised double-blind placebo-controlled crossover study which compared co-enzyme Q10 at a dose of 600 mg twice daily with placebo (each taken for 60 days) in 30 adults with mitochondrial disorders. After 60 days treatment there was no statistically significant difference between co-enzyme Q10 and placebo for mitochondrial disease-specific activities of daily living, quality of life assessment scores or handgrip fatigue tests. See the results tables for more details. This study was included in a Cochrane review on treatment for mitochondrial disorders (Pfeffer et al. 2012).

Chen et al. (1997) reported a double-blind placebo-controlled crossover study which compared co-enzyme Q10 at a dose of 160 mg daily taken for 3 months with placebo taken for 1 month in 8 adults and young people (age range 17 to 68) with mitochondrial encephalomyopathy. There was no statistically significant difference between co-enzyme Q10 and placebo for sustained endurance strength (defined as the mean time taken in seconds to perform specified activities) or fatigability in activities of daily living assessment score. There was a statistically significant increase in the global Medical Research Council (MRC) muscle scale score with co-enzyme Q10 compared with placebo. However, the clinical significance of this increase (from approximately 83% to 87%) is unclear. When the proximal and distal limb muscle groups were assessed individually there was no statistical significant difference between co-enzyme Q10 and placebo for the MRC muscle scale scores for any of the muscle groups. See the results tables for more details.

In Bresolin et al. (1990), during the first phase of the study 59 adults and young people

with mitochondrial myopathies took co-enzyme Q10 at a dose of 2 mg per kg daily for 6 months. Results were presented for the 44 participants who completed this phase of the study. After 6 months treatment with co-enzyme Q10 there was a statistically significant increase in the global MRC muscle scale score (from approximately 89% to 91%) and a statistically significant decrease in post-exercise serum lactate levels. However, the clinical significance of these changes is unclear. Sixteen participants classed as responders to co-enzyme Q10 (defined as at least a 25% reduction in post-exercise serum lactate after 6 months treatment) were entered into the comparative phase of the study which compared co-enzyme Q10 with placebo for 3 months. There was no significant change in the global MRC muscle scale score in either the co-enzyme Q10 or placebo groups after entering this phase of the study. In the group that received a total of 9 months treatment with co-enzyme Q10, there was a statistically significant decrease in post-exercise serum lactate from baseline to 9 months. However, in the group that received 6 months treatment with co-enzyme Q10 followed by 3 months of placebo, the decrease in post-exercise serum lactate from baseline to 9 months was not statistically significant. See the results tables for more details.

Safety and tolerability

The BNF for children (BNFc) lists side effects of co-enzyme Q10 as nausea, diarrhoea, heartburn and rarely causing headache, irritability, agitation and dizziness. The BNFc recommends that the dose of co-enzyme Q10 should be reduced in people with moderate or severe renal impairment. Co-enzyme Q10 may reduce insulin requirement in people with diabetes and may enhance or reduce the anticoagulant effect of warfarin (BNFc).

Bresolin et al. (1990), Chen et al. (1997) and Glover et al. (2010) provided no information on the safety and tolerability of co-enzyme Q10. The 3 case reports in children (Montini et al. 2008, Papadimitriou et al. 1996 and Rotig et al. 2000) also provided no information on this.

The summary of product characteristics (SPC) for idebenone (Raxone), a synthetic analogue of co-enzyme Q10 which is licensed for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON) lists nasopharyngitis and cough as very common adverse reactions (1 in 10 or more) and diarrhoea and back pain as common adverse reactions (between 1 in 100 and 1 in 10). The SPC reports that clinical trial data in children with LHON is limited to children and young people aged 14 years and older and that no data is available on the use of this product in people with hepatic or renal impairment. It also reports that there is no available data from controlled clinical trials on treatment with idebenone for longer than 6 months. Evaluation

of data from people taking idebenone for treatment of Friedreich's ataxia and LHON led to the inclusion of blood count abnormalities and abnormal liver function and hepatitis as potential safety concerns for idebenone in the European Public Assessment Report (EPAR: Raxone).

Evidence strengths and limitations

The studies included in the evidence summary have many limitations that affect their application to clinical practice. In addition, mitochondrial disorders are a heterogeneous group of rare diseases and participants included in the studies many not represent all types of patients seen in clinical practice.

Very limited evidence was found on the use of co-enzyme Q10 for mitochondrial disorders in children. Three case reports in children were found and are discussed in this evidence summary (Montini et al. 2008, Papadimitriou et al. 1996 and Rotig et al. 2000). As uncontrolled observational studies in individual patients these case reports are prone to bias and other methodological problems. Whilst they did report some changes in functional ability, they provided very limited data on objective measurable outcomes.

Because of the very limited evidence found specific to the use of co-enzyme Q10 for mitochondrial disorders in children, the best available evidence in adults and young people was also included. This comprised 2 RCTs (Chen et al. 1997 and Glover et al. 2010) and a non-randomised study (Bresolin et al. 1990). Mitochondrial diseases are chronic conditions but all 3 were short-term studies that may have been of insufficient length to fully evaluate the efficacy of co-enzyme Q10. In addition, they recruited small numbers of participants and therefore may have been insufficiently powered to reliably detect any differences between placebo and co-enzyme Q10. All 3 studies included several outcomes measures, including objective measurements of muscle power. However none of the studies defined a primary outcome measure, and the clinical relevance of some of the outcomes reported is also unclear.

In Chen et al. (1997) there was a washout period of 1 month between treatments if the participant was randomised to co-enzyme Q10 first (but not if they received placebo first). This may have allowed a blinded assessor to know whether a participant was taking treatment or placebo depending on the duration of time in the study. Bresolin et al. (1990) was a 2-part study with an open label non-comparative phase and a comparative phase. The comparative phase of the study was stated to be 'blind' but insufficient information was provided to assess whether this was single or double blinding. This phase was at high

risk of bias because entry eligibility depended upon the results of the open-label phase and though comparative it was not randomised.

In Glover et al. (2010) participants had previously received nutritional supplements including co-enzyme Q10 for several years. In Chen et al. (1997) participants included in the study also had a disease duration of several years, however no information was provided in the paper about current medication (including nutritional supplements) that participants may have been taking prior to entering the study. For both studies, there was insufficient information provided in the paper to assess if the groups were similar at the start of the trial with respect to previous supplements taken.

None of the studies included in this evidence summary provided information on the safety and tolerability of co-enzyme Q10, making it difficult to establish the safety of co-enzyme Q10 for treating mitochondrial disorders from the available data. The studies used a wide variety of different doses of co-enzyme Q10.

An overview of the quality assessment for Bresolin et al. (1990), Chen et al. (1997) and Glover et al. (2010) can be found in the evidence tables.

Estimated impact for the NHS

Other treatment

There is currently no established treatment for mitochondrial disorders and clinical management is largely supportive. Interventions used to modify the disease process include dietary modification, pharmacological agents and a variety of nutritional supplements such as co-enzyme Q10, thiamine, vitamin C and vitamin E and exercise therapy (Pfeffer et al. 2012).

Costs of other treatment

Co-enzyme Q10 is available from 'special-order' manufacturers or specialist importing companies. Costs will vary depending on the brand or manufacturer.

Idebenone is a synthetic analogue of co-enzyme Q10. It is licensed for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic

Neuropathy (summary of product characteristics [SPC]: Raxone). Idebenone costs £6,364.00 for 180×150 mg tablets (MIMs, March 2017). This is £6,364.00 for 30 days' treatment at the SPC recommended dose of 300 mg three times a day.

Current or estimated usage

It is not possible to provide estimated usage based on the available data.

Likely place in therapy

There is currently no established treatment for mitochondrial disorders; clinical management, which may include dietary modification and nutritional supplements, is largely supportive.

There was very limited evidence found on the use of co-enzyme Q10 for mitochondrial disorders in children. The case reports included in this evidence summary have limited applicability to clinical practice.

Overall, the studies on the use of co-enzyme Q10 for mitochondrial disorders in adults and young people showed no advantage over placebo for the majority of outcomes assessed. However, these studies also had a number of limitations which restrict their applicability to clinical practice. The studies included in this evidence summary provide no information on the safety and tolerability of co-enzyme Q10 for the treatment of mitochondrial disorders.

Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

Information about licensing of medicines

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on NHS Choices.

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's good practice guidelines. These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

Questions that might be useful to ask about medicines

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?

