QUESTION

Should strengthening and stretching (including standing machine exercises and serial casting) with or without pharmacological therapy vs. pharmacological therapy only or no intervention be used for people with spasticity with Friedreich ataxia?

POPULATION:	people with spasticity with Friedreich ataxia
INTERVENTION:	strengthening and stretching (including standing machine exercises and serial casting) with or without pharmacological therapy
COMPARISON:	pharmacological therapy only or no intervention
MAIN OUTCOMES:	Mobility related to spasticity ; Frequency and severity of spasms; Pain; Frequency and severity of cramps; Severity of spasticity; Severity of spasticity; Upper limb function;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Data from the FA Clinical Outcome Measures (FA-COMS) registry found in individuals still ambulating, 68.2% (230/337) adults and 55.9% (157/281) children reported leg spasms. The incidence of spasms was higher for individuals not ambulating, with 80.0% (340/425) adults and 57.1% (44/77) children reporting leg spasms. In adults still ambulating, 55.1% (207/376) had pes cavus, while 61.4% (183/298) children had pes cavus. In individuals no longer ambulating, 67.6% (288/426) adults and 73.3% (55/75) children had pes cavus. https://clinicaltrials.gov/ct2/show/NCT03090789 Publications that report the prevalence of spasticity in individuals with FRDA include: Geoffroy and colleagues (1976) described 33 individuals with 'typical' FRDA of whom 15.1% had spasticity. Harding (1981) found increased lower limb muscle tone in 12.2% of 115 individuals with FRDA from 90 families in the UK. Bhidayasiri and colleagues (2005) studied 13 patients with late onset FRDA (LOFA) and compared them with 13 individuals with typical onset FRDA. Lower limb spasticity was significantly more common in the late-onset group. Klockgether and colleagues (1993) found similar results in their study examining 13 individuals with typical onset FRDA and three with LOFA. A 2016 cross-sectional study of 31 people with FRDA (typical onset n=23 and LOFA n=8) in Australia found a greater incidence of spasticity when assessing spasticity with the Modified Tardieu Scale. All participants had spasticity present in at least one of the calf muscles (Milne et al, 2016). Seven out of 18 (39%) ambulant and nine out of 13 (69%) non-ambulant individuals had muscle length shortening indicative of contracture (Milne et al, 2016). In the same study, reduced muscle length and worsening spasticity of the calf musculature was significantly associated with decreased ability to transfer, ambulate and climb stairs.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic. 1/7 indicated spasticity and spasms were probably not serious, 2/7 indicated spasticity and spasms were probably serious, 4/7 indicated spasticity and spasms were serious. 3/7 indicated spasticity and spasms were probably not urgent, 2/7 indicated spasticity and spasms were probably urgent, 2/7 indicated spasticity and spasms were urgent. 1/7 indicated spasticity and spasms were not a priority, 2/7 indicated spasticity and spasms were probably not a priority, 1/7 indicated spasticity and spasms were probably a priority, 3/7 indicated spasticity and spasms were a priority. (Aug 2020). The clinicians' experience from clinic practice suggests that lower limb spasticity and abnormal posturing can be a common and distressing feature of the condition.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

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

RESEARCH EVIDENCE

A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies examining physiotherapy combined with pharmacotherapy for spasticity published from 2014 through to 9 October 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.

For the comparison of stretching and strengthening (without pharmacotherapy) versus no intervention.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with strengthening and stretching
Mobility related to spasticity assessed with: Amended Motor Club Assessment follow-up: 36 weeks	122 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	-	122 people with multiple sclerosis were randomised to either usual care or usual care plus standing programme (n=61 for both). Assessments were done at baseline, 20 weeks post randomisation and 36 weeks post randomisation. An ANCOVA identified a significant increase in AMCA score in the standing frame group compared with usual care group. Between-group difference at 36 weeks was 4.7 points (95% CI 1.9-7.5, *p*=0.0014).	
Frequency and severity of spasms assessed with: Penn Spasm Frequency Scale	122 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	-	122 people with multiple sclerosis were randomised to either usual care or usual care plus standing programme (n=61 for both). Assessments were done at baseline, 20 wks post randomisation and 36 wks post randomisation. Logistic regression was used to analyse the dichotomised Penn Spasm Frequency Scale (no or mild spasms	

ADDITIONAL CONSIDERATIONS

Although there is no published evidence of the intervention in individuals with FRDA, it is common practice to provide physiotherapy interventions to enhance the effects of botulinum toxin injection in both ambulant and non-ambulant individuals with FRDA. There is less consistency with using physiotherapy interventions following systemic pharmacotherapy interventions.

