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Pharmacological treatments for Friedreich ataxia (Review)

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[Intervention Review]

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% of people with the disorder. There is no easily defined clinical or biochemical marker and no known treatment. This is the second update of a review first published in 2009 and previously updated in 2012.

Objectives

To assess the effects of pharmacological treatments for Friedreich ataxia.

Search methods

On 29 February 2016 we searched The Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, EMBASE and CINAHL Plus. On 7 March 2016 we searched ORPHANET and TRIP. We also checked clinical trials registers for ongoing studies.

Selection criteria

We considered randomised controlled trials (RCTs) or quasi-RCTs of pharmacological treatments (including vitamins) in people with genetically-confirmed Friedreich ataxia. The primary outcome was change in a validated Friedreich ataxia neurological score after 12 months. Secondary outcomes were changes in cardiac status as measured by magnetic resonance imaging or echocardiography, quality of life, mild and serious adverse events, and survival. We excluded trials of duration shorter than 12 months.

Data collection and analysis

Three review authors selected trials and two review authors extracted data. We obtained missing data from the two RCTs that met our inclusion criteria. We collected adverse event data from included studies. We used standard methodological procedures expected by Cochrane.

Main results

We identified more than 12 studies that used antioxidants in the treatment of Friedreich ataxia, but only two small RCTs, with a combined total of 72 participants, both fulfilled the selection criteria for this review and published results. One of these trials compared idebenone with placebo, the other compared high-dose versus low-dose coenzyme Q10 and vitamin E (the trialists considered the low-

dose medication to be the placebo). We identified two other completed RCTs, which remain unpublished; the interventions in these trials were pioglitazone (40 participants) and idebenone (232 participants). Other RCTs were of insufficient duration for inclusion.

In the included studies, the primary outcome specified for the review, change in a validated Friedreich ataxia rating score, was measured using the International Co-operative Ataxia Rating Scale (ICARS). The results did not reveal any significant difference between the antioxidant-treated and the placebo groups (mean difference 0.79 points, 95% confidence interval -1.97 to 3.55 points; low-quality evidence).

The published included studies did not assess the first secondary outcome, change in cardiac status as measured by magnetic resonance imaging. Both studies reported changes in cardiac measurements assessed by echocardiogram. The ejection fraction was not measured in the larger of the included studies (44 participants). In the smaller study (28 participants), it was normal at baseline and did not change with treatment. End-diastolic interventricular septal thickness showed a small decrease in the smaller of the two included studies. In the larger included study, there was no decrease, showing significant heterogeneity in the study results; our overall assessment of the quality of evidence for this outcome was very low. Left ventricular mass (LVM) was only available for the smaller RCT, which showed a significant decrease. The relevance of this change is unclear and the quality of evidence low.

There were no deaths related to the treatment with antioxidants. We considered the published included studies at low risk of bias in six of seven domains assessed. One unpublished included RCT, a year-long study using idebenone (232 participants), published an interim report in May 2010 stating that the study reached neither its primary endpoint, which was change in the ICARS score, nor a key cardiological secondary endpoint, but data were not available for verification and analysis.

Authors' conclusions

Low-quality evidence from two small, published, randomised controlled trials neither support nor refute an effect from antioxidants (idebenone, or a combination of coenzyme Q10 and vitamin E) on the neurological status of people with Friedreich ataxia, measured with a validated neurological rating scale. A large unpublished study of idebenone that reportedly failed to meet neurological or key cardiological endpoints, and a trial of pioglitazone remain unpublished, but on publication will very likely influence quality assessments and conclusions. A single study of idebenone provided low-quality evidence for a decrease in LVM, which is of uncertain clinical significance but of potential importance that needs to be clarified. According to low-quality evidence, serious and non-serious adverse events were rare in both antioxidant and placebo groups. No non-antioxidant agents have been investigated in RCTs of 12 months' duration.

PLAIN LANGUAGE SUMMARY

Pharmacological treatments for Friedreich ataxia

Review question

We reviewed the evidence about the effect of antioxidants and other medicines for Friedreich ataxia.

Background

Friedreich ataxia is a rare inherited neurological condition, which first presents between 5 and 15 years of age. It initially causes clumsiness of movement, and progresses to unsteadiness in standing and walking, with wheelchair dependency by late teens or early twenties. Speech usually becomes slurred. A specific faulty gene must be inherited from each parent for the disease to develop in their child (autosomal recessive inheritance). Other major problems which can develop include a curved spine (scoliosis), foot deformity (a high arch), and heart problems, which are a cause of death in 60% of people. Friedreich ataxia has no known effective treatment. Clinical examination and laboratory tests are not very useful for assessing disease progression, and this in turn makes interpreting clinical trial results difficult.

Antioxidants are thought to reduce damage to cells from harmful 'free radicals'. Antioxidants occur naturally in foods in very low levels. Recent studies have found conflicting results about the effect that the antioxidants idebenone, coenzyme Q10 and vitamin E have on the heart in Friedreich ataxia, as measured by thickening of the interventricular septum (the wall between two chambers of the heart), and increased left ventricular mass (the left ventricle is the chamber of the heart that pumps blood around the body).

Study characteristics

We decided to review clinical trials that had participants who took antioxidants for at least 12 months, as Friedreich ataxia is a slowly progressing condition. A wide search of the medical literature found four randomised controlled trials, but only two of them had published results in medical journals. One trial, involving 28 participants, compared idebenone to a placebo. The other, involving 44 participants, compared high-dose and very low-dose combined coenzyme Q10 and vitamin E. The two unpublished trials studied pioglitazone in 40 participants and idebenone in 232 participants, but we had no data.

Key results and quality of the evidence

According to low quality evidence from two small published trials included in the review, antioxidants did not improve neurological symptoms in Friedreich ataxia. An additional large, unpublished study of idebenone reportedly found no benefit from idebenone for heart

or neurological symptoms, but data are not available for checking and analysis. When published this trial will very likely influence our quality assessments and conclusions.

Although some measures of heart wall thickness and mass decreased in the smaller of the two published trials, the quality of this evidence was low or very low and the importance of these findings is not clear. .

Numbers of serious or non-serious adverse events were low and similar with antioxidants and placebo. The only serious adverse event that required withdrawal of an antioxidant was increased bowel frequency in one person receiving coenzyme Q with vitamin E.

The evidence in the review is up to date to February 2016.

Summary of findings for the main comparison. Antioxidant versus placebo for Friedreich ataxia

Antioxidant versus placebo for Friedreich ataxia

Patient or population: people with Friedreich ataxia
Settings: hospital outpatients
Intervention: antioxidant[1] versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Antioxidant				
Ataxia rating score ICARS; range 0 to 100) Follow-up: 1 year	The mean change in ataxia rating score in the control groups was a **4.5-point decrease** and ranged from **0** to **-9 points** [2]	The mean change in ataxia rating score in the intervention groups was **0.79 points higher** (1.97 lower to 3.55 higher)	-	72 (2 studies)	⊕⊕⊖⊖ **low** [3,4]	Decrease in score indicates improvement
Ejection fraction Follow-up: 1 year	The mean change in ejection fraction in the control group was a **0.64% increase**	The mean change in ejection fraction in the intervention group was **0.21% lower** (5.55% lower to 5.13% higher)	-	28 (1 study)	⊕⊖⊖⊖ **very low** [5]	Mariotti 2003 reported no statistically significant difference between treatment and placebo groups in ejection fraction. Baseline levels were normal.
End-diastolic interventricular septal thickness (IVSTd) Measured in mm Follow-up: 1 year	The mean change in IVSTd in the control groups was 0.47 mm and ranged[6] from **0.27 to -0.71 mm**	The mean change in IVSTd in the intervention groups was **-0.65 mm lower** (-2.00 lower to 0.70 higher)	-	72 (2 studies)	⊕⊖⊖⊖ **very low** [3,7]	The clinical relevance of the change in IVSTd is difficult to interpret (see Methods section for details)
Left ventricular mass (LVM) Measured in g Follow-up: 1 year	The mean change in LVM in the control group was an increase of **16.28 g**	The mean change in LVM in the intervention group was **-30.3 g** (53.34 g lower to 7.26 g lower)	-	28 (1 study)	⊕⊕⊖⊖ **low** [4,8]	A decrease in mass indicates improvement. In percentage terms, the MD was a decrease of 16.37% (95% CI 2% to 31%) with antioxidant

Survival (not measured)	-	-	-	-	-	Not an outcome in either study
Severe adverse events Follow-up: 1 year	One event was reported in the control groups; the assumed risk was **3 out of 100**	One event was reported in the intervention groups; the risk was 1.00, 0.07 lower to 15.00 higher	RR 1.00 (0.07 to 15.00)	72 (2 studies)	⊕⊕⊖⊖ **low** [9]	There were 2 adverse events leading to withdrawal (placebo group: prolonged nausea; antioxidant group: increased bowel frequency)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **ICARS:** International Cooperative Ataxia Rating Scale; **MD**: mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Antioxidants were idebenone and a combination of coenzyme Q10 and vitamin E.
[2] The assumed risk is the mean score across control groups in Cooper 2008 and Mariotti 2003.
[3] We downgraded the evidence for risk of bias (study limitations) and heterogeneity (imprecision).
[4] A large completed trial of idebenone involving 232 participants with Friedreich ataxia failed to reach its primary endpoint and remains unpublished. We were unable to obtain data, rendering the results of our review at risk of publication bias. As the quality of the evidence from included studies is already low or very low, and the reported lack of efficacy in the unpublished trial tends to support the findings of our review, we have not further downgraded our assessments. A smaller trial (planned enrolment 40 participants) investigating pioglitazone is also unreported.
[5] Downgraded twice for imprecision (wide CIs in a single small study), and for the indirectness of ejection fraction as a cardiac measure in Friedreich ataxia.
[6] The assumed risk is the mean score across control groupsin the two included studies.
[7] We downgraded the evidence because of the high degree of heterogeneity in the analysis, and inconsistency (the 2 trials show very different effects).
[8] We downgraded the evidence because the outcome measure is of uncertain clinical relevance (indirectness) and the wide CIs encompass both large and very small effects.
[9] We downgraded the evidence twice for imprecision. CIs were very wide. There was one event in each group and the analysis included 72 participants.

