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Antioxidants and other pharmacological treatments for Friedreich ataxia

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ABSTRACT

Background
Friedreich ataxia is a rare inherited autosomal recessive neurological disorder, characterised initially by unsteadiness in standing and walking, slowly progressing to wheelchair dependency usually in the late teens or early twenties. It is associated with slurred speech, scoliosis and pes cavus. Heart abnormalities cause premature death in 60% to 80% of people with the disorder. There is no easily defined clinical or biochemical marker and no known treatment. This is the first update of a review published in 2009.

Objectives
To examine the efficacy of antioxidants and other pharmacological treatments for Friedreich ataxia.

Search methods

Selection criteria
Randomised controlled trials (RCTs) or quasi-RCTs of drug treatment in people with genetically confirmed Friedreich ataxia. The primary outcome was change in ataxia rating scale as measured by the International Co-operative Ataxia Rating Scale (ICARS) after 12 months. Secondary outcomes included change in left ventricular heart mass as measured by magnetic resonance imaging or echocardiography. We excluded trials of shorter duration than 12 months.

Data collection and analysis
Three authors selected the trials and two authors extracted data. We obtained missing data from the one RCT that met our inclusion criteria. We planned to collect adverse event data from included studies.
Main results

More than 10 studies used idebenone in the treatment of Friedreich ataxia but only one small RCT, with 29 participants, using the synthetic antioxidant idebenone 5 mg/kg, fulfilled the selection criteria for this review. Other RCTs were of insufficient duration. We identified no additional RCT when the searches were updated in 2011. In the included study, the primary outcome specified for this review, change in ICARS scale, did not reveal any significant differences with idebenone treatment compared to placebo. The secondary outcome of change in left ventricular heart mass index as measured by magnetic resonance spectroscopy was not assessed. The secondary outcome, change in left ventricular mass as measured by echocardiography, did improve significantly; there was a 10.7% worsening after 12 months of treatment in the placebo group and a 5.6% improvement in the idebenone group. The mean difference was 16.37% (95% CI 95% 2% to 31%). There were no adverse events. We considered the included study at low risk of bias in five of the seven domains assessed. A larger trial using idebenone published an interim report in May 2010 stating that the study had failed to reach its primary endpoint, which was change in the ICARS scale.

Authors’ conclusions

No RCT using idebenone or any other pharmacological treatment has shown significant benefit on neurological symptoms associated with Friedreich ataxia. Idebenone has shown a positive effect on left ventricular heart mass but the clinical relevance of this change was not assessed in the included study.

PLAIN LANGUAGE SUMMARY

Antioxidants and other pharmacological treatment for Friedreich ataxia

Friedreich ataxia is a rare progressive condition that causes damage to the nervous system. It is inherited in an autosomal recessive pattern, meaning that an affected gene must be inherited from each parent for the disease to develop in their child. It is the most common recessively inherited ataxia worldwide. It usually presents between the ages of 5 and 15 years with clumsiness of movement, progressing to unsteadiness in standing and walking. Speech usually becomes slurred. Most people with the condition become wheelchair-dependent in their late teens or early twenties. Heart abnormalities cause premature death in 60% to 80% of people with the disorder. Other significant problems which may develop include scoliosis (curvature of the spine), and pes cavus (high arched foot deformity). The progression of the disease cannot be easily assessed by clinical examination or a laboratory test. Evaluation of disease progress using standard neurological scales is made more difficult when the person is wheelchair-dependent.

Recent studies have suggested that a synthetic antioxidant idebenone may help the most frequent heart abnormality, enlargement of the left ventricle. Antioxidants occur naturally in foods but do not reach a level that would be considered necessary to alter the progress of Friedreich ataxia.

A review of the medical literature revealed one small randomised controlled trial with 29 participants that used idebenone for a sufficient period, 12 months, and the review authors identified no new studies when the searches were updated in 2011. Randomised controlled trials are studies in which people are allocated at random to receive one of several clinical interventions. One of these interventions is a control. The control may be a standard practice, a placebo (for example a sugar coated pill) or no intervention at all. Randomised controlled trials are generally accepted as the most valid method of determining the efficacy of a treatment, because the biases associated with other experimental designs can be avoided.

The included randomised controlled trial showed that idebenone did not help the neurological symptoms associated with Friedreich ataxia. We considered it at low risk of bias on five of the seven criteria assessed. Idebenone showed a positive effect on heart muscle but the clinical relevance of this change was not assessed in the study. There were no adverse events.
by a slowly progressive neurological disability. Heart abnormalities cause premature death in 60% to 80% of people with the disorder. The first symptoms usually present between the ages of five and 15 years with unsteadiness in standing or walking. It is followed by progressive limb and gait ataxia, as well as slurred speech. Most patients are wheelchair-dependent by their late teens or early twenties. Other significant problems which may develop include scoliosis and pes cavus in 10% of people with Friedreich ataxia.

Friedreich ataxia is the most common recessively inherited ataxia worldwide and was first described in 1863 by the German neurologist and pathologist Nicholas Friedreich. It has a prevalence of approximately 1 in 40,000 in Caucasians populations. It is thought that about 50,000 individuals worldwide are affected but more exact figures are not available. There is no biochemical biomarker or easily defined clinical marker for this small patient population. Mutations in the Frataxin gene (FXN) on chromosome 9q13 were found to cause Friedreich ataxia in 1996 (Camuzano 1996). Most people with Friedreich ataxia are homozygous for expansions of a GAA repeat in the first intron of the FXN gene. Normal alleles have 40 or fewer GAA repeats while disease alleles have from 100 to more than 1700 repeats. These repeat expansions induce a packaging of the involved genomic regions into inaccessible heterochromatin structure leading to gene silencing. In rare cases, other loss-of-function mutations are found in heterozygosity with a GAA repeat expansion. FXN encodes for a small mitochondrial protein called frataxin, whose expression is reduced in Friedreich ataxia (Schulz 2000). Frataxin is ubiquitous, with high levels in the central and peripheral nervous systems and in some non-neuronal tissues, such as the heart, pancreas, liver, muscle, thymus and brown fat. Some but not all of these tissues are affected in Friedreich ataxia; for example, in the nervous system, primary sensory neurons, the dentate nucleus and pyramidal tracts undergo atrophy, while other neuronal systems are much more resistant despite similar levels of frataxin expression.

Cellular frataxin deficiency has a deleterious effect on mitochondrial function. In the cells of Friedreich ataxia patients and in animal models there is loss of iron sulphur proteins, including the respiratory chain complexes I, II, III and aconitase. This results in reduced adenosine triphosphate (ATP) generation, as confirmed in patients by magnetic resonance spectroscopy (Lodi 2001). In addition, mitochondria become overloaded with iron, leading to the formation of reactive oxygen species as indicated by increased concentrations of the oxidative damage markers plasma malondialdehyde (Emond 2000) and urinary 8-hydroxy-2-deoxyguanosine. Both respiratory chain dysfunction and oxidative stress are likely to result in cardiac or cardiomyocyte hypertrophy and neuronal cell dysfunction. Antioxidants are postulated to protect against these effects. In 2000, Schulz treated 48 Friedreich ataxia patients with the antioxidant idebenone over an eight-week period and found a significant decrease in urinary 8-hydroxy-2-deoxyguanosine (Schulz 2000). A more recent study studied 48 participants over six months and did not observe significant changes in the concentrations of this biochemical marker after idebenone treatment (Di Prospero 2007).

