QUESTION

Should pharmaceutical intervention vs. no pharmaceutical intervention be used for all people with Friedreich ataxia?	
POPULATION:	all people with Friedreich ataxia
INTERVENTION:	pharmaceutical intervention
COMPARISON:	no pharmaceutical intervention
MAIN OUTCOMES:	Acoustic analysis of speech and voice ; Clinician rating of speech severity ; Clinician rating of speech severity ; Clinician rating of speech severity ; Patient self-rating of speech ;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Dysarthria remains a significant and important issue for people with FA. Speech disorder is prevalent across the disease course, gradually worsening as the disease progresses. There are several pharmaceutical treatment clinical trials currently underway.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic. 7/7 indicated dysarthria was serious. 1/7 indicated dysarthria was probably not urgent, 1/7 indicated probably urgent, 4/7 indicated urgent, 1/7 indicated varies/sometimes urgent. 2/7 indicated dysarthria was probably a priority, 5/7 indicated 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		

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no pharmaceutical intervention	Risk difference with pharmaceutical intervention
Acoustic analysis of	24 (1	⨁◯◯◯	-	27 individuals with Friedreich ataxia completed an open-label trial of two	

	speech and voice assessed with: Speech recordings of four speech tasks	observational study)[1]	Very low[a]		different doses (1g or 5g) of resveratrol over a 12-week period. For each dosage group, the mean absolute change from baseline to 12 weeks in all outcome measures was calculated. Paired t tests were used to test the null hypothesis of no absolute change in each of these parameters from baseline to 12 weeks, carried out separately for each dosage group. In the high dose group, the speech variable mean silence length (p=0.007) was reduced in two out of three speech tasks. This finding, in combination with a trend to a reduction in percentage silence time (p=0.017) in the same speech tasks reflects improved speech efficiency. (Yiu et al 2015).	
	Clinician rating of speech severity assessed with: Friedreich Ataxia Rating Scale	24 (1 observational study)[1]	⊕◯◯◯ Very low[a,b]	-	27 individuals with Friedreich ataxia completed an open-label trial of two different doses (1g or 5g) of resveratrol over a 12-week period. For each dosage group, the mean absolute change from baseline to 12 weeks in all outcome measures was calculated. Paired t tests were used to test the null hypothesis of no absolute change in each of these parameters from baseline to 12 weeks, carried out separately for each dosage group. There was an improvement in neurologic deficit after 12 weeks of treatment in participants receiving high-dose resveratrol as measured by the FARS [change in score -3.4 points, 95 % CI (-6.6, -0.3), p = 0.036]. Improvements were seen predominantly in the 'Neurological Examination' subscale of the FARS (upper limb and bulbar components). (Yiu et al 2015).	
	Clinician rating of speech severity assessed with: Scale for the Assessment	48 (2 observational studies)[1,2]	⊕◯◯◯ Very low[a,c,d,e]	-	27 individuals with Friedreich ataxia completed an open-label trial of two different doses (1g or 5g) of resveratrol over a 12-week period. For each dosage group, the mean absolute change from baseline to 12 weeks in all outcome measures was calculated. Paired t tests were used to test the null hypothesis of no	

and Rating of Ataxia				absolute change in each of these parameters from baseline to 12 weeks, carried out separately for each dosage group. There was also a trend for improvement in the SARA in the high dose group, however this was not statistically significant. (Yiu et al 2015). 21 people with spinocerebellar ataxia 3 were enrolled in this open-label prospective study of nerve growth factor (NGF) administered by intramuscular injection (18 µg once daily for 28 consecutive days). Patients were evaluatied at baseline, 2 weeks and 4 weeks after treatment using the Chinese version of the SARA. The mean total SARA score decreased significantly from a baseline of 8.48 ± 2.40 to 6.30 ± 1.87 (p<0.001). (Tan et al 2015).
Clinician rating of speech severity assessed with: International Cooperative Ataxia Rating Scale	29 (2 observational studies)[1,3]	⨁◯◯◯ Very low[a,f,g]	-	27 individuals with Friedreich ataxia completed an open-label trial of two different doses (1g or 5g) of resveratrol over a 12-week period. For each dosage group, the mean absolute change from baseline to 12 weeks in all outcome measures was calculated. Paired t tests were used to test the null hypothesis of no absolute change in each of these parameters from baseline to 12 weeks, carried out separately for each dosage group. There was an improvement in neurologic deficit after 12 weeks of treatment in participants receiving high-dose resveratrol as measured by the ICARS [change in score -1.9 points, 95 % CI (-3.1, -0.8), p=0.004]. (Yiu et al 2015). A 60 year old woman with multisystem atrophy (MSA) type C (patient 1) and a 54 year old woman with spinocerebellar ataxia (SCA) type 6 (patient 2) who had histories of ginseng intake (5 years and 30 months respectively) were examined, In patient 1, ICARS score improved from 21 to 17.5 (±1.8) in the 5 years. Patient 2 showed an improvement in ICARS from 22 to 6.0 (±1.0) over 30 months. However upon ceasing ginseng, patient 2's ICARS score progressed up to 13 points in 2