BACKGROUND

Description of the condition

Friedreich ataxia (FA) is a rare inherited recessive disorder characterised by a slowly progressive neurological disability, but the most common recessively inherited ataxia worldwide. It was first described in 1863 by the German neurologist and pathologist Nicholas Friedreich. It has a prevalence of approximately 1 in 50,000 in European populations (Dürr 1996). It is thought that about 50,000 individuals worldwide are affected, but more exact figures are not available. There is no biomarker or easily defined clinical marker for this small patient population (Di Prospero 2007; Pandolfo 2008).

Friedreich ataxia age of onset varies. It can present from early infancy to adulthood with unsteadiness in standing or walking. It is followed by progressive limb and gait ataxia, as well as slurred speech. Most people with Friedreich ataxia are wheelchair dependent by their late teens or early twenties. Cardiac dysfunction in the form of congestive cardiac failure and arrhythmia is common. Cardiac complications are the most common cause of death in patients with FA (59% of deaths are from a cardiac cause (Tsou 2011)). Other significant medical problems which may develop include scoliosis and pes cavus in 55%, diabetes in 12% to 30% and impaired glucose tolerance in 49% of people with Friedreich ataxia (Cnop 2012; Dürr 1996).

Mutations in the*Frataxin* gene (*FXN*) on chromosome 9q13 were found to cause Friedreich ataxia in 1996 (Campuzano 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, point mutations are found in heterozygosity with a GAA repeat expansion. The*Frataxin* gene encodes for a small mitochondrial protein called frataxin, whose expression is reduced in Friedreich ataxia (Schulz 2000).

Description of the intervention

Until 2009, the pharmacological treatments most commonly used in clinical trials were antioxidants, of which there were many, including pioglitazone. Since 2009, other agents have been used. The most common drugs are deferiprone, erythropoietin, and histone deacetylase inhibitors, of which there are many, including nicotinamide.

Antioxidants

Antioxidants are biological and chemical compounds that reduce oxidative damage. They are a group of organic nutrients that include vitamins. 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 lipo peroxidation 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 that 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 used as a treatment, for example, in liver, heart, and lung disease.
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 neuro protective antioxidant properties. Its clinical efficacy in Parkinsonism is only apparent when prescribed with levo-dopa (Drugs.com).
6. Dehydroepiandrosterone, a steroid synthesised in brain glial cells.
7. Alpha-tocopheryl quinine EPI-A0001 (A0001), a potent antioxidant and metabolic stimulator.
8. Pioglitazone, a peroxisome proliferator-activated receptor gamma (PPARϒ) 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. It is proposed that this agent could be therapeutic in neurological disease by improving the antioxidant defence mechanism. Pioglitazone crosses the blood-brain barrier in humans (Grommes 2013). A randomised control clinical trial using pioglitazone in Friedreich ataxia was completed in March 2013 (NCT00811681).
9. Some studies have used antioxidants in combination with other pharmacological treatments (Arpa 2014).

Non antioxidant treatment

The most common other pharmaceuticals that have been proposed as treatment for Friedreich ataxia are as follows:

1. Deferiprone, an iron chelator, is a small molecule that preferentially binds iron, a toxic metal, over other metals and prevents a build-up of reactive oxygen species, thereby reducing oxidative stress. Deferiprone can cross the blood-brain barrier.
2. Erythropoietin (EPO), a glycoprotein hormone produced in the kidney that principally regulates red blood cell production. Other biological functions include playing an important part in the brain's response to neuronal injury and in the wound healing process. Recombinant human erythropoietin (rHuEPO) was found to increase frataxin in open-label studies in Friedreich ataxia patients (Boesch 2007; Nachbauer 2011; Saccà 2010). Recombinant DNA (rDNA) molecules are formed by laboratory

methods of genetic recombination to bring together genetic material from multiple sources.

3. Histone deacetylase inhibitors (HDACis) modulate the level of acetylation of chromosomal proteins and other cellular targets, and can revert the silent heterochromatin to an active chromatin conformation and restore the normal function of the silenced genes (Robinson 2014). This results in a raised fraxin level, which is the underlying problem in Friedreich ataxia (Campuzano 1997). The HDACis used to date are nicotinamide and 2-aminobenzamide (109/RG2833).
4. Resveratrol, a plant-derived compound that increased the level of frataxin in cell and mouse models of Friedreich ataxia.
5. Interferon gamma-1b, a compound currently used to treat chronic granulomatous disease and severe malignant osteopetrosis (BNF 2016).

How the intervention might work

Antioxidants are postulated to protect against oxidative stress in neuronal and cardiomyocytes, which is caused by a loss of frataxin in Friedreich ataxia. 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.

When frataxin is deficient, the mitochondrial function of the cell is severely affected. There is a loss of iron sulphur proteins, respiratory chain I, II, III complexes, and aconitase. This causes a reduction in adenosine triphosphate generation. This reduction was confirmed using magnetic resonance spectroscopy on cardiac muscle (Lodi 2001). Mitochondria also become overloaded with iron. This causes an increase in reactive oxygen species which has been verified by increased levels of plasma malondialdehyde and urinary 8-hyroxy-2-deoxyguanosine (Emond 2000). 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.

Deferiprone is proposed to work in Friedreich ataxia by redistributing iron from the overloaded mitochondrial compartment to the cytosol (Kakhlon 2008). Using regimens suitable for patients with no iron overload, deferiprone has been associated with an imaging reduction of iron signal in the dentate nuclei of people with Friedreich ataxia as well as a reduction in neuropathy and ataxia in one open study (Boddaert 2007). Deferiprone does not cause overall iron depletion, unlike other iron chelators, and this makes it an interesting candidate for Friedreich ataxia treatment (Pandolfo 2014).

Erythropoetin, in the form of recombinant human erythropoietin (rhuEPO), has been shown in open label studies to significantly increase frataxin expression in many cells, including lymphocytes from Friedriech ataxia patients in vitro (Boesch 2007; Nachbauer 2011; Saccà 2010).

Histone deacetylase inhibitors (HDACis) work by raising the frataxin level. Herman 2006 showed that in human lymphoblastoid cells from Friedreich ataxia patients, it was possible to revert the FXN gene silencing and raise the low frataxin level. A report from the 2014 Annual American Neurology meeting further confirmed that HDACis induce increased expression of frataxin gene in the participants (Robinson 2014).

Interferon gamma-1b has been found to increase frataxin expression in dorsal root ganglion neurons in treated mouse models and these models also had improved sensorimotor performance (Tomassini 2012).

Why it is important to do this review

Currently, there is conflicting evidence about the value of different treatments in Friedreich ataxia, and in particular, the value of antioxidants. Clinical trials using antioxidants in Friedreich ataxia have been ongoing since the late 1990s and have suggested that idebenone, an antioxidant, may help left ventricular hypertrophy, the most frequent heart abnormality (Buyse 2003; Hausse 2002; Mariotti 2003; Pineda 2008; Ribai 2007; Rustin 1999). However, Ribai 2007 found that even though left ventricular mass improved, cardiac function, as measured by ejection fraction, did not improve. Artuch 2002 and Lynch 2010 did not demonstrate an improvement in cardiac measures with idebenone. Schulz 2000 treated 48 people with Friedreich ataxia with the antioxidant idebenone over an eight-week period and found a significant decrease in urinary 8-hydroxy-2-deoxyguanosine. A more recent study assessed 48 participants over six months and did not observe significant changes in the concentrations of urinary 8-hydroxy-2-deoxyguanosine after idebenone treatment (Di Prospero 2007).

Quebec licensed the antioxidant idebenone from July 2008 for the treatment of Friedreich ataxia. Initial licensing was conditional upon the outcome of clinical trials (Health Canada 2009). During that period, idebenone was provided free of charge, but Quebec withdrew the licence in April 2013. In November 2008, the European Medicines Agency refused marketing authorisation for idebenone in Europe (EMA 2009). The US Food and Drugs Administration has never authorised idebenone for use in Friedreich ataxia.

This is the second update of a review first published in 2009 and previously updated in 2012 (Kearney 2009; Kearney 2012).

OBJECTIVES

To assess the effects 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 of antioxidants and other pharmacological treatments for Friedreich ataxia. Quasi-RCTs are studies that use semi-systematic methods of allocation to treatments, for example, alternation, or allocation by case record number of date of birth.

Types of participants

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

Types of interventions

Any pharmacological treatment compared with any other pharmacological treatment, placebo, or no treatment. We included any form of treatment considered to have an antioxidant effect (including vitamins) as well as other pharmacological treatments.

We analysed antioxidants as a group. We would have performed additional subgroup analyses of individual antioxidants if the review had included sufficient trials. We would have considered other pharmacological treatments individually, or within therapeutic groups, as appropriate.

Types of outcome measures

Primary outcomes

Change in score on validated Friedreich ataxia rating scales after 12 months of treatment. We considered the following scales:

- Scale for the Assessment and Rating of Ataxia (SARA);
- Friedreich Ataxia Rating Scale (FARS);
- International Cooperative Ataxia Rating Scale (ICARS).

An absolute reduction in these scores indicates improvement.

Friedreich ataxia is a slowly progressive disorder. There is no biochemical or simple clinical measure of progression. Current scoring systems are composite scores of disability and impairment measures: the ataxia rating scales. The SARA, which is primarily, but not exclusively, an impairment scale, has been validated for both spinocerebellar ataxia and Friedreich ataxia (Bürk 2009), and is the preferred scale in the most recent trials. The FARS was validated in 2006 (Fahey 2006). The ICARS was developed for neurological conditions by a committee of the World Federation of Neurology in 1997 and was validated (Trouillas 1997). In future, pure disability or impairment scales would be preferable as primary outcome measures in the review. If these are used in trials, currently reported mixed scales will become secondary outcome measures.

Secondary outcomes

We also assessed secondary outcomes after 12 months of treatment.

1. Change in cardiac measures: ejection fraction, end-diastolic interventricular septal thickness (IVSTd) and left ventricular mass (LVM), as measured by cardiac magnetic resonance imaging (cMRI).
2. Change in cardiac measures: ejection fraction, end-diastolic IVSTd, LVM as measured by echocardiogram.
3. Improvement in any validated quality of life score.
4. Mild adverse effects (medication continued).
5. Severe adverse affects (defined as leading to cessation of medication).
6. Survival.

