

QUESTION

Should botulinum toxin, stretching (including standing machine) and prescription of ankle-foot orthotics vs. no treatment be used for non-ambulant people with lower limb spasticity with Friedreich ataxia?

POPULATION:	non-ambulant people with lower limb spasticity with Friedreich ataxia
INTERVENTION:	botulinum toxin, stretching (including standing machine) and prescription of ankle-foot orthotics
COMPARISON:	no treatment
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>In a cohort of 111 individuals with FRDA, quality of life (QOL), as measured by the PedsQL 4.0 GCM, was significantly lower for those who used a mobility device as compared to those who did not require a mobility device. Of the 47 participants who reported they had transitioned to a mobility device, 43 reported that this was a wheelchair, suggesting decreased QOL may be in part due to loss of ability to ambulate (Ejax et al, 2018).</p> <p>In a 2016 cross-sectional study of 31 people with FRDA, 100% of participants had spasticity present in at least one of the calf muscles (Milne et al, 2016). Nine out of 13 (69%) of non-ambulant individuals had muscle length shortening indicative of contracture. In the same study, reduced muscle length and worsening spasticity of the calf musculature was significantly associated with decreased ability to transfer or mobilise (Milne et al, 2016).</p>	<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 type="radio"/> Don't know 	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 24 September 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know 	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 24 September 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	<p>As per the below survey, 1 out of 26 clinicians working with patients found a harmful effect on the capacity to stand following botulinum toxin injections. No other harms were noted on other outcomes or from the other management strategies targeting ankle range of movement or spasticity in non-ambulant people with FRDA.</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 	<p>No published evidence.</p>	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS									
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability 	<table border="1"> <thead> <tr> <th>Outcomes</th> <th>Importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Independence in transfers - not measured</td> <td>CRITICAL^a</td> <td>-</td> </tr> <tr> <td>Pain - not measured</td> <td>IMPORTANT^b</td> <td>-</td> </tr> </tbody> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)	Independence in transfers - not measured	CRITICAL ^a	-	Pain - not measured	IMPORTANT ^b	-	
Outcomes	Importance	Certainty of the evidence (GRADE)									
Independence in transfers - not measured	CRITICAL ^a	-									
Pain - not measured	IMPORTANT ^b	-									

	<table border="1"> <tr> <td>Independence in activities of daily living - not measured</td> <td>CRITICAL^a</td> <td>-</td> </tr> <tr> <td>Capacity to stand - not measured</td> <td>IMPORTANT^c</td> <td>-</td> </tr> <tr> <td>Sitting balance - not measured</td> <td>IMPORTANT^c</td> <td>-</td> </tr> <tr> <td>Quality of life - not measured</td> <td>CRITICAL^d</td> <td>-</td> </tr> </table> <p>a. Identified as critical (4/6) and 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) and important (3/6) by people with FA and important by expert authors on this topic d. Identified as critical (3/6) and important (3/6) by people with FA and critical by expert authors on this topic</p>	Independence in activities of daily living - not measured	CRITICAL ^a	-	Capacity to stand - not measured	IMPORTANT ^c	-	Sitting balance - not measured	IMPORTANT ^c	-	Quality of life - not measured	CRITICAL ^d	-	
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Capacity to stand - not measured	IMPORTANT ^c	-												
Sitting balance - not measured	IMPORTANT ^c	-												
Quality of life - not measured	CRITICAL ^d	-												

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>No published evidence.</p>	<p>A survey designed to systematically collect expert-based opinions from clinicians involved in developing the recommendations for this topic and providing clinical care for individuals with Friedreich ataxia, was conducted. Clinical experts from Australia, Europe and the USA were asked to consider the harms/benefits of Botulinum toxin as a management strategy for non-ambulant individuals with lower limb spasticity.</p> <p>Reflecting on the impact of Botulinum toxin on Independence in transfers, 50% (1/2) clinical experts reported a benefit (large, moderate or small), 50% (1/2) reported no effect and, 0% (0/2) reported observing a harm (large, moderate or small). Reflecting on the impact on Pain, 100% (2/2) clinical experts reported a benefit. Reflecting on the impact on Independence in activities of daily living, 50% (1/2) clinical experts reported a benefit, 50% (1/2) reported no effect. Reflecting on the impact on Sitting balance, 50% (1/2) clinical experts reported a benefit, 50% (1/2) reported no effect. Reflecting on the impact on Quality of life, 100% (2/2) clinical experts reported a benefit.</p> <p>Reflecting on the impact of botulinum toxin on Capacity to stand, 42.31% (11/26) clinical experts reported a benefit (large,</p>

moderate or small), 7.69% (2/26) reported no effect and, 3.85% (1/26) reported observing a harm (large, moderate or small). 12 clinicians could not provide any information on this outcome.

