Treatment for mitochondrial disorders (Review)

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[Intervention Review]

Treatment for mitochondrial disorders

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Cochrane Database of Systematic Reviews, Issue 4, 2009 (Status in this issue: *Unchanged*)

DOI: 10.1002/14651858.CD004426.pub2
This version first published online: 25 January 2006 in Issue 1, 2006.
Last assessed as up-to-date: 11 September 2005. (Help document - Dates and Statuses explained)

This record should be cited as: Chinnery PF, Majamaa K, Turnbull D, Thorburn D. Treatment for mitochondrial disorders. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD004426. DOI: 10.1002/14651858.CD004426.pub2.

ABSTRACT

Background

Mitochondrial respiratory chain disorders are the most prevalent group of inherited neurometabolic diseases. They present with central and peripheral neurological features usually in association with other organ involvement including the eye, the heart, the liver, and kidneys, diabetes mellitus and sensorineural deafness. Current treatment is largely supportive and the disorders progress relentlessly causing significant morbidity and premature death. Vitamin supplements, pharmacological agents and exercise therapy have been used in isolated cases and small clinical trials, but the efficacy of these interventions is unclear.

Objectives

To determine whether there is objective evidence to support the use of current treatments for mitochondrial disease.

Search strategy

We searched the Cochrane Neuromuscular Disease Group trials register (searched September 2003), the Cochrane Central Register of Controlled Trials, MEDLINE (January 1966 to October 3 2003), EMBASE (January 1980 to October 3 2003) and the European Neuromuscular Centre (ENMC) clinical trials register, and contacted experts in the field.

Selection criteria

We included randomised controlled trials (including crossover studies) and quasi-randomised trials comparing pharmacological treatments, and non-pharmacological treatments (vitamins and food supplements), and physical training in individuals with mitochondrial disorders. The primary outcome measures included an improvement in muscle strength and/or endurance, or neurological clinical features. Secondary outcome measures included quality of life assessments, biochemical markers of disease and negative outcomes.

Data collection and analysis

Details of the number of randomised patients, treatment, study design, study category, allocation concealment and patient characteristics were extracted. Analysis was based on intention to treat data. We planned to use meta-analysis, but this did not prove necessary.

Main results

Six hundred and seventy-eight abstracts were reviewed, and six fulfilled the entry criteria. Two trials studied the effects of co-enzyme Q10 (ubiquinone), one reporting a subjective improvement and a significant increase in a global scale of muscle strength, but the other trial did not show any benefit. Two trials used creatine, with one reporting improved measures of muscle strength and post-exercise

lactate, but the other reported no benefit. One trial of dichloroacetate showed an improvement in secondary outcome measures of mitochondrial metabolism, and one trial using dimethylglycine showed no significant effect.

Authors' conclusions

There is currently no clear evidence supporting the use of any intervention in mitochondrial disorders. Further research is needed to establish the role of a wide range of therapeutic approaches.

PLAIN LANGUAGE SUMMARY

No clear evidence from randomised trials for the use of any intervention in mitochondrial disorders

There is currently no established treatment for mitochondrial disorders, a group of diseases particularly affecting muscles but also every other part of the body. They can cause progressive disability and premature death, due to the involvement of multiple organ systems. Dietary modifications, pharmacological agents and exercise therapy have been tried in individual cases and small cohorts. We identified six randomised controlled trials. Two trials studying co-enzyme Q10 and two studying creatine produced conflicting outcomes, one trial using dimethylglycine showed no positive effect, and one studying dichloroacetate improved some outcomes. Further randomised controlled trials of a range of therapies are needed.

BACKGROUND

General introduction

Mitochondria are responsible for converting food into energy within human cells. There are a number of genetically determined abnormalities of mitochondria that cause human diseases. These diseases usually involve organs that are heavily dependent upon the energy produced by mitochondria such as the brain, peripheral nerves, limb muscles, heart and hormone-producing glands. Mitochondrial disorders can cause muscle weakness on its own, but this is usually associated with neurological, heart and hormone problems including diabetes. There is currently no established treatment for mitochondrial disorders, but there have been a number of case reports and small trials describing the positive effects of a number of different drugs, vitamins and food supplements. Exercise therapy has also been shown to help with the muscle symptoms. The purpose of this review is to objectively assess the available evidence for the various treatments that have been tried in mitochondrial myopathy and mitochondrial encephalomyopathy. Leber hereditary optic neuropathy (LHON) is also a primary mitochondrial disorder that usually just affects the eye. This disease has also been included in this study.

Mitochondria and human disease

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 (DiMauro 2001; Leonard 2000). Based upon recent epidemiological studies, mitochondrial disorders affect at least 1 in 8000 of the general population (Chinnery 2000; Darin 2001; Skladal 2003).

Mitochondrial function and biogenesis

Mitochondria are complex ubiquitous intracellular organelles that perform an essential role in a number of cellular processes (Wallace 1999). They contain enzymes involved in cellular metabolism, and are involved in many cell death pathways. It is therefore possible that mitochondria play a central role in many disease processes. Mitochondria also play a pivotal role in the final common pathway of aerobic metabolism - oxidative phosphorylation (OXPHOS). Oxidative phosphorylation is carried out by the mitochondrial respiratory chain, which is a group of five multi-subunit enzyme complexes situated on the inner mitochondrial membrane that generate adenosine triphosphate (ATP) from intermediary metabolites. Adenosine triphosphate is a high-energy phosphate molecule that provides an energy source for all active cellular processes. The term "mitochondrial disorders" usually refers to primary disorders of the mitochondrial respiratory chain.

