QUESTION

Should pharmacological intervention (antioxidants, antidepressants eg: idebenone, citalopram) vs. No pharmacological intervention (antioxidants, antidepressants eg: idebenone, citalopram) be used for all individuals who report fatigue with Friedreich ataxia?	
POPULATION:	all individuals who report fatigue with Friedreich ataxia
INTERVENTION:	pharmacological intervention (antioxidants, antidepressants eg: idebenone, citalopram)
COMPARISON:	No pharmacological intervention (antioxidants, antidepressants eg: idebenone, citalopram)
MAIN OUTCOMES:	Reported fatigue; Reported fatigue; Improved quality of life; Improved energy levels; Improved physical capacity; Improved physical capacity; Improved physical capability; Improved physical capability; Improved physical capacity; Improved physical capacity; Improved capacity to participate in daily tasks; Improved capacity to participate in daily tasks; Improved capacity to participate in daily tasks; Reduced falls;

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Fatigue may be a rather frequent and often under recognized feature in individuals with FRDA (da Silva et al, 2013).	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of fatigue. 4/7 indicated that the problem was serious, 3/7 indicated probably serious. 3/7 indicated that the problem was urgent, 2/7 indicated probably urgent, 2/7 indicated probably not urgent. 4/7 indicated that the problem was a priority, 3/7 indicated probably a priority. (Aug 2020)

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	(see table below)	Expert authors do not consider the ICARS/mFARS/SARA scales (as used in studies of pharmacological intervention) to be sensitive enough to measure fatigue accurately. In unpublished evidence, one expert author found several patients reported that when they started using a wheelchair or a walker, their fatigue actually improved, despite their ataxia severity score probably getting worse. This suggests that fatigue improvements may not be reflected in the FRDA measurement scales. Also, there is a lot of day to day fluctuation in fatigue, whereas there isn't likely to be

Outcomes	№ of	Certainty of	Relative	Anticipated absolute effects* (95% CI)

	participants (studies) Follow-up	the evidence (GRADE)	effect (95% CI)	Risk with No pharmacological intervention (antioxidants, antidepressants eg: idebenone, citalopram)	Risk difference with pharmacological intervention (antioxidants, antidepressants eg: idebenone, citalopram)
Reported fatigue assessed with: Modified Fatigue Impact Scale	29 (1 RCT)[1]	⊕⊕◯◯ Low[a,b,c]	-	29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. The MFIS was analysed using an analysis of covariance (ANCOVA) model with the baseline value as a covariate. No significant differences wereobserved between treatments for the MFIS. (Cook et al 2019)	
Reported fatigue assessed with: Adverse events	108 (3 RCTs)[1,2,3]	⊕⊕◯◯ Low[a,d,e]	-	10 people with Friedreich ataxia were given single doses (phase 1) and repeated daily doses of 2-8g oral nicotinamide for 5 days (phase 2) and 8 weeks (phase 3). Doses were gradually escalated during phases 1 and 2 with individual maximum tolerated doses used in phase 3. There were 4 total reported episodes of fatigue (7%) in phase 1 and 6 events of fatigue in phases 2 and 3. (Libri et al 2014) 69 patients with Friedreich ataxia were randomised 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. 4/52 (8%) in treatment group and 2/17 (12%) in placebo group reported fatigue as an adverse event. (Lynch et al 2019)29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. Fatigue (4 patients treated with idebenone and 1 patient treated with placebo) were the adverse events most	

much fluctuation in ataxia severity scores.