- What are the risks of the treatment?
- Are the risks minor or serious? How likely are they to happen?
- What could happen if I don't have the treatment?

Relevance to other programmes

NICE guidance programmes

This use of co-enzyme Q10 is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

There is currently no NICE guidance on the management of mitochondrial disorders.

NHS England commissioning policies

NHS England has produced a service specification for the rare mitochondrial disorders service (all ages).

References

Bresolin N, Doriguzzi C, Ponzetto C et al. (1990) Ubidecarenone in the treatment of mitochondrial myopathies: A multi-center double-blind trial. Journal of the Neurological Sciences 100 (1–2): 70–78

Chen RS, Huang CC, Chu N S (1997) Coenzyme Q10 treatment in mitochondrial encephalomyopathies. Short-term double-blind, crossover study. European neurology 37 (4): 212–18

Glover EI, Martin J, Maher A et al. (2010) A randomized trial of coenzyme Q10 in mitochondrial disorders. Muscle and Nerve 42 (5): 739–48

Montini G, Malaventura C, Salviati L. (2008) Early coenzyme Q10 supplementation in primary coenzyme Q10 deficiency. New England Journal of Medicine 358 (26): 2849–50

Papadimitriou A, Hadjigeorgiou G M, Divari R et al. (1996) The influence of coenzyme Q10 on total serum calcium concentration in two patients with Kearns-Sayre Syndrome and hypoparathyroidism. Neuromuscular Disorders 6 (1): 49–53

Pfeffer G, Majamaa K, Turnbull D M et al. (2012) Treatment for mitochondrial disorders (review). Cochrane Database of Systematic Reviews Issue 4. No: CD004426

Rotig A, Appelkvist EL, Geromel V et al. (2000) Quinone-responsive multiple respiratory chain deficiency due to widespread coenzyme Q10 deficiency. Lancet 356 (9227): 391–95

Salviati L, Sacconi S, Murer L, et al. (2005) Infantile encephalomyopathy and nephropathy with CoQ10 deficiency: a CoQ10-responsive condition. Neurology 65 (4): 606–08

Evidence tables

Table 3 Bresolin et al. 1990

Study reference	Bresolin N, Doriguzzi C, Ponzetto C et al. (1990) Ubidecarenone in the treatment of mitochondrial myopathies: A multi-center double-blind trial. Journal of the Neurological Sciences 100 (1–2): 70–78
Unique identifier	Not provided
Study type	2 phase study. Phase 1 was an open-label non-comparative, before and after investigation, phase 2 was a blind comparative non-randomised investigation
Aim of the study	To evaluate the effects of treatment with co-enzyme Q10 in people with mitochondrial myopathies
Study dates	Not provided
Setting	5 centres in Italy
Number of participants	59 participants entered the open label phase and 44 completed it. The 16 participants who were selected as responders entered the comparative phase

Population	In the open label phase there were 59 participants (33 female and 26 male, age range 16 to 82 years) with mitochondrial myopathies. Of these 41 people had CPEO with proximal limb weakness, 9 people had clinical features of KSS, 6 people had mitochondrial myopathy without ophthalmoplegia and 3 people had MERRF syndrome. In the group of 16 participants who were selected for the comparative phase, 13 had CPEO with muscle weakness, 1 had MERRF syndrome, 1 had KSS and 1 had mitochondrial myopathy without CPEO	
Inclusion criteria	Inclusion criteria for the comparative phase was a response to co-enzyme Q10 defined as at least a 25% reduction in post-exercise serum lactate after 6 months' treatment	
Exclusion criteria	No exclusion criteria provided	
Intervention(s)	Co-enzyme Q10 at a dose of 2 mg per kg daily in both the open-label and comparative phases[a]	
Comparator(s)	Placebo in the comparative phase	
Length of follow-up	6 months in the open-label phase and 3 months in the comparative phase	
Outcomes	The primary outcome was not specified. The study assessed several functional and biochemical measures including: • Medical Research Council muscle scale scores[b] • Serum lactate levels after exercise[c]	
Source of funding	Details not provided	
Overall risk of bias/quality assessment of double-blind phase of study (CASP RCT checklist)	Did the trial address a clearly focused issue?	No
	Was the assignment of participants to treatments randomised?	No
	Were participants, health workers and study personnel blinded?	Unclear[d]
	Were the groups similar at the start of the trial?	Unclear[e]

	Aside from the experimental intervention, were the groups treated equally?	Unclear[f]
	Were all of the participants who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See tables 6 and 7
	How precise was the estimate of the treatment effect?	See tables 6 and 7
	Can the results be applied in your context? (or to the local population)	Unclear[f]
	Were all clinically important outcomes considered?	Unclear[f]
	Are the benefits worth the harms and costs?	See key points
Study limitations	• Entry to the comparative phase of the study was contingent on a pre-determined response to the study medicine in the open-label phase • The comparative phase was not randomised • Insufficient information is provided to assess whether the comparative phase was single or double-blinded or if the co-enzyme Q10 and placebo groups were similar at the start of study	

Comments	[a] Participants took co-enzyme Q10 for 6 months during the open-label phase of the study. Participants who entered the comparative phase then took either co-enzyme Q10 or placebo for 3 months. [b] Two neurologists completed the Medical Research Council muscle scale for different muscle groups. This was conducted at the beginning of the trial then every 2 months during the open-label phase and monthly during the comparative phase. [c] Serum lactate levels were measured at baseline and 5 and 60 minutes after standard exercise on a bicycle ergometer. This test was conducted at the beginning of the trial and then every 2 months during the open-label phase and monthly during the comparative phase. [d] Insufficient information provided in paper to assess whether this was single or double blinding. [e] The paper reports that the 2 groups in the comparative phase were balanced for clinical and biochemical parameters. However, insufficient information is provided in the paper to be able to assess this, for example there are no baseline characteristics tables. [f] Insufficient information provided in the paper to assess.
Abbreviations: CPEO, chronic progressive external ophthalmoplegia syndromes; KSS, Kearns-Sayre syndrome; MERRF, myoclonus epilepsy with ragged-red fibres; RCT, randomised controlled trial.	

Table 4 Chen et al. 1997

Study reference	Chen RS, Huang CC, Chu N S (1997) Coenzyme Q10 treatment in mitochondrial encephalomyopathies. Short-term double-blind, crossover study. European neurology 37 (4): 212–18
Unique identifier	Not provided
Study type	Double-blind placebo-controlled crossover study
Aim of the study	To evaluate the effectiveness of treatment with co-enzyme Q10 in people with mitochondrial encephalomyopathies
Study dates	Not provided

Setting	1 centre in Taiwan	
Number of participants	8 participants included in study, results presented for 7 participants (1 participant died from intracerebral haemorrhage)	
Population	Eight participants (5 female and 3 male, age range 17 to 68 years) with mitochondrial encephalomyopathy. Four participants had MERRF, 3 had MELAS and 1 had CPEO. Disease duration ranged from 2 to 33 years	
Inclusion criteria	No inclusion criteria provided	
Exclusion criteria	No exclusion criteria provided	
Intervention(s)	Co-enzyme Q10 at a dose of 160 mg daily for 3 months[a]	
Comparator(s)	Placebo for 1 month[a]	
Length of follow-up	3 months while taking co-enzyme Q10, 1 month while taking placebo	
Outcomes	The primary outcome was not specified. Study outcomes included the following which were assessed each month: • Patient assessment of fatigue[b] • Medical Research Council muscle scale scores[c] • Sustained endurance strength[d]	
Source of funding	Grant from the National Service Council	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	No
	Was the assignment of participants to treatments randomised?	Yes
	Were participants, health workers and study personnel blinded?	Unclear[e]
	Were the groups similar at the start of the trial?	Yes

	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the participants who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 8
	How precise was the estimate of the treatment effect?	See table 8
	Can the results be applied in your context? (or to the local population)	Unclear[f]
	Were all clinically important outcomes considered?	Unclear[f]
	Are the benefits worth the harms and costs?	See key points
Study limitations	• The study included only 8 participants therefore it may have been insufficiently powered to reliably detect any differences in effect between placebo and co-enzyme Q10 • Several outcomes were assessed and the primary endpoint was not defined • The study design may have allowed a blinded assessor to know whether a participant was on treatment or placebo. If participants were randomised to receive co-enzyme Q10 first and placebo second, there was a wash-out period of 1 month before the placebo phase started • Participants included in the study had a disease duration of several years. No information was provided in the paper on current medication including nutritional supplements that participants may have been taking prior to entering study • Treatment and follow-up period may have been too short to fully assess effectiveness of co-enzyme Q10	