Molecular pathology of mitochondrial disorders

The last ten years have seen major advances in our understanding of the biochemical and molecular basis of mitochondrial disease. The respiratory chain has a dual genetic basis (DiMauro 1998). The vast majority of the respiratory chain subunits (greater than

70) are the products of nuclear genes. These subunits are synthesised within the cytosol and are delivered into mitochondria by a peptide targeting sequence. By contrast, thirteen essential respiratory chain subunits are synthesised within the mitochondrial matrix from small 16.5 kb circles of double-stranded DNA called mitochondrial DNA (mtDNA) (Anderson 1981). MtDNA is different to nuclear DNA in a number of respects. First, there are many thousands of copies of mtDNA within each cell. MtDNA mutations may only affect a proportion of the mtDNA molecules, leading to a mixture of mutant and wild-type mtDNA within the cell (heteroplasmy) (Holt 1988). Single cell studies have shown that the proportion of mutant mtDNA must exceed a critical threshold level before the cell expresses a biochemical defect of the mitochondrial respiratory chain (Schon 1997). This threshold varies from tissue to tissue, and partly explains the tissue-selectivity seen in mitochondrial disorders (Wallace 1994). The percentage level of mutant mtDNA can also vary between and within individuals harbouring a pathogenic mtDNA defect, and this partly explains the clinical variability that is a hallmark of mtDNA disorders (Macmillan 1993).

Clinical features of mitochondrial diseases

Mitochondrial disorders principally affect tissues that are heavily dependent upon oxidative metabolism. These tissues include the central nervous system, peripheral nerves, eye, skeletal and cardiac muscle, and endocrine organs. Many individuals with mitochondrial respiratory chain disease have a multi-system disorder that often involves skeletal muscle and the central nervous system, but some individuals have a disorder that only affects one organ system (DiMauro 2001; Leonard 2000). In general terms, the clinical features of mitochondrial disease can be divided into two groups: central neurological features (including encephalopathy, stroke-like episodes, seizures, dementia and ataxia), and peripheral neurological features (including myopathy, ophthalmoplegia, and peripheral neuropathy). Some individuals have a mixture of central and peripheral features, whereas others have a pure central or peripheral phenotype.

Many individuals with mitochondrial disease have a clearly defined clinical phenotype (summarised in the table: clinical syndromes associated with mitochondrial disease). Chronic Progressive External Ophthalmoplegia (CPEO), the Kearns-Sayre syndrome (KSS) and Pearson syndrome are usually due to a deletion of mtDNA (Moraes 1989; Zeviani 1988). Leber hereditary optic neuropathy (LHON), Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes (MELAS), Myoclonic Epilepsy with Ragged-Red Fibres (MERRF), Maternally Inherited Diabetes and Deafness (MIDD), and Neurogenic (or neuropathy) Ataxia with Retinitis Pigmentosa (NARP) are usually due to point mutations of mtDNA (Lamantea 2002). Unlike nuclear DNA, mtDNA is inherited down the maternal line, so these disorders either affect sporadic cases or they are passed from mother to child (Chinnery 1998). Children presenting with a relapsing encephalopathy with prominent brain stem signs and lactic acidosis (Leigh syndrome) may have a mtDNA defect, or an underlying nuclear genetic defect causing a respiratory chain deficiency. These mutations can affect the genes that code for the subunits themselves (complexes I and II), genes important for the assembly of an intact respiratory chain (complexes III and IV), or genes involved in mitochondrial transcription or translation, and they are usually autosomal recessive (Dahl 1998; Thorburn 2001). Mutations in the gene LPPRC cause a specific form of infantile COX deficiency found in the Saguenay-Lac-Saint-Jean region of Canada (Mootha 2003).

A further group of mitochondrial disorders have recently been defined at the molecular level. These disorders result from a disorder of mtDNA maintenance. For some of these diseases the primary defect is an abnormality of the intra-mitochondrial nucleoside pool. Most individuals with autosomal dominant PEO have a mutation in one of three genes: C10ORF2, ANT1 or POLG, which lead to the formation of multiple mtDNA deletions in muscle (Kaukonen 2000; Spelbrink 2001; Van Goethem 2001). Children presenting with mtDNA depletion syndrome may have mutations in the nuclear genes Thymidine kinase 2 (TK2) in the myopathic form, or Deoxyguanosine kinase (DGUOK) or POLG in the hepatic form (Mandel 2001; Naviaux 2004; Saada 2001). Secondary mtDNA multiple deletions are also a feature of Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE) which is also due to a disturbance of the intra-mitochondrial nucleoside pool secondary to thymidine phosphorylase (TP) deficiency (Nishino 1999). A final important group are the disorders associated with co-enzyme Q10 (ubiquinone) deficiency. This may present with childhood encephalopathy and seizures, recurrent rhabdomyolysis or ataxia with seizures. Case reports suggest that this disorder responds to Q10 replacement therapy (Musumeci 2001).

A large proportion of individuals with mitochondrial disease do not have a clearly defined phenotype. There may be single or multi-organ involvement including the heart, endocrine organs (particularly the pancreas), and the nervous system. Gastrointestinal complications are an under recognised but common feature of mitochondrial disorders. Mitochondrial disease should be considered in any patient presenting with an unexplained progressive multi-system disorder with prominent neurological features (Chinnery 1997).

Secondary mitochondrial disorders

Many other genetic disorders are also associated with abnormal mitochondrial function either as a secondary phenomenon, or because mitochondria play a crucial role in the pathophysiology of the disorder. To date these include three X-linked conditions (Barth syndrome, sideroblastic anaemia with ataxia, deafness and dystonia) and a number of autosomal recessive (Friedreich's ataxia, spastic paraparesis SPG4 and SPG13, Wilson's disease) and au-

tosomal dominant conditions (optic atrophy OPA1, hereditary paragangliomas). These disorders will not be considered in this Cochrane review.

The clinical management of mitochondrial disease

There is currently no established treatment for mitochondrial disorders, and the clinical management of individuals is largely supportive. The aims are to provide prognostic information and genetic counselling.

Treatments used to modify the underlying disease process fall into three groups: pharmacological and nutritional agents, modification of macronutrient composition in the diet (dietary supplementation with vitamins and co-factors) and exercise therapy. A number of different pharmacological treatments and nutritional supplements have been used in individuals with mitochondrial disease, with varying reports of success. These include antioxidants (co-enzyme Q10, idebenone, vitamin C, vitamin E and menadione), agents that specifically improve lactic acidosis (dichloroacetate and dimethylglycine, which is a component of pangamic acid (vitamin B15)), agents that correct secondary biochemical deficiencies (carnitine, creatine), respiratory chain co-factors (nicotinamide, thiamine, riboflavin, succinate, and co-enzyme Q10), and hormones (growth hormone and corticosteroids) (reviewed in (Chinnery 2001)). Much of the evidence used to support specific treatments comes from single case reports, but there have been a number of small quasi-randomised trials and open-labelled case series. Improvements following dietary modification (for example, a ketogenic diet) and exercise therapy (for example, endurance training) have also been documented in individual cases, and open-labelled trials (Taivassalo 2001). These reports suggest that there might be benefits from these treatments.

Novel treatment strategies

A number of groups are developing treatments that act on the genetic level, but it is unlikely that these will be available for individuals in the near future (Chinnery 2001; Taylor 2000).

The aim of this review is to critically appraise the available evidence from randomised controlled trials for currently available treatments for individuals with mitochondrial disorders with peripheral neurological features. Our initial protocol subdivided mitochondrial disorders into encephalopathies and myopathies. After completing the review, we amalgamated our results into a single report because (a) only a small number of studies were identified; (b) the majority of participants in these studies had both central neurological and neuromuscular features which were both assessed in the same trial. The myopathic and encephalopathic groups may be separated in future revisions of the review.

OBJECTIVES

This Cochrane review will focus on the treatment of all primary mitochondrial disorders, including specific syndromes, complex multi-system disorders and specific phenotypes such as LHON.

The objective of this review is to examine the effects of pharmacological treatments, and non-pharmacological treatments (vitamins and food supplements), and physical training in improving the symptoms, signs, disability and quality of life in individuals with mitochondrial disorders.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (including crossover studies) and quasi-randomised trials (trials in which randomisation is intended but which might be flawed, such as alternate allocation).

Types of participants

We included participants of any age with a confirmed diagnosis of primary respiratory chain disease based upon muscle histochemistry and/or respiratory chain complex analysis of tissues or cell lines and/or DNA studies.

Types of interventions

We included any pharmacological agent, dietary modification, nutritional supplement, exercise therapy or other treatment. We did not study the effects of treatments for the complications of mitochondrial disorders (such as ptosis surgery, or cardiac pacing).

Types of outcome measures

Primary outcomes

We chose primary outcome measures related to neuromuscular function. For peripheral neurological involvement, the primary outcome measures included an improvement in muscle strength and/or endurance (including the MRC muscle strength scale, isometric dynamometer, custom made strain device, vital capacity or maximal voluntary inspiratory or expiratory capacity, or walking speed). For central neurological features, our primary end points were an improvement in a system-specific neurological function score, a reduction of paroxysmal events (such as seizures or stroke-like episodes), visual acuity, pure tone audiometry or improved cognitive performance. We chose a number of outcome measures

because a preliminary literature search only identified a few studies, and each one incorporated different outcome measures. Focussing on one outcome measure would severely limit the scope of this review for a group of disorders with such a complex clinical phenotype. We also did not choose a specific time point for the primary outcomes because we were aware that a specific time point would exclude most of the identified studies, as no universal time point has been agreed upon for the assessment of treatments in these disorders.

Secondary outcomes

We also studied a number of secondary outcome measures.

1. An improvement in quality of life as measured by a recognised scale (e.g. SF36).
2. Biochemical markers of disease (normalisation of plasma lactate/pyruvate ratio, lowered Vmax as measured by magnetic resonance spectroscopy).
3. Negative outcomes. This included all adverse events attributable to the treatment. Serious adverse events, namely disabling or life-threatening complications, complications which require hospitalisation, and death will be recorded separately. A record was made if it were not possible to determine whether the negative outcome is a consequence of the treatment or part of the natural history of the disease.

These measures were considered secondary because they either reflect an indirect and non-specific consequence of the disorder (1), are surrogate markers of disease activity which correlate poorly with functional ability (2), or relate to the negative effects of treatment.

Search methods for identification of studies

We searched the Cochrane Neuromuscular Disease Group trials register (searched September 2003) using the terms 'mitochondrial disease' or 'mitochondrial myopathy' or 'mitochondrial disorder' or 'Disorders of mitochondrial function', or 'chronic progressive external ophthalmoplegia' or 'CPEO' or 'Kearns syndrome' or 'KSS' or 'Kearns Sayre syndrome' or 'Pearson syndrome' or 'Leber hereditary optic neuropathy' or 'LHON' or 'MELAS syndrome' or 'MERRF syndrome' or 'MIDD' or 'NARP' or 'Leigh syndrome' or 'MNGIE'. We adapted this strategy to search the Cochrane Central Register of Controlled Trials (Issue 3,2003), MEDLINE (January 1966 to October 3 2003), EMBASE (January 1980 to October 3 2003) and the European Neuromuscular Centre (ENMC) clinical trials register. We searched for randomised controlled clinical trials and quasi-randomised trials for possible inclusion in the analysis. We also searched for informative single case reports and observational studies, and incorporated these in the discussion. Wherever possible we contacted the authors of these studies for long-term follow up on the individual cases. We also planned to include any unpublished studies conducted by experts in the field by contacting the authors of all published studies and other experts in the field.

The strategy in Appendix 1 was used to search MEDLINE to October 3 2003 in combination with the strategy for identifying rcts on OVID MEDLINE listed in the Neuromuscular Disease Group module.

Data collection and analysis

All four authors checked titles and abstracts identified using the search strategy. All four authors independently decided which trials fitted the inclusion criteria and graded the methodological quality using the Cochrane approach:
(A) adequate
(B) unclear
(C) inadequate
(D) not done

The methodological quality assessment took into account and graded: security of randomisation, allocation concealment, observer blinding, patient/participant blinding, completeness of follow-up, intention to treat analysis, explicit diagnostic criteria, and explicit outcome criteria. Data extraction was performed by all four authors and was concordant in each case. We obtained missing data from the trial authors wherever possible. If there had been adequate data we planned to carry out a meta-analysis using weighted mean differences to analyse continuous data and relative risks to analyse dichotomous data. If data were available for more than one trial with a specific intervention, we planned to use the Cochrane Review Manager 4.2 (RevMan) software using a fixed effect model. If heterogeneity was identified we planned to explore possible reasons for differences between studies such as type of participants, intervention or quality, and we planned to perform sensitivity analyses by omitting trials which lacked one or more of the methodological attributes. Uncertainty would have been expressed as 95% confidence intervals.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Six hundred and seventy-eight abstracts were reviewed, identifying eleven studies. Six were included in the review. *See* table 'Characteristics of included studies'. The studies evaluated the following

treatments: Co-enzyme Q10 (ubiquinone), creatine, dichloroacetate (DCA) and dimethylglycine (DMG). The excluded studies were single case reports (2), open studies (2), retrospective studies (1) and one of these excluded studies did not include patients with mitochondrial disease.

Risk of bias in included studies

The methodological rating for the included studies is summarised in Table 1. The majority of studies included only a small number of participants. The methodological criteria were assessed and graded according to Cochrane criteria where: A is adequate, B is unclear, C is inadequate and D is not done. Two studies used co-enzyme Q10 (ubiquinone) and two used creatine. Given the limited size of these studies, the heterogeneous patient groups, and the different end points, we elected not to perform meta-analysis.

Table 1. Methodological quality scores

Study ID	Secure randomisation	Allocat Concealment	Observer blinding	Participant blinding	Patient blinding	Follow-up	Intention to treat	Diagnostic criteria	Outcome criteria
Chen 1997	B	A	A	A	A	A	D	A	A
DeStefano 1995	B	A	A	A	A	A	D	A	A
Klopstock 2000	B	A	A	A	A	A	D	A	A
Leit 2003	B	A	A	A	A	A	D	A	A
Muller 1990	B	B	A	A	A	A	D	B	A
Tarnopolsky 1997	B	A	A	A	A	A	D	A	A

Effects of interventions

All of six studies involved an oral agent (either a pharmacological agent, or a food supplement). The studies are reported in alphabetical order according to the treatment used.

Co-enzyme Q10 (ubiquinone)

Chen et al (Chen 1997) studied eight participants with mitochondrial encephalomyopathies. Four had MERRF, three had MELAS and one had CPEO with myopathy. The study was a randomised, double-blind crossover trial. The participants were given co-enzyme Q10 160 mg/day orally for three months and placebo for one month, with a one month wash out period. Results were subjectively assessed on entry and monthly by the participants using a six-point score of fatigability in activities of daily living. The results were also objectively assessed on entry and monthly by two neurologists blind to the treatment using a global score based upon the Medical Research Council (MRC) scale for proximal (biceps/triceps, quadriceps/hamstrings), distal muscles (forearm flexors/forearm extensors, anterior tibial.gastrocnemius) and neck muscles, endurance performing standardised bedside activities (the duration of raising the head 30 to 45º from the bed, raising the legs 30 to 45º from the bed, holding a 0.5 kg object with arms

outstretched, and finger tapping), an exercise lactate test (using a standard Bruce exercise ECG protocol), and the serum level of co-enzyme Q10. Both subjective and objective measures showed a trend towards improvement on treatment, but the global MRC index score was the only measure reaching statistical significance (P value < 0.05, no means and SD shown graphically). The serum co-enzyme Q10 levels were significantly lower in the participants than controls before treatment, and significantly increased during treatment. No adverse events were noted.

Muller et al (Muller 1990) reported in abstract form a double-blind crossover trial using co-enzyme Q10. They studied 11 women and 6 men with CPEO using 100 mg/day for nine months and placebo for nine months. Assessments were made every three months, involving muscle power, serum lactate, electromyogram, nerve conduction studies, evoked potential studies, exercise electrocardiogram, electroretinogram and magnetic resonance imaging of the muscles. Seven participants completed the study. No benefit was noted, although the results of statistical analyses were not reported. Adverse events were not commented on. It was not explained why only seven completed the study.

Creatine

Tarnopolsky et al (Tarnopolsky 1997) studied the effects of creatine monohydrate on seven patients with mitochondrial disease, including six with MELAS and one with a mitochondrial myopathy. The participants were given 5 g creatine twice daily for two weeks followed by 2 g twice daily for one week in a randomised crossover design. Measurements included activities of daily living on a visual analogue scale, ischaemic isometric handgrip strength for 1 minute, evoked and voluntary contraction strength of dorsiflexor muscles using a dynamometer, nonischaemic isometric dorsiflexion torque for 2 minutes (NIDFT), and aerobic cycle ergometry (15 to 30W for 5 to 10 mins) with basal and post-ischaemic lactate measurements. Creatine resulted in significantly increased handgrip strength (19%, P value < 0.01, SD not reported), NIDFT (11%, P value < 0.01, SD not reported) and post-exercise lactate (P value <0.05, means shown graphically, SD not reported) with no change in the other variables. No side effects were noted.

Klopstock et al (Klopstock 2000) studied the effects of creatine monohydrate in 13 participants with CPEO and three with mitochondrial myopathy in a randomised placebo controlled crossover trial. Participants received either 20 g of creatine/day or placebo for four weeks. Measurements included visual analogue scales of subjective weakness and general activity, testing muscle strength in 32 muscles according to the Medical Research Council (MRC) scale, the Hammersmith motor ability score, a neuromuscular symptom score, a function time test, a function ranking test and an ataxia score. Resting and post exercise lactate was determined following cycle ergometry, and maximal voluntary muscle torque was measured for elbow flexion (biceps at 90º) and knee extension (quadriceps at 110º) using the multifunctional training machine. Aerobic exercise was tested by nonischaemic isokinetic biceps flexion and knee extension (at a speed of 80 deg/sec with 15% of maximal muscle force until muscular exhaustion). Eye motility and eyelid drooping, and the velocity, gain and latency of visually guided horizontal saccades were also measured. No significant effects of treatment were noted. Two participants experienced muscle cramps whilst being treated with creatine.

Dichloroacetate

De Stefano et al (DeStefano 1995) studied 11 participants with mitochondrial disease, including four with myopathy, one with chronic CPEO and myopathy, two with KSS, two with Leigh syndrome, one with mitochondrial MELAS, and one with the mitochondrial depletion syndrome. The study was a double-blind placebo controlled trial using 25 mg/kg twice daily of dichloroacetate (DCA) or placebo for one week, followed by a three month wash out period before the second arm. Assessments were performed prior to each arm and on termination of the treatment, and included: a complete neurological examination, isometric force generation on dynamometry in proximal muscles (deltoid and iliopsoas), gait performance evaluation, resting venous blood lactate, alanine and pyruvate; incremental exercise in four participants with measurements of venous blood lactate, alanine and pyruvate; phosphorus magnetic resonance spectroscopy (MRS) of muscle and proton MRS of the brain. The DCA produced significant decreases in blood lactate, pyruvate and alanine at rest and after exercise (P value < 0.05, values for each individual shown graphically), and improvements on brain MRS were also noted in seven patients, including a reduction of the brain lactate/creatine ratio (42%, P value < 0.05, mean shown graphically), an increase in brain choline/creatine ratio (18%, P value < 0.01), and increase in the acetylaspartate/creatine ratio (8%, P value < 0.05). In two participants similar results were seen in a different volume of interest including the basal ganglia. Muscle MRS and self-assessed clinical disability were unchanged. No adverse effects were reported.

Dimethylglycine

Based on anecdotal reports of an improvement in patients with congenital lactic acidosis, Liet et al (Liet 2003) studied five children with Saguenay-Lac-Saint-Jean cytochrome c oxidase (SLSJ-COX) deficiency in a randomised double-blind study comparing dimethylglycine (DMG) to placebo. Children weighing < 33 kg were given 50 mg/kg/day in three divided doses, and those weighing > 33 kg were given 5 g per day in three doses over three days. The wash out period was at least two weeks. Four measurements of oxygen consumption (VO2) were performed using indirect calorimetry before and after treatment, and blood lactate, pyruvate, bicarbonate and pH. Dietary caloric intake was calculated for three days prior to each measurement. The mean VO2 was lower after administration of both DMG and placebo, but neither value reached statistical significance. There was no detectable effect on

blood lactate, pyruvate, bicarbonate or pH. No significant side effects were noted.

Statistical analysis

We were not able to perform meta-analysis because of the different treatments used and different outcomes measured in each study. It was also not possible to perform composite analysis based upon means and standard deviations because measurements of the variance were not always stated in tabular form, and in some studies the precise meaning of the error bars on the figures was not clear.

DISCUSSION

Assessing the efficacy of treatment for mitochondrial disorders is difficult for a number of reasons. First, the complex and variable phenotypes make it difficult to compare two or more individuals. Second, many mitochondrial disorders affect multiple organ systems which are difficult to compare (for example, it is difficult to compare an improvement in diabetic control with a reduction in seizure frequency). Thirdly, there is a lack of natural history data on individuals with mitochondrial disease, and related to this, many mitochondrial disorders involve infrequent paroxysmal events (such as stroke like episodes, encephalopathy or seizures), making short studies unhelpful. Finally, and partly because of these problems, there is no recognised disease rating scale for mitochondrial disorders to aid a comparison between different groups of individuals subjected to different treatments. These difficulties explain why we were only able to find six studies fulfilling our entry criteria, and most of these focussed on peripheral neuromuscular features, which are easier to assess.

The six studies assessed the effect of four oral agents: co-enzyme Q10 (ubiquinone, Q10), creatine monohydrate (Cr), dichloroacetate (DCA), and dimethylglycine (DMG). There was objective evidence of locomotor functional improvement with Q10 and Cr, but there were conflicting data for both agents. Q10 improved global muscle strength in one study, and Cr improved handgrip strength and nonischaemic isometric dorsiflexion torque (NIDFT) but did not improve muscle strength in another study. Paradoxically, the trials showing no effect used higher doses of the oral agent, ruling out inadequate dosage as an explanation for the lack of response. Although differences in study design may explain the discrepancies, it is intriguing, that the two longer trials showed no effect, possibly indicating that if there is a treatment response to Q10 or Cr, it is not sustained. Although secondary measures were shown to improve with DCA this was not associated with any improvement in physical function. There was no evidence of a positive response to DMG. On the other hand, there was no evidence that any of these agents are harmful.

The literature contains hundreds of case studies describing benefits and harmful effects of a wide range of different therapies in the treatment of mitochondrial disease (examples: Abe 1991; Barbiroli 1995; Barshop 2004; Bendahan 1992; Bernsen 1993; Curless 1986; Eleff 1984; Gubbay 1989; Hsu 1995; Ihara 1989; Kurlemann 1995; Lou 1981; Majamaa 1997; Mashima 1992; Mashima 2000; Mathews 1993; Mitsui 2002; Mori 2004; Mowat 1999; Nishikawa 1989; Ogasahara 1986; Ogasahara 1989; Oguro 2004; Panetta 2004; Papadimitriou 1996; Penn 1992; Remes 2002; Rotig 2000; Shoffner 1989; Sobreira 1997; Tarnopolsky 1999 are summarised in Table 2). There have also been a number of open studies showing improvement with pharmacological and non-pharmacological treatments, including a recent study of L-arginine for the acute and long-term treatment of stroke-like episodes in patients with MELAS (Koga 2005). Given the inherent bias in studies of this type, we have deliberately not used these reports when reaching a view about treatment. These interventions should be studied rigorously in randomised controlled trials, particularly to evaluate the longer term effects.

Table 2. Oral agents used in single case studies and open trials

Class	Agent (route)	Indication	Proposed mechanism	Dose	Effects	
Quinone derivatives	Ubiquinone (Coenzyme Q10)(Oral)	Isolated ubiquinone deficiency	Redox bypass corrects the deficiency	60 - 250 mg/day	Significant clinical improvement (Ogasahara et al. 1989; Sobreira et al. 1997; Rotig et al. 2000).	

Table 2. Oral agents used in single case studies and open trials (*Continued*)

		All mitochondrial disorders	Redox bypass, free radical scavenger	30 - 260 mg/day	Subjective improvement, particularly reduced fatigue and reduced muscle cramps. Isolated reports of clinical and metabolic improvement (Ogasahara et al. 1986; Ihara et al. 1989; Nishikawa et al. 1989; Abe et al. 1991; Bendahan et al. 1992; Gold et al. 1996; Papadimitriou et al. 1996).	
	Idebenone (Oral)	All mitochondrial disorders, especially LHON	Free radical scavenger, Redox bypass of complex I	90 - 270 mg/day	Improved brain and skeletal muscle metabolism in isolated cases (Ihara et al. 1989; Cortelli et al. 1997). May enhance the rate and degree of visual recovery in LHON (Mashima et al. 1992; Mashima et al. 2000)	
Vitamin supplements	Thiamine (B1)(Oral)	KSS and other mitochondrial disorders	Co-enzyme for pyruvate deydrogenase complex (PDHC)	Up to 900 mg/day	Isolated reports of improvement (Lou 1981). No significant effect in a larger study (Mathews et al. 1993).	

Table 2. Oral agents used in single case studies and open trials (*Continued*)

	Riboflavin (B2)(Oral)	Complex I and complex II deficiency	Acts as flavin precursor for complex I and II	100 mg/day	Clinical and biochemical improvements in small groups of patients (Penn et al. 1992; Bernsen et al. 1993). A larger study of 16 different patients failed to show a benefit (Mathews et al. 1993).	
	Ascorbate (C) and Menadione (K3)(Oral)	Complex III deficiency. Other mitochondrial disorders	Antioxidant By-pass of complex III (with Vit. C)	10 mg qds (four times daily)	Symptomatic and bioenergetic improvements in isolated cases (Eleff et al. 1984; Mowat et al. 1999).	
	Nicotinamide (B3) (Oral)	MELAS and Complex I deficiency	Increase of NAD + NADH pool		Clinical and biochemical improvements in isolated cases treated with nicotinamide alone (Majamaa et al. 1997) or in combination with ubiquinone (Remes et al. 2002) or riboflavin (Penn et al. 1992).	
Metabolic supplements	Succinate (Oral)	Complex I deficiency, KSS and MELAS	Donates electrons directly to complex II	6 g/day	Improvements reported in isolated cases (Shoffner et al. 1989; Oguro et al. 2004).	

Table 2. Oral agents used in single case studies and open trials (*Continued*)

	Creatine	Mitochondrial myopathy	Enhances muscle phosphocreatine	Up to 10 g/day	Reduced fatigue and enhanced muscle strength and aerobic exercise capacity (Tarnopolsky and Martin 1999)	
	Carnitine	Secondary carnitine deficiency	Replacement	Up to 3 g/day	Improvements in isolated cases (Hsu et al. 1995).	
	Lipoic acid (Oral)	CPEO	Enhancing PDHC activity	600 mg/day	Clinical and biochemical improvement in an isolated case (Barbiroli et al. 1995).	
	High Fat Diet	Mitochondrial disorders, especially Complex I deficiency	Increased proportion of electrons donated after (ie bypass) Complexes I and II	50 - 60% of caloric intake	Short-term clinical improvement in small series treated with high-fat diet plus ubiquinone and vitamins B1, B1 and C (Panetta et al. 2004).	
Dichloroacetate		Mitochondrial disorders especially with lactic acidosis	Reduces lactic acidosis by enhancing PDHC activity	25 mg/kg/day	Short-term improvements in muscle and brain oxidative metabolism (DeStefano et al. 1995). Potential complications include a painful peripheral neuropathy (Kurlemann et al. 1995). Temporary ben-	

Table 2. Oral agents used in single case studies and open trials (*Continued*)

					efits noted in two recent open trials (Barshop et al. 2004; Mori et al. 2004).	
Corticosteroids		No clear indication	Unclear, if any	Up to 100 mg/day Prednisone	Improvements have been reported in isolated cases (Gubbay et al. 1989), but steroids may exacerbate the metabolic encephalopathy (Curless et al. 1986) and have long-term consequences (Mitsui et al. 2002).	
Vasodilators	L-Arginine	3243A>G MELAS stroke-like episodes	Endothelial relaxation through enhanced nitric oxide production	0.15-0.3 g/kg/d IV in the acute phase, oral between episodes	Improved stroke-like symptoms (Koga et al. 2005)	

Over the last five years a number of multi-centre research collaborations have been forged throughout Europe and North America, and clinical rating scales are under construction through an EU consortium (EUmitocombat www.eumitocombat.org and MITOCIRCLE http://mitocircle.unimaas.nl). These developments will facilitate multi-centre trials on larger cohorts of phenotypically similar patients, providing hope of progress in the future.

AUTHORS' CONCLUSIONS

Implications for practice

There have been very few randomised controlled clinical trials for the treatment of mitochondrial disease. Those that have been performed were short, and involved fewer than 20 study participants with heterogeneous phenotypes. We conclude that there is currently no clear evidence supporting or refuting the use of any of these agents in mitochondrial disorders. No major side effects of these treatments were recorded.

Implications for research

Further research is needed to establish the role of a wide range of therapeutic approaches in the treatment of mitochondrial disorders.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chen 1997

Methods	Randomised placebo controlled double-blind crossover
Participants	8 participants (4 MERRF, 3 MELAS, 1 CPEO)
Interventions	Co-enzyme Q10 (ubiquinone) 160 mg/day for three months or placebo for one month. 1 month wash out.
Outcomes	Subjective fatigability in ADL score. Global muscle strength based on MRC scale. Bedside endurance tests, exercise lactate test, serum Q10 level.
Notes	Improved global muscle score (actual means and SD not reported). Q10 levels increased during treatment.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

DeStefano 1995

Methods	Randomised placebo controlled double-blind crossover
Participants	11 participants (4 myopathy, one CPEO, 2 KSS, 2 Leigh, one MELAS)
Interventions	Dichloroacetate 25 mg/kg twice daily or placebo for one week. 3 month washout.
Outcomes	Neurological exam, dynamometry, gait evaluation, venous blood lactate, alanine and pyruvate at rest and on incremental exercise; phosphorus magnetic resonance spectroscopy (MRS) of muscle and proton MRS of the brain.
Notes	Decreased blood lactate, pyruvate and alanine at rest and after exercise (P value <0.05), and improvements on brain MRS (Brain lactate/creatine ratio fell by 42%, P value <0.05; brain choline/creatine ratio increased by 18%, P value < 0.01; brain acetylaspartate/creatine ratio increased by 18%, P value < 0.05).

Risk of bias

DeStefano 1995 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Klopstock 2000

Methods	Randomised placebo controlled double-blind crossover
Participants	16 participants (13 CPEO, 3 myopathy)
Interventions	Creatine monohydrate 20 g /day or placebo for four weeks. Washout = 24 days in all participants
Outcomes	Visual analogue scales of subjective weakness and general activity, neuromuscular symptom score, function time test, function ranking test, ataxia score, muscle strength, motor ability score. Resting and post exercise lactate, maximal voluntary muscle torque, aerobic exercise performance, eye motility and eyelid drooping.
Notes	No effect.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Liet 2003

Methods	Randomised placebo controlled crossover study
Participants	5 children with SLSJ-COX deficiency
Interventions	Dimethylglycine or placebo (50 mg/kg/day in <33 kg, 5g/day if >33 kg). Two week washout.
Outcomes	Oxygen consumption (VO2) by indirect calorimetry, Venous lactate, pyruvate, bicarbonate and pH.
Notes	No significant effect.