				commonly considered by the investigator to be treatment-related. (Cook et al 2019)	
Improved quality of life assessed with: SF-36V2	82 (2 RCTs)[3,4]	⊕⊕◯◯ Low[d,e,f]	-	13 patients with Friedreich ataxia were treated with deferiprone at 5-25 mg/kg/day, idebenone at 10–20 mg/kg/day and riboflavin at 10–15 mg/kg/day for 15–45 months. Efficacy analyses were performed on per protocol (PP) population, defined as patients who had completed at least one year in the study and had no major protocol violations. For the efficacy parameters, to compare the change from baseline to post-baseline visits, nonparametric Wilcoxon–Mann–Whitney tests were used. In the SF-36, 61.5% reported dissatisfaction, the satisfaction was fair in 19.25% and poor in 19.25%. (Arpa et al 2014). 69 patients with Friedreich ataxia were randomised 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. The pairwise dose group comparisons with placebo were estimated using the difference in adjusted means and 95% confidence intervals for the difference in changes from baseline to Week 12. After 12 weeks of treatment, patients treated with Omav 160 mg/day did not show improvements versus placebo in SF-36 (*p* = 0.19). (Lynch et al 2019)	
Improved energy levels - not measured	-	-	-	-	-
Improved physical capacity assessed with: International Cooperative Ataxia Rating	29 (1 RCT)[1]	⊕⊕◯◯ Low[a,c]	-	29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. The ICARS was analysed using an analysis of covariance (ANCOVA) model with the baseline value	

Scale				as a covariate. For ICARS, the mean difference (-2.2 points) between idebenone and placebo for the analysis using observed cases was not statistically significant, but for ambulatory patients, the mean difference between treatments (-6.4 points) was statistically significant (p = 0.0121) in favour of idebenone. (Cook et al 2019)
Improved physical capacity assessed with: Scale for the Assessment and Rating of Ataxia	23 (2 RCTs)[2,4]	⨁◯◯◯ Very low[a,e,f]	-	13 patients with Friedreich ataxia were treated with deferiprone at 5-25 mg/kg/day, idebenone at 10–20 mg/kg/day and riboflavin at 10–15 mg/kg/day for 15–45 months. Efficacy analyses were performed on per protocol (PP) population, defined as patients who had completed at least one year in the study and had no major protocol violations. For the efficacy parameters, to compare the change from baseline to post-baseline visits, nonparametric Wilcoxon–Mann–Whitney tests were used. Statistically significant ($p < 0.05$) worsening of ataxia as evaluated by the SARA was observed from the fourth quarter of the study. (Arpa et al 2014) 10 people with Friedreich ataxia were given single doses (phase 1) and repeated daily doses of 2-8g oral nicotinamide for 5 days (phase 2) and 8 weeks (phase 3). Doses were gradually escalated during phases 1 and 2 with individual maximum tolerated doses used in phase 3. Comparison of clinical scores between baseline and week 8 was done using a two-tailed paired Student's t test. No significant effects were seen on the clinical scale ratings for disease progression over study phases 2 and 3. (Libri et al 2014)
Improved physical capability	10 (1 observational	⨁◯◯◯ Very low[a,b,e]	-	10 people with Friedreich ataxia were given single doses (phase 1) and repeated daily doses of 2-8g oral

assessed with: Spinocerebellar ataxia functional index	study)[2]			nicotinamide for 5 days (phase 2) and 8 weeks (phase 3). Doses were gradually escalated during phases 1 and 2 with individual maximum tolerated doses used in phase 3. Comparison of clinical scores between baseline and week 8 was done using a two-tailed paired Student's t test. No significant effects were seen on the clinical scale ratings for disease progression over study phases 2 and 3. (Libri et al 2014)
Improved physical capability assessed with: Modified Friedreich Ataxia Rating Scale	69 (1 RCT)[3]	⊕⊕⊕◯ Moderate[d]	-	69 patients with Friedreich ataxia were randomised 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. The mFARS was analyzed using repeated measures analysis of variance. Analysis visits at baseline, weeks 4, 8, and 12 were used in the repeated measures analysis, with an unstructured covariance structure. Omav significantly improved mFARS scores from baseline in a dose-dependent manner ($p < 0.001$). Overall, dose-dependent improvements at Week 12 were maximal at 160 mg/day. When compared to the placebo-corrected change at 160 mg/day), the improvement in mFARS approached statistical significance ($p = 0.06$) and was equivalent to an improvement of about 1 year of progression in FRDA based on comparisons to natural history data. The improvements in mFARS were time dependent, as the mFARS improved by week 4 and further improved by week 12. In addition, the improvement compared to placebo increased over this time. (Lynch et al 2019)
Improved physical capacity assessed with: Timed 25 Foot Walk	69 (1 RCT)[3]	⊕⊕⊕◯ Moderate[d]	-	69 patients with Friedreich ataxia were randomised 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. The T25FW was analyzed using repeated measures analysis of variance. Analysis visits at baseline, weeks 4, 8, and 12 were used in the repeated measures analysis, with an

				unstructured covariance structure. After 12 weeks of treatment, patients treated with Omav 160 mg/day did not show improvements versusplacebo in 25-foot timed walk test (*p* = 0.64). (Lynch et al 2019)
Improved physical capacity assessed with: 9-Hole Peg Test	0 (1 RCT)[3]	⊕⊕⊕◯ Moderate[d]	-	69 patients with Friedreich ataxia were randomised 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. The T25FW was analyzed using repeated measures analysis of variance. Analysis visits at baseline, weeks 4, 8, and 12 were used in the repeated measures analysis, with an unstructured covariance structure. After 12 weeks of treatment, patients treated with Omav 160 mg/day did not show improvements versus placebo in 9-hole peg test time for dominant (*p* = 0.20) or nondominant hand (*p* = 0.89). (Lynch et al 2019)
Improved capacity to participate in daily tasks assessed with: Activities of Daily Living	10 (1 observational study)[2]	⊕◯◯◯ Very low[a,b,e]	-	10 people with Friedreich ataxia were given single doses (phase 1) and repeated daily doses of 2-8g oral nicotinamide for 5 days (phase 2) and 8 weeks (phase 3). Doses were gradually escalated during phases 1 and 2 with individual maximum tolerated doses used in phase 3. Comparison of clinical scores between baseline and week 8 was done using a two-tailed paired Student's t test. No significant effects were seen on the clinical scale ratings for disease progression over study phases 2 and 3. (Libri et al 2014)
Improved capacity to participate in daily tasks assessed with: Status questionnaire	29 (1 RCT)[1]	⊕⊕◯◯ Low[a,b,c]	-	29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. The Status Questionnaire were analysed using logistic regression. The majority of patients reported no worsening in all

				categories, irrespective of their treatment. (Cook et al 2019)
Improved capacity to participate in daily tasks assessed with: Change questionnaire	29 (1 RCT)[1]	⊕⊕◯◯ Low[a,b,c]	-	29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. The Change Questionnaire were analysed using logistic regression. The majority of patients reported no worsening in all categories, irrespective of their treatment. (Cook et al 2019)
Reduced falls assessed with: Self report	29 (1 RCT)[1]	⊕⊕◯◯ Low[a,b,c]	-	29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. Falls (4 patients treated with idebenone and 2 patients treated with placebo) were the adverse events most commonly considered by the investigator to be treatment-related. (Cook et al 2019)

1. Cook A, Boesch S Heck S Brunt E Klockgether T Schöls L et al. Patient-reported outcomes in Friedreich's ataxia after withdrawal from idebenone. Acta Neurologica Scandinavica; 2019.
2. Libri V., Yandim C. Athanasopoulos S. et al. Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: An exploratory, open-label, dose-escalation study. Lancet; 2014.
3. Lynch D.R., Farmer J. Hauser L. et al. Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. Annals of Clinical and Translational Neurology; 2019.
4. Arpa J., Sanz-Gallego I. Rodriguez-de-Rivera F.J. et al. Triple therapy with deferiprone, idebenone and riboflavin in Friedreich's ataxia - open-label trial. Acta Neurologica Scandinavica; 2014.

a. Small sample size.
b. Single study published.
c. No confidence intervals reported with low absolute numbers of participants and events.
d. Small sample size in subgroups.
e. One open label trial.
f. High number of withdrawals.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	See table below	Fatigue (4 patients treated with idebenone and 1 patient treated with placebo) were the adverse events most commonly considered by the investigator to be treatment-related (Cook et al 2019).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with No pharmacological intervention (antioxidants, antidepressants eg: idebenone, citalopram)	Risk difference with pharmacological intervention (antioxidants, antidepressants eg: idebenone, citalopram)
Reported fatigue assessed with: Modified Fatigue Impact Scale	29 (1 RCT)[1]	⊕⊕◯◯ Low[a,b,c]	-	29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. The MFIS was analysed using an analysis of covariance (ANCOVA) model with the baseline value as a covariate. No significant differences wereobserved between treatments for the MFIS. (Cook et al 2019)	
Reported fatigue assessed with: Adverse events	108 (3 RCTs)[1,2,3]	⊕⊕◯◯ Low[a,d,e]	-	10 people with Friedreich ataxia were given single doses (phase 1) and repeated daily doses of 2-8g oral nicotinamide for 5 days (phase 2) and 8 weeks (phase 3). Doses were gradually escalated during phases 1 and 2 with individual maximum tolerated doses used in phase 3. There were 4 total reported episodes of fatigue (7%) in phase 1 and 6 events of fatigue in phases 2 and 3. (Libri et al 2014) 69 patients with Friedreich ataxia were	

				randomised 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. 4/52 (8%) in treatment group and 2/17 (12%) in placebo group reported fatigue as an adverse event. (Lynch et al 2019)29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. Fatigue (4 patients treated with idebenone and 1 patient treated with placebo) were the adverse events most commonly considered by the investigator to be treatment-related. (Cook et al 2019)
Improved quality of life assessed with: SF-36V2	82 (2 RCTs)[3,4]	⨁⨁◯◯ Low[d,e,f]	-	13 patients with Friedreich ataxia were treated with deferiprone at 5-25 mg/kg/day, idebenone at 10–20 mg/kg/day and riboflavin at 10–15 mg/kg/day for 15–45 months. Efficacy analyses were performed on per protocol (PP) population, defined as patients who had completed at least one year in the study and had no major protocol violations. For the efficacy parameters, to compare the change from baseline to post-baseline visits, nonparametric Wilcoxon–Mann–Whitney tests were used. In the SF-36, 61.5% reported dissatisfaction, the satisfaction was fair in 19.25% and poor in 19.25%. (Arpa et al 2014). 69 patients with Friedreich ataxia were randomised 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. The pairwise dose group comparisons with placebo were estimated using the difference in adjusted means and 95% confidence intervals for the difference in changes from baseline to Week 12. After 12 weeks of treatment, patients treated with Omav 160 mg/day did not show improvements versus placebo in SF-36

				(p = 0.19). (Lynch et al 2019)	
Improved energy levels - not measured	-	-	-	-	-
Improved physical capacity assessed with: International Cooperative Ataxia Rating Scale	29 (1 RCT)[1]	⊕⊕◯◯ Low[a,c]	-	29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. The ICARS was analysed using an analysis of covariance (ANCOVA) model with the baseline value as a covariate. For ICARS, the mean difference (-2.2 points) between idebenone and placebo for the analysis using observed cases was not statistically significant, but for ambulatory patients, the mean difference between treatments (-6.4 points) was statistically significant (p = 0.0121) in favour of idebenone. (Cook et al 2019)	
Improved physical capacity assessed with: Scale for the Assessment and Rating of Ataxia	23 (2 RCTs)[2,4]	⊕◯◯◯ Very low[a,e,f]	-	13 patients with Friedreich ataxia were treated with deferiprone at 5-25 mg/kg/day, idebenone at 10–20 mg/kg/day and riboflavin at 10–15 mg/kg/day for 15–45 months. Efficacy analyses were performed on per protocol (PP) population, defined as patients who had completed at least one year in the study and had no major protocol violations. For the efficacy parameters, to compare the change from baseline to post-baseline visits, nonparametric Wilcoxon–Mann–Whitney tests were used. Statistically significant (p < 0.05) worsening of ataxia as evaluated by the SARA was observed from the fourth quarter of the study. (Arpa et al 2014) 10 people with Friedreich ataxia were given single doses (phase 1) and repeated daily doses of 2-8g oral nicotinamide for 5 days (phase 2) and 8	