				years. (Min et al 2015).
Patient self-rating of speech assessed with: Friedreich Ataxia Impact Scale	24 (1 observational study)[1]	⨁◯◯◯ Very low[a]	-	27 individuals with Friedreich ataxia completed an open-label trial of two different doses (1g or 5g) of resveratrol over a 12-week period. For each dosage group, the mean absolute change from baseline to 12 weeks in all outcome measures was calculated. Paired t tests were used to test the null hypothesis of no absolute change in each of these parameters from baseline to 12 weeks, carried out separately for each dosage group. There were no significant changes in any components of the FAIS or SF-36 in either dosage group (Yiu et al 2015).

1. Yiu E.M., Tai G.,Peverill R.E. et al. An open-label trial in Friedreich ataxia suggests clinical benefit with high-dose resveratrol, without effect on frataxin levels. Journal of Neurology; 2015.
2. Tan S, Wang RH,Niu HX,et al. Nerve growth factor for the treatment of spinocerebellar ataxia type 3: An open-label study. Chinese Medical Journal; 2015.
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a. Small sample size/s.
b. Outcome measure not specific to measuring speech severity.
c. Twenty-seven participants had a diagnosis of FRDA out of total sample of 48 participants (spinocerebellar ataxia type III n=21)
d. In one study the outcome measure was not specific to measuring speech severity.
e. No short or long term follow up.
f. For the study evaluating the impact of ginseng, none of the participants had a diagnosis of FRDA (total sample n=2).
g. One study was a case series (n=2).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no pharmaceutical intervention	Risk difference with pharmaceutical intervention
Acoustic analysis of speech and voice assessed with: Speech recordings of four speech tasks	24 (1 observational study)[1]	⨁◯◯◯ Very low[a]	-	27 individuals with Friedreich ataxia completed an open-label trial of two different doses (1g or 5g) of resveratrol over a 12-week period. For each dosage group, the mean absolute change from baseline to 12 weeks in all outcome measures was calculated. Paired t tests were used to test the null hypothesis of no absolute change in each of these parameters from baseline to 12 weeks, carried out separately for each dosage group. In the high dose group, the speech variable mean silence length (p=0.007) was reduced in two out of three speech tasks. This finding, in combination with a trend to a reduction in percentage silence time (p=0.017) in the same speech tasks reflects improved speech efficiency. (Yiu et al 2015).	
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				limb and bulbar components). (Yiu et al 2015).
Clinician rating of speech severity assessed with: Scale for the Assessment and Rating of Ataxia	48 (2 observational studies)[1,2]	⨁◯◯◯ Very low[a,c,d,e]	-	27 individuals with Friedreich ataxia completed an open-label trial of two different doses (1g or 5g) of resveratrol over a 12-week period. For each dosage group, the mean absolute change from baseline to 12 weeks in all outcome measures was calculated. Paired t tests were used to test the null hypothesis of no absolute change in each of these parameters from baseline to 12 weeks, carried out separately for each dosage group. There was also a trend for improvement in the SARA in the high dose group, however this was not statistically significant. (Yiu et al 2015). 21 people with spinocerebellar ataxia 3 were enrolled in this open-label prospective study of nerve growth factor (NGF) administered by intramuscular injection (18 µg once daily for 28 consecutive days). Patients were evaluatied at baseline, 2 weeks and 4 weeks after treatment using the Chinese version of the SARA. The mean total SARA score decreased significantly from a baseline of 8.48 ± 2.40 to 6.30 ± 1.87 (p<0.001). (Tan et al 2015).
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				A 60 year old woman with multisystem atrophy (MSA) type C (patient 1) and a 54 year old woman with spinocerebellar ataxia (SCA) type 6 (patient 2) who had histories of ginseng intake (5 years and 30 months respectively) were examined, In patient 1, ICARS score improved from 21 to 17.5 (±1.8) in the 5 years. Patient 2 showed an improvement in ICARS from 22 to 6.0 (±1.0) over 30 months. However upon ceasing ginseng, patient 2's ICARS score progressed up to 13 points in 2 years. (Min et al 2015).
Patient self-rating of speech assessed with: Friedreich Ataxia Impact Scale	24 (1 observational study)[1]	⊕◯◯◯ Very low[a]	-	27 individuals with Friedreich ataxia completed an open-label trial of two different doses (1g or 5g) of resveratrol over a 12-week period. For each dosage group, the mean absolute change from baseline to 12 weeks in all outcome measures was calculated. Paired t tests were used to test the null hypothesis of no absolute change in each of these parameters from baseline to 12 weeks, carried out separately for each dosage group. There were no significant changes in any components of the FAIS or SF-36 in either dosage group (Yiu et al 2015).