Comments	[a] Participants took co-enzyme Q10 for 3 months and placebo for 1 month. If participants were randomised to receive co-enzyme Q10 first and placebo second, there was a wash-out period of 1 month before the placebo phase started. [b] Patient assessment of fatigability after continuous exercise, usual ADL and capacity of activity in the upper and lower limbs. All scored on a 6 point scale from Grade 1 normal or no fatigue in ADL to Grade 6 severe impairment of activities of daily living and use of walking assistance or in wheelchair. [c] Two neurologists completed the Medical Research Council muscle scale for different muscle groups at enrolment to study and monthly after treatment. The muscle scale grades muscle power on a scale of 0 to 5 in relation to the maximum expected for that muscle. [d] Time taken (in seconds) to complete the following movements: raising head from bed to a 30 to 45 degree angle in the supine position, lifting legs from bed to a 30 to 45 degree angle in the supine position, stretching out arms horizontally holding a 0.5 kg weight in each hand and preforming rapid thumb tapping on a special counter for 30 seconds. [e] The study was reported to be double-blind. Information is provided on how the treatment protocol was blinded to physicians. However, blinding may have been unmasked by use of a washout period after treatment in participants initially randomised to co-enzyme Q10 but not those participants initially randomised to placebo. [f] Insufficient information provided in paper to assess.
Abbreviations: ADL, activities of daily living; CPEO, chronic progressive external ophthalmoplegia syndromes; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes; MERRF, myoclonus epilepsy with ragged-red fibres; RCT, randomised controlled trial.	

Table 5 Glover et al. 2010

Study reference	Glover EI, Martin J, Maher A et al. (2010) A randomized trial of coenzyme Q10 in mitochondrial disorders. Muscle and Nerve 42 (5): 739–48

Unique identifier	Not provided
Study type	Randomised double-blind placebo-controlled crossover study
Aim of the study	To evaluate the effectiveness of treatment with co-enzyme Q10 in people with mitochondrial disease
Study dates	Not provided
Setting	1 centre in Canada
Number of participants	30 participants
Population	People with mitochondrial disease. Fifteen participants (9 female and 6 male) had MELAS, the remaining participants (11 female and 4 male) had other mitochondrial diseases. The mean age in the population with MELAS was 48 ±3 years and the mean age for the remaining participants was 56 ±3 years. Most participants had previously taken nutritional supplements including co-enzyme Q10 for several years. All supplements were stopped 6 weeks prior to starting the study. Participants were allowed to continue other medication
Inclusion criteria	Diagnosis of mitochondrial disease confirmed using a combination of clinical symptoms, fasting serum lactate concentration, muscle biopsy findings and mitochondrial DNA analysis
Exclusion criteria	No exclusion criteria provided
Intervention(s)	Co-enzyme Q10 at a dose of 600 mg twice daily[a]
Comparator(s)	Placebo[a]
Length of follow-up	60 days[b]

Outcomes	Primary outcome not specified. The study assessed a variety of functional and biochemical measures including: • Mitochondrial disease-specific activity of daily living and quality of life questionnaires[c] • Forearm isometric fatigue test[d]	
Source of funding	Donation from an individual and family	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	No
	Was the assignment of participants to treatments randomised?	Yes
	Were participants, health workers and study personnel blinded?	Unclear[e]
	Were the groups similar at the start of the trial?	Yes
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the participants who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 9
	How precise was the estimate of the treatment effect?	See table 9
	Can the results be applied in your context? (or to the local population)	Unclear[f]
	Were all clinically important outcomes considered?	Unclear[f]
	Are the benefits worth the harms and costs?	See key points

Study limitations	• Participants had previously received nutritional supplements including co-enzyme Q10 for several years • Several outcomes were assessed and the primary endpoint was not defined • No power calculation was presented in the paper • The outcomes assessed may not be applicable to clinical practice • Treatment and follow-up period of 60 days may be too short to fully assess effectiveness of co-enzyme Q10
Comments	[a] Participants took both co-enzyme Q10 and placebo for 60 days with a mean washout period of 67±8.3 days between each treatment. [b] Functional and biochemical measures were assessed after 60 days taking placebo and after 60 days taking co-enzyme Q10. Each testing day followed the same testing order. [c] Activities of daily living and quality of life questionnaires consisted of a series of questions that assessed capacity to perform tasks such as cooking and housework and perceived health and well-being measured on a visual-analogue scale from 0 to 100 mm. [d] Ninety second (9 second contraction and 1 second rest) isometric handgrip fatigue test. [e] The study was reported to be double-blind. Information is provided on how the co-enzyme Q10 capsules were blinded but insufficient information was provided in the paper to assess blinding of study personnel. [f] Insufficient information provided in paper to assess.
Abbreviations: HR, heart rate; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes; RCT, randomised controlled trial; RER; respiratory exchange rate; VE, minute ventilation; VO_2; oxygen uptake.	

Results tables

Table 6 Bresolin et al. 1990 (open label phase)

	Co-enzyme Q10 2 mg per kg daily	Analysis
N[a]	**44**	
Selected outcomes		
Global MRC muscle scale score (%)[b]	Results presented graphically. No absolute values reported	Statistically significant increase from baseline after 6 months treatment (from approximately 89% to 91%[c] p<0.01)
Mean serum lactate levels 5 minutes after exercise (mg %)	Results presented graphically. No absolute values reported	Statistically significant decrease from baseline after 6 months treatment (from approximately 68 to 52 mg %[c] p<0.0001)
[a] Fifty-nine participants entered study. However, 15 participants did not complete the study and results were only reported for the 44 remaining participants. [b] MRC muscle scale grades muscle power on a scale of 0 to 5 in relation to the maximum expected for that muscle. Study results were presented as a percentage. It is unclear from the information provided in the paper what these percentages represent and the clinical significance of any reported improvements. Five muscle groups were assessed and a global score was presented for all muscle groups. [c] Figures estimated from inspection of graph.		
Abbreviations: MRC, Medical Research Council.		

Table 7 Bresolin et al. 1990 (comparative phase)

	Co-enzyme Q10 2 mg per kg daily[a]	Placebo[a]	Analysis
N	**8**	**8**	
Selected outcomes			

Global MRC muscle scale score (%)[b]	Results presented graphically. No absolute values reported	No significant change in either group after entering comparative phase
Mean serum lactate levels 5 minutes after exercise (mg %)	Results presented graphically. No absolute values reported	All participants showed a statistically significant decrease from baseline after 6 months treatment with co-enzyme Q10. In the group treated with a further 3 months of co-enzyme Q10, the decrease from baseline to 9 months was statistically significant ($p<0.01$). In the group switched to placebo for 3 months, the decrease from baseline to 9 months was not statistically significant (p value not stated)
[a] Participants had all completed open-label phase so had all received 6 months of co-enzyme Q10. Co-enzyme Q10 group therefore had 9 months of co-enzyme Q10 and placebo group had 6 months of co-enzyme Q10 and 3 months of placebo. [b]MRC muscle scale grades muscle power on a scale of 0 to 5 in relation to the maximum expected for that muscle. Study results were presented as a percentage. It is unclear from the information provided in the paper what these percentages represent and the clinical significance of any reported improvements. Five muscle groups were assessed and a global score was presented for all muscle groups.		
Abbreviations: MRC, Medical Research Council.		

Table 8 Chen et al. 1997

	Co-enzyme Q10 160 mg daily	**Placebo**	**Analysis**
N	**8**	**8**	
Selected outcomes			

Fatigability in ADL[a]	Results presented graphically. No absolute values reported	No statistical significant difference between co-enzyme Q10 and placebo
Score on MRC muscle scale (%)[b]	Results presented graphically. No absolute values reported	After 3 months treatment with co-enzyme Q10 there was no statistically significant change in the score for the 4 individual muscle groups assessed. There was a statistically significant increase in the global score from all muscle groups combined (from approximately 83% to 87%)[b,c]
Sustained endurance strength (mean time taken in seconds to perform specified activities)	Results presented graphically. No absolute values reported	No statistical significant difference between co-enzyme Q10 and placebo
[a] Scored on a 6 point scale from 1 (minimal or no fatigue) to 6 (severe impairment of activities of daily living and use of walking assistance or in wheelchair). [b] MRC muscle scale grades muscle power on a scale of 0 to 5 in relation to the maximum expected for that muscle. Study results were presented as a percentage. It is unclear from the information provided in the paper what these percentages represent and the clinical significance of any reported improvements. Four muscle group were assessed: upper extremity distal and proximal muscles and lower extremity distal and proximal muscles. A global score was presented for all muscle groups. [c] Figures estimated from inspection of graph.		
Abbreviations: ADL, activities of daily living; MRC, Medical Research Council.		