				weeks (phase 3). Doses were gradually escalated during phases 1 and 2 with individual maximum tolerated doses used in phase 3. Comparison of clinical scores between baseline and week 8 was done using a two-tailed paired Student's t test. No significant effects were seen on the clinical scale ratings for disease progression over study phases 2 and 3. (Libri et al 2014)
Improved physical capability assessed with: Spinocerebellar ataxia functional index	10 (1 observational study)[2]	⨁◯◯◯ Very low[a,b,e]	-	10 people with Friedreich ataxia were given single doses (phase 1) and repeated daily doses of 2-8g oral nicotinamide for 5 days (phase 2) and 8 weeks (phase 3). Doses were gradually escalated during phases 1 and 2 with individual maximum tolerated doses used in phase 3. Comparison of clinical scores between baseline and week 8 was done using a two-tailed paired Student's t test. No significant effects were seen on the clinical scale ratings for disease progression over study phases 2 and 3. (Libri et al 2014)
Improved physical capability assessed with: Modified Friedreich Ataxia Rating Scale	69 (1 RCT)[3]	⨁⨁⨁◯ Moderate[d]	-	69 patients with Friedreich ataxia were randomised 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. The mFARS was analyzed using repeated measures analysis of variance. Analysis visits at baseline, weeks 4, 8, and 12 were used in the repeated measures analysis, with an unstructured covariance structure. Omav significantly improved mFARS scores from baseline in a dose-dependent manner ($p < 0.001$). Overall, dose-dependent improvements at Week 12 were maximal at 160 mg/day. When compared to the placebo-corrected change at 160 mg/day), the improvement in mFARS approached statistical significance ($p = 0.06$) and was equivalent to an improvement of about 1 year of progression in FRDA based on comparisons to natural history data. The improvements in mFARS were time

				dependent, as the mFARS improved by week 4 and further improved by week 12. In addition, the improvement compared to placebo increased over this time. (Lynch et al 2019)
Improved physical capacity assessed with: Timed 25 Foot Walk	69 (1 RCT)[3]	⊕⊕⊕◯ Moderate[d]	-	69 patients with Friedreich ataxia were randomised 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. The T25FW was analyzed using repeated measures analysis of variance. Analysis visits at baseline, weeks 4, 8, and 12 were used in the repeated measures analysis, with an unstructured covariance structure. After 12 weeks of treatment, patients treated with Omav 160 mg/day did not show improvements versusplacebo in 25-foot timed walk test ($p = 0.64$). (Lynch et al 2019)
Improved physical capacity assessed with: 9-Hole Peg Test	0 (1 RCT)[3]	⊕⊕⊕◯ Moderate[d]	-	69 patients with Friedreich ataxia were randomised 3:1 to either omaveloxolone or placebo administered once daily for 12 weeks. The T25FW was analyzed using repeated measures analysis of variance. Analysis visits at baseline, weeks 4, 8, and 12 were used in the repeated measures analysis, with an unstructured covariance structure. After 12 weeks of treatment, patients treated with Omav 160 mg/day did not show improvements versus placebo in 9-hole peg test time for dominant ($p = 0.20$) or nondominant hand ($p = 0.89$). (Lynch et al 2019)
Improved capacity to participate in daily tasks assessed with: Activities of Daily Living	10 (1 observational study)[2]	⊕◯◯◯ Very low[a,b,e]	-	10 people with Friedreich ataxia were given single doses (phase 1) and repeated daily doses of 2-8g oral nicotinamide for 5 days (phase 2) and 8 weeks (phase 3). Doses were gradually escalated during phases 1 and 2 with individual maximum tolerated doses used in phase 3. Comparison of clinical scores between baseline and week 8 was done using a two-tailed paired

				Student's t test. No significant effects were seen on the clinical scale ratings for disease progression over study phases 2 and 3. (Libri et al 2014)
Improved capacity to participate in daily tasks assessed with: Status questionnaire	29 (1 RCT)[1]	⨁⨁◯◯ Low[a,b,c]	-	29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. The Status Questionnaire were analysed using logistic regression. The majority of patients reported no worsening in all categories, irrespective of their treatment. (Cook et al 2019)
Improved capacity to participate in daily tasks assessed with: Change questionnaire	29 (1 RCT)[1]	⨁⨁◯◯ Low[a,b,c]	-	29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. The Change Questionnaire were analysed using logistic regression. The majority of patients reported no worsening in all categories, irrespective of their treatment. (Cook et al 2019)
Reduced falls assessed with: Self report	29 (1 RCT)[1]	⨁⨁◯◯ Low[a,b,c]	-	29 patients with Friedreich ataxia taking idebenone for at least 12 months as part of an open label extension study were randomised to receive either placebo or idebenone continuation for 2-month treatment cycles. Falls (4 patients treated with idebenone and 2 patients treated with placebo) were the adverse events most commonly considered by the investigator to be treatment-related. (Cook et al 2019)

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2. Libri V., Yandim C. Athanasopoulos S. et al. Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: An exploratory, open-label, dose-escalation study. Lancet; 2014.

	3. Lynch D.R., Farmer J. Hauser L. et al. Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. Annals of Clinical and Translational Neurology; 2019. 4. Arpa J., Sanz-Gallego I. Rodriguez-de-Rivera F.J. et al. Triple therapy with deferiprone, idebenone and riboflavin in Friedreich's ataxia - open-label trial. Acta Neurologica Scandinavica; 2014. a. Small sample size. b. Single study published. c. No confidence intervals reported with low absolute numbers of participants and events. d. Small sample size in subgroups. e. One open label trial. f. High number of withdrawals.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Moderate to very low certainty of the evidence of effects as per the evidence profile table.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	<table><tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Reported fatigue</td><td>IMPORTANT[a]</td><td>⨁⨁◯◯</td></tr></table>	

	assessed with: Modified Fatigue Impact Scale		LOW[b,c,d]	
	Reported fatigue assessed with: Adverse events	IMPORTANT[a]	⨁⨁◯◯ LOW[b,e,f]	
	Improved quality of life assessed with: SF-36V2	IMPORTANT[g]	⨁⨁◯◯ LOW[e,f,h]	
	Improved energy levels - not measured	IMPORTANT[i]	-	
	Improved physical capacity assessed with: International Cooperative Ataxia Rating Scale	IMPORTANT[a]	⨁⨁◯◯ LOW[b,d]	
	Improved physical capacity assessed with: Scale for the Assessment and Rating of Ataxia	IMPORTANT[a]	⨁◯◯◯ VERY LOW[b,f,h]	
	Improved physical capability assessed with: Spinocerebellar ataxia functional index	IMPORTANT[a]	⨁◯◯◯ VERY LOW[b,c,f]	
	Improved physical capability assessed with: Modified Friedreich Ataxia Rating Scale	IMPORTANT[a]	⨁⨁⨁◯ MODERATE[e]	
	Improved physical capacity assessed with: Timed 25 Foot Walk	IMPORTANT[a]	⨁⨁⨁◯ MODERATE[e]	
	Improved physical capacity assessed with: 9-Hole Peg Test	IMPORTANT[a]	⨁⨁⨁◯ MODERATE[e]	
	Improved capacity to participate in daily tasks assessed with: Activities of Daily Living	IMPORTANT[a]	⨁◯◯◯ VERY LOW[b,c,f]	
	Improved capacity to participate in daily tasks assessed with: Status questionnaire	IMPORTANT[a]	⨁⨁◯◯ LOW[b,c,d]	
	Improved capacity to participate in daily tasks assessed with: Change questionnaire	IMPORTANT[a]	⨁⨁◯◯ LOW[b,c,d]	
	Reduced falls	CRITICAL[j]	⨁⨁◯◯	

	assessed with: Self report		LOW[b,c,d]

a. Identified as important (6/6) by people with FA and critical by expert authors on this topic
b. Small sample size.
c. Single study published.
d. No confidence intervals reported with low absolute numbers of participants and events.
e. Small sample size in subgroups.
f. One open label trial.
g. Identified as important (5/6) and critical (1/6) by people with FA and important by expert authors on this topic
h. High number of withdrawals.
i. Identified as important (6/6) by people with FA and important by expert authors on this topic
j. Identified as important (3/6) and critical (3/6) by people with FA and critical by expert authors on this topic

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		A survey designed to systematically collect expert-based opinions from clinicians involved in the development of these guidelines and providing clinical care for individuals with Friedreich ataxia, was conducted. Clinical experts from Australia, Europe, UK, South America, Canada and the USA were asked to consider the harms/benefits of Pharmacological intervention (antioxidants, antidepressants eg: idebenone, citalopram) as a management strategy for all individuals. Reflecting on the impact of Pharmacological intervention (antioxidants, antidepressants eg: idebenone, citalopram) on Reported fatigue, 43.48% (10/23) clinical experts reported a benefit (large, moderate or small), 4.35% (1/23) reported no effect and, 0% (0/23) reported observing a harm (large, moderate or small). 12 clinicians could not provide any information on this outcome. Reflecting on the impact on Improved quality of life, 39.13% (9/23) clinical experts reported a benefit, 8.7% (2/23) reported no effect and, 0% (0/23) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on energy levels, 39.13% (9/23) clinical

		experts reported a benefit, 8.7% (2/23) reported no effect and, 0% (0/23) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on physical capacity, 30.44% (7/23) clinical experts reported a benefit, 17.39% (4/23) reported no effect and, 0% (0/23) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on capacity to participate in daily tasks, 39.13% (9/23) clinical experts reported a benefit, 8.7% (2/23) reported no effect and, 0% (0/23) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on falls, 17.39% (4/23) clinical experts reported a benefit, 30.43% (7/23) reported no effect and, 0% (0/23) reported observing a harm. 12 expert clinicians could not provide any information on this outcome.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No published evidence.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using medication in people who report fatigue was acceptable (weighing up the balance between benefits, harms and costs). 1/4 indicated the intervention was probably acceptable, 1/4 indicated probably not acceptable, 2/4 indicated they didn't know if acceptable. (Aug 2020).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or**			

	JUDGEMENT						
				variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest some pharmacological intervention (antioxidants, antidepressants) may have limited value in managing fatigue related to Friedreich ataxia.

Justification

Based on current small studies, there is only low certainty of evidence of small desirable effects of pharmacological intervention (antioxidants, antidepressants) for individuals with Friedreich ataxia reporting fatigue; thus, only a conditional recommendation can be made.

Most studies of pharmacological interventions use clinical scales such as the ICARS/mFARS/SARA as outcome measures. Expert authors do not consider these scales to be sensitive enough to capture the extent and impact of fatigue. Indeed, in as yet unpublished evidence, one expert author found several patients reported that when they started using a wheelchair or a walker, their fatigue actually improved. So, although their ataxia severity score was likely to have got worse (reflected by moving to a wheelchair), their fatigue improved. Also, there is a lot of day to day fluctuation in fatigue, whereas there is unlikely to be comparable daily fluctuation in the ataxia severity score.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia who report fatigue.

Research priorities

Targeted measures of fatigue are required in future studies evaluating efficacy of pharmaceuticals on fatigue in FRDA.

Reference

da Silva CB, Chevis CF, D'Abreu A, Lopes-Cendes I, Franca MC, Jr. Fatigue is frequent and multifactorial in Friedreich's ataxia. Parkinsonism Relat Disord. 2013;19(8):766-7.