### Antioxidants

The best known antioxidants are vitamins A, C and E, which are found in fruit, vegetables, cereals, some teas, grape seed extract and red wine. However, the antioxidant activity levels in these foods do not reach what would be considered therapeutic levels, capable of modifying the rate of disease progression in Friedreich ataxia. Vitamin C increases lipoperoxidation by reducing Fe^{3+} to Fe^{2+}. This decreases the activity of respiratory complex II. Furthermore, cellular studies have indicated that ascorbic acid may increase some of the iron-associated adverse effects seen in Friedreich ataxia (Rustin 1999). The most commonly considered antioxidant medications for Friedreich ataxia include the following.

1. **Idebenone**, a short chain quinone analogue which acts as a free-radical scavenger. It is a synthetic analogue of coenzyme Q10, a potent antioxidant and may act as an electron carrier in the respiratory chain. It has been used in recent studies in Friedreich ataxia.
2. **Coenzyme Q10**, a naturally occurring compound found in every cell in the body. It carries electrons from complexes I and II to complex III in the respiratory chain, playing a role in mitochondrial adenosine triphosphate production. It is fat soluble.
3. **Vitamin E**, a naturally occurring lipid soluble antioxidant. Its deficiency causes a spinocerebellar phenotype with peripheral neuropathy that clinically resembles Friedreich ataxia.
4. **N-acetylcysteine**, a precursor of glutathione, a natural intracellular antioxidant whose protective properties have been demonstrated in a number of cellular models. It has been proposed as a treatment for various conditions, including liver, kidney and lung diseases and as a supportive treatment for HIV infection and cancer.
5. **Selegiline**, a selective monoamine oxidase B inhibitor. Selegiline increases superoxide dismutase and catalase activity and probably has additional antioxidant properties. It was initially used in Parkinson's disease for presumed neuroprotective antioxidant properties. Its clinical efficacy has been questioned and is currently under review.
7. **Combination antioxidant therapy.** The value of antioxidants in amyotrophic lateral sclerosis, another degenerative neurological condition, has been the subject of a Cochrane review (Orrell 2011). This review concluded that there was insufficient evidence of efficacy of individual antioxidants or antioxidants as a group in the treatment of amyotrophic lateral sclerosis. Clinical trials using antioxidants in Friedreich ataxia have been ongoing since the late 1990s and have included Rustin 1999, Buyse 2003, Mariotti 2010 and Ribai 2007; these have suggested
that idebenone, an antioxidant, may help cardiac hypertrophy, the most frequent heart abnormality. Artuch 2002 and Lynch 2010 did not demonstrate an improvement in cardiac hypertrophy with idebenone. In July 2008 idebenone was licensed provisionally in Canada for treatment of Friedreich ataxia. Since then it has been provided free of charge in one of the ten provinces, Quebec, but in the other provinces it is only provided by private insurers. In November 2008, the European Medicines Agency refused marketing authorisation for idebenone in Europe (EMA 2009). The US Food and Drugs Administration has not authorised idebenone for use in Friedreich ataxia. This review will examine the available evidence concerning idebenone, other antioxidants and other pharmacological treatment for Friedreich ataxia.

**Other pharmacological treatments for Friedreich ataxia**

In the last five years, there has been considerable interest in researching the compounds detailed below in Friedreich ataxia. These compounds have been licensed for use in other diseases. Deferiprone is an iron chelator: a small molecule that preferentially binds iron, a toxic metal, over other metals and prevents its reaction with reactive oxygen species. Deferiprone can cross the blood-brain barrier. The rationale for its use in Friedreich ataxia is its ability to redistribute iron from the overloaded mitochondrial compartment to the cytosol (Kakhlon 2008). Using regimens suitable for patients with no iron overload, deferiprone has been shown to reduce iron accumulation in the brain, specifically in the dentate nuclei, of Friedreich ataxia patients and to reduce neuropathy and ataxic gait in the youngest patients (Boddaert 2007). Erythropoietin (EPO) is a glycoprotein that is produced in the kidney. It is also a hormone, regulating red blood cell production. It has other biological functions; for example, it plays an important part in the brain's response to neuronal injury and in the wound healing process. Recombinant human erythropoietin (rhuEPO) significantly increases frataxin expression in many cells, including lymphocytes from Friedreich ataxia patients in vitro (Boesch 2007). Pioglitazone is a peroxisome proliferator-activated receptor gamma (PPAR) molecule that is currently licensed for treatment of diabetes mellitus. It induces the expression of enzymes involved in mitochondrial metabolism, including superoxide dismutase, which is an important antioxidant defence in nearly all cells exposed to oxygen. Pioglitazone crosses the blood-brain barrier in humans. It is proposed that this agent could be therapeutic in neurological disease by improving the antioxidant defence mechanism. A single case report has shown that daily treatment with pioglitazone for three years induced apparent clinical improvement without adverse events in a patient with multiple sclerosis (Pershadingh 2004). In cultured human cells with low frataxin, pioglitazone showed no increase in toxicity compared to controls. A clinical trial using pioglitazone is currently recruiting participants with Friedreich ataxia (NCT 00811681). Histone deacetylase inhibitors (HDACis) modulate the level of acetylation of chromosomal proteins as well as other cellular targets and can revert the silent heterochromatin to an active chromatin conformation and restore the normal function of the silenced genes. Herman 2006 showed that in human lymphoblastoid cells from Friedreich ataxia patients with a new HDACi, it was possible to revert the FXN gene silencing. This provides an innovative approach to the treatment of Friedreich ataxia that results in raised frataxin levels. Full pharmacology and toxicology have been completed for one of the HDACi. An application has been made to the US FDA for permission to carry out a phase I safety trial in human subjects (www.naf.org). This is the first update of a review first published in 2009.

**OBJECTIVES**

To examine the efficacy of antioxidants and other pharmacological treatments for Friedreich ataxia.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All randomised controlled trials (RCTs) or quasi-RCTs (using, for example, alternate allocation) of antioxidant and other pharmacological treatments for Friedreich ataxia.

**Types of participants**

Participants with genetically confirmed Friedreich ataxia at all stages of their illness, both genders and any age.

**Types of interventions**

Any treatment compared with any other pharmacological treatment, placebo or no treatment. We specifically focused on antioxidants because there have been more clinical trials using these than any other agent. We included any form of treatment considered to have an antioxidant effect as well as other pharmacological treatments.
Types of outcome measures
Antioxidants were analysed initially as a group, with additional subgroup analysis of individual antioxidants. Other pharmacological treatments were considered individually, or within therapeutic groups as appropriate.

Primary outcomes
Change in ataxia rating scale after 12 months of treatment as measured by the International Cooperative Ataxia Rating Scale (ICARS) score. An absolute reduction in this scale indicates improvement.

Secondary outcomes
1. Change in left ventricular mass index of the heart as measured by a $^{31}$P magnetic resonance spectroscopy after 12 months of treatment. It has been shown that cardiac bioenergetics, measured in vivo, are abnormal in Friedreich ataxia patients in the absence of any discernible deterioration in cardiac contractile performance as measured by echocardiography (Lodi 2001). These bioenergetics are measured by the research biomarker $^{31}$P using a magnetic resonance spectroscopy. This spectroscopy can measure the ratio of phosphocreatine (PCr) to adenosine triphosphate (ATP), a reliable measure of the bioenergetic state of cardiac muscle. It has also been shown that cardiac magnetic resonance has excellent inter-study reproducibility in normal, dilated and hypertrophic hearts and is superior to two-dimensional echocardiography (Grothues 2002).
2. Change in left ventricular mass of the heart as measured by echocardiography after 12 months of treatment.
3. Improvement in any validated quality of life score after 12 months of treatment.
4. Severe adverse effects (leading to cessation of medication).
5. Mild adverse effects (medication continued) after 12 months of treatment.
We will include a 'Summary of findings' table in a future update if more data emerge and will present the following outcomes: change in ataxia rating scale, change in left ventricular mass of the heart, improvement in quality of life, and adverse events.

Search methods for identification of studies

Electronic searches
We searched The Cochrane Neuromuscular Disease Group Specialized Register (11 July 2011) using Friedreich's ataxia or Friedreich ataxia for trials of the following agents using the search terms idebenone, co-enzyme Q10, vitamin A, vitamin C, ascorbic acid, vitamin E, alpha-tocopherol, seligline, deprenyl, n-acetyl cysteine, n-acetyl-l-cysteine, n-acetylcysteine, acetylcysteine, superoxide dismutase, SOD, dehydroepiandrosterone, glutathione, urea, uric acid, selenium, carotenoids, flavonoids, tau- rine, recombinant human erythropoietin, iron chelation, deferiprone, pioglitazone, histone deacetylase inhibitors, HDACi, antioxidant treatment and pharmacological therapy.

We adapted this strategy to search the following electronic databases:

For search strategies, see Appendix 1 (CENTRAL), Appendix 2 (MEDLINE), Appendix 3 (EMBASE), Appendix 4 (CINAHL Plus), Appendix 5 (AMED), Appendix 6 (LILACS), Appendix 7 (ORPHANET), Appendix 8 (TRIP) and Appendix 9 (PEDRO).

We decided in advance that if we included clinical trials conducted prior to 1996 (genetic diagnosis of Friedreich ataxia became available in 1996), it would be necessary to exclude the results of these trials from further analysis if genetic confirmation had not been subsequently carried out.

As searching AMED, LILACS and PEDRO has produced no useful results to date we will remove these databases from our searches at the next update.

Searching other resources
Three review authors inspected the reference lists of all papers selected from the searches. We performed a search of the references listed in the published studies, reviews and relevant conference proceedings. We also considered studies in other languages for inclusion. We consulted the Clinical Trials Registry of the U.S. National Institute of Health (www.ClinicalTrials.gov) to identify additional trials that had not yet been published. We obtained the latest results from the RCTs by searching conference proceedings and canvassing colleagues.

Data collection and analysis
Three review authors (MK, RO and MF) independently checked titles and abstracts obtained from literature searches to identify potentially relevant trials for the review. All authors obtained the full text of all potentially relevant studies for independent assessment. The authors resolved disagreements about inclusion criteria by discussion.

We completed a 'Risk of bias' assessment on the included study according to the guidance in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We assessed the RCT for random sequence generation, allocation concealment, blinding...
(participants and outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias. We made a judgement on each of these criteria relating to the risk of bias, rating studies as at ‘High risk of bias’, ‘Low risk of bias’ or ‘Unclear risk of bias’ for each criterion.

Two authors (MK and RO) extracted data independently from the included study onto a specially designed data extraction form. Both found that there were no published data in the manuscript on the primary outcome, change in ICARS score in the included study. The lead author emailed Dr Mariotti who supplied missing data which we subsequently included on the data extraction sheet. If relevant trials were available we intended to conduct statistical analysis as described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) using Review Manager 5 (RevMan 5) software. We would have used the $I^2$ test for heterogeneity and if its value has been greater than 50% we would have inspected trials and forest plots for differences between trials which could explain heterogeneity. If we had been unable to find any explanation, we would have repeated the analysis with a random-effects model.

If no heterogeneity had been demonstrated we intended to use a fixed-effect model. We would have performed sensitivity analysis if there had been significant heterogeneity in the outcomes. We would have assessed antioxidants as a group with additional subgroup analysis of individual antioxidant agents and other pharmacological treatments. Using the Cochrane statistical package, RevMan, we would have calculated risk ratios (RRs) for binary outcomes such as survival, and a difference in means for continuous outcomes like the ICARS score, to determine the treatment effect across trials. If we had analysed survival data using Cox regression methods, we may have had to use the generic inverse variance (GIV) method in RevMan to combine estimated hazard ratios and their standard errors. We would have expressed results as RRs with 95% confidence intervals (CI), risk differences with 95% CI for dichotomous outcomes and mean differences (MDs), and 95% CI for continuous outcomes. We would have analysed all the primary and secondary outcomes under consideration whenever the data allowed.

**Results**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

**Results of the search**

The number of papers found by the new, current strategies are: Cochrane Neuromuscular Disease Group Specialized Register, 3 (0 new); MEDLINE, 148 papers (38 new); EMBASE, 306 (116 new); AMED, 4 (0 new); CINAHL Plus, 54 (27 new); CENTRAL, 35; ORPHANET, 29 (16 new); TRIP, 189 (82 new); PEDRO, 9 (1 new) and 12 additional records through other sources.

**Included studies**

From the searches, two authors independently screened 789 references to potential studies and found that 148 merited further analysis. Three authors screened 148 papers and found that four studies (reported in five full-text articles) should be studied in detail for eligibility (see PRISMA flow chart Figure 1). We identified no additional RCTs when the searches were updated in 2011. There was only one RCT (Mariotti 2003) that fulfilled the criteria set by this review. In this RCT, the antioxidant idebenone 5 mg/kg was compared to placebo. There were 29 participants, who had genetically confirmed, homozygous expansion for Friedreich ataxia, which had been present for more than 10 years. Eighteen of them were wheelchair-dependent at the onset of the study. See Characteristics of included studies. The manuscript did not provide the actual data about the primary outcome for this review, change in the ataxia rating scale ICARS, but we subsequently obtained these data directly from the lead author (Mariotti 2003). The data confirmed that there was no significant difference between the treated and the placebo group (Table 1).
Figure 1. Study flow diagram.

777 records identified through database searching

12 additional records identified through other sources

799 records in total

588 after duplicates were removed

148 records after initial screening

143 records excluded

4 studies (5 full-text articles) assessed for eligibility

3 studies (4 full-text articles) excluded with reasons

1 study included in qualitative synthesis

No study included in quantitative synthesis (meta-analysis)
Excluded studies
There were three excluded studies described in four reports (two of the reports were from the same study (Lynch 2010)). Two excluded RCTs (Di Prospero 2007; Lynch 2010) compared different doses of idebenone to placebo over a six-month period in 48 and 72 participants respectively. They did not fulfil the duration criteria of 12 months set for this review. The third excluded study (Schöls 2005) compared different doses of L-carnitine and creatine over a four-month period and was therefore excluded as it did not fulfil the duration criteria of 12 months. See Characteristics of excluded studies.

