

## QUESTION

Should local pharmacotherapy vs. no intervention be used for people who have focal spasticity and this is impacting on function or pain with Friedreich ataxia?

POPULATION:	people who have focal spasticity and this is impacting on function or pain with Friedreich ataxia
INTERVENTION:	local pharmacotherapy
COMPARISON:	no intervention
MAIN OUTCOMES:	Mobility related to spasticity; Frequency and severity of spasms; Pain; Frequency and severity of cramps; Severity of spasticity; UL function;

## ASSESSMENT

### Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>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. <a href="https://clinicaltrials.gov/ct2/show/NCT03090789">https://clinicaltrials.gov/ct2/show/NCