

QUESTION

Should cardio-pulmonary exercise vs. no exercise be used for non-ambulant people with Friedreich ataxia?

POPULATION:	non-ambulant people with Friedreich ataxia
INTERVENTION:	cardio-pulmonary exercise
COMPARISON:	no exercise
MAIN OUTCOMES:	Independence in transfers; Pain; Independence in activities of daily living; Capacity to stand; Sitting balance; Quality of life;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 		<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic.</p> <p>1/7 indicated non-ambulant mobility was not serious, 2/7 indicated probably serious, 4/7 indicated serious.</p> <p>3/7 indicated non-ambulant mobility was probably not urgent, 4/7 indicated urgent.</p> <p>2/7 indicated non-ambulant mobility was probably not a priority, 1/7 indicated probably a priority, 4/7 indicated priority. (Aug 2020).</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																		
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input checked="" type="radio"/> Don't know 	<table border="1"> <thead> <tr> <th>Outcomes</th> <th>No of participants (studies) Follow up</th> <th>Certainty of the evidence (GRADE)</th> <th>Relative effect (95% CI)</th> <th colspan="2">Anticipated absolute effects* (95% CI)</th> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <th>Risk with no exercise</th> <th>Risk difference with cardio-pulmonary exercise</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)						Risk with no exercise	Risk difference with cardio-pulmonary exercise							<p>Minimal evidence for the effectiveness of cardio-pulmonary exercise on functional outcomes, quality of life or capacity to stand or balance. Many rehabilitation programs include exercises that cover multiple domains such as strengthening and balance training, rather than examine cardio-pulmonary exercise as a stand-alone approach.</p>
Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)																
				Risk with no exercise	Risk difference with cardio-pulmonary exercise															

Independence in transfers - not measured	-	-	-	-	-
Pain - not measured	-	-	-	-	-
Independence in activities of daily living - not measured	- ¹	-	-	-	-
Capacity to stand assessed with: Scale for Assessment and the Rating of Ataxia	0 (1 observational study) ²	⊕○○○ VERY LOW ^a	-	A 29-year old male with Friedreich ataxia underwent intensive rehabilitation training. The effects of stand-along robotic gait training with Lokomat-Pro preceded by cerebellar anodal tDCS was compared to training with Lokomat-Pro preceded by cathodal tDCS. At baseline, SARA score was 28. Following Lokomat and anodal tDCS training, SARA score was 24.	
Sitting balance assessed with: Scale for the Assessment and Rating of Ataxia	0 (1 observational study) ²	⊕○○○ VERY LOW ^a	-	A 29-year old male with Friedreich ataxia underwent intensive rehabilitation training. The effects of stand-along robotic gait training with Lokomat-Pro preceded by cerebellar anodal tDCS was compared to training with Lokomat-Pro preceded by cathodal tDCS. At baseline, SARA score was 28. Following Lokomat and anodal tDCS training, SARA score was 24.	
Quality of life - not measured	-	-	-	-	-

1. Seco J, Fernández IG, Atutxa AF, Torres-Unda J, Verdejo IC et al. Improvements in Quality of Life in Individuals with Friedreich's Ataxia after Participation in a 5-Year Program of Physical Activity: An observational Study Pre-Post Test Design, and Two Years Follow-Up. . Int J Neurorehabilitation. ; 2014.
2. Portaro S., Russo M., Bramanti A., et al. The role of robotic gait training and tDCS in Friedrich ataxia rehabilitation: A case report. . Medicine (Baltimore); 2019.

a. Case study only (n=1).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- Large
- Moderate
- Small
- Trivial
- Varies
- Don't know

RESEARCH EVIDENCE

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no exercise	Risk difference with cardio-pulmonary exercise
Independence in transfers - not measured	-	-	-	-	-
Pain - not measured	-	-	-	-	-
Independence in activities of daily living - not measured	- ¹	-	-	-	-
Capacity to stand assessed with: Scale for Assessment and the Rating of Ataxia	0 (1 observational study) ²	⊕○○○ VERY LOW ^a	-	A 29-year old male with Friedreich ataxia underwent intensive rehabilitation training. The effects of stand-alone robotic gait training with Lokomat-Pro preceded by cerebellar anodal tDCS was compared to training with Lokomat-Pro preceded by cathodal tDCS. At baseline, SARA score was 28. Following Lokomat and anodal tDCS training, SARA score was 24.	
Sitting balance assessed with: Scale for the	0 (1 observational	⊕○○○ VERY LOW ^a	-	A 29-year old male with Friedreich ataxia underwent intensive rehabilitation training. The effects of	

ADDITIONAL CONSIDERATIONS

A large cohort of 650 patients with FRDA studied in the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS), 40.3% had cardiomyopathy/cardiac hypertrophy. This is more prevalent in individuals with typical onset FRDA (46.1%) than in late onset FRDA (11.1%) (Reetz et al, 2018).

Due to the incidence of cardiomyopathy in FRDA, seeking cardiologist advice when prescribing cardio-pulmonary exercise to non-ambulant individuals with FRDA is warranted. However, the neurological impairments in FRDA may preclude exercising at high enough levels to stress these systems.

The judgement has been marked as moderate due to the potential consequences of exercise as opposed to the likely frequency of undesirable effects.