Studies awaiting classification
Regarding the use of antioxidants other than idebenone in the treatment of Friedreich ataxia, one RCT (Cooper 2008) fulfilled the duration criteria set by this review. There were 50 participants with genetically confirmed Friedreich ataxia in the study. High- and low-dose coenzyme Q10 and vitamin E antioxidants were compared over a two-year period. There was a lack of a true placebo group in this study. The primary endpoint, change in ICARS score, was not significantly different between the therapy groups. Two of the authors of this review have looked for details of ICARS score and left ventricular mass after 12 months, but to date have not received any results. On the data supplied from the published work we were not able to include the study in this update. See Characteristics of studies awaiting classification.

Ongoing studies
See Characteristics of ongoing studies for details of five ongoing studies of antioxidants in Friedreich ataxia. Among these is a recently completed RCT using idebenone (Schulz ongoing). This study, which was originally called MICONOS, recruited 232 participants in 13 centres in six European countries. An optional two-year open-label extension study with high dose idebenone is still ongoing in several centres. An interim report (Schulz ongoing) confirmed that idebenone was well tolerated by participants with Friedreich ataxia. Although the results of this study have not yet (October 2011) been published, a press release by the sponsor, Santhera Pharmaceuticals, in May 2010 stated that: “This study failed to reach its primary endpoint”. The primary endpoint was improvement in the ICARS score from baseline. A detailed analysis of the cardiac endpoint is still ongoing (www.santhera.com). Published results of this study are expected later in 2011 or 2012. A double-blind clinical trial (NCT00530127) using three different doses of deferasiprone, 20, 40 and 60 mg/kg/day, is completed but full results are not yet available. However, at the euro-ATAXIA conference (October 2010 in Cervia, Italy) the study investigators told the gathering that participants who were taking the highest dose of deferasiprone developed a worsening of ataxic symptoms leading to a premature termination of their participation in this study.
A study using epoetin alfa in Friedreich ataxia patients is active but not recruiting at present (NCT01016366). A RCT using pioglitazone (NCT 00811681) is currently recruiting participants with Friedreich ataxia. The estimated study completion date is December 2012. A clinical trial of EGb 761 is recruiting participants (NCT00824512) (May 2011).

Risk of bias in included studies
The risk of bias table for the included study is summarised in Figure 2. The method of measuring the primary outcome was not described in the manuscript and the lead review author sought data. The study author’s response revealed that the assessors of the primary outcome were blind to the participants’ assignment. The method of measuring the secondary outcome was outlined in the manuscript. The outcome assessors were blinded to the participants’ assignment. No reference was made as to how allocation concealment was carried out.
Effects of interventions

We could not perform a meta-analysis because only one study was included (Mariotti 2003). For this study we calculated the mean improvement and the level of significance. Values < 0.05 were considered significant.

Idebenone versus placebo

Primary outcome measure: change in ataxia rating scale

This study measured change in ataxia rating scale using the ICARS scale. The scores are outlined in Table 1 and do not reveal any significant difference between the idebenone-treated and placebo groups.

Secondary outcome measures

Change in left ventricular mass index of the heart as measured by $^{31}$P magnetic resonance spectroscopy after 12 months of treatment

Magnetic resonance spectroscopy was not carried out in this study.

Change in left ventricular mass of the heart as measured by echocardiography after 12 months of treatment

Change in left ventricular mass was measured by echocardiography. There was a 10.7% ($P = 0.01$) worsening in left ventricular mass (Table 2) after 12 months of treatment in the placebo group and a 5.6% improvement in the idebenone-treated group after 12 months of treatment. The MD was 16.37% (95% CI 2% to 31%). On multivariate regression analysis, the effect of idebenone treatment after adjusting for age of enrolment, gender, disease and baseline value of ultrasound measures showed an independent significant effect ($P = 0.007$).


**Improvement in quality of life score after 12 months**
This was not assessed by this study.

**Severe adverse effects**
There were no severe adverse effects due to idebenone or placebo.

**Mild adverse effects**
There were no reported mild adverse effects.

**Survival**
One of the placebo study participants died during the study due to diabetic ketoacidosis five months after enrolment.

**DISCUSSION**

The one eligible trial of the treatment of Friedreich ataxia showed no improvement in the primary outcome with the antioxidant idebenone. The study (Mariotti 2003) compared treatment with idebenone 5 mg/kg versus placebo. It evaluated the primary outcome, change in ataxia rating scale using the ICARS scale. The second secondary outcome, change in left ventricular mass of the heart as measured by echocardiography, showed a significant improvement at six months when idebenone was used and this trend was confirmed at 12 months. The clinical relevance of this effect was not evaluated in the included study. The author of the included study provided us with information on improvement in the interventricular septal (IVS) thickness of the heart, which also showed significant improvement after 12 months of treatment with idebenone (Table 3). IVS thickness was not a secondary outcome in our review, but we have presented details of IVS thickness in the Discussion as idebenone had a significant effect on it in this RCT. A recent study, Lynch 2010, did not support this finding from the Mariotti 2003 study. Lynch 2010 showed that idebenone did not reduce left ventricular hypertrophy or improve cardiac function in patients with Friedreich ataxia over a period of six months. This study could not be included in the review owing to its short duration.

We excluded the two six-month RCTs (Di Prospero 2007; Lynch 2010) from the review because of their short duration. However, both studies provided important new information about Friedreich ataxia. The Di Prospero 2007 study showed that idebenone did not decrease the urinary biomarker, 8-hydroxy-2-deoxyguanosine. The Lynch 2010 study revealed that the sensitivity of the ICARS and Friedreich Ataxia Rating Scale (FARS) to change was limited. The ICARS and FARS take a longer time to complete than the more recently developed and shorter Scale for Assessment and Rating of Ataxia (SARA) which has been validated for use in Friedreich ataxia (Bürk 2009). The ICARS has a 100-point scale, FARS a 122-point scale and SARA a 40-point scale. The scales are based on standard neurological examination and aim to provide a quantitative estimate of the severity of neurological symptoms.

The Friedreich ataxia composite test (FACT) measures performance in specific tasks. It comprises a timed 25-foot walk, a hand dexterity test using a nine-hole peg board, a quantitative measure of dysarthria by repeating the word PATA several times and a low contrast vision test. It takes 5 to 10 minutes to carry out. One could argue that a well designed assessment of functional abilities is a more appropriate outcome measure for a clinical trial. FACT was validated in 2005 (Lynch 2005) as an accurate assessment of disease progression in Friedreich ataxia.

Despite the recognised value of these studies, there is some disagreement about the validity of these ataxia rating scales and the functional composite scale in providing a clinically meaningful measure of disease severity and progression, which is appropriate as primary outcome for clinical trials. A collaborative project, funded by the European Union, called European Friedreich’s Ataxia Consortium for Transitional Studies (EFACTS) (http://ec.europa.eu) is going to test the validity of the SARA in a four-year prospective study, while an American network of clinical centres is using the FARS for long-term follow-up.

The ongoing RCT (Schulz ongoing) in Friedreich ataxia is using change in ICARS scale after 12 months as its primary endpoint. Its results and those of the other ongoing studies we identified (NCT00530127; NCT 00811681; NCT00824512; NCT01016366) will be discussed in this review as soon as they become available.