Risk of bias

Item	Authors' judgement	Description

Liet 2003 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Muller 1990

Methods	Double-blind crossover
Participants	17 participants with CPEO
Interventions	Co-enzyme Q10 (ubiquinone) 100 mg/day or placebo for nine months.
Outcomes	Muscle power, serum lactate, electromyogram, nerve conduction studies, evoked potential studies, exercise electrocardiogram, electroretinogram and muscle magnetic resonance imaging.
Notes	Seven completed. No response. No statistical analysis reported or data shown.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Tarnopolsky 1997

Methods	Randomised placebo controlled double-blind crossover
Participants	7 participants (6 MELAS, 1 myopathy)
Interventions	Creatine monohydrate 5 g twice daily for two weeks followed by 2 g twice daily for 1 week.
Outcomes	Visual analogues ADL scale, ischaemic isometric handgrip strength, evoked and voluntary muscle contraction strength, nonischaemic isometric dorsiflexion torque (NIDFT), aerobic cycle ergometry with basal and post-ischaemic lactate measurements.
Notes	Significantly increased handgrip strength (19%, P value < 0.01), NIDFT (11%, P value < 0.01) and post-exercise lactate (P value < 0.05).

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

ADL = activites of daily living
CPEO = chronic progressive external ophthalmoplegia

MELAS = mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
MERRF = myoclonic epilepsy with ragged-red fibres
MRC = UK Medical Research Council
SLSJ-COX = Saguenay-Lac-Saint-Jean cytochrome c oxidase deficiency

Characteristics of excluded studies *[ordered by study ID]*

Cortelli 1997	No patients with mitochondrial disease
Dunlop 1995	Open trial
Folkers 1985	Single case study
Gold 1996	Single case study
Komura 2003	Retrospective open trial

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. OVID MEDLINE strategy

1. exp Mitochondrial Diseases/
2. mitochondrial myopath$.mp
3. (mitochondrial encephalomyopath$ or mitochondrial encephalopath$).mp
4.(mitochondrial disease$ or mitochondrial disorder$).mp
5. or/1-4
6. ((CPEO or opthalmoplegia) adj5 progressive).mp
7. cytochrome-c oxidase deficiency.mp. or Ubiquinol-Cytochrome-c reductase/df
8. (Kearns adj3 syndrome$).mp
9. KSS.mp
10. or/6-9
11. ((Pearson adj5 syndrome$) or (pearson adj5 disease$)).mp
12. (leber adj5 neuropath$).mp. or optic nerve atrophy/
13. LHON.mp
14. (MELAS adj6 syndrome$).mp
15. lactic acidosis.mp. or Lactic Acidosis/
16. (stroke adj episode$).mp
17. 15 and 16
18. 11 or 12 or 13 or 14 or 17
19. ((MERFF adj5 syndrome$) or MERFF).mp
20. MIDD.mp
21. (maternal$ adj5 diabetes adj5 deafness).mp
22. or/19-21
23. ((leigh adj5 syndrome$) or (leigh adj5 disease$)).mp
24. MNGIE.mp
25. (mitochondrial adj5 neurogastrointestinal adj5 encephalomyopath$).mp
26.or/23-25
27. retinitis pigmentosa.mp. or Retinitis Pigmentosa/
28. ATAXIA/
29. ataxia.mp
30. 27 and (28 or 29)
31. NARP.mp
32. (pyruvate adj5 carboxylase adj5 deficiency adj5 disease).mp
33. pyruvate dehydrogenase complex deficiency disease.mp
34. or/30-33
35. 5 or 10 or 18 or 22 or 26 or 34
36.drug$.mp. or Drug Therapy/
37. treatment.mp. or Therapeutics/
38. (coenzyme Q10 or co enzyme Q10 or carnitine$ or creatine$ or idebenone$ or ubidecarenone$ or vitamin C or vitamin E or menadione$ or nicotinamide$ or dichloracetate$ or thiamine$ or riboflavin$ or succinate$ or corticosteroid$).mp
39. (growth adj5 hormone$).mp.
40. exercise.mp. or Exercise Therapy/
41. diet$.mp. or Diet Therapy/

42. or/36-41
43. 35 and 42

WHAT'S NEW

Last assessed as up-to-date: 11 September 2005.

27 April 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 1, 2006

12 September 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All four authors agreed the criteria for inclusion of studies and their methodological quality. All four authors independently assessed all of the studies reviewed. PFC completed the first draft which was modified with comments from the other authors.

DECLARATIONS OF INTEREST

DMT is involved in a publicly funded trial of exercise therapy for the treatment of mitochondrial myopathy. KM has carried out publicly funded open trials in the treatment of mitochondrial disease.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Wellcome Trust, UK.
- Muscular Dystrophy Campaign, UK.
- Medical Research Council, UK.
- Ataxia, UK.
- Association Francaise contre les myopathies, France.
- Council for Health Research, Finland.
- Sigrid Juselius Foundation, Finland.
- Australian National Health and Medical Research Council, Australia.
- Muscular Dystrophy Association, USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Creatine [therapeutic use]; Dichloroacetate [therapeutic use]; Mitochondrial Diseases [*drug therapy]; Sarcosine [analogs & derivatives; therapeutic use]; Ubiquinone [therapeutic use]

MeSH check words

Humans