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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	Very low certainty of the evidence of effects as per the evidence profile.	

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		

Outcomes	Importance	Certainty of the evidence (GRADE)
Acoustic analysis of speech and voice assessed with: Speech recordings of four speech tasks	IMPORTANT[a]	⨁◯◯◯ VERY LOW[b]
Clinician rating of speech severity assessed with: Friedreich Ataxia Rating Scale	IMPORTANT[c]	⨁◯◯◯ VERY LOW[b,d]

Clinician rating of speech severity assessed with: Scale for the Assessment and Rating of Ataxia	IMPORTANT[c]	⨁◯◯◯ VERY LOW[b,e,f,g]
Clinician rating of speech severity assessed with: International Cooperative Ataxia Rating Scale	IMPORTANT[c]	⨁◯◯◯ VERY LOW[b,h,i]
Patient self-rating of speech assessed with: Friedreich Ataxia Impact Scale	IMPORTANT[c]	⨁◯◯◯ VERY LOW[b]

a. Identified as important (3/6) and critical (3/6) by people with FA and important by expert authors on this topic
b. Small sample size/s.
c. Identified as important (4/6) and critical (2/6) by people with FA and important by expert authors on this topic
d. Outcome measure not specific to measuring speech severity.
e. Twenty-seven participants had a diagnosis of FRDA out of total sample of 48 participants (spinocerebellar ataxia type III n=21)
f. In one study the outcome measure was not specific to measuring speech severity.
g. No short or long term follow up.
h. For the study evaluating the impact of ginseng, none of the participants had a diagnosis of FRDA (total sample n=2).
i. One study was a case series (n=2).

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	There is some preliminary evidence to suggest that speech can change because of pharmaceutical treatment, however the evidence is inconclusive. Data are derived from only one small open label trial. Improvements to speech were observed in the high dose group and not the low dose group.	

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 the intervention was acceptable (weighing up the balance between benefits, harms and costs). 1/4 indicated pharmaceutical intervention was probably reasonable, 3/4 didn't know if reasonable. (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 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

For people with Friedreich ataxia, we suggest that pharmaceutical therapies are not used to treat dysarthria.

Justification

Very few published studies have used speech as an outcome measure in pharmaceutical trials for FRDA. There is very low evidence supporting the use of any pharmaceutical therapies to improve dysarthria in FRDA. One open-label trial showed minor changes in acoustic outcomes related to timing in the high-dose group (versus low-dose group) (Yiu et al, 2015). These findings were not verified against listener-based judgements.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia with dysarthria.

Research priorities

Future pharmaceutical trials in FA should include objective markers of speech as outcome measures. This would provide evidence supporting or refuting the efficacy of new therapies in this domain.

References

Yiu EM, Tai G, Peverill RE, Lee KJ, Croft KD, Mori TA, et al. An open-label trial in Friedreich ataxia suggests clinical benefit with high-dose resveratrol, without effect on frataxin levels. J Neurol. 2015;262(5):1344-53.