Other studies using idebenone in the treatment of Friedreich ataxia were open label prospective, non randomised controlled trials (Artuch 2002; Buyse 2003; Hauses 2002; Pineda 2008; Ribai 2007). We did not include these studies in the review as they were not RCTs. They varied in length from six months to five years (Ribai 2007). They all used idebenone 5 mg/kg with one exception (Pineda 2008). Ribai 2007 treated 88 people with Friedreich ataxia over a five-year period and reported that the neurological condition deteriorated over time, even taking idebenone. An improvement was noted in left ventricular mass of the heart but cardiac function as measured by ejection fraction did not improve.

Deferiprone 30 mg/kg was used in an open study (Christou 2010) for one year with six Friedreich ataxia patients. The study reported no improvement in ICARS score but some improvement in cardiac parameters as measured by echocardiogram. Full results of the ongoing clinical trial (NCT00530127) described in the ongoing studies are not yet available.

In addition to the ongoing study of epoetin alfa (NCT01016366) in Friedreich ataxia patients, erythropoietin was used in a double-blind, placebo-controlled study (Mariotti 2010) with 16 participants over a six-month period. This study showed that the doses...
and the drug schedules were safe. However, erythropoietin was not
effective in increasing the levels of frataxin protein in lymphocytes
of Friedreich ataxia patients.

RCTs using pioglitazone (NCT 00811681) and Egb 761 (NCT00824512) are mentioned in the Characteristics of ongoing
studies. As researchers await a decision from the US FDA regarding
a phase I clinical trial using HDACi, Pandolfo et al have shown
that nucleic acids and protein-based biomarkers could be used to
monitor the clinical evaluation of HDACi in Friedreich ataxia pa-
tients (Pandolfo 2010).

A collaborative gene therapy project between Oxford, England and
Madrid, Spain demonstrated that vectors carrying the full frataxin
gene led to persistent expression of frataxin in vivo after injection
into a mouse cerebellum (Gimenez-Cassina 2011). A further study
in Bristol, England aims to establish whether transplantation of
human bone marrow-derived stem cells will protect against pro-
gression of disease in an animal model of Friedreich ataxia (Ataxia
UK 2012).

The authors of this review felt that all relevant studies were iden-
tified. Further data requested from authors of the only included
clinical trial (Mariotti 2003) were obtained and confirmed that
idebenone produced no significant change in ICARS score. The
quality of evidence presented on the change in ICARS score and
left ventricular heart mass (Mariotti 2003) showed no obvious po-
tential for bias in its compilation. The evidence about idebenone
from the included study has been confirmed in the open clinical
trials described above.

The open clinical trials were not included in this Cochrane sys-
tematic review because the lack of randomisation excluded them
from consideration in any formal meta-analysis. There was signif-
icant variance in these open trials due to the variation in genetic
severity, the differing age of onset of the condition, the individual
clinical progression of Friedreich ataxia, the heterogeneity of clin-
ical features in Friedreich ataxia and the variation in ICARS scores
at the start of the study for each individual. In the Schulz ongoing
study an effort was made to eliminate some of these variables by
enrolling a specific percentage of mobile participants.

Currently, idebenone is available to some people with Friedreich
ataxia free of charge while others have to pay for it (Euro-ATAXIA
2009). Idebenone is expensive when purchased through the phar-
maceutical company and therefore costs countries who supply it
to people with Friedreich ataxia a significant amount of money.
It may be more appropriate for people with Friedreich ataxia who
could benefit from idebenone to receive it as part of a RCT. There
has been further confirmation of this opinion from the press re-
lease issued by Santhera Santhera 2010 about the MICONOS
RCT (Schulz ongoing), in which the company said that this trial
had missed its primary end point, change in the ataxia rating scale
ICARS.

Over the last decade, researchers all over the world have co-op-
erted to the extent that there have been a number of multicen-
tre RCTs (NCT00530127; NCT01016366; Lynch 2010; Schulz
ongoing) in Friedreich ataxia. One of them is an international trial
(NCT00530127). The research on HDACi is also international.

AUTHORS’ CONCLUSIONS

Implications for practice

There is no evidence in one small RCT that idebenone has a sig-
nificant effect on the neurological status of people with Friedreich
ataxia. The second secondary outcome change in left ventricular
heart mass showed a significant improvement but the clinical re-
levance of this change was not assessed in the included study. To
date, there is no clear evidence to recommend idebenone for the
treatment of Friedreich ataxia.

Implications for research

Friedreich ataxia is a slowly progressive disorder that affects a
small patient population. The progress of the condition cannot
be assessed by an easily defined clinical marker or biochemical
biomarker. Clinical assessment is even more difficult when the
patient is wheelchair-dependent. In view of these factors, large,
placebo-controlled RCTs of 12 months duration are needed to
show the efficacy of drug treatment in Friedreich ataxia. One of
the excluded RCTs (Lynch 2010) has demonstrated that the cur-
rent ataxia scales have limitations.

In May 2010, a collaborative project for translational research
in Friedreich ataxia was granted funding to the value of almost
EURO6,000,000 by the European Union in the VII framework
programme for research and technological development. This
money will be used to explore the pathogenesis of the disease,
the functions of frataxin, make new cellular and animal disease
models, study the natural history of the disease, develop potential
therapies, explore biomarkers and validate clinical outcomes for
future clinical trials in Friedreich ataxia.

ACKNOWLEDGEMENTS

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Disease Review Group for their availability and guidance at all
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Neuromuscular Disease Group was funded by the TREAT NMD
European Union Grant 036825. At the time of the update editor-
ial support was funded by the MRC Centre for Neuromuscular
Diseases. We wish to thank Dr Lynn Killen, Lecturer in Statistics,
Dublin City University, and the Irish College of General practi-
tioners, Dublin, Ireland for their help. We would like to thank our

Antioxidants and other pharmacological treatments for Friedreich ataxia (Review)

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peer reviewers for their comments and help in producing the final review.

The editorial base of the Cochrane Neuromuscular Disease Group is supported by the MRC Centre for Neuromuscular Diseases.

REFERENCES

References to studies included in this review

Mariotti 2003 [published and unpublished data]

References to studies excluded from this review

Di Prospero 2007 [published data only]

Lynch 2010 [published data only]

Schöls 2005 [published data only]

References to studies awaiting assessment

Cooper 2008 [published data only]

References to ongoing studies

NCT00530127 [unpublished data only]

NCT00811681 [unpublished data only]

NCT00824512 [unpublished data only]

NCT01016366 [unpublished data only]

Schulz ongoing [published data only]

Additional references

Artuch 2002

Ataxia UK 2012

Boddaert 2007

Boesch 2007

Buyse 2003

Bürk 2009
Bürk K, Mälzig U, Wolf S, Heck S, Dimitriadis K, Schmitz-Hübsch T at al. Comparison of three clinical rating scales...

Campuzano 2009

Christou 2010

EMA 2009

Emond 2000

Euro-ATAXIA 2009
Euro-ATAXIA newsletter no. 34. www.euro-ataxia.eu/ in Friedreich's ataxia.

Gimenez-Cassina 2011

Grothues 2002

Hausse 2009

Herman 2006

Higgins 2008

Kahlton 2008

Lodi 2001

Lynch 2005

Mariotti 2010

Orrell 2011

Pandolfo 2010

Pershadingh 2004

Pineda 2008

Ribai 2007

Rustin 1999

Santhera 2010
Santhera. May 20, 2010: Santhera’s MICONOS Trial with Catena®/Sovrima® in Friedreich's Ataxia Misses...

Schulz 2000

References to other published versions of this review

Kearney 2009

* Indicates the major publication for the study
## Characteristics of included studies

### Mariotti 2003

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, double-blind, placebo-controlled clinical trial</td>
</tr>
<tr>
<td>Participants</td>
<td>29 participants: 14 received idebenone, 15 received placebo; mean age 26.2 years (range 20.8 to 31.8 years); mean duration of illness 15.1 years (range 10.6 to 20.1)</td>
</tr>
<tr>
<td>Interventions</td>
<td>5 mg/kg idebenone three times daily for one year</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Change in ataxia rating scale as measured by ICARS</td>
</tr>
<tr>
<td></td>
<td>Change in left ventricular heart mass as measured by echocardiography</td>
</tr>
<tr>
<td>Notes</td>
<td>ICARS: International Co-operative Ataxia Rating Score</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Randomization of patients, stratified according to IVS thickness at baseline (IVS =12 to 14 mm, and &gt;14 mm) was computer generated” Comment: probably done</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No mention of it in report so probably not done</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Quote: “Idebenone 60 mg/capsule) and identical placebo capsules were prepackaged and provided by Takeda” Comment: probably done</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Data on primary outcome sought and obtained</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Selective reporting, as figures not provided for the primary outcome in the published report. However, the trial author supplied the data to the review authors</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>The proportion of wheelchair-dependent and non-wheelchair-dependent participants was significantly different in each group. Seven of the fourteen participants were wheelchair-dependent in the</td>
</tr>
</tbody>
</table>
idebenone treated group. Eleven of the fifteen participants in the placebo group were wheelchair-dependent.

<table>
<thead>
<tr>
<th>Blinding of outcome assessors</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quote “Echocardiographers... were blinded to patient’s assignment” Dr Mariotti informed the authors of this review that the outcome assessors for the change in ataxia scale were blinded to the patient's assignment. Comment: probably done</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Prospero 2007</td>
<td>Duration of RCT insufficient</td>
</tr>
<tr>
<td>Lynch 2010</td>
<td>Duration of RCT insufficient</td>
</tr>
<tr>
<td>Schöls 2005</td>
<td>Duration of RCT insufficient</td>
</tr>
</tbody>
</table>

### Characteristics of studies awaiting assessment  * [ordered by study ID] *

#### Cooper 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>Pilot study. Randomised double-blind trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>50 Friedreich ataxia patients</td>
</tr>
<tr>
<td>Interventions</td>
<td>High or low dose coenzyme Q10 or vitamin E</td>
</tr>
<tr>
<td>Outcomes</td>
<td>International Co-operative Ataxia Ratings Scale (ICARS) was assessed over two years as the primary end-point</td>
</tr>
<tr>
<td>Notes</td>
<td>Unable to obtain details from the trial author of the change in ICARS score after 12 months of treatment</td>
</tr>
</tbody>
</table>
## Characteristics of ongoing studies  *(ordered by study ID)*

### NCT 00811681

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Effect of pioglitazone administered to patients with Friedreich's ataxia: proof of concept (ACTFRIE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, double-blind, controlled clinical trial</td>
</tr>
<tr>
<td>Participants</td>
<td>Genetically confirmed Friedreich ataxia with GAA repeat length on the shorter allele of ≥ 300</td>
</tr>
<tr>
<td>Interventions</td>
<td>Pioglitazone and placebo</td>
</tr>
</tbody>
</table>
| Outcomes            | Change in ataxia rating scale as measured by ICARS and FARS scales every 6 months over a 2-year period  
|                     | Change in cardiac parameters as measured by electrocardiography, 24 hour Holter, echocardiography with tissue doppler or cardiac magnetic resonance spectroscopy  
|                     | Change in quality of life scale measured by the Short Form 36 (SF-36) score after 12 months of treatment |
| Starting date       | Dec 2008                                                                                         |
| Contact information | pierre.rustin@inserm.fr or www.orpha.net                                                          |
| Notes               | French national multicentre study, estimated study completion date December 2012               |

### NCT00530127

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>A study investigating the safety and tolerability of deferiprone in patients with Friedreich ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, double-blind, placebo-controlled clinical trial</td>
</tr>
<tr>
<td>Participants</td>
<td>80 participants with genetically confirmed Friedreich ataxia with confirmed mutation (excludes point mutation) in the frataxin gene and with GAA repeats ≥ 400 on the shorter allele</td>
</tr>
<tr>
<td>Interventions</td>
<td>3 different doses of deferiprone and a placebo</td>
</tr>
</tbody>
</table>
| Outcomes            | Participants’ tolerance of treatment  
|                     | Change in ataxia rating scale as measured by ICARS after 6 months                               |
| Starting date       | April 2008                                                                                       |
| Contact information | Dian Shaw, ApoPharma telephone +1 416 401 7283 dshaw@apotex.com                                  |
| Notes               | International multicentre study with centres in Australia, Belgium, France and Italy            |
### NCT00824512

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Efficacy of EGb 761 in patients suffering from Friedreich ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, double-blind, placebo-controlled trial</td>
</tr>
<tr>
<td>Participants</td>
<td>20 ambulatory participants with genetically confirmed Friedreich ataxia</td>
</tr>
<tr>
<td>Interventions</td>
<td>EGb 761 120mg twice daily, placebo 1 tablet twice daily</td>
</tr>
</tbody>
</table>
| Outcomes            | Primary outcome: creatine re-phosphorylation rate post exercise using P-31 NMR spectroscopy after 12 weeks of treatment  
Secondary outcome: skeletal muscle perfusion post exercise |
| Starting date       | June 2008                                                     |
| Contact information | Ipsen Recruitment Enquiries [clinical.trials@ipsen.com](mailto:clinical.trials@ipsen.com) |
| Notes               | This study is currently recruiting participants in the Hospital Necker Enfants Malades, Paris, France, 75015. Study director is Dr Philippe Garnier |

### NCT01016366

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Safety study of carbamylated erythropoietin to treat patients with the neurodegenerative disorder Friedreich's ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Double-blind placebo-controlled phase II clinical trial</td>
</tr>
<tr>
<td>Participants</td>
<td>36 participants with genetically confirmed Friedreich ataxia with a nucleotide triplet repeat size greater than 400</td>
</tr>
<tr>
<td>Interventions</td>
<td>Erythropoetin 325 µg Lu AA24493 dose injected 3 times per week for 2 weeks or a placebo 3 times a week for 2 weeks</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Measure frataxin and biomarkers of oxidative stress</td>
</tr>
<tr>
<td>Starting date</td>
<td>October 2009</td>
</tr>
<tr>
<td>Notes</td>
<td>Expected completion date March 2011</td>
</tr>
</tbody>
</table>
Schulz ongoing