Strengthening and stretching exercises are thought to improve the secondary consequences of spasticity such as decreased range of movement, increase strength and subsequently improve mobility and function.

This is a similar approach used in other neurological conditions even though the evidence is similarly limited. A 2014 systematic review examined rehabilitation therapies after botulinum toxin injection for the management of spasticity in adults with neurological impairments (Kinnear et al, 2014). The study found combining rehabilitation therapies with botulinum toxin was slightly better than providing botulinum toxin alone. However, the majority of studies of included participants post-stroke, and the heterogeneity of rehabilitation interventions limited the conclusions that could be drawn.

It was noted in the paper by Manca and colleagues (2020) that passive and active range of motion of the elbow was improved after eccentric strength training, even though scores on Modified Ashworth Scale did not change in individuals with MS.

A 2019 systematic review on non-pharmacological interventions for spasticity found 'low' evidence for stretching programs in individuals with various neurological conditions (based on the findings from three prior systematic reviews) (Khan et al, 2019).

				vs infrequent or >1/hr or >10/hr).	
Pain assessed with: Adverse events	122 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	-	122 people with multiple sclerosis were randomised to either usual care or usual care plus standing programme (n=61 for both). Assessments were done at baseline, 20 wks post randomisation and 36 weeks post randomisation. Pain was collected as adverse events reported in patient diaries. Short-term musculoskeletal pain was noted in 41% of adverse events in the standing frame group compared to 22% in the usual care group. Musculoskeletal pain lasated longer than 7 days in 5 pts.	
Frequency and severity of cramps - not measured	-	-	-	-	-
Severity of spasticity assessed with: Modified Ashworth Scale	6 (1 observational study)[2]	⊕◯◯◯ Very low[a,b]	-	6 people with multiple sclerosis underwent a 6-week eccentric strength training of the spastic muscles. Non-parametric Wilcoxon signed-rank tests detected no change in the MAS scores.	
Severity of spasticity assessed with: Numerical Rating Scale	6 (1 observational study)[2]	⊕◯◯◯ Very low[a,b]	-	6 people with multiple sclerosis underwent a 6-week eccentric strength training of the spastic muscles. Non parametric Wilcoxon signed-rank test detected a reduction in spasticity NRS scores - 4 participants reported a reduction by at least 1 point.	
Upper limb function - not measured	-	-	-	-	-

1. Freeman JA, Hendrie W,Jarrett L et al. Assessment of a home-based standing frame programme in people with progressive multiple sclerosis (SUMS): a pragmatic, multi-centre, randomised, controlled trial and cost-effectiveness analysis. Lancet Neurology; 2019.
2. Manca A., Martinez G.,Aiello E.,Ventura L.,Deriu F. Effect of Eccentric

Strength Training on Elbow Flexor Spasticity and Muscle Weakness in People With Multiple Sclerosis: Proof-of-Concept Single-System Case Series. Physical Therapy; 2020.

a. All participants had a diagnosis of multiple sclerosis (none with FRDA).
b. Small sample size

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

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

RESEARCH EVIDENCE

A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies examining stretching and strengthening with pharmacotherapy published from 2014 through to 9 October 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.

For the comparison of stretching and strengthening (without pharmacotherapy) versus no intervention.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with strengthening and stretching
Mobility related to spasticity assessed with:	122 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	-	122 people with multiple sclerosis were randomised to either usual care or usual care plus standing programme (n=61 for both). Assessments were done at baseline, 20 weeks post randomisation and 36	

ADDITIONAL CONSIDERATIONS

No published evidence on the undesirable effects of stretching and strengthening in combination with pharmacological interventions.

As per the survey responses collected from clinical experts in FRDA, there appears to be no harm seen in clinical practice as a consequence of this intervention.

Serial casting

Clinicians discussed possible negative effects of serial casting include pressure areas, difficultly mobilising while casting in situ.

Standing machine stretch

Freeman and colleagues (11) (Freeman et al, 2019) reported an increased frequency of short-term musculoskeletal pain in the group completing the standing frame intervention. However, the 20-week program was monitored with phone calls only and this may have contributed to incorrect standing postures during the intervention.