	Assessment and Rating of Ataxia	study) ²				stand-alone robotic gait training with Lokomat-Pro preceded by cerebellar anodal tDCS was compared to training with Lokomat-Pro preceded by cathodal tDCS. At baseline, SARA score was 28. Following Lokomat and anodal tDCS training, SARA score was 24.
	Quality of life - not measured	-	-	-	-	-
<p>1. Seco J, Fernández IG, Atutxa AF, Torres-Unda J, Verdejo IC et al.. Improvements in Quality of Life in Individuals with Friedreich's Ataxia after Participation in a 5-Year Program of Physical Activity: An observational Study Pre-Post Test Design, and Two Years Follow-Up. . Int J Neurorehabilitation. ; 2014.</p> <p>2. Portaro S., Russo M., Bramanti A., et al. The role of robotic gait training and tDCS in Friedrich ataxia rehabilitation: A case report. . Medicine (Baltimore); 2019.</p> <p>a. Case study only (n=1).</p>						

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 	Very low certainty of evidence as per 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

Outcomes	Importance	Certainty of the evidence (GRADE)
Independence in transfers - not measured	CRITICAL ^a	-
Pain - not measured	IMPORTANT ^b	-
Independence in activities of daily living - not measured	CRITICAL ^a	-
Capacity to stand assessed with: Scale for Assessment and the Rating of Ataxia	IMPORTANT ^c	⊕○○○ VERY LOW ^d
Sitting balance assessed with: Scale for the Assessment and Rating of Ataxia	IMPORTANT ^c	⊕○○○ VERY LOW ^d
Quality of life - not measured	CRITICAL ^e	-

- a. Identified as critical (4/6), important (2/6) by people with FA and critical by expert authors on this topic
- b. Identified as critical (2/6), important (2/6), and low importance (2/6) by people with FA and important by expert authors on this topic
- c. Identified as critical (3/6), important (3/6) by people with FA and important by expert authors on this topic
- d. Case study only (n=1).
- e. Identified as critical (3/6), important (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

<ul style="list-style-type: none"> ○ 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 		<p>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 Cardio-pulmonary exercise as a management strategy for non-ambulant individuals.</p> <p>Reflecting on the impact of Cardio-pulmonary exercise on Independence in transfers, 64% (16/25) clinical experts reported a benefit (large, moderate or small), 4% (1/25) reported no effect and, 0% (0/25) reported observing a harm (large, moderate or small). 8 clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Pain, 40% (10/25) clinical experts reported a benefit, 28% (7/25) reported no effect and, 0% (0/25) reported observing a harm. 8 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Independence in activities of daily living, 60% (15/25) clinical experts reported a benefit, 8% (2/25) reported no effect and, 0% (0/25) reported observing a harm. 8 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Capacity to stand, 48% (12/25) clinical experts reported a benefit, 20% (5/25) reported no effect and, 0% (0/25) reported observing a harm. 8 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Sitting balance, 44% (11/25) clinical experts reported a benefit, 20% (5/25) reported no effect and, 0% (0/25) reported observing a harm. 9 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Quality of life, 60% (15/25) clinical experts reported a benefit, 4% (1/25) reported no effect and, 0% (0/25) reported observing a harm. 9 expert clinicians could not provide any information on this outcome.</p> <p>Based on clinical experience of the intervention from the survey above and the limited evidence on undesirable effects of the intervention, the balance of effects probably favours the intervention.</p>
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Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	No published evidence.	<p>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).</p> <p>1/5 indicated cardio-pulmonary exercise were probably reasonable; 3/5 indicated reasonable; 1/5 didn't know if reasonable. (Aug 2020).</p>
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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 <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input checked="" type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
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CONCLUSIONS

Recommendation

We conditionally recommend cardio-pulmonary exercise over no cardio-pulmonary exercise in individuals with Friedreich ataxia who are no longer ambulant. Gradual onset and increase in the level of activity, with monitoring for any adverse symptoms, is likely to be a safe approach in those with and without cardiac abnormalities.

Justification

There is limited published evidence and some uncertainty in clinical practice regarding the efficacy of this exercise focus. However, case studies have demonstrated beneficial effects without significant adverse effects (Fillyaw & Ades, 1989; Portaro et al, 2019).

Subgroup considerations

This recommendation is for non-ambulant individuals with Friedreich ataxia.

Research priorities

There is a lack of published evidence focusing on therapeutic approaches for individuals who are non-ambulant. Outcomes from currently recruiting randomised, placebo-controlled trial 'NAD+ and Exercise in FA' may provide further evidence for the effectiveness of cardio-pulmonary exercise in non-ambulant individuals with FRDA (<https://clinicaltrials.gov/ct2/show/NCT04192136>).

References

Fillyaw MJ, Ades PA. Endurance exercise training in Friedreich ataxia. *Arch Phys Med Rehabil.* 1989;70(10):786-8.

Portaro S, Russo M, Bramanti A, Leo A, Billeri L, Manuli A, et al. The role of robotic gait training and tDCS in Friedrich ataxia rehabilitation: A case report. *Medicine (Baltimore).* 2019;98(8):e14447.

Reetz K, Dogan I, Hohenfeld C, Didszun C, Giunti P, Mariotti C, et al. Nonataxia symptoms in Friedreich Ataxia: Report from the Registry of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS). *Neurology.* 2018;91(10):e917-e30.