There has been much debate about how best to quantify the cardiomyopathy in Friedreich ataxia. Weidemann 2012 reviewed the cardiac status of 205 people with Friedreich ataxia in detail. The study found that IVSTd, as measured by echocardiogram, was a reliable predictor of LVM when the results were correlated with those from cMRI. The latter has been shown to be the more sensitive and accurate in determining the severity of cardiomyopathy in Friedreich ataxia (Grothues 2002). Cardiac assessment is complicated, as there is not a single cut-off point for defining normal versus abnormal IVSTd in this group of people. The clinical phenotype varies, disease progression is variable, and with the passage of time, people with Friedreich ataxia develop a worsening cardiomyopathy. People with Friedreich ataxia commonly develop myocardial fibrosis with a subsequent decrease in IVSTd, which could be mistaken for a positive treatment effect (Weidemann 2012).

An ejection fraction of 55% or higher is considered normal (Mayo Clinic 2015). For this review, we selected ejection fraction as the principal criterion for defining the severity of cardiomyopathy and measuring heart function in Friedreich ataxia (Weidemann 2012), in conjunction with IVSTd.

Search methods for identification of studies

Electronic searches

We searched The Cochrane Neuromuscular Specialised Register (29 February 2016), CENTRAL (29 February 2016 in the Cochrane Register of Controlled Trials Online (CRSO)), MEDLINE (January 1966 to February 2016), EMBASE (January 1980 to February 2016), CINAHL Plus (January 1937 to February 2016), ORPHANET (1990 to September 2015), and TRIP (1998 to September 2015).

We have presented the detailed search strategies in the appendices: Appendix 1 (Cochrane Neuromuscular Specialised Register), Appendix 2 (CENTRAL), Appendix 3 (MEDLINE), Appendix 4 (EMBASE), Appendix 5 (CINAHL Plus), Appendix 6 (ORPHANET) and Appendix 7 (TRIP).

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

As searching AMED, LILACS and PEDRO produced no useful results, we did not search these databases after the first version of this review.

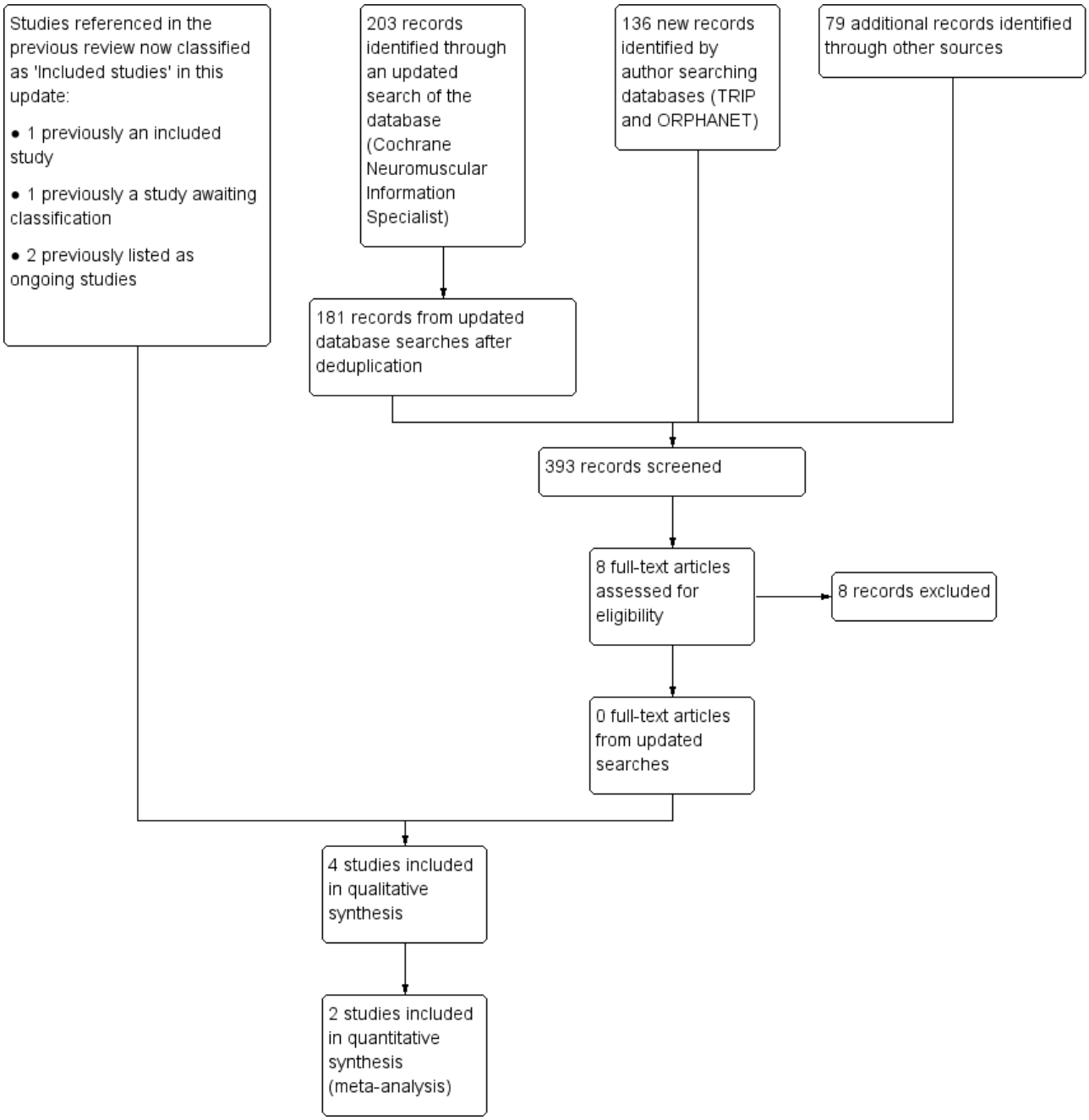
Searching other resources

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 languages other than English for inclusion. We consulted the Clinical Trials Registry of the U.S. National Institute of Health (Clinical trials) to identify additional trials that had not yet been published. We searched the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) (last search March 2016). We obtained the latest results from the RCTs by searching conference proceedings, canvassing colleagues, and reviewing the websites of the patient organisations, Friedreich Ataxia Research Alliance and euro-ataxia.

Data collection and analysis

We conducted data collection and analysis in accordance with the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011). Figure 1 shows the flow of information through the different phases of the systematic review.

Figure 1. A flow diagram illustrating the study selection process.



Selection of studies

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

Data extraction and management

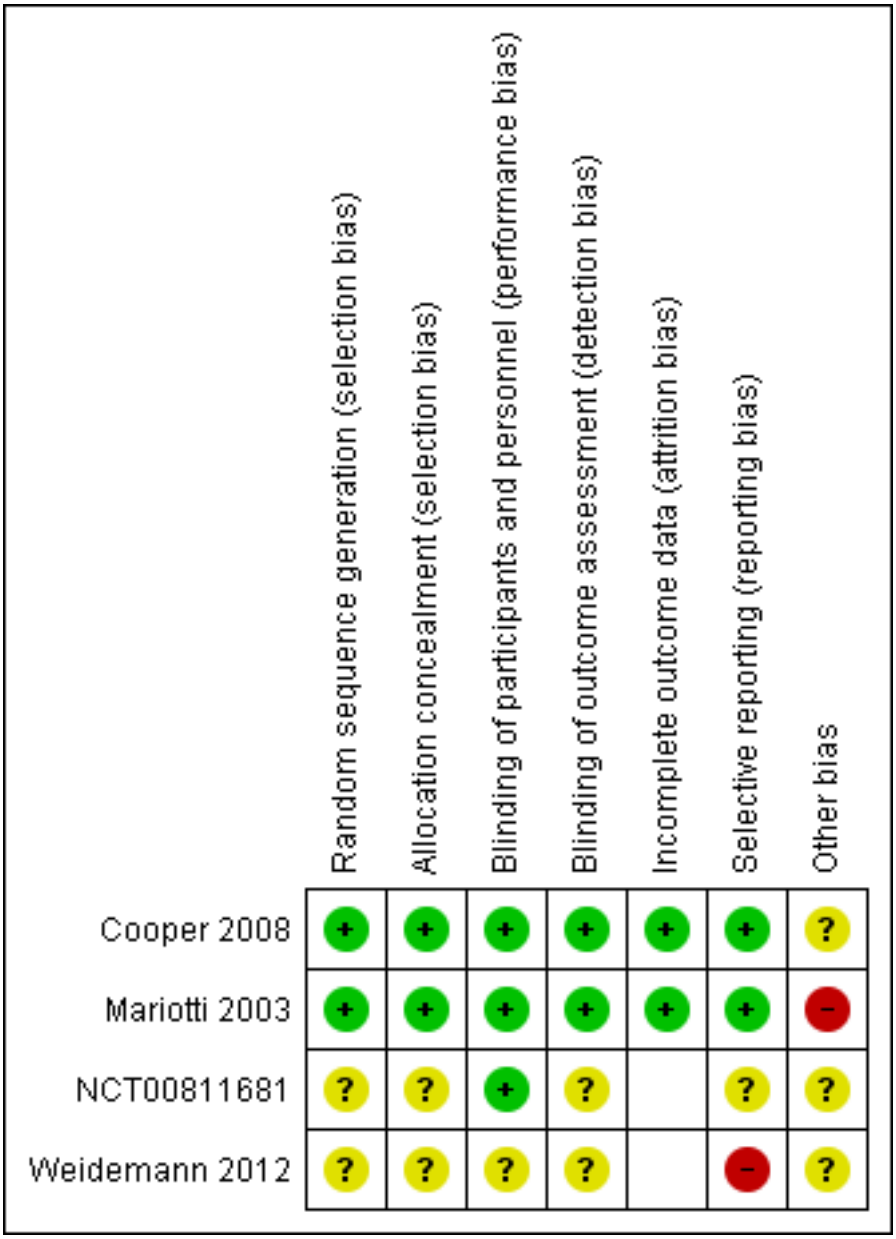
Two authors (MK and RO) independently extracted data from the included studies onto a specially designed data extraction form. They resolved disagreements by discussion. Review authors sought further data from the lead author of Cooper 2008, as the study report provided outcome data at two years rather than at one year as specified in our protocol.

Assessment of risk of bias in included studies

We assessed risk of bias in the included studies using the Cochrane `Risk of bias' tool, considering the domains of random sequence generation, allocation concealment, blinding (investigators, participants, and outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias. We made a judgment on each of these criteria, rating studies

as at `High risk of bias', `Low risk of bias' or `Unclear risk of bias' for each criterion (Figure 2).

Figure 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study. We could not evaluate attrition bias in the unpublished studies.



Measures of treatment effect

We reported risk ratios (RRs) with 95% confidence intervals (CIs) for binary outcomes such as adverse events. For continuous outcomes, such as ICARS scores, ejection fraction, IVSTd, and LVM, we calculated mean differences with 95% CI. If trials had reported the same outcome using different measurement tools, we would have combined data using standardised mean differences and 95% CIs.

We analysed all the primary and secondary outcomes under consideration whenever the data allowed.

Unit of analysis issues

The unit of analysis was a participant. To prevent unit-of-analysis issues related to repeated measures, we chose to analyse outcome data after 12 months of treatment.

Dealing with missing data

Since completion of the previous review update in 2012, Dr Cooper provided raw data on the change in the ICARS score and IVSTd after 12 months (Cooper 2008). We completed the data extraction form and determined that we could include this study in this updated review.

We sought details of the primary outcome of Mariotti 2003 from Dr Mariotti in 2009, who supplied the mean, standard deviation and P value for ICARS scores at the start and after 12 months for both the placebo and the treatment groups. We included these details on the data extraction sheet for the initial publication of this review in 2009. We sought details of ejection fraction measurements for the 2015 update and the raw data on these measurements were supplied.

Weidemann 2012 was completed in 2009, We contacted the trialists several times, and on our last contact in January 2016, the lead investigator, Dr Frank Weideman, responded to our query, advising that the manuscript was in preparation.

We contacted the authors of NCT00811681 in January 2016. Dr Pierre Rustin responded by email, and told us that the clinical trial had missed its primary endpoint, change in neurological score.

Assessment of heterogeneity

We used the I^2 test for heterogeneity. We considered that an I^2 greater than 50% suggested that variations in the effect estimates of the different studies were due to differences between trials rather than to chance alone. We initially used a fixed-effect model and repeated the analysis with a random-effects model.

Assessment of reporting biases

The search strategies covered multiple sources without language or publication restrictions. We were alert to the possibility of duplication of studies. We did not produce a funnel plot, as the review included too few studies for an analysis of small study effects to be meaningful (Sterne 2011).

Data synthesis

We performed statistical analyses of the data using Review Manager 5 (RevMan 5). We combined data from primary studies of antioxidants versus placebo and reported the results of analyses using a random-effects model.

`Summary of findings' table

We created a `Summary of findings' table for each comparison using the following outcomes: change in ICARS score, change in cardiac measures (ejection fraction, IVSTd, and LVM), severe adverse events, and survival. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software. We justified all decisions to downgrade or up-grade the quality of studies using footnotes, and we made comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was not relevant. We investigated heterogeneity by inspecting trials and the forest plot. We reviewed the clinical and methodological characteristics of the included studies.

Sensitivity analysis

Sensitivity analysis was not relevant.

RESULTS

Description of studies

Results of the search

The numbers of papers found by the update searches run by the Cochrane Neuromuscular Information Specialist were: Cochrane Neuromuscular Specialised Register = 34, CENTRAL = 24, MEDLINE = 64, EMBASE = 41, CINAHL Plus = 33, DARE = 6, HTA = 1, for a total of 203 new records (181 after deduplication). The review authors identified 135 new records in TRIP, 1 new record in ORPHANET, and 79 additional records through searching other sources. The review authors identified eight studies (reported in nine full-text articles) to be studied in detail for eligibility (see PRISMA flow chart Figure 1). From these, we identified no new studies through the searches for this update. To the one study included in the last version of this review, we added three other studies previously identified as either awaiting classification or ongoing.

Included studies

In the initial review and first update, we included one study (Mariotti 2003), and one other study awaited classification (Cooper 2008). As a result of information from the trial author, we included Cooper 2008 in this update of the review. We reviewed the information on Weidemann 2012 and NCT00811681 and found that they also met our selection criteria.

Cooper 2008 initially included 50 participants with genetically-confirmed homozygous expansion for Friedreich ataxia. The trial compared high-dose and a very low-dose of coenzyme Q10 and vitamin E antioxidants over a two-year period. The trial authors considered the very low dose coenzyme Q10 and very low dose vitamin E as placebos. The authors justified this, citing recruitment difficulties for a trial involving a placebo group.

Mariotti 2003 compared the antioxidant idebenone 5 mg/kg to placebo in 29 participants with genetically-confirmed homozygous expansion for Friedreich ataxia. In all participants, the condition had been present for over 10 years. Eighteen participants were wheelchair dependent at the onset of the study.

In Weidemann 2012, 232 participants were randomised to receive idebenone or placebo (dosage adjusted for weight) and 205 provided outcome data. At the planning stage of this study, the trialists decided to enrol a significant number of ambulatory participants, as defined by a person who could walk at least 10 meters with or without a walking aid but without the help of an accompanying person.

NCT00811681 was a double-blind clinical trial of pioglitazone over a two-year period, involving 40 participants with confirmed Freidreich ataxia. The pioglitazone dose was increased to a maximum of 45 mg/day and the primary endpoint was change in ataxia rating scale score (ICARS) after two years. The study was completed in March 2013 but to date, remains unpublished.

Both published trial reports provided details of funding sources. Cooper 2008 was funded by Ataxia UK, the Wellcome Trust, and the Medical Research Council in the UK, and Pharma Nord supplied

the medication. Mariotti 2003 was funded by the Italian Ministry of Health, and Takeda-Italy supplied the trial medication.

See Characteristics of included studies.

Excluded studies

There were five excluded studies, described in six reports (two of the reports were from the same study (Lynch 2010)). We excluded these trials because they did not fulfil the duration criterion of 12 months. See Characteristics of excluded studies.

Di Prospero 2007 was a six-month, open-label, dose-escalation trial of idebenone involving 48 people (9 to 17 years) with genetically-confirmed Friedreich ataxia. Participants received 5 mg/kg, 15 mg/kg, or 45 mg/kg idebenone, or placebo. Outcomes were change in a urinary marker of oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine, and changes from baseline in ICARS and FARS scores, and in activities of daily living,

In Lynch 2010, 70 ambulant participants with genetically-confirmed Friedreich ataxia (aged 8 to 18 years) were enrolled in a six-month double-blind, parallel-group RCT. The trial compared two different doses of idebenone (450 mg/day or 900 mg/day for body weight less than 45 kg; 1350 mg/day or 2250 mg/day for body weight greater than 45 mg/kg), and placebo. The primary outcome was the ICARS score; FARS, Friedreich's Ataxia Composite Test (FACT-Z_3), and activities of daily living scores were secondary outcomes.

Pandolfo 2014 was a six-month double-blind RCT in which 72 participants (7 to 35 years of age) with genetically-confirmed Friedreich ataxia received deferiprone (20 mg/kg/day, 40 mg/kg/day, or 60 mg/kg/day) or placebo, divided into two daily doses. The main aim of the study was to determine safety and tolerability. Changes in 9-hole peg test, timed 25-foot walk, low-contrast letter acuity, ICARS, and FARS scores were secondary outcomes. Cardiac measures and activities of daily living were also assessed.

Mariotti 2010 was a randomised, double-blind, placebo-controlled, dose-finding trial. Sixteen adults with Friedreich ataxia received erythropoietin in three consecutive cycles intravenously (20,000 to 40,000 units every two weeks) or placebo over a six-month period, followed by a six-month phase of subcutaneous treatment. All patients were also treated with idebenone (5 mg/kg/day). The study assessed safety and frataxin levels in lymphocytes.

Schöls 2005 was a randomised, placebo-controlled, cross-over study comparing L-carnitine (3 g daily), creatine (6.75 g daily) and placebo over a four-month period. Participants were 16 ambulant adults with genetically-confirmed Friedreich ataxia. The trialists assessed "mitochondrial ATP production measured as phosphocreatine recovery by ^{31}Phosphorus magnetic resonance spectroscopy," ICARS scores, and cardiac hypertrophy by echocardiography.

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

None of the several ongoing studies in Friedreich ataxia fulfil the selection criteria set by this review as being an RCT of at least one year's duration.

Risk of bias in included studies

The review authors' `Risk of bias' judgements for the included studies are summarised in Figure 2. See Characteristics of included studies for detailed assessments of each study.

Allocation

The two included published studies provided sufficient detail of the randomisation of participants to consider them probably at low risk of bias from sequence generation and allocation concealment.

Blinding

Cooper 2008 reported that participants were blinded until the end of the trial and that the placebo medication was indistinguishable from the active medication. The Mariotti 2003 manuscript did not mention whether participants were blinded but the contact author stated in an email that the assessors of the primary and secondary outcomes were blind to the participants' assignment.

Incomplete outcome data

In the Cooper 2008 study, six of the original 50 participants withdrew, three from high dose group and three from the low dose group. In the Mariotti 2003 study one participant withdrew from the placebo group.

Selective reporting

Trial protocols were unavailable for Cooper 2008 and Mariotti 2003, therefore, it is not possible on the basis of the published reports alone to determine whether all expected outcomes were reported. For each trial, investigators provided raw data for the outcomes of interest in the review. The unpublished but completed study Weidemann 2012 represented a high risk of reporting bias. We assessed NCT00811681 as unclear.

Other potential sources of bias

In Mariotti 2003, the proportion of ambulant versus wheelchair-dependent participants was different in the intervention and placebo groups. Cooper 2008 did not provide this information.

In Cooper 2008, the authors reported no conflict of interest. Mariotti 2003 made no reference to conflicts of interest.

Effects of interventions

See: **Summary of findings for the main comparison** Antioxidant versus placebo for Friedreich ataxia

Antioxidants versus placebo

Outcome data were not available for Weidemann 2012 or NCT00811681, which were unpublished trials.

Primary outcome measure: change in ataxia rating scale after 12 months

Changes in the ataxia rating scales SARA or FARS after 12 months treatment were not measured in either Cooper 2008 or Mariotti 2003.

Data for the change in ICARS scores were available for two studies (Cooper 2008; Mariotti 2003). The ICARS score ranges from 0 to 100, with higher scores indicating greater severity.

In the published studies, the scores did not reveal any significant difference between the antioxidant and placebo groups at 12 months. The individual participant ICARS scores before and after treatment were provided for Cooper 2008, after contact with the author. These scores were not available for Mariotti 2003, for which the trial author supplied the mean change in ICARS scores for each group, but not the change in score for each participant. We estimated the within-group SD for Mariotti 2003 using the observed correlation in the Cooper study (using rho = 0.94). The MD for the change from baseline in the ICARS for antioxidant versus placebo in Cooper 2008 was -0.64 (95% CI -3.66 to 2.38). Mariotti 2003 reported a 9-point decrease in the ICARS score from baseline to 12 months in the placebo group and a 0.8 point decrease in the antioxidant group. The MD for change from baseline to 12 months in Mariotti 2003 was 8.20 (95% CI 1.35 to 15.05). Pooling data from the two trials, the MD was 0.79 points, 95% CI -1.97 to 3.55 (N = 72). We considered the evidence as low quality, downgrading for heterogeneity (Chi^2 = 5.36, df = 1 (P = 0.02); I^2 = 81%) (Analysis 1.1 and Summary of findings for the main comparison).

Changes in ICARS and FARS scores from baseline to week 52 were both outcomes in Weidemann 2012. The study sponsors, Santhera, reported in a press release that "the primary endpoint of the study, mean change in the International Cooperative Ataxia Rating Scale (ICARS) score from baseline, did not detect any significant difference between the active dose arms and placebo" and secondary endpoints "including the proportion of patients improving on ICARS score (responder analysis) and change in the Friedreich's Ataxia Rating Scale also did not show statistically significant differences between the placebo and active dose groups". These statements are consistent with the findings from included studies, but data were not available to the review authors for independent analysis.

NCT00811681 measured the change in ataxia rating scales as measured by ICARS and FARS every six months over a two-year period. We were unable to obtain data for analysis.

Secondary outcome measures: change in cardiac measure

Change in cardiac status using cMRI was not measured in Cooper 2008 or Mariotti 2003, but both studies assessed change in cardiac status using echocardiogram.

Change in ejection fraction

Ejection fraction data were only available for Mariotti 2003.

None of the participants in Mariotti 2003 had "pathologic ejection fraction at baseline", as the ejection fraction remained above 50% in all trial participants over the year of follow-up. Ejection fraction increased by 0.64% in the placebo group and 0.43% in the antioxidant group, a mean difference (MD) of -0.21% (95% CI -5.55 to 5.13) (Analysis 1.2). We assessed the quality of the evidence as very low. Cooper 2008 measured fractional shortening at 12 months rather than ejection fraction; the latter is considered to be a more accurate reflection of heart function (Mayo Clinic 2015). We were unable to obtain fractional shortening data for Cooper 2008.

Change in interventricular septal thickness as measured by echocardiography

Cooper 2008 and Mariotti 2003 measured change in IVSTd, in which a decrease indicates improvement. The scores revealed a small difference between the antioxidant treated groups and the placebo groups at 12 months in favour of idebenone in Mariotti 2003. In Cooper 2008, there was no improvement. The MD (mm) of the combined measures was -0.65 (95% CI -2.00 to 0.70, N = 72, random-effects) in favour of antioxidant treatment (Analysis 1.3). We considered this evidence as very low quality because of risk of bias, marked statistical heterogeneity (I^2 statistic = 74%), and inconsistency (one trial shows a strong effect, the other none) (Analysis 1.3; Summary of findings for the main comparison). The CIs are wide, including both the possibility of change that might be clinically important and no effect.

Change in left ventricular mass

Results for left ventricular mass were available from Mariotti 2003. Left ventricular mass increased by 16.28 g (SD 29.37) in the placebo group and decreased by 14 g (SD 32.75) in the antioxidant group (MD -30.30 g, 95% CI -53.34 to -7.26, in favour of the antioxidant) (Analysis 1.4). There was a 10.7% (P = 0.01) increase in left ventricular mass after 12 months of treatment in the placebo group and a 5.6% decrease in the idebenone-treated group after 12 months of treatment. The MD was 16.37% (95% CI 2% to 31%). The potential importance of these results needs to be clarified in view of the fact that people with Friedreich ataxia commonly develop myocardial fibrosis with a subsequent decrease in LVM, which could be mistaken for a positive treatment effect.

The press release reporting the failure of Weidemann 2012 to reach its endpoints reported "no difference between the active and placebo groups in the key cardiological secondary endpoint assessing a combination of anatomical and functional cardiac parameters". We were unable to obtain data for analysis. See Characteristics of included studies for details of cardiac measures listed in the trial registry entry.

Cardiac outcomes in NCT00811681 were not fully described in the clinical trials registry entry.

Improvement in quality of life score after 12 months

Not assessed by Cooper 2008 or Mariotti 2003.

Change in quality of life scale measured by the Short Form 36 (SF-36) score after 12 months of treatment was among the listed outcomes in NCT00811681. No data were available.

Mild adverse effects

In Cooper 2008, the authors reported the intervention to be well tolerated and provided details of withdrawals, but did not specifically report the occurrence of mild adverse events. In Mariotti 2003, one participant experienced occasional tachycardia, which did not require treatment modification (Analysis 1.5).

Severe adverse effects

In Cooper 2008, one participant in the placebo group withdrew due to prolonged nausea, and one participant in the treatment group withdrew due to increased bowel frequency. In Mariotti 2003, there were no severe adverse effects due to idebenone or placebo.

One of the placebo participants in Mariotti 2003 died during the study as a result of diabetic ketoacidosis five months after enrolment. The trial authors considered the death to be unrelated to the clinical trial.

Survival

Survival was not an outcome in the included studies.

DISCUSSION

Summary of main results

Effectiveness of pharmacological treatments versus placebo

Neither of the published included studies showed that antioxidants were effective for treating Friedreich ataxia using the primary outcome, change in the validated Friedreich ataxia neurological scale, International Cooperative Ataxia Rating Scale (ICARS; Cooper 2008; Mariotti 2003). The included studies showed contradictory evidence in the secondary outcome, change in interventricular septal thickness as measured by echocardiography. Mariotti 2003 (28 participants) did show a significant change in left ventricular mass (LVM). This is of uncertain clinical significance, but of potential importance that needs to be clarified.

Among the secondary cardiac outcomes, change in ejection fraction using echocardiogram was not measured in the Cooper 2008 study. Ejection fraction was measured in Mariotti 2003, but was normal at the outset of the study, so was not likely to demonstrate change after 12 months' treatment. Results confirmed this.

Both reported studies measured change in end-diastolic interventricular septal thickness (IVSTd). There was no improvement in IVSTd in Cooper 2008. In Mariotti 2003, it showed a small improvement in favour of the antioxidant group. When we reviewed this result, we considered that in the absence of any improvement in ejection fraction, the improvement in IVSTd was of no clear clinical significance, although the result was too imprecise to rule out the possibility of an effect.

We were not successful in our attempts to obtain data from two unpublished studies, which involved a combined total of approximately 272 participants.

Overall completeness and applicability of evidence

The low- or very low-quality evidence in this review is currently insufficient to support or refute an effect of antioxidants in Friedreich ataxia. The authors felt that all relevant studies were identified but the evidence is incomplete, as Weidemann 2012 and NCT00811681 had no published results as of May 2016. Santhera, the sponsors of Weidemann 2012, published an interim report in May 2010 stating that the study had failed to reach its primary endpoint, which was change in ICARS score (Santhera 2010). The company also reported no change in secondary endpoints Friedreich Ataxia Rating Score (FARS), and cardiac parameters. The results of these unpublished trials, particularly Weidemann 2012, which involved 232 participants with Friedreich ataxia, represent important missing data.

For years, idebenone was available to some people with Friedreich ataxia free of charge, while others had to pay for it. After the European Medicines Agency refused marketing authorisation for idebenone, several European countries and some private insurance companies reviewed their policies on reimbursement and no longer supply this medication to people with Friedreich ataxia (EMA 2009). The evidence seems to suggest that idebenone is not effective, and this is supported rather than refuted by the unpublished study (Weidemann 2012).

We identified no trials of non-antioxidant agents eligible for inclusion in the review.

Evidence from excluded studies

We limited this review to studies at least a year long, as shorter studies in this slowly progressive condition are unlikely to demonstrate clinical benefit. As this potentially excludes short-term trials signalling clinical efficacy, we briefly described excluded studies here as they have helped considerably to add to the body of knowledge about clinical trials in Friedreich ataxia.

Di Prospero 2007 was a six-month, open-label dose-escalation trial involving 48 people with genetically-confirmed Friedreich ataxia. Higher doses of idebenone led to a proportional increase in plasma levels and were well tolerated. One child on a high dose of idebenone experienced neutropenia, which recovered when treatment was stopped. Overall, ICARS, FARS, and total activity of daily living (ADL) scores did not improve with idebenone. Improvement in ICARS scores but not FARS or ADL scores showed dose dependence and the difference from placebo was statistically significant at the higher doses. The subgroup of ambulant but symptomatic participants (baseline ICARS score more than 10 but less than 54), showed improvement in ICARS but not in FARS or ADL scores.

Lynch 2010 reported that idebenone did not alter neurological function in Friedreich ataxia after six months of treatment. It also demonstrated that the sensitivity of the ataxia rating scales to change is limited, and suggested that in future studies, inclusion of a higher percentage of ambulant participants would be desirable. Idebenone did not decrease left ventricular hypertrophy or improve heart function in this study.

Recombinant human erythropoietin (rHuEPO) was used in two RCTs, which found acceptable safety and tolerability of rHuEPO derivatives in Friedreich ataxia, but did not find any increase in frataxin levels or improvement in the clinical condition of participants over a two-week RCT (Boesch 2014), or over the six-month period in Mariotti 2010.

There is rationale for deferiprone as a therapy for Friedreich ataxia; however, its safety and appropriate dosing need to be assessed prior to another large scale trial. Pandolfo 2014 was a six-month study involving 74 randomised adults and children with Friedreich ataxia. A dose of 20 mg/kg/day was well tolerated, whereas 40 mg/kg/day produced a worsening of ataxia scores (ICARS and FARS). The highest dose, 60 mg/kg/day dose was discontinued as a precautionary measure, because two participants experienced a worsening of ataxia. Ataxia in the placebo group did not deteriorate over the six-month period and this prevented the researchers from detecting any potential protective effect of deferiprone. Left ventricular mass decreased in treatment versus placebo arms, but the clinical significance of this is unclear. The trial produced inconclusive efficacy results, with no improvement over placebo at 20 mg/day, but it was too short to rule out an effect. Based on subgroup analyses, the trial authors considered that lower doses warranted further investigation.

A cross-over trial comparing L-carnitine (3 g daily in three doses), creatine (6.75 g daily in three doses), and placebo over a four-month

period among 16 ambulant adults with genetically-confirmed Friedreich ataxia, found that neither echocardiographic data nor ICARS scores demonstrated an improvement over baseline or placebo (Schöls 2005).

Evidence from other studies

A histone deacetylase inhibitor (HDACi),109/RG 2833 was well-tolerated in a phase 1 trial (Soragni 2014), but Robinson 2014 reported that two drug metabolites persisted in the serum for hours after the compound was broken down, one a suspected cardiotoxin and the other a suspected carcinogen. This led the group to begin developing related compounds that penetrate the blood-brain barrier but which are without these effects. Libri 2014 used the HDACi nicotinamide in an open-label, dose-escalation study over an eight-week period. This study showed a sustained improvement in frataxin concentration over the course of the treatment.

Gene therapy research in Friedreich ataxia has been ongoing for the last 10 years. A GAA-expanded frataxin genomic DNA reporter model of Friedreich ataxia has been developed. which would lead the way to identification of novel therapies (Lufino 2013). In Friedreich ataxia, protection for nerve cells would be a priority. Kemp 2011 looked to see if bone marrow-derived cells might be able to protect cerebellar neurons in vitro. He demonstrated "that normal human mesenchymal stem cells (MSCs) induce both an increase in frataxin gene and protein expression in Friedreich ataxia fibroblasts via secretion of soluble factors". The most recent study, Perdomini 2014, reported that cardiomyocytes from mice with severe energy failure and ultra structural disorganisation, can be rapidly rescued and remodelled by gene therapy. This established pre-clinical proof of concept for the potential of gene therapy in treating Friedreich ataxia cardiomyopathy.

Many of the studies referenced in this section have been based at multiple centres in different countries and continents. In recent years, clinicians have been keen to organise double-blind clinical trials. Patient organisations have come together internationally to make patient recruitment for clinical trials possible.

Quality of the evidence

The quality of the evidence from the results of the two included and reported studies was low for the validated Friedreich ataxia neurological scale score, ICARS, and low or very low for other outcomes. As Friedreich ataxia varies considerably in genetic severity, has a varying age of onset from 5 to 60 years, has a variable clinical progression, and is heterogeneous in its clinical features, much of the recent research has focused on finding an accurate measure of disease progression (Bürk 2009). Lynch 2010 revealed that the sensitivity of the neurological examination when using the ICARS and the FARS was limited, and each scale had a variety of other drawbacks. When the participants are wheelchair-dependent, posture and gait scores in the ICARS are redundant, leading to a sudden, significant deterioration in the person's ICARS score when they become wheelchair-dependent, followed by a period where there is almost no change in the score, which is know as a ceiling effect. In the planning stage of Weidemann 2012, an effort was made to eliminate this ceiling effect by enrolling a significant percentage of ambulatory participants. Weidemann 2012 reported that 51.8% of participants were ambulatory. In Mariotti 2003, 37% were ambulatory, that is, 11 out of 29 participants.

A collaborative project funded by the European Commission, called the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS; www.e-facts.eu), is testing the validity of ataxia rating scales in a four-year prospective study from 2012 to 2016. It reviews its Friedreich ataxia participants on an annual basis. An American network, Collaborative Clinical Research Network in Friedreich Ataxia (CCRN in FA; www.curefa.org), is testing the validity of the FARS for measuring long-term follow-up in Friedreich ataxia. As a result of the different variables in design and implementation in the included studies, which we assessed as a potential risk of bias, we downgraded the quality of the evidence for change in the ICARS score.

The evidence published in the included studies was direct. There was significant heterogeneity in the study participants and considerable inconsistency in the results for change in the cardiac measure, interventricular thickness, and as a result we found it necessary to downgrade the quality of evidence for these outcomes. As there were so few participants (N = 72), only two of whom experienced events, we downgraded the results due to imprecision for the outcomes mild adverse events and severe adverse events. The larger of the two unpublished studies appeared likely to strengthen a finding of no effect for idebenone on both neurological (the ICARS and FARS) and "anatomical and functional cardiological parameters" (Weidemann 2012). On this basis, we chose not to downgrade the evidence for publication bias, although these results were mentioned in a press release and not available for verification.

Potential biases in the review process

There may be some potential for bias in this review process as there were changes to the protocol. These included additions and deletions to the outcomes, as reported in Differences between protocol and review. None of these changes were made as a result of the findings of the included studies but rather to improve the structure of the review. We are confident that we have identified all clinically relevant trials, as we conducted a comprehensive search of all published literature and clinical trials registers for potentially relevant clinical trials and three of the review authors regularly attend international conferences on Friedrieich ataxia.

As the review includes data from only two small RCTs, it is possible that our methods have not detected all rare and serious adverse events. This review defines severe adverse events as those leading to withdrawal, which has been adequate for describing serious adverse events in currently included trials. We will widen our definition to also include adverse events that are fatal, life threatening, or require prolonged hospitalisation in future updates, if they are measured in newly included studies.

Agreements and disagreements with other studies or reviews

Some open-label trials of idebenone found an improvement in cardiac measures (Buyse 2003; Mariotti 2003; Pineda 2008; Ribai 2007; Rustin 1999), but others, Lynch 2010, a six-month RCT and Artuch 2002, did not. Lynch 2010 found that idebenone at similar or higher doses than those that were used in Mariotti 2003 did not improve ejection fraction over a period of six months, in participants with Friedreich ataxia. As mentioned previously, we did not include Lynch 2010 in the review owing to its short duration.

AUTHORS' CONCLUSIONS

Implications for practice

Low-quality evidence from the two small, published, included randomised controlled trials neither supported nor refuted an effect from antioxidants (idebenone, or a combination of coenzyme Q10 and vitamin E) on the neurological status of people with Friedreich ataxia, measured with a validated neurological rating scale. A large unpublished study of idebenone that reportedly failed to meet neurological endpoints, and a trial of pioglitazone remain unpublished, but on publication will very likely influence quality assessments and conclusions. Cardiac changes were based on low- and very low-quality evidence of uncertain clinical significance. According to low-quality evidence, serious and non-serious adverse events were rare in both antioxidant and placebo groups. Other classes of agents have not been tested in clinical trials eligible for inclusion in this review.

Implications for research

Publication of data from unpublished trials is highly desirable, as important data may be missing from this review. The clinical importance of observed cardiac changes with antioxidants might warrant further investigation. Future studies might also investigate whether pharmacological interventions such as antioxidants have any complementary or adjunctive role in the treatment of Friedreich ataxia.

Friedreich ataxia is a rare, slowly progressive disorder. Researchers have not yet defined a suitable clinical marker or biomarker to assess disease progression. Clinical assessment becomes even more difficult when the patient is wheelchair-dependent. In view of these factors, and in order to evaluate the effects of other pharmacological treatments in Friedreich ataxia, we need large, placebo-controlled RCTs of 12 months' duration, using clinical scales that are both valid and responsive to change

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CHARACTERISTICS OF STUDIES

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

Cooper 2008

Methods	Randomised, double-blind trial
Participants	50 people with Friedreich ataxia
Interventions	High-dose or low-dose coenzyme Q10 or vitamin E
Outcomes	Outcomes of relevance to this review: • Primary - change in ICARS score after 12 months' treatment • Secondary - change in IVS thickness
Funding	Pharma Nord provided vitamin E, coenzyme Q10 and placebo tablets Grant from Ataxia UK, Wellcome Trust and Medical Research Council
Conflicts of interest	None
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Statistician external to the study randomised patients to give 2 groups of 24 and 26"
Allocation concealment (selection bias)	Low risk	"double blind was maintained until all evaluations were complete at the 2 years time point". Allocation concealment not precisely stated, but external personnel were responsible for randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind was maintained until all evaluations were complete at the 2 years time point". Report states that 'placebo' and active tables were "indistinguishable"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double blind was maintained until all evaluations were complete at the 2 years time point"
Incomplete outcome data (attrition bias) Neuological outcome	Low risk	7 withdrawals: 6 withdrew within the first 6 months and a further participant did not complete the final assessment. 4 withdrawals were voluntary, 1 participant with severe Friedreich ataxia was unable to continue with the assessments, and 2 had adverse reactions (1 in the high dose group, 1 in the low dose group)
Selective reporting (reporting bias)	Low risk	Reporting was selective in the published material but we judge there to be a low risk of bias for this domain following provision of additional data
Other bias	Unclear risk	The manuscript does not report what percentage of each group were wheelchair-dependent and this could have a significant effect on the results.

Mariotti 2003

Methods	Randomised, double-blind, placebo-controlled clinical trial
Participants	29 participants with Friedreich ataxia: 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)
Interventions	5 mg/kg idebenone three times daily for one year or identical placebo
Outcomes	Outcomes of relevance to this review: • Change in ICARS score • Change in left ventricular mass as measured by echocardiography
Funding	Supported by a grant from the Italian Ministry of Health. Takeda-Italy provided idebenone and placebo
Conflicts of interest	Not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization of patients, stratified according to IVS thickness at baseline (IVS = 12 to 14 mm, and > 14 mm) was computer generated" Comment: probably done
Allocation concealment (selection bias)	Low risk	Study author told review authors that outcome assessors were blinded to participants' assignment until the end of the study. Not described, but assessed as low risk because of computer-generated randomisation, and maintenance of blinding.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Idebenone 60 mg/capsule and identical placebo capsules were prepackaged and provided by Takeda" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "were blind to patient assignment"
Incomplete outcome data (attrition bias) Neuological outcome	Low risk	Data on primary outcome sought and obtained, 1 placebo assignee died from diabetic ketoacidosis 5 months after enrolment
Selective reporting (reporting bias)	Low risk	Data for change in ICARS score were not shown in the published report but were supplied by the trial author.
Other bias	High risk	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 idebenone treated group. Eleven of the fifteen participants in the placebo group were wheelchair-dependent

NCT00811681

Methods	Randomised, double-blind, placebo-controlled clinical trial
Participants	40 participants with genetically-confirmed Friedreich ataxia with GAA repeat length of the shorter allele of frataxin gene ≥ 300
Interventions	Pioglitazone and placebo
Outcomes	Outcomes of relevance to this review: • Change in ataxia rating scales as measured by ICARS and FARS 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 spectroscope • Change in quality of life scale measured by the Short Form 36 (SF-36) health survey after 12 months of treatment
Funding	Assistance Publique - Hôpitaux de Paris
Conflicts of interest	Not stated in clinical trials registration
Notes	French national multi-centre study, final data collection March 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Clinicial trials registration reported study design "allocation: Randomized"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinicial trial registration reported study design "Masking: Double blind (Subject, Investigator)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	Study completed March 2013, no publication to date (December 2015)
Other bias	Unclear risk	No information

Weidemann 2012

Methods	Randomised, double-blind, placebo-controlled clinical trial
Participants	232 enrolled participants with genetically-confirmed Friedreich ataxia
Interventions	Placebo or weight-adjusted daily doses of idebenone as follows (for participants with ≤ and >45 kg body weight): Low dose: 180 mg or 360 mg

Weidemann 2012 *(Continued)*

	Mid dose: 450 mg or 900 mg High dose: 1350 mg or 2250 mg
Outcomes	Outcomes of relevance to this review, measured from baseline to week 52: • change in ataxia rating scale as measured by ICARS • change in FARS scores • proportion of improving on ICARS "by a clinically relevant margin" (of 2.5 ICARS points) In participants presenting with cardiac involvement: • proportion improving on LV peak systolic strain rate or showing a reduction in LVM index with no worsening in strain rate • change in peak systolic strain rate • change in peak workload as assessed by a modified exercise test
Funding	Santhera Pharmaceuticals
Conflicts of interest	Unpublished - not reported
Notes	ClinicalTrials.gov identifier: NCT00905268 European multi-centre study with 13 centres in Belgium, France, Germany, Netherlands, and UK. Study completion date January 2010. Santhera, the pharmaceutical company organising the study issued a statement in May 2010 stating that "the study failed to reach its primary endpoint".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	High risk	Study completed Spring 2010, no publication to date (December 2015)
Other bias	Unclear risk	No information

ICARS: International Co-operative Ataxia Rating Scale; FARS: Friedreich Ataxia Rating Scale; IVS: interventricular septum; LVM: left ventricular mass; LV: left ventricular

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

Study	Reason for exclusion
Di Prospero 2007	Duration of RCT insufficient (6 months)
Lynch 2010	Duration of RCT insufficient (6 months)
Mariotti 2010	Duration of RCT insufficient (6 months)
Pandolfo 2014	Duration of RCT insufficient (6 months)
Schöls 2005	Duration of RCT insufficient (4 months)

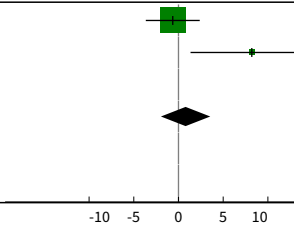
DATA AND ANALYSES

Comparison 1. Antioxidant versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ICARS score	2	72	Mean Difference (IV, Fixed, 95% CI)	0.79 [-1.97, 3.55]
2 Ejection fraction	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-5.55, 5.13]
3 Interventricular septal thickness	2	72	Mean Difference (IV, Random, 95% CI)	-0.65 [0.00, 0.70]
4 Left ventricular mass	1	28	Mean Difference (IV, Fixed, 95% CI)	-30.3 [-53.34, -7.26]
5 Mild adverse events	2	72	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Severe adverse events	2	72	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.00]

Analysis 1.1. Comparison 1 Antioxidant versus placebo, Outcome 1 ICARS score.

Study or subgroup	Antioxidant N	Antioxidant Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cooper 2008	22	-0.6 (4.6)	22	0 (5.6)		83.77%	-0.64[-3.66,2.38]
Mariotti 2003	14	-0.8 (9.2)	14	-9 (9.3)		16.23%	8.2[1.35,15.05]
Total ***	**36**		**36**			**100%**	**0.79[-1.97,3.55]**
Heterogeneity: Tau^2=0; Chi^2=5.36, df=1(P=0.02); I^2=81.33%							
Test for overall effect: Z=0.56(P=0.57)							



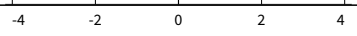
Analysis 1.2. Comparison 1 Antioxidant versus placebo, Outcome 2 Ejection fraction.

Study or subgroup	Antioxidant N	Antioxidant Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Mariotti 2003	14	0.4 (8.5)	14	0.6 (5.6)		100%	-0.21[-5.55,5.13]
Total ***	**14**		**14**			**100%**	**-0.21[-5.55,5.13]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.08(P=0.94)							

Favours placebo — Favours antioxidant

Analysis 1.3. Comparison 1 Antioxidant versus placebo, Outcome 3 Interventricular septal thickness.

Study or subgroup	Antioxidant N	Antioxidant Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Mariotti 2003	14	-0.7 (1.6)	14	0.7 (1)		46.94%	-1.38[-2.38,-0.38]
Cooper 2008	22	0.3 (1.4)	22	0.3 (1.1)		53.06%	0[-0.75,0.75]
Total ***	**36**		**36**			**100%**	**-0.65[-2,0.7]**
Heterogeneity: Tau^2=0.75; Chi^2=4.69, df=1(P=0.03); I^2=78.68%							
Test for overall effect: Z=0.94(P=0.35)							



Favours antioxidant — Favours placebo

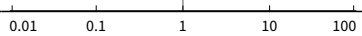
Analysis 1.4. Comparison 1 Antioxidant versus placebo, Outcome 4 Left ventricular mass.

Study or subgroup	Antioxidant N	Antioxidant Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Mariotti 2003	14	-14 (32.8)	14	16.3 (29.4)		100%	-30.3[-53.34,-7.26]
Total ***	**14**		**14**			**100%**	**-30.3[-53.34,-7.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.58(P=0.01)							

Favours antioxidant — Favours placebo

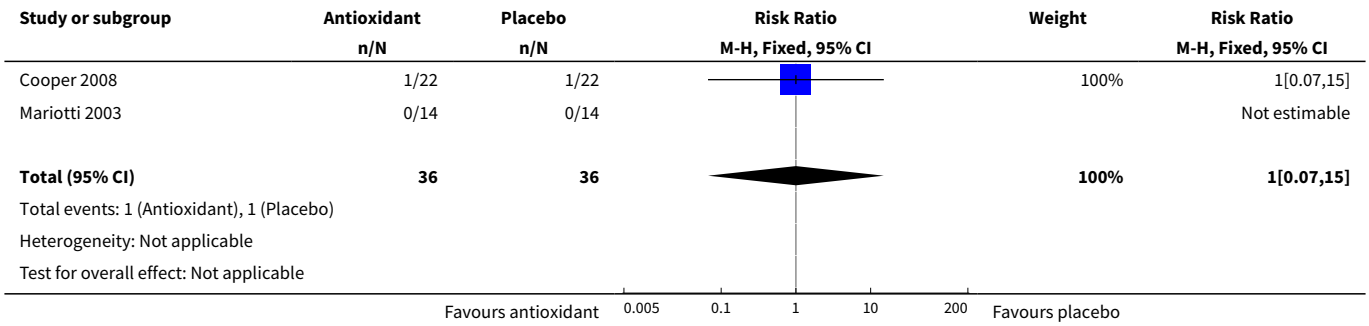
Analysis 1.5. Comparison 1 Antioxidant versus placebo, Outcome 5 Mild adverse events.

Study or subgroup	Antioxidant n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cooper 2008	0/22	0/22			Not estimable
Mariotti 2003	0/14	0/14			Not estimable
Total (95% CI)	**36**	**36**			**Not estimable**
Total events: 0 (Antioxidant), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Favours antioxidant — Favours placebo

Analysis 1.6. Comparison 1 Antioxidant versus placebo, Outcome 6 Severe adverse events.



APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register (CRS)

#1 friedreich NEAR ataxia* [REFERENCE] [STANDARD]
#2 freidreich NEAR ataxia* [REFERENCE] [STANDARD]
#3 #1 or #2 [REFERENCE] [STANDARD]
#4 idebenone or noben or "ascorbic acid" "vitamin C" or "vitamin E" or "vitamin A" [REFERENCE] [STANDARD]
#5 "alpha Tocopherol" or alphatocopherol [REFERENCE] [STANDARD]
#6 Selegiline or "Superoxide Dismutase" or Dehydroepiandrosterone or Glutathione or Urea or "Uric Acid" or Selenium or Erythropoietin [REFERENCE] [STANDARD]
#7 "Iron Chelating Agents" or "Chelation Therapy" or deferiprone or Pyridones or pioglitazone [REFERENCE] [STANDARD]
#8 MeSH DESCRIPTOR Antioxidants Explode All [REFERENCE] [STANDARD]
#9 MeSH DESCRIPTOR Therapeutics Explode All [REFERENCE] [STANDARD]
#10 n NEAR1 acetyl NEAR3 cysteine [REFERENCE] [STANDARD]
#11 n NEAR1 acetylcysteine [REFERENCE] [STANDARD]
#12 deprenyl or carotene or carotenoids or flavonoids or taurine [REFERENCE] [STANDARD]
#13 "recombinant human erythropoietin" [REFERENCE] [STANDARD]
#14 "iron chelat*" [REFERENCE] [STANDARD]
#15 deferiprone or pioglitazone or therapy or treatment [REFERENCE] [STANDARD]
#16 "Histone Deacetylase" NEAR1 Inhibitor* [REFERENCE] [STANDARD]
#17 deacetylase NEAR1 Inhibitor* NEAR1 histone [REFERENCE] [STANDARD]
#18 hdac NEAR1 inhibitor* [REFERENCE] [STANDARD]
#19 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 [REFERENCE] [STANDARD]
#20 #3 and #19 [REFERENCE] [STANDARD]
#21 (#3 and #19) AND (INREGISTER) [REFERENCE] [STANDARD]

Appendix 2. CENTRAL (CRSO) search strategy

Search run on Mon Feb 29 2016

#1 (Friedreich NEAR ataxia*):TI,AB,KY57
#2 (idebenone or noben or "ascorbic acid" "vitamin C" or "vitamin E" or "vitamin A"):TI,AB,KY 4474
#3 ("alpha Tocopherol" or alphatocopherol):TI,AB,KY 1989
#4 (Selegiline or "Superoxide Dismutase" or Dehydroepiandrosterone or Glutathione or Urea or "Uric Acid" or Selenium or Erythropoietin):TI,AB,KY 14263
#5 ("Iron Chelating Agents" or "Chelation Therapy" or deferiprone or Pyridones or pioglitazone):TI,AB,KY 1778
#6 MESH DESCRIPTOR Antioxidants EXPLODE ALL TREES 11256
#7 MESH DESCRIPTOR Therapeutics EXPLODE ALL TREES 238526
#8 n NEAR1 acetyl NEAR3 cysteine 191
#9 n NEAR1 acetylcysteine 845
#10 deprenyl or carotene or carotenoids or flavonoids or taurine 3101
#11 ("recombinant human erythropoietin"):TI,AB,KY 842
#12 ("iron chelat*"):TI,AB,KY 313