Strengthening program

Manca and colleagues (9) (2020) did not report on adverse events during their 6-week eccentric strength training program.

Amended Motor Club Assessment follow-up: 36 weeks				weeks post randomisation. An ANCOVA identified a significant increase in AMCA score in the standing frame group compared with usual care group. Between-group difference at 36 weeks was 4.7 points (95% CI 1.9-7.5, *p*=0.0014).	
Frequency and severity of spasms assessed with: Penn Spasm Frequency Scale	122 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	-	122 people with multiple sclerosis were randomised to either usual care or usual care plus standing programme (n=61 for both). Assessments were done at baseline, 20 wks post randomisation and 36 wks post randomisation. Logistic regression was used to analyse the dichotomised Penn Spasm Frequency Scale (no or mild spasms vs infrequent or >1/hr or >10/hr).	
Pain assessed with: Adverse events	122 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	-	122 people with multiple sclerosis were randomised to either usual care or usual care plus standing programme (n=61 for both). Assessments were done at baseline, 20 wks post randomisation and 36 weeks post randomisation. Pain was collected as adverse events reported in patient diaries. Short-term musculoskeletal pain was noted in 41% of adverse events in the standing frame group compared to 22% in the usual care group. Musculoskeletal pain lasated longer than 7 days in 5 pts.	
Frequency and severity of cramps - not measured	-	-	-	-	-
Severity of spasticity assessed with: Modified Ashworth Scale	6 (1 observational study)[2]	⨁◯◯◯ Very low[a,b]	-	6 people with multiple sclerosis underwent a 6-week eccentric strength training of the spastic muscles. Non-parametric Wilcoxon signed-rank tests detected no change in the MAS scores.	
Severity of spasticity	6 (1	⨁◯◯◯	-	6 people with multiple sclerosis underwent a 6-week eccentric strength training of the	

assessed with: Numerical Rating Scale	observational study)[2]	Very low[a,b]		spastic muscles. Non parametric Wilcoxon signed-rank test detected a reduction in spasticity NRS scores - 4 participants reported a reduction by at least 1 point.	
Upper limb function - not measured	-	-	-	-	-

1. Freeman JA, Hendrie W,Jarrett L et al. Assessment of a home-based standing frame programme in people with progressive multiple sclerosis (SUMS): a pragmatic, multi-centre, randomised, controlled trial and cost-effectiveness analysis. Lancet Neurology; 2019.
2. Manca A., Martinez G.,Aiello E.,Ventura L.,Deriu F. Effect of Eccentric Strength Training on Elbow Flexor Spasticity and Muscle Weakness in People With Multiple Sclerosis: Proof-of-Concept Single-System Case Series. Physical Therapy; 2020.

a. All participants had a diagnosis of multiple sclerosis (none with FRDA).
b. Small sample size

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	No published evidence for strengthening and stretching in combination with pharmacotherapy. Moderate to very low certainty of evidence as per the evidence profile table.	Based on moderate to very low certainty of evidence as per the evidence profile table. No studies examining the effect of this intervention on individuals with FRDA.

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)
Mobility related to spasticity assessed with: Amended Motor Club Assessment follow up: 36 weeks	IMPORTANT[a]	⨁⨁⨁◯ MODERATE[b]
Frequency and severity of spasms assessed with: Penn Spasm Frequency Scale	IMPORTANT[c]	⨁⨁⨁◯ MODERATE[b]
Pain assessed with: Adverse events	IMPORTANT[d]	⨁⨁⨁◯ MODERATE[b]
Frequency and severity of cramps - not measured	IMPORTANT[e]	-
Severity of spasticity assessed with: Modified Ashworth Scale	IMPORTANT[f]	⨁◯◯◯ VERY LOW[b,g]
Severity of spasticity assessed with: Numerical Rating Scale	IMPORTANT[f]	⨁◯◯◯ VERY LOW[b,g]
Upper limb function - not measured	CRITICAL[h]	-