Table 9 Glover et al. 2010

	Co-enzyme Q10 600 mg twice daily	Placebo	Analysis
N[a]	**30**	**30**	
Selected outcomes[b]			
Mean (SEM) mitochondrial disease specific ADL questionnaire score[c]	5.14 (0.19)	4.73 (0.19)	No statistical significant difference between co-enzyme Q10 and placebo (p=0.26)
Mean (SEM) mitochondrial disease specific QOL questionnaire score[c]	5.06 (0.16)	4.66 (0.27)	No statistical significant difference between co-enzyme Q10 and placebo (p=0.09)
Mean (SEM) maximal isometric forearm strength (Nm)[d]	23.8 (1.8)	24.6 (1.6)	No statistical significant difference between co-enzyme Q10 and placebo (p=0.27)
[a] Not all participants completed all outcomes. Complete data for the ADL and QOL questionnaires was available for 22 participants. [b] All outcomes assessed after 60 days taking co-enzyme Q10 and after 60 days taking placebo. [c] These consisted of a series of questions that assessed the participants' capacity to perform tasks such as cooking and housework and perceived health and well-being measured on a visual-analogue scale from 0 to 100 mm. [d] Ninety second (9 second contraction and 1 second rest) isometric handgrip fatigue test.			
Abbreviations: ADL, activities of daily living; HR, heart rate (beats per minute); Nm, maximal isometric grip strength in newton; QOL, quality of life; RER; respiratory exchange rate (VCO_2/VO_2); SEM, standard error of the mean; VE, minute ventilation (litre/minute); VO_2; oxygen uptake (ml/kg lean body mass).			

Excluded studies

Study reference	Reason for exclusion

Abe K, Fujimura H, Nishikawa Y et al. (1991) Marked reduction in CSF lactate and pyruvate levels after CoQ therapy in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). Acta Neurologica Scandinavica (6): 356–9	Study not prioritised (not the best available evidence: case report in an adult)
Abe K, Matsuo Y, Kadekawa J et al. (1999) Effect of coenzyme Q10 in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): evaluation by noninvasive tissue oximetry. Journal of the Neurological Sciences (1): 65–8	Study not prioritised (not the best available evidence: case reports in adults)
Apetauerova D, Scala S, Standaert D et al. (2015) Effects of coenzyme Q10 in PSP, A multicenter, randomized, placebo controlled, double-blind study. European journal of neurology (22): 292–	Poor relevance against search terms (not mitochondrial disorders)
Bendahan D, Desnuelle C, Vanuxem D et al. (1992) 31P NMR spectroscopy and ergometer exercise test as evidence for muscle oxidative performance improvement with coenzyme Q in mitochondrial myopathies. Neurology (6): 1203–8	Study not prioritised (not the best available evidence: case reports in adults)
Butler MG, Dasouki M, Bittel D et al. (2003) Coenzyme Q10 levels in Prader-Willi syndrome: comparison with obese and non-obese subjects. American journal of medical genetics. Part A 119A (2): 168–71	Poor relevance against search terms (not mitochondrial disorders)
Chan A, Reichmann H, Kogel A et al. (1998) Metabolic changes in patients with mitochondrial myopathies and effects of coenzyme Q10 therapy. Journal of neurology (10): 681–685	Study not prioritised (not the best available evidence: non-comparative study in 9 adults)
Costeff H, Apter N, Elpeleg ON et al. (1998) Ineffectiveness of oral coenzyme Q10 supplementation in 3-methylglutaconic aciduria, type 3. Brain and Development (1): 33–35	Poor relevance against search terms (not mitochondrial disorders)
Emmanuele V, Lopez LC, Lopez L et al. (2012) Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. Archives of neurology (8): 978–83	Not a relevant study (narrative review)

Gempel K, Topaloglu H, Talim B et al. (2007) The myopathic form of coenzyme Q10 deficiency is caused by mutations in the electron-transferring-flavoprotein dehydrogenase (ETFDH) gene. Brain: A journal of neurology 130 (Pt 8): 2037–44	Study not prioritised (not the best available evidence: case reports of 7 adults and children)
Gold R, Seibel P, Reinelt G et al. (1996) Phosphorus magnetic resonance spectroscopy in the evaluation of mitochondrial myopathies: results of a 6-month therapy study with coenzyme Q. European Neurology (4): 191–6	Study not prioritised (not the best available evidence: non-comparative study in 8 adults)
Ihara Y, Namba R, Kuroda S et al. (1989) Mitochondrial encephalomyopathy (MELAS): pathological study and successful therapy with coenzyme Q10 and idebenone. Journal of the Neurological Sciences (3): 263–71	Study not prioritised (not the best available evidence: case reports in adults and young people)
Li CW, Zhuang ZY, Zhang SK (2009) [Clinical study on treatment of Leber hereditary optic neuropathy]. Chinese journal of integrated traditional and Western (12): 1078–80	Non- English language study
Muller W, Reimers CD, Berninger T et al. (1990) Coenzyme Q10 in ophthalmoplegia plus - a double blind, cross over therapeutic trial. Journal of the Neurological Sciences 98 Supplement: 442	Abstract only
Neustadt J (2006) Mitochondrial dysfunction and disease. Integrative Medicine (3): 14–20	Unable to source study
Newman NJ (2011) Treatment of Leber hereditary optic neuropathy. Brain: A journal of neurology 134 (Pt 9): 2447–50	Not a relevant study (a narrative review)
Nishikawa K, Takahashi M, Yorifuji S et al. (1989) Long-term coenzyme Q10 therapy for a mitochondrial encephalomyopathy with cytochrome coxidase deficiency: a 31P NMR study. Neurology (3): 399–403	Study not prioritised (not the best available evidence: case report in an adult)

Ogasahara S, Engel AG, Frens D et al. (1989) Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy. Proceedings of the National Academy of Sciences of the United States of America (7): 2379–82	Poor relevance against search terms (study assessing co-enzyme Q10 levels in muscle not assessing treatment with co-enzyme Q10)
Ogasahara S, Nishikawa Y, Yorifuji S et al. (1986) Treatment of Kearns-Sayre syndrome with coenzyme Q10. Neurology (1): 45–53	Study not prioritised (not the best available evidence: non-comparative study in 5 adults)
Omata T, Fujii K, Takanashi J-I et al. (2016) Drugs indicated for mitochondrial dysfunction as treatments for acute encephalopathy with onset of febrile convulsive status epileptics. Journal of the Neurological Sciences (360): 57–60	Poor relevance against search terms (not mitochondrial disorders)
Panetta J, Smith LJ, Boneh A (2004) Effect of high-dose vitamins, coenzyme Q and high-fat diet in paediatric patients with mitochondrial diseases. Journal of Inherited Metabolic Disease (4): 487–98	Study not prioritised (not the best available evidence: study assessing combination of treatments)
Peterson PL (1995) The treatment of mitochondrial myopathies and encephalomyopathies. Biochimica et biophysica acta (1): 275–80	Study not prioritised (not the best available evidence: study assessing combination of treatments)
Pineda M, Montero R, Aracil A et al. (2010) Coenzyme Q (10)-responsive ataxia: 2-year-treatment follow-up. Movement disorders : Official journal of the Movement Disorder Society (9): 1262–68	Poor relevance against search terms (not mitochondrial disorders)
Rodriguez MC, MacDonald JR, Mahoney DJ et al. (2007) Beneficial effects of creatine, CoQ10, and lipoic acid in mitochondrial disorders. Muscle and Nerve (2): 235–42	Study not prioritised (not the best available evidence: study assessing combination treatment)

Sacconi S, Trevisson E, Salviati L et al. (2010) Coenzyme Q10 is frequently reduced in muscle of patients with mitochondrial myopathy. Neuromuscular disorders: NMD (1): 44–48	Poor relevance against search terms (study assessing co-enzyme Q10 levels in muscle not assessing treatment with co-enzyme Q10)
Scarlato G, Bresolin N, Moroni I et al. (1991) Multicenter trial with ubidecarenone: treatment of 44 patients with mitochondrial myopathies. Revue neurologique (6–7): 542–48	Duplicate study
Shults CW, Haas R (2005) Clinical trials of coenzyme Q10 in neurological disorders. BioFactors (1–4): 117–26	Not a relevant study (a narrative review)
Sobreira C, Hirano M, Shanske S et al. (1997) Mitochondrial encephalomyopathy with coenzyme Q10 deficiency. Neurology (5): 1238–43	Study not prioritised (not the best available evidence: case report in adult)
Sommerville RB, Zaidman CM, Pestronk A (2013) Coenzyme Q10 deficiency in children: frequent type 2C muscle fibers with normal morphology. Muscle & nerve (5): 722–726	Poor relevance against search terms (study assessing co-enzyme Q10 deficiency)
Suzuki S, Hinokio Y, Ohtomo M et al. (1998) The effects of coenzyme Q10 treatment on maternally inherited diabetes mellitus and deafness, and mitochondrial DNA 3243 (A to G) mutation. Diabetologia 5:584–8	Study not prioritised (not the best available evidence: non-comparative study in adults)

Terms used in this evidence summary

Chronic progressive external ophthalmoplegia syndromes (CPEO)

Chronic progressive external ophthalmoplegia is a condition characterised mainly by a loss of the muscle functions involved in eye and eyelid movement. Signs and symptoms tend to begin in early adulthood and most commonly include weakness or paralysis of the muscles that move the eye (ophthalmoplegia) and drooping of the eyelids (ptosis). Some people also have general weakness of the skeletal muscles (myopathy), which may be especially noticeable during exercise. Muscle weakness may also cause difficulty swallowing (dysphagia).

Kearns-Sayre syndrome (KSS)

Kearns-Sayre syndrome is a condition that affects many parts of the body, especially the eyes. The features of Kearns-Sayre syndrome usually appear before the age of 20, and the condition is diagnosed by a few characteristic signs and symptoms. People with Kearns-Sayre syndrome have progressive external ophthalmoplegia and pigmented retinopathy. In addition, there is at least one of the following signs or symptoms: cardiac conduction defects, ataxia, or abnormally high levels of protein in the cerebrospinal fluid. People with Kearns-Sayre syndrome may also have muscle weakness, deafness, kidney problems or cognitive function decline.

Medical Research Council muscle scale

The Medical Research Council muscle scale grades muscle power on a scale of 0 to 5 in relation to the maximum expected for that muscle. The studies in the evidence summary presented results for this outcome as a percentage. It is unclear from the information provided in the papers what the percentages represent.

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)

MELAS is one well known clinical manifestation of mitochondrial disease. People with MELAS usually have the following clinical features: stroke-like episodes, encephalopathy with seizures or dementia, mitochondrial myopathy and recurrent headache.

Myoclonic epilepsy with ragged-red fibres (MERRF)

The clinical features that people with MERRF syndrome develop are mainly characterised by generalised seizures, myoclonus, ataxia and muscle weakness.

Search strategy

Database: Medline Version: Ovid MEDLINE(R) <1946 to September Week 4 2016> Search date: 12/10/16

1 exp Mitochondrial Diseases/ (13217)

2 (mitochondrial and (disease* or disorder* or myopath* or encephalomyopath* or encephalopath*)).ti,ab. (34162)

3 ("chronic progressive external opthalmoplegia" or CPEO or (opthalmoplegia adj5 progressive)).ti,ab. (279)

4 "cytochrome-c oxidase deficien*".ti,ab. (390)

5 "infantile myopathy".ti,ab. (19)

6 Acidosis, Lactic/ (2890)

7 lactic acidosis.ti,ab. (5130)

8 Optic Atrophy, Hereditary, Leber/ or (optic nerve/ and (atrophy/ or optic atrophy/)) (1545)

9 "retinitis pigmentosa".ti,ab. (6032)

10 retinitis pigmentosa/ (6652)

11 ataxia.ti,ab. (26804)

12 ataxia/ (7189)

13 ("leber hereditary optic neuropathy" or LHON or (leber adj5 neuropath*)).ti,ab. (922)

14 MERRF syndrome/ (325)

15 Kearns-Sayre syndrome/ (615)

16 Leigh disease/ (901)

17 (((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 syndrome*) or ((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 disease*)).ti,ab. (2157)

18 (MIDD or MNGIE or MERRF or NARP or KSS).ti,ab. (1812)

19 (maternal* adj5 diabetes adj5 deafness).ti,ab. (177)

20 ((pyruvate adj5 carboxylase adj5 deficiency adj5 disease) or "pyruvate dehydrogenase complex deficiency disease*").ti,ab. (4)

21 or/1-20 (82470)

22 Ubiquinone/ (8104)

23 ("coenzyme Q10" or "coenzyme Q" or "co enzyme Q10" or CoQ or CoQ10 or ubiquinone or ubidecarenone).ti,ab. (9869)

24 or/22-23 (11944)

25 21 and 24 (1331)

26 (infant* or newborn or "new-born*" or perinat or neonat or baby or babies or toddler* or minor or minors or boy or boys or boyhood or girl* or kid or kids or child or children or schoolchild* or "school age" or schoolage* or adolescen* or juvenil* or youth* or "young person*" or "young people" or youngster* or teen* or "under*age" or pubescen* or pediatric* or paediatric* or peadiatric* or preterm*).ti,ab,jw. (1985217)

27 Pediatrics/ (47831)

28 exp Child/ (1713193)

29 exp Infant/ (1034267)

30 Adolescent/ (1782191)

31 or/26-30 (3679621)

32 25 and 31 (361)

33 limit 32 to english language (326)

34 animals/ not humans/ (4292287)

35 33 not 34 (321)

36 letter/ or historical article/ or comment/ or editorial/ (1766982)

37 35 not 36 (312)

Medline Version: Ovid MEDLINE(R) <1946 to September Week 4 2016> Search date: 12/10/16

1 exp Mitochondrial Diseases/ (13217)

2 (mitochondrial and (disease* or disorder* or myopath* or encephalomyopath* or encephalopath*)).ti,ab. (34162)

3 ("chronic progressive external opthalmoplegia" or CPEO or (opthalmoplegia adj5 progressive)).ti,ab. (279)

4 "cytochrome-c oxidase deficien*".ti,ab. (390)

5 "infantile myopathy".ti,ab. (19)

6 Acidosis, Lactic/ (2890)

7 lactic acidosis.ti,ab. (5130)

8 Optic Atrophy, Hereditary, Leber/ or (optic nerve/ and (atrophy/ or optic atrophy/)) (1545)

9 "retinitis pigmentosa".ti,ab. (6032)

10 retinitis pigmentosa/ (6652)

11 ataxia.ti,ab. (26804)

12 ataxia/ (7189)

13 ("leber hereditary optic neuropathy" or LHON or (leber adj5 neuropath*)).ti,ab. (922)

14 MERRF syndrome/ (325)

15 Kearns-Sayre syndrome/ (615)

16 Leigh disease/ (901)

17 (((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 syndrome*) or

((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 disease*)).ti,ab. (2157)

18 (MIDD or MNGIE or MERRF or NARP or KSS).ti,ab. (1812)

19 (maternal* adj5 diabetes adj5 deafness).ti,ab. (177)

20 ((pyruvate adj5 carboxylase adj5 deficiency adj5 disease) or "pyruvate dehydrogenase complex deficiency disease*").ti,ab. (4)

21 or/1-20 (82470)

22 Ubiquinone/ (8104)

23 ("coenzyme Q10" or "coenzyme Q" or "co enzyme Q10" or CoQ or CoQ10 or ubiquinone or ubidecarenone).ti,ab. (9869)

24 or/22-23 (11944)

25 21 and 24 (1331)

26 (infant* or newborn or "new-born*" or perinat or neonat or baby or babies or toddler* or minor or minors or boy or boys or boyhood or girl* or kid or kids or child or children or schoolchild* or "school age" or schoolage* or adolescen* or juvenil* or youth* or "young person*" or "young people" or youngster* or teen* or "under*age" or pubescen* or pediatric* or paediatric* or peadiatric* or preterm*).ti,ab,jw. (1985217)

27 Pediatrics/ (47831)

28 exp Child/ (1713193)

29 exp Infant/ (1034267)

30 Adolescent/ (1782191)

31 or/26-30 (3679621)

32 25 and 31 (361)

33 limit 32 to english language (326)

34 animals/ not humans/ (4292287)

35 33 not 34 (321)

36 letter/ or historical article/ or comment/ or editorial/ (1766982)

37 35 not 36 (312)

Embase <1974 to 2016 Week 41> Search date: 4/10/16

1 exp "disorders of mitochondrial functions"/ (32159)

2 (mitochondrial and (disease* or disorder* or myopath* or encephalomyopath* or encephalopath*)).ti,ab. (50908)

3 enchephalomyopathy/ (0)

4 ("chronic progressive external opthalmoplegia" or CPEO or (opthalmoplegia adj5 progressive)).ti,ab. (373)

5 external opthalmoplegia/ (0)

6 "cytochrome-c oxidase deficien*".ti,ab. (457)

7 "infantile myopathy".ti,ab. (20)

8 lactic acidosis/ (11066)

9 lactic acidosis.ti,ab. (7311)

10 Leber hereditary optic neuropathy/ or optic nerve atrophy/ (8154)

11 ("leber hereditary optic neuropathy" or LHON or (leber adj5 neuropath*)).ti,ab. (1225)

12 retinitis pigmentosa.ti,ab. (7265)

13 retinisis pigmentosa/ (0)

14 ataxia.ti,ab. (37143)

15 ataxia/ (25219)

16 MERRF syndrome/ (592)

17 Kearns Sayre syndrome/ (1231)

18 Leigh disease/ (2082)

19 NARP syndrome/ (188)

20 (((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 syndrome*) or ((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 disease*)).ti,ab. (3087)

21 (MIDD or MNGIE or MERRF or NARP or KSS).ti,ab. (2713)

22 (maternal* adj5 diabetes adj5 deafness).ti,ab. (217)

23 ((pyruvate adj5 carboxylase adj5 deficiency adj5 disease) or "pyruvate dehydrogenase complex deficiency disease*").ti,ab. (6)

24 or/1-23 (140126)

25 ubidecarenone/ or ubiquinone/ (13870)

26 ("coenzyme Q10" or "coenzyme Q" or "co enzyme Q10" or CoQ orCoQ10 or ubiquinone or ubidecarenone).ti,ab. (11361)

27 or/25-26 (16990)

28 24 and 27 (2911)

29 (infant* or newborn or "new-born*" or perinat or neonat or baby or babies or toddler* or minor or minors or boy or boys or boyhood or girl* or kid or kids or child or children or schoolchild* or "school age" or schoolage* or adolescen* or juvenil* or youth* or "young

person*" or "young people" or youngster* or teen* or "under*age" or pubescen* or pediatric* or paediatric* or peadiatric* or preterm*).ti,ab,jw. (2595442)

30 pediatrics/ (81865)

31 child/ (1611104)

32 infant/ (594689)

33 adolescent/ (1390268)

34 or/29-33 (3704989)

35 28 and 34 (680)

36 limit 35 to english language (642)

37 nonhuman/ not human/ (3671252)

38 36 not 37 (634)

39 limit 38 to (editorial or letter) (10)

40 38 not 39 (624)

Cochrane/CRD databases Version: CDSR – october 16

CENTRAL – September 16

#1 [mh "mitochondrial diseases"] 100

#2 (mitochondrial and (disease* or disorder* or myopath* or encephalomyopath* or encephalopath*)):ti,ab 295

#3 ("chronic progressive external opthalmoplegia" or CPEO or (opthalmoplegia adj5 progressive)):ti,ab 4

#4 "cytochrome-c oxidase deficien*":ti,ab 0

#5 "infantile myopathy":ti,ab 0

#6 [mh "acidosis, lactic"] 66

#7 lactic acidosis:ti,ab 240

#8 [mh "optic atrophy, hereditary, leber"] or [mh "optic atrophy"] 33

#9 "retinitis pigmentosa":ti,ab 121

#10 [mh "retinitis pigmentosa"] 67

#11 ataxia:ti,ab 415

#12 [mh ataxia] 157

#13 ("leber hereditary optic neuropathy" or LHON or (leber adj5 neuropath*)):ti,ab 15

#14 [mh "MERRF syndrome"] 0

#15 [mh "kearns-sayre syndrome"] 0

#16 [mh "leigh disease"] 0

#17 (((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 syndrome*) or ((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 disease*)):ti,ab 0

#18 (MIDD or MNGIE or MERRF or NARP or KSS):ti,ab 147

#19 (maternal* adj5 diabetes adj5 deafness):ti,ab 0

#20 ((pyruvate adj5 carboxylase adj5 deficiency adj5 disease) or "pyruvate dehydrogenase complex deficiency disease*"):ti,ab 0

#21 {or #1-#20} 1342

#22 [mh ubiquinone] 348

#23 ("coenzyme Q10" or "coenzyme Q" or "co enzyme Q10" or CoQ or CoQ10 or ubiquinone or ubidecarenone):ti,ab 581

#24 {or #22-#23} 640

#25 #21 and #24 76

#26 (infant* or newborn or "new-born*" or perinat or neonat or baby or babies or toddler* or minor or minors or boy or boys or boyhood or girl* or kid or kids or child or children or schoolchild* or "school age" or schoolage* or adolescen* or juvenil* or youth* or "young person*" or "young people" or youngster* or teen* or "under*age" or pubescen* or pediatric* or paediatric* or peadiatric* or preterm*):ti,ab 112733

#27 [mh paediatrics] 0

#28 [mh child] 200

#29 [mh infant] 14594

#30 [mh adolescent] 86804

#31 {or #26-#30} 182210

#32 #25 and #31 27

Updated searches

Searches run on 1/12/16. This looked for coenzyme and mitochondrial terms without the children limit, but with the original searches added on afterwards to exclude anything already sifted. In Medline and Embase these searches were limited just to RCTs since 2011. In both databases this includes an 'entry date' limit rather than just a year limit, this allows for anything added to the database since the specified date.

Medline Version: Ovid MEDLINE(R) 1946 to November Week 4 2016 Search date: 01/12/16

1 exp Mitochondrial Diseases/ (14816)

2 (mitochondrial and (disease* or disorder* or myopath* or encephalomyopath* or

encephalopath*)).ti,ab. (40138)

3 ("chronic progressive external opthalmoplegia" or CPEO or (opthalmoplegia adj5 progressive)).ti,ab. (312)

4 "cytochrome-c oxidase deficien*".ti,ab. (454)

5 "infantile myopathy".ti,ab. (20)

6 Acidosis, Lactic/ (3037)

7 lactic acidosis.ti,ab. (5404)

8 Optic Atrophy, Hereditary, Leber/ or (optic nerve/ and (atrophy/ or optic atrophy/)) (1710)

9 "retinitis pigmentosa".ti,ab. (6899)

10 retinitis pigmentosa/ (7367)

11 ataxia.ti,ab. (29767)

12 ataxia/ (7673)

13 ("leber hereditary optic neuropathy" or LHON or (leber adj5 neuropath*)).ti,ab. (1074)

14 MERRF syndrome/ (350)

15 Kearns-Sayre syndrome/ (647)

16 Leigh disease/ (976)

17 (((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 syndrome*) or ((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 disease*)).ti,ab. (2318)

18 (MIDD or MNGIE or MERRF or NARP or KSS).ti,ab. (1973)

19 (maternal* adj5 diabetes adj5 deafness).ti,ab. (188)

20 ((pyruvate adj5 carboxylase adj5 deficiency adj5 disease) or "pyruvate dehydrogenase complex deficiency disease*").ti,ab. (4)

21 or/1-20 (93103)

22 Ubiquinone/ (8664)

23 ("coenzyme Q10" or "coenzyme Q" or "co enzyme Q10" or CoQ or CoQ10 or ubiquinone or ubidecarenone).ti,ab. (10649)

24 or/22-23 (12891)

25 21 and 24 (1521)

26 exp Mitochondrial Diseases/ (14816)

27 (mitochondrial and (disease* or disorder* or myopath* or encephalomyopath* or encephalopath*)).ti,ab. (40138)