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>12-month European phase III clinical study on SNT-MC17/idebenone in the treatment of Friedreich’s ataxia: baseline neurology data and interim safety results. Original Title :MICONOS (Mitochondrial Protection with Idebenone In Cardiac Or Neurological Outcome Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, double-blind, placebo-controlled clinical trial</td>
</tr>
<tr>
<td>Participants</td>
<td>A total of 232 patients who were older than 8 years of age with 60 places reserved for participants who can still walk</td>
</tr>
<tr>
<td>Interventions</td>
<td>3 different doses of idebenone and a placebo</td>
</tr>
</tbody>
</table>
| Outcomes            | Change in ataxia rating scale as measured by ICARS scale after 12 months of treatment  
Change in left ventricular mass index as measured by cardiac magnetic resonance spectroscopy  
Change in quality of life scale after 12 months of treatment                                                                                                                                               |
| Starting date       | December 2005  
Some of the participants at the centre in Germany finished the trial in July 2008 and were then enrolled in an extension study. In the UK the first patient was recruited in September 2008                                                                 |
| Contact information | www.santhera.com  
Klaus Schollmeier, Chief Executive Officer  
Phone: +41 (0)61 906 89 52 or klaus.schollmeier@santhera.com                                                                                                                                                      |
| Notes               | European multicentre study with centres in Belgium, France, Germany, Netherlands and UK  
Results of this trial are expected in Autumn 2011                                                                                                                                                             |
DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Mariotti 2003, ICARS\(^a\) scores

<table>
<thead>
<tr>
<th>Placebo group n = 14</th>
<th>Baseline score, mean ± SD(^b)</th>
<th>Score after 6 months, mean ± SD</th>
<th>Change in score after 6 months, mean ± SD</th>
<th>Per cent change</th>
<th>Score after 12 months Mean ± SD</th>
<th>Change in score after 12 months, mean ± SD</th>
<th>Per cent change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>58.8 ± 21.7</td>
<td>57.1 ± 20.6</td>
<td>-1.7</td>
<td>-2.9%</td>
<td>49.8 ± 26.1</td>
<td>-9.0</td>
<td>-15.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idebenone group n = 14</td>
<td>Baseline score, mean ± SD</td>
<td>Score after 6 months, mean ± SD</td>
<td>Change in score after 6 months, mean ± SD</td>
<td>Per cent change</td>
<td>Score after 12 months, mean ± SD</td>
<td>Change in score after 12 months, mean ± SD</td>
<td>Per cent change</td>
</tr>
<tr>
<td></td>
<td>53.7 ± 25.5</td>
<td>52.4 ± 26.6</td>
<td>-1.3</td>
<td>-2.4%</td>
<td>52.9 ± 26.6</td>
<td>-0.8</td>
<td>-1.5%</td>
</tr>
</tbody>
</table>

\(^a\) ICARS: International Ataxia Co-operative Rating Scale; a decrease in ICARS score indicates improvement.
\(^b\) SD: standard deviation.

Table 2. Mariotti 2003, left ventricular mass\(^a\) results

<table>
<thead>
<tr>
<th>Placebo group n = 14</th>
<th>Baseline score, mean ± SD(^b)</th>
<th>Score after 6 months, mean ± SD</th>
<th>Change in score after 6 months, mean ± SD</th>
<th>Per cent change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>187.2 ± 27.1</td>
<td>192.4 ± 22.2</td>
<td>5.2 ± 18.2</td>
<td>3.1% ± 9.7</td>
<td>P = 0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idebenone group n = 14</td>
<td>Baseline score, mean ± SD</td>
<td>Score after 6 months, mean ± SD</td>
<td>Change in score after 6 months, mean ± SD</td>
<td>Per cent change</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>203.5 ± 27.2</td>
<td>163.6 ± 9.2</td>
<td>10.7 ± 16.3</td>
<td>P = 0.01</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) SD: standard deviation.
### Table 2. Mariotti 2003, left ventricular mass results (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Score after 12 months, mean ± SD</th>
<th>Change in score after 12 months, mean ± SD</th>
<th>Per cent change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>184.2 ± 30.1</td>
<td>-14.0 ± 33.9</td>
<td>-5.6 ± 16.9</td>
<td>P = 0.01</td>
</tr>
</tbody>
</table>

*A decrease in left ventricular mass indicates improvement.

*SD: standard deviation.

### Table 3. Mariotti 2003, interventricular septum thickness results

<table>
<thead>
<tr>
<th>Placebo group n = 14</th>
<th>Baseline score, mean ± SD</th>
<th>Score after 6 months, mean ± SD</th>
<th>Change in score after 6 months, mean ± SD</th>
<th>Per cent change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>14.0 ± 2.1</td>
<td>14.5 ± 2.5</td>
<td>0.5 ± 1.0</td>
<td>3.3 ± 7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Score after 12 months, mean ± SD</td>
<td>Change in score after 12 months, mean ± SD</td>
<td>Per cent change</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.7 ± 1.6</td>
<td>0.7 ± 1.0</td>
<td>5.5 ± 7.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Idebenone group n = 14</th>
<th>Baseline score, mean ± SD</th>
<th>Score after 6 months, mean ± SD</th>
<th>Change in score after 6 months, mean ± SD</th>
<th>Per cent change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13.9 ± 1.5</td>
<td>13.3 ± 1.9</td>
<td>-0.6 ± 1.0</td>
<td>-4.3 ± 11.1</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Score after 12 months, mean ± SD</td>
<td>Change in score after 12 months, mean ± SD</td>
<td>Per cent change</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.2 ± 1.5</td>
<td>-0.7 ± 1.6</td>
<td>-4.5 ± 12.3</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

*A decrease in interventricular septum thickness of the heart indicates improvement.

*SD: standard deviation.
APPENDICES

Appendix 1. CENTRAL search strategy
#1 friedreich* near ataxia*

Appendix 2. MEDLINE (OvidSP) search strategy
1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 drug therapy.fs.
6 randomly.ab.
7 trial.ab.
8 groups.ab.
9 or/1-8
10 exp animals/ not humans.sh.
11 9 not 10
12 Friedreich Ataxia/
13 (friedreich adj5 ataxia).tw.
14 12 or 13
15 (idebenone or noben).mp.
16 Ascorbic Acid/ or Vitamin E/ or Vitamin A/
17 alpha-Tocopherol/
18 Selegiline/
19 Acetylcysteine/
20 Superoxide Dismutase/
21 Dehydroepiandrosterone/
22 Glutathione/
23 Urea/
24 Uric Acid/
25 Selenium/
26 Carotenoids/
27 Flavonoids/
28 Taurine/
29 Erythropoietin/
30 Iron Chelating Agents/
31 Chelation Therapy/
32 deferiprone.mp.
33 Pyridones/
34 pioglitazone.mp.
35 exp Antioxidants/
36 exp Therapeutics/
37 (vitamin adj5 (a or c or e)).mp.
38 ascorbic acid.mp.
39 (alhydracopherol or alpha-tocopherol).mp.
40 (selegiline or deprenyl or superoxide dismutase or dehydroepiandrosterone or glutathione).mp.
41 ((n adj acetyl adj3 cysteine) or n adh acetylcysteine).mp.
42 (urea or uric acid or selenium or carotene or carotenoids or flavinoids or taurine).mp.
43 (recombinant human erythropoietin or iron chelat$ or deferiprone or pioglitazone).mp.
44 (therapy or treatment).tw.
45 Histone Deacetylase Inhibitors/
Appendix 3. EMBASE (OvidSP) search strategy