a. Identified as important (5/6) and low importance (1/6) by people with FA and critical by expert authors on this topic
b. All participants had a diagnosis of multiple sclerosis (none with FRDA).
c. Identified as critical (2/6), important (3/6) and low importance (1/6) by people with FA and critical by expert authors on this topic
d. Identified as critical (2/6), important (2/6) and low importance (2/6) by people with FA and critical by expert authors on this topic
e. Identified as critical (1/6) and important (5/6) by people with FA and critical by expert authors on this topic
f. Identified as critical (3/6), important (2/6) and low importance (1/6) by people with FA and important by expert authors on this topic
g. Small sample size
h. Identified as critical (3/6) and 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
○ 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	No published evidence.	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 strengthening and stretching as a management strategy for people with spasticity. Reflecting on the impact of **strengthening and stretching** on mobility related to spasticity, 50% (13/26) clinical experts reported a benefit (large, moderate or small), 3.85% (1/26) reported no effect and, 0% (0/26) reported observing a harm (large, moderate or small). 12 clinicians could not provide any information on this outcome. Reflecting on the impact on frequency & severity of spasms, 42.31% (11/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on pain, 42.3% (11/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on severity of spasticity, 42.31% (11/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on upper limb function, 46.15% (12/26) clinical experts reported a benefit, 3.85% (1/26) reported no effect and, 0% (0/26) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact of **strengthening and stretching (including standing machine exercises and serial casting) in combination with pharmacological therapy** on mobility related to spasticity, 53.85% (14/26) clinical experts reported a benefit (large, moderate or small), 0% (0/26) reported no effect and, 0%

		(0/26) reported observing a harm (large, moderate or small). 12 clinicians could not provide any information on this outcome. Reflecting on the impact on frequency & severity of spasms, 46.16% (12/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on pain, 50% (13/26) clinical experts reported a benefit, 0% (0/26) reported no effect and, 0% (0/26) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on severity of spasticity, 53.85% (14/26) clinical experts reported a benefit, 0% (0/26) reported no effect and, 0% (0/26) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on upper limb function, 50% (13/26) clinical experts reported a benefit, 0% (0/26) reported no effect and, 0% (0/26) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Although there are no studies that have directly examined stretching and strengthening with or without pharmacological therapies for the management of spasticity in individuals with FRDA, it is common practice to trial more conservative therapies prior to initiating pharmacological treatment and combine physiotherapy with pharmacotherapies targeting spasticity. This is consistent with the Ataxia UK Medical Guidelines (de Silva et al, 2019) which also recommends: • Consider physiotherapy first to treat spasticity, and if that does not provide complete benefit use pharmacological treatment • To treat focal spasticity, particularly in small muscles, refer to a specialised clinic for treatment with intramuscular botulinum toxin injections, followed by physiotherapy. These recommendations are “good practice points” based on clinical expertise (de Silva et al, 2019). This criterion has been marked as ‘probably favours the intervention’. The most appropriate approach should be based on an individualised assessment considering the severity of spasticity and its impact on function and quality of life.

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 research.	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 strengthening and stretching were probably reasonable, 3/4 indicated reasonable. 1/4 indicated strengthening and stretching in combination with pharmacological therapy was probably not reasonable, 1/4 indicated probably reasonable, 1/4 indicated reasonable, 1/4 indicated they 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

We suggest non-pharmacological treatment, such as strengthening and stretching, should be used as a first option in the management of spasticity (and its secondary consequences such as mobility decline), prior to considering pharmacological interventions for individuals with FRDA with spasticity.

We suggest physiotherapy/rehabilitation interventions (such as strengthening, stretching, serial casting and standing machine stretch) are used to enhance the effects of pharmacological therapy for management of spasticity in individuals with Friedreich ataxia. This should occur when non-pharmacological treatment alone does not address the individual's problems and/or treatment goals.

Justification

Although there are no studies that have directly examined stretching and strengthening for the management of spasticity in individuals with FRDA, it is common practice to trial more conservative therapies prior to initiating pharmacological treatment.

There are no published studies in FRDA; however clinical expert observations in clinical practice suggests that physiotherapy interventions as an adjunct to pharmacotherapy is a beneficial approach in managing spasticity. Similarly, a 2014 systematic review (Kinnear et al, 2014) suggests this approach may be slightly more effective than pharmacotherapy management alone.

Clinicians noted there were regional differences in the approach to supplement pharmacotherapy with physiotherapy interventions. A case by case review was recommended to ensure the appropriate therapy was provided to each individual. Use of adjunctive physiotherapy usually comes after a stretching intervention.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia with spasticity.

Research priorities

A further examination of both non-pharmacological and pharmacological approaches to the management of spasticity in individuals with FRDA is warranted to ensure appropriately targeted therapy.

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