28 ("chronic progressive external opthalmoplegia" or CPEO or (opthalmoplegia adj5 progressive)).ti,ab. (312)

29 "cytochrome-c oxidase deficien*".ti,ab. (454)

30 "infantile myopathy".ti,ab. (20)

31 Acidosis, Lactic/ (3037)

32 lactic acidosis.ti,ab. (5404)

33 Optic Atrophy, Hereditary, Leber/ or (optic nerve/ and (atrophy/ or optic atrophy/)) (1710)

34 "retinitis pigmentosa".ti,ab. (6899)

35 retinitis pigmentosa/ (7367)

36 ataxia.ti,ab. (29767)

37 ataxia/ (7673)

38 ("leber hereditary optic neuropathy" or LHON or (leber adj5 neuropath*)).ti,ab. (1074)

39 MERRF syndrome/ (350)

40 Kearns-Sayre syndrome/ (647)

41 Leigh disease/ (976)

42 (((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 syndrome*) or ((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 disease*)).ti,ab. (2318)

43 (MIDD or MNGIE or MERRF or NARP or KSS).ti,ab. (1973)

44 (maternal* adj5 diabetes adj5 deafness).ti,ab. (188)

45 ((pyruvate adj5 carboxylase adj5 deficiency adj5 disease) or "pyruvate dehydrogenase complex deficiency disease*").ti,ab. (4)

46 or/26-45 (93103)

47 Ubiquinone/ (8664)

48 ("coenzyme Q10" or "coenzyme Q" or "co enzyme Q10" or CoQ or CoQ10 or ubiquinone or ubidecarenone).ti,ab. (10649)

49 or/47-48 (12891)

50 46 and 49 (1521)

51 (infant* or newborn or "new-born*" or perinat or neonat or baby or babies or toddler* or minor or minors or boy or boys or boyhood or girl* or kid or kids or child or children or schoolchild* or "school age" or schoolage* or adolescen* or juvenil* or youth* or "young person*" or "young people" or youngster* or teen* or "under*age" or pubescen* or pediatric* or paediatric* or peadiatric* or preterm*).ti,ab,jw. (2118308)

52 Pediatrics/ (52714)

53 exp Child/ (1803789)

54 exp Infant/ (1084154)

55 Adolescent/ (1893732)

56 or/51-55 (3900787)

57 50 and 56 (419)

58 limit 57 to english language (381)

59 animals/ not humans/ (4636427)

60 58 not 59 (375)

61 letter/ or historical article/ or comment/ or editorial/ (1994865)

62 60 not 61 (362)

63 randomized controlled trial.pt. (469510)

64 randomized controlled trial/ (469510)

65 controlled clinical trial.pt. (95053)

66 random allocation/ (95156)

67 Placebos/ (35356)

68 clinical trial, phase ii/ or clinical trial, phase iii/ (43306)

69 63 or 64 or 65 or 66 or 67 or 68 (667071)

70 Observational Study as Topic/ (1999)

71 Observational Study/ (30201)

72 Epidemiologic Studies/ (7951)

73 exp Case-Control Studies/ (876991)

74 exp Cohort Studies/ (1714267)

75 Cross-Sectional Studies/ (255001)

76 Comparative Study.pt. (1882146)

77 case control*.tw. (101250)

78 case series.tw. (44269)

79 (cohort adj (study or studies)).tw. (124992)

80 cohort analy*.tw. (5123)

81 (follow up adj (study or studies)).tw. (42365)

82 (observational adj (study or studies)).tw. (61166)

83 longitudinal.tw. (179019)

84 prospective.tw. (424945)

85 retrospective.tw. (336596)

86 cross sectional.tw. (220130)

87 or/70-86 (3970287)

88 62 and 87 (56)

89 62 and 69 (26)

90 88 or 89 (73)

91 25 not 90 (1448)

92 Randomized Controlled Trial.pt. (469510)

93 Controlled Clinical Trial.pt. (95053)

94 Clinical Trial.pt. (527441)

95 exp Clinical Trials as Topic/ (323082)

96 Placebos/ (35356)

97 Random Allocation/ (95156)

98 Double-Blind Method/ (147714)

99 Single-Blind Method/ (24543)

100 Cross-Over Studies/ (42595)

101 ((random* or control* or clinical*) adj3 (trial* or stud*)).tw. (938615)

102 (random* adj3 allocat*).tw. (25283)

103 placebo*.tw. (182790)

104 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (144623)

105 (crossover* or (cross adj over*)).tw. (67837)

106 or/92-105 (1681657)

107 animals/ not humans/ (4636427)

108 106 not 107 (1565539)

109 91 and 108 (198)

110 limit 109 to ed=20110711-20161120 (71)

Embase 1974 to 2016 Week 48 Search date 01/12/16

1 exp "disorders of mitochondrial functions"/ (32770)

2 (mitochondrial and (disease* or disorder* or myopath* or encephalomyopath* or encephalopath*)).ti,ab. (51789)

3 enchephalomyopathy/ (0)

4 ("chronic progressive external opthalmoplegia" or CPEO or (opthalmoplegia adj5 progressive)).ti,ab. (375)

5 external opthalmoplegia/ (0)

6 "cytochrome-c oxidase deficien*".ti,ab. (462)

7 "infantile myopathy".ti,ab. (20)

8 lactic acidosis/ (11181)

9 lactic acidosis.ti,ab. (7379)

10 Leber hereditary optic neuropathy/ or optic nerve atrophy/ (8241)

11 ("leber hereditary optic neuropathy" or LHON or (leber adj5 neuropath*)).ti,ab. (1242)

12 retinitis pigmentosa.ti,ab. (7325)

13 retinisis pigmentosa/ (0)

14 ataxia.ti,ab. (37565)

15 ataxia/ (25521)

16 MERRF syndrome/ (599)

17 Kearns Sayre syndrome/ (1239)

18 Leigh disease/ (2105)

19 NARP syndrome/ (188)

20 (((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 syndrome*) or ((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 disease*)).ti,ab. (3126)

21 (MIDD or MNGIE or MERRF or NARP or KSS).ti,ab. (2755)

22 (maternal* adj5 diabetes adj5 deafness).ti,ab. (218)

23 ((pyruvate adj5 carboxylase adj5 deficiency adj5 disease) or "pyruvate dehydrogenase complex deficiency disease*").ti,ab. (6)

24 or/1-23 (142101)

25 ubidecarenone/ or ubiquinone/ (14037)

26 ("coenzyme Q10" or "coenzyme Q" or "co enzyme Q10" or CoQ orCoQ10 or ubiquinone or ubidecarenone).ti,ab. (11489)

27 or/25-26 (17169)

28 24 and 27 (2952)

29 exp "disorders of mitochondrial functions"/ (32770)

30 (mitochondrial and (disease* or disorder* or myopath* or encephalomyopath* or encephalopath*)).ti,ab. (51789)

31 enchephalomyopathy/ (0)

32 ("chronic progressive external opthalmoplegia" or CPEO or (opthalmoplegia adj5 progressive)).ti,ab. (375)

33 external opthalmoplegia/ (0)

34 "cytochrome-c oxidase deficien*".ti,ab. (462)

35 "infantile myopathy".ti,ab. (20)

36 lactic acidosis/ (11181)

37 lactic acidosis.ti,ab. (7379)

38 Leber hereditary optic neuropathy/ or optic nerve atrophy/ (8241)

39 ("leber hereditary optic neuropathy" or LHON or (leber adj5 neuropath*)).ti,ab. (1242)

40 retinitis pigmentosa.ti,ab. (7325)

41 retinisis pigmentosa/ (0)

42 ataxia.ti,ab. (37565)

43 ataxia/ (25521)

44 MERRF syndrome/ (599)

45 Kearns Sayre syndrome/ (1239)

46 Leigh disease/ (2105)

47 NARP syndrome/ (188)

48 (((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 syndrome*) or ((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 disease*)).ti,ab. (3126)

49 (MIDD or MNGIE or MERRF or NARP or KSS).ti,ab. (2755)

50 (maternal* adj5 diabetes adj5 deafness).ti,ab. (218)

51 ((pyruvate adj5 carboxylase adj5 deficiency adj5 disease) or "pyruvate dehydrogenase complex deficiency disease*").ti,ab. (6)

52 or/29-51 (142101)