1 Randomized Controlled Trial/
2 Clinical Trial/
3 Multicenter Study/
4 Controlled Study/
5 Crossover Procedure/
6 Double Blind Procedure/
7 Single Blind Procedure/
8 exp RANDOMIZATION/
9 Major Clinical Study/
10 PLACEBO/
11 Meta Analysis/
12 phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
13 (clin$ adj25 trial$).tw. (233136)
14 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.
15 placebo$.tw.
16 random$.tw.
17 control$.tw.
18 (meta$analys$ or systematic review$).tw.
19 (cross$over or factorial or sham$ or dummy).tw.
20 ABAB design$.tw.
21 or/1-20
22 human/
23 nonhuman/
24 22 or 23
25 21 not 24
26 21 and 22
27 25 or 26
28 Friedreich Ataxia/
29 (friedreich adj5 ataxia).tw.
30 28 or 29
31 (idebenone or noben).mp.
32 Ascorbic Acid/ or Vitamin D/ or Alpha Tocopherol/
33 SELEGILINE/
34 Acetylcysteine/
35 Superoxide Dismutase/
36 Prasterone/
37 GLUTATHIONE/
38 UREA/
39 Uric Acid/
40 SELENIUM/
41 CAROTENE/
42 Carotenoid/
43 Flavonoid/
44 TURINE/
Appendix 4. CINAHL (EBSCOhost) search strategy

S22. S18 and S21
S21. S19 or S20
S20. friedreich* ataxia
S19. (MH “Friedreich’s Ataxia”)
S18. S17 or S16 or S15 or S14 or S13 or S12 or S11 or S10 or S9 or S8 or S7 or S6 or S5 or S4 or S3 or S2 or S1
S17. TI random* or AB random*
S16. (TI (cross*over or placebo* or control* or factorial or sham? or dummy) ) or (AB (cross*over or placebo* or control* or factorial or sham? or dummy) )
S15. (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic) ) and (TI (trial*) or AB (trial*) )
S14. (TI (meta*analysis* or systematic review*) ) or (AB (meta*analysis* or systematic review*) )
S13. (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*) ) and (TI (blind* or mask*) or AB (blind* or mask*) )
S12. ABAB design*
S11. PT clinical trial or PT systematic review
S10. (MH “Factorial Design”)
S9. (MH “Concurrent Prospective Studies”) or (MH “Prospective Studies”)
S8. (MH “Meta Analysis”)
S7. (MH “Solomon Four-Group Design”) or (MH “Static Group Comparison”)  
S6. (MH “Quasi-Experimental Studies”)
S5. (MH “Placebos”)
S4. (MH “Double-Blind Studies”) or (MH “Triple-Blind Studies”)
S3. (MH “Clinical Trials+”)  
S2. (MH “Crossover Design”)
S1. (MH “Random Assignment”) or (MH “Random Sample”) or (MH “Simple Random Sample”) or (MH “Stratified Random Sample”) or (MH “Systematic Random Sample”)
Appendix 5. AMED (OvidSP) search strategy

1. Randomized controlled trials/
2. Random allocation/
3. Double blind method/
4. Single-Blind Method/
5. exp Clinical Trials/
7. ((singl$ or doubl$ or treb$ or trip$) adj25 (blind$ or mask$ or dummy)).tw.
8. placebo$.
9. placebo$.tw.
10. random$.tw.
11. research design/
12. Prospective Studies/
13. meta analysis/
14. (meta2analys$ or systematic review$).tw.
15. control$.tw.
16. (multicenter or multicentre).tw.
17. ((study or studies or design$) adj25 (factorial or prospective or intervention or crossover or cross-over or quasi-experiment$)).tw.
18. or/1-17
19. friedreich$.mp.
20. 18 and 19

Appendix 6. LILACS search strategy

Mh friedreich ataxia or Tw friedreich* [Palavras]

Appendix 7. ORPHANET search strategy

1. Simple Search: Friedreich's ataxia by disease name
2 Result(s)
   • Ataxia, Friedreich-like, with selective vitamin E deficiency
   • Friedreich ataxia

Appendix 8. TRIP search strategy

Search Strategy for TRIP
1. Quick Search: Friedreich's ataxia by Title [43 Records]
2. Quick Search: Friedreich ataxia by Title[53 Records]
3. Quick Search: Idebenone by Title [23 Records]
Appendix 9. PEDRO search strategy

1. Simple Search: Friedreich’s ataxia [0 Results]
2. Simple Search: Friedreich ataxia [0 Results]
3. Simple Search: Ataxia [6 Results]

WHAT’S NEW

Last assessed as up-to-date: 11 July 2011.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>7 December 2011</td>
<td>New citation required but conclusions have not changed</td>
<td>New search, no new studies included</td>
</tr>
<tr>
<td>4 October 2011</td>
<td>New search has been performed</td>
<td>We updated the searches to 11 July 2011. No new studies were identified for inclusion. We included more detail on ataxia rating scales and a PRISMA flow diagram</td>
</tr>
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HISTORY

Protocol first published: Issue 2, 2009
Review first published: Issue 4, 2009

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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<tr>
<td>18 January 2010</td>
<td>Amended</td>
<td>Figures in Table 1 corrected. Other minor changes.</td>
</tr>
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</table>

CONTRIBUTIONS OF AUTHORS

Dr Mary Kearney with the help of Prof Massimo Pandolfo wrote the first draft of the protocol, Dr Richard Orrell and Dr Michael Fahey edited the protocol. Dr Mary Kearney edited the final text and all agreed to the final version submitted on 2nd November 2008 and published in April 2009. Dr Mary Kearney and Dr Richard Orrell performed data extraction and analyses. Dr Mary Kearney wrote the first draft of the review, and the other co-authors contributed to subsequent revisions for important intellectual content. Dr Mary Kearney, Dr Richard Orrell and Dr Michael Fahey inspected the list of clinical trials. Dr Mary Kearney wrote the draft for the updated version of the review and all authors contributed to subsequent revisions for important intellectual content.
DECLARATIONS OF INTEREST

Dr Richard Orrell and Dr Mary Kearney have no conflicts of interest.

Professor Massimo Pandolfo was an investigator in the MICONOS (Santhera, idebenone) and LA-29 (Apopharma, deferiprone) trials, for which his institution received funding. His institution has received a research grant from Repligen Corporation for testing novel HDAC inhibitors in patients’ cells and in mouse models of Friedreich’s ataxia. He has received honoraria from Santhera and Apopharma. He has received royalties from Athena Diagnostics for granting an exclusive license to commercially perform genetic testing for Friedreich ataxia. None of the declared relationships have influenced this review in any way.

Dr Michael Fahey has served on a scientific advisory board and acted as a consultant for Actelion Pharmaceuticals Ltd and also received funding for travel. He receives research support from NHMRC and the NIH (1R03HD058625-01, CI). He has held/holds stock in Sigma Pharmaceuticals and has given expert testimony on behalf of the Therapeutic Goods Administration.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.
  No internal source of support

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Three of the four authors inspected the list of potentially relevant studies.

The NORD database was not searched for the review or the update.

We have included a 'Summary of findings' table. We have also added a PRISMA flow chart to show the study selection process.

INDEX TERMS

Medical Subject Headings (MeSH)

Antioxidants [*therapeutic use]; Friedreich Ataxia [*drug therapy]; Hypertrophy, Left Ventricular [drug therapy; ultrasonography]; Randomized Controlled Trials as Topic; Rare Diseases [*drug therapy]; Ubiquinone [*analogs & derivatives; therapeutic use]

MeSH check words

Humans