Clinical experts were asked to consider the harms/benefits of stretching (including standing machine) as a management strategy for non-ambulant individuals with lower limb spasticity.

Reflecting on the impact of stretching (including standing machine) on Independence in transfers, 100% (2/2) clinical experts reported a benefit (large, moderate or small), 0% (0/2) reported no effect and, 0% (0/2) reported observing a harm (large, moderate or small). Reflecting on the impact on Pain, 100% (2/2) clinical experts reported a benefit. Reflecting on the impact on Independence in activities of daily living, 0% (0/2) clinical experts reported a benefit, 100% (2/2) reported no effect. Reflecting on the impact on Capacity to stand, 50% (1/2) clinical experts reported a benefit, 50% (1/2) reported no effect. Reflecting on the impact on Sitting balance, 0% (0/2) clinical experts reported a benefit, 100% (2/2) reported no effect. Reflecting on the impact on Quality of life, 100% (2/2) clinical experts reported a benefit.

Clinical experts were asked to consider the harms/benefits of prescription of ankle-foot orthotics as a management strategy for Non-ambulant individuals with lower limb spasticity.

Reflecting on the impact of prescription of ankle-foot orthotics on Independence in transfers, 100% (2/2) clinical experts reported a benefit (large, moderate or small). Reflecting on the impact on Pain, 50% (1/2) clinical experts reported a benefit, 50% (1/2) reported no effect. Reflecting on the impact on Independence in activities of daily living, 100% (2/2) clinical experts reported a benefit. Reflecting on the impact on Capacity to stand, 100% (2/2) clinical experts reported a benefit.

Reflecting on the impact on Sitting balance, 0% (0/2) clinical experts reported a benefit, 100% (2/2) reported no effect. Reflecting on the impact on Quality of life, 100% (2/2) clinical experts reported a benefit.

In clinical practice, there is some uncertainty about the benefits of botulinum toxin, stretching and prescribing ankle-foot orthoses. This potentially highlights the need to choose these management strategies based on a complete assessment of the individual with FRDA and the importance of discussing potential risks and benefits.

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Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" 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>2/5 indicated botulinum toxin, stretching and prescription of ankle foot orthotics were probably reasonable; 3/5 indicated that the interventions were reasonable. (Aug 2020).</p>

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 botulinum toxin injections, stretching, and prescription of ankle-foot orthoses for individuals with Friedreich ataxia who are no longer ambulant and who have spasticity and reduced length of the calf muscles. A comprehensive physiotherapy and medical assessment of impairments, mobility status and patient goals should be done to determine the appropriateness of this treatment.

Justification

There is no published evidence examining the effect of this group of management strategies (either as single interventions or as a group) for individuals with FRDA with lower limb spasticity. However, approximately 40-50% of clinicians who work with individuals with FRDA have found beneficial effects from these treatments.

Subgroup considerations

For non-ambulant individuals with FRDA who have difficulty transferring due to foot placement and/or ankle or foot pain, treatment including botulinum toxin injections as an adjunct to stretching and orthotic prescription may warrant greater consideration. However, individuals who present with spasticity or muscle length changes who do not have difficulty transferring may warrant a conservative approach, including stretching and orthotic prescription, prior to trialling botulinum toxin injections.

Research priorities

Given the uncertainty on the effects of botulinum toxin injections, stretching and orthotic prescription, further research should examine the effects of these interventions on individuals with FRDA, including the specific factors that indicate these treatments will provide a beneficial effect in an individual.

References

Ejaz R, Chen S, Isaacs CJ, Carnevale A, Wilson J, George K, et al. Impact of mobility device use on quality of life in children with Friedreich ataxia. *J Child Neurol.* 2018;33(6):397-404.

Milne SC, Corben LA, Yiu E, Delatycki MB, Georgiou-Karistianis N. Gastrocnemius and soleus spasticity and muscle length in Friedreich's ataxia. *J Clin Neurosci.* 2016;29:29-34.