#13 (deferiprone or pioglitazone or therapy or treatment):TI,AB,KY 508710
#14 ("Histone Deacetylase" NEAR1 Inhibitor*):TI,AB,KY 74
#15 (deacetylase NEAR1 Inhibitor* NEAR1 histone):TI,AB,KY 1
#16 (hdac NEAR1 inhibitor*):TI,AB,KY 14
#17 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 566110
#18 #1 AND #17 46
#19 sr-neuromusc:cc 5822
#20 #18 not #19 18

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to February Week 3 2016>
Search Strategy:
---
1 randomized controlled trial.pt. (406624)
2 controlled clinical trial.pt. (90068)
3 randomized.ab. (303867)
4 placebo.ab. (155146)
5 drug therapy.fs. (1821266)
6 randomly.ab. (215136)
7 trial.ab. (313195)
8 groups.ab. (1362139)
9 or/1-8 (3453304)
10 exp animals/ not humans.sh. (4189142)
11 9 not 10 (2940585)
12 Friedreich Ataxia/ (2246)
13 (friedreich adj5 ataxia).tw. (721)
14 12 or 13 (2423)
15 (idebenone or noben).mp. (405)
16 Ascorbic Acid/ or Vitamin E/ or Vitamin A/ (76994)
17 alpha-Tocopherol/ (4395)
18 Selegiline/ (2277)
19 Acetylcysteine/ (10972)
20 Superoxide Dismutase/ (42033)
21 Dehydroepiandrosterone/ (8861)
22 Glutathione/ (48333)
23 Urea/ (39831)
24 Uric Acid/ (20792)
25 Selenium/ (17636)
26 Carotenoids/ (15664)
27 Flavonoids/ (31297)
28 Taurine/ (8687)
29 Erythropoietin/ (21625)
30 Iron Chelating Agents/ (5391)
31 Chelation Therapy/ (1227)
32 deferiprone.mp. (915)
33 Pyridones/ (5772)
34 pioglitazone.mp. (3895)
35 exp Antioxidants/ (379084)
36 exp Therapeutics/ (3610513)
37 (vitamin adj5 (a or c or e)).mp. (92827)
38 ascorbic acid.mp. (46493)
39 (alphatocopherol or alpha-tocopherol).mp. (13896)
40 (selegiline or deprenyl or superoxide dismutase or dehydroepiandrosterone or glutathione).mp. (170930)
41 ((n adj acetyl adj3 cysteine) or (n adj acetylcysteine)).mp. (13647)
42 (urea or uric acid or selenium or carotene or carotenoids or flavonoids or taurine).mp. (210103)
43 (recombinant human erythropoietin or iron chelat$ or deferiprone or pioglitazone).mp. (17259)
44 (therapy or treatment).tw. (3652967)
45 Histone Deacetylase Inhibitors/ (7162)
46 (histone deacetylase adj1 Inhibitor$).tw. (5172)
47 (deacetylase adj1 Inhibitor$ histone).tw. (33)
48 (hdac adj1 inhibitor$).tw. (3586)

49 or/15-48 (6513415)
50 14 and 49 (550)
51 Friedreich Ataxia/dt [Drug Therapy] (157)
52 11 and (50 or 51) (218)
53 remove duplicates from 52 (216)

Appendix 4. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2016 Week 09>
Search Strategy:
---
1 crossover-procedure.sh. (46158)
2 double-blind procedure.sh. (126385)
3 single-blind procedure.sh. (21564)
4 randomized controlled trial.sh. (393423)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (1223922)
6 trial.ti. (193286)
7 or/1-6 (1370827)
8 (animal/ or nonhuman/ or animal experiment/) and human/ (1446761)
9 animal/ or nonanimal/ or animal experiment/ (3498115)
10 9 not 8 (2901774)
11 7 not 10 (1261401)
12 limit 11 to embase (1041826)
13 Friedreich Ataxia/ (3589)
14 (friedreich adj5 ataxia).tw. (984)
15 13 or 14 (3694)
16 (idebenone or noben).mp. (1211)
17 Ascorbic Acid/ or Vitamin D/ or Alpha Tocopherol/ (166246)
18 SELEGILINE/ (8761)
19 Acetylcysteine/ (27733)
20 Superoxide Dismutase/ (63090)
21 Prasterone/ (13044)
22 GLUTATHIONE/ (73101)
23 UREA/ (57055)
24 Uric Acid/ (30264)
25 SELENIUM/ (30785)
26 CAROTENE/ (2097)
27 Carotenoid/ (17745)
28 Flavonoid/ (38647)
29 TAURINE/ (11676)
30 Recombinant Erythropoietin/ (18331)
31 Iron Chelation/ (5247)
32 DEFERIPRONE/ (2466)
33 PIOGLITAZONE/ (14801)
34 exp Antioxidant/ (118651)
35 or/16-34 (579260)
36 15 and 35 (572)
37 (vitamin adj (a or c or e)).mp. (66264)
38 (ascorbic acid or selegiline or deprenyl superoxide dismutase or dehydroepiandrosterone).mp. (101221)
39 ((alpha adj tocopherol) or (n adj acetyl adj3 l adj3 cysteine) or (n adj acetylcysteine)).mp. (77957)
40 (glutathione or urea or uric acid or selenium or carotene or carotenoid$1 or flavonoid$1 or taurine).mp. (427286)
41 (recombinant human erythropoietin or iron chelat$ or deferiprone or pioglitazone or antioxidant$1 or (anti adj oxidant$1)).mp. (255515)
42 (therapy or treatment).mp. (6748927)
43 histone deacetylase inhibitor/ (12403)
44 (histone deacetylase adj1 Inhibitor$).mp. (15381)
45 (deacetylase adj1 Inhibitor$ histone).mp. (59)
46 (hdac adj1 inhibitor$).mp. (6742)
47 or/16-46 (7313230)
48 15 and 47 (1178)
49 Friedreich ataxia/dt [Drug Therapy] (347)
50 12 and (48 or 49) (97)
51 remove duplicates from 50 (97)

Appendix 5. CINAHL (EBSCOhost) search strategy

Monday, February 29, 2016 10:42:46 AM

S22 S18 and S21 90
S21 S19 or S20 247
S20 friedreich* ataxia 247
S19 (MH "Friedreich's Ataxia") 194
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 812,608
S17 ABAB design* 91
S16 TI random* or AB random* 166,706
S15 (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)) 331,594
S14 (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*)) 118,835
S13 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*)) 43,606
S12 (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*)) 25,698
S11 PT ("clinical trial" or "systematic review") 131,468
S10 (MH "Factorial Design") 967
S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") 278,869
S8 (MH "Meta Analysis") 24,148
S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison") 49
S6 (MH "Quasi-Experimental Studies") 7,730
S5 (MH "Placebos") 9,644
S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies") 33,107
S3 (MH "Clinical Trials+") 196,275
S2 (MH "Crossover Design") 13,598
S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample") 71,958

Appendix 6. 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 7. 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]
4. Quick Search: friedreich ataxia AND antioxidant treatment [11 Records]

Appendix 8. Clinical Trials Registries

ClinicalTrials.gov

International Clinical Trials Registry Platform (ICTRP)

1 Simple search : Friedreich's Ataxia by disease name

WHAT'S NEW

Date	Event	Description
10 October 2016	Amended	Revision to sentence in Background regarding action of deferiprone

HISTORY

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

Date	Event	Description
2 September 2016	Amended	Correction to information about interferon gamma-1b in the background.
11 March 2015	New citation required and conclusions have changed	Searches updated to 29 February 2016. Three additional included studies.
11 March 2015	New search has been performed	The text was revised throughout and 'Summary of findings' tables included
7 December 2011	New citation required but conclusions have not changed	New search, no new studies included
4 October 2011	New search has been performed	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.
18 January 2010	Amended	Figures in Table 1 corrected. Other minor changes.

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 2 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, Dr Ruth Brassington assisted with presenting data and creating 'Summary of findings' tables, and all authors contributed to 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 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 holds stock in Sigma Pharmaceuticals and has given expert testimony on behalf of the Therapeutic Goods Administration.

Dr Ruth Brassington has no known financial or intellectual conflicts of interest. She is Managing Editor of Cochrane Neuromuscular, of which The National Institute for Health Research (NIHR) is the largest single founder. A grant from the Motor Neurone Disease Association also contributes to her salary.

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Internal sources

- Ruth Brassington, UK.

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- Ruth Brassington, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

We did not search the NORD databasefor this or the previous update.

As searching AMED, LILACS, and PEDRO produced no useful results, we did not search these databases for the 2015 update.

We included a `Summary of findings' table. We added a PRISMA flow chart in the 2012 update to show the study selection process.

In the 2015 update, we changed the primary outcome to

Change in validated Friedreich ataxia neurological score such as:

- ataxia rating score, Scale for the Assessment and Rating of Ataxia (SARA) after 12 months treatment
- ataxia rating score, Friedreich Ataxia Rating Scale (FARS) after 12 months treatment
- ataxia rating score, International Cooperative Ataxia Rating Scale (ICARS) after 12 months treatment

and we changed the secondary outcomes:

1. Change in cardiac measures, ejection fraction, interventricular septal wall thickness (IVSTd), and left ventricular mass (LVM), after 12 months treatment as measured by cardiac magnetic resonance imaging (cMRI):
2. Change in cardiac measures, ejection fraction, IVSTd, LVM after 12 months' treatment as measured by echocardiogram.

Change in authorship: addition of Dr Ruth Brassington.

INDEX TERMS

Medical Subject Headings (MeSH)

Antioxidants [adverse effects] [*therapeutic use]; Friedreich Ataxia [*drug therapy]; Heart [drug effects]; Hypertrophy, Left Ventricular [diagnostic imaging] [drug therapy]; Randomized Controlled Trials as Topic; Rare Diseases [drug therapy]; Ubiquinone [adverse effects] [*analogs & derivatives] [therapeutic use]; Ultrasonography; Vitamin E [adverse effects] [*therapeutic use]

MeSH check words

Humans