53 ubidecarenone/ or ubiquinone/ (14037)

54 ("coenzyme Q10" or "coenzyme Q" or "co enzyme Q10" or CoQ orCoQ10 or ubiquinone or ubidecarenone).ti,ab. (11489)

55 or/53-54 (17169)

56 52 and 55 (2952)

57 (infant* or newborn or "new-born*" or perinat or neonat or baby or babies or toddler* or minor or minors or boy or boys or boyhood or girl* or kid or kids or child or children or schoolchild* or "school age" or schoolage* or adolescen* or juvenil* or youth* or "young person*" or "young people" or youngster* or teen* or "under*age" or pubescen* or pediatric* or paediatric* or peadiatric* or preterm*).ti,ab,jw. (2625864)

58 child/ (1632862)

59 infant/ (600884)

60 adolescent/ (1403108)

61 pediatrics/ (82903)

62 or/57-61 (3742342)

63 56 and 62 (692)

64 limit 63 to english language (654)

65 nonhuman/ not human/ (3701938)

66 64 not 65 (646)

67 limit 66 to (editorial or letter) (10)

68 66 not 67 (636)

69 exp Clinical Trials/ (266512)

70 Randomization/ (83503)

71 Placebo/ (327021)

72 Double Blind Procedure/ (138148)

73 Single Blind Procedure/ (27452)

74 Crossover Procedure/ (53925)

75 ((random* or control* or clinical*) adj3 (trial* or stud*)).tw. (1297010)

76 (random* adj3 allocat*).tw. (33873)

77 placebo*.tw. (249179)

78 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (196414)

79 (crossover* or (cross adj over*)).tw. (85870)

80 or/69-79 (1745911)

81 nonhuman/ not human/ (3701938)

82 80 not 81 (1687757)

83 Clinical study/ (255141)

84 Case control study/ (122832)

85 Family study/ (28253)

86 Longitudinal study/ (105793)

87 Retrospective study/ (515538)

88 comparative study/ (741516)

89 Prospective study/ (387235)

90 Randomized controlled trials/ (125077)

91 89 not 90 (382491)

92 Cohort analysis/ (301895)

93 cohort analy*.tw. (7801)

94 (Cohort adj (study or studies)).tw. (179438)

95 (Case control* adj (study or studies)).tw. (103148)

96 (follow up adj (study or studies)).tw. (53636)

97 (observational adj (study or studies)).tw. (101335)

98 (epidemiologic* adj (study or studies)).tw. (89042)

99 (cross sectional adj (study or studies)).tw. (131599)

100 case series.tw. (67177)

101 prospective.tw. (627888)

102 retrospective.tw. (574088)

103 or/83-88,91-102 (2973667)

104 68 and 82 (77)

105 68 and 103 (71)

106 104 or 105 (131)

107 28 not 106 (2821)

108 exp Clinical Trials/ (266512)

109 Randomization/ (83503)

110 Placebo/ (327021)

111 Double Blind Procedure/ (138148)

112 Single Blind Procedure/ (27452)

113 Crossover Procedure/ (53925)

114 ((random* or control* or clinical*) adj3 (trial* or stud*)).tw. (1297010)

115 (random* adj3 allocat*).tw. (33873)

116 placebo*.tw. (249179)

117 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (196414)

118 (crossover* or (cross adj over*)).tw. (85870)

119 or/108-118 (1745911)

120 nonhuman/ not human/ (3701938)

121 119 not 120 (1687757)

122 107 and 121 (403)

123 (2011* or 2012* or 2013* or 2014* or 2015* or 2016*).dd. (22194878)

124 122 and 123 (223)

125 limit 124 to english language (215)

Cochrane /CRD databasesVersion: Wiley Search date: 01/12/16

#1 [mh "mitochondrial diseases"] 100

#2 (mitochondrial and (disease* or disorder* or myopath* or encephalomyopath* or encephalopath*)):ti,ab 304

#3 ("chronic progressive external opthalmoplegia" or CPEO or (opthalmoplegia adj5 progressive)):ti,ab 4

#4 "cytochrome-c oxidase deficien*":ti,ab 0

#5 "infantile myopathy":ti,ab 0

#6 [mh "acidosis, lactic"] 66

#7 lactic acidosis:ti,ab 248

#8 [mh "optic atrophy, hereditary, leber"] or [mh "optic atrophy"] 33

#9 "retinitis pigmentosa":ti,ab 125

#10 [mh "retinitis pigmentosa"] 69

#11 ataxia:ti,ab 441

#12 [mh ataxia] 157

#13 ("leber hereditary optic neuropathy" or LHON or (leber adj5 neuropath*)):ti,ab 15

#14 [mh "MERRF syndrome"] 0

#15 [mh "kearns-sayre syndrome"] 0

#16 [mh "leigh disease"] 0

#17 (((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 syndrome*) or ((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 disease*)):ti,ab 0

#18 (MIDD or MNGIE or MERRF or NARP or KSS):ti,ab 155

#19 (maternal* adj5 diabetes adj5 deafness):ti,ab 0

#20 ((pyruvate adj5 carboxylase adj5 deficiency adj5 disease) or "pyruvate dehydrogenase complex deficiency disease*"):ti,ab 0

#21 {or #1-#20} 1397

#22 [mh ubiquinone] 350

#23 ("coenzyme Q10" or "coenzyme Q" or "co enzyme Q10" or CoQ or CoQ10 or ubiquinone or ubidecarenone):ti,ab 596

#24 {or #22-#23} 655

#25 #21 and #24 78

#26 [mh "mitochondrial diseases"] 100

#27 (mitochondrial and (disease* or disorder* or myopath* or encephalomyopath* or encephalopath*)):ti,ab 304

#28 ("chronic progressive external opthalmoplegia" or CPEO or (opthalmoplegia adj5 progressive)):ti,ab 4

#29 "cytochrome-c oxidase deficien*":ti,ab 0

#30 "infantile myopathy":ti,ab 0

#31 [mh "acidosis, lactic"] 66

#32 lactic acidosis:ti,ab 248

#33 [mh "optic atrophy, hereditary, leber"] or [mh "optic atrophy"] 33

#34 "retinitis pigmentosa":ti,ab 125

#35 [mh "retinitis pigmentosa"] 69

#36 ataxia:ti,ab 441

#37 [mh ataxia] 157

#38 ("leber hereditary optic neuropathy" or LHON or (leber adj5 neuropath*)):ti,ab 15

#39 [mh "MERRF syndrome"] 0

#40 [mh "kearns-sayre syndrome"] 0

#41 [mh "leigh disease"] 0

#42 (((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 syndrome*) or ((Kearns or Leigh or Pearson or MELAS or MERRF or NARP) adj5 disease*)):ti,ab 0

#43 (MIDD or MNGIE or MERRF or NARP or KSS):ti,ab 155

#44 (maternal* adj5 diabetes adj5 deafness):ti,ab 0

#45 ((pyruvate adj5 carboxylase adj5 deficiency adj5 disease) or "pyruvate dehydrogenase complex deficiency disease*"):ti,ab 0

#46 {or #26-#45} 1397

#47 [mh ubiquinone] 350

#48 ("coenzyme Q10" or "coenzyme Q" or "co enzyme Q10" or CoQ or CoQ10 or ubiquinone or ubidecarenone):ti,ab 596

#49 {or #47-#48} 655

#50 #46 and #49 78

#51 (infant* or newborn or "new-born*" or perinat or neonat or baby or babies or toddler* or minor or minors or boy or boys or boyhood or girl* or kid or kids or child or children or schoolchild* or "school age" or schoolage* or adolescen* or juvenil* or youth* or "young

person*" or "young people" or youngster* or teen* or "under*age" or pubescen* or pediatric* or paediatric* or peadiatric* or preterm*):ti,ab 115004

#52 [mh paediatrics] 0

#53 [mh child] 208

#54 [mh infant] 14681

#55 [mh adolescent] 87542

#56 {or #51-#55} 184998

#57 #50 and #56 28

#58 #25 not #57 Publication Year from 2011 to 2016 24

Development of this evidence summary

The evidence summary: process guide (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

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Declarations of interest

Dr Enrico Bugiardini: no relevant interests declared.

Professor Chinnery: principal investigator on an industry-led study in the treatment of mitochondrial disease. This was not a paid role.

Professor Michael G Hanna: no relevant interests declared.

About this evidence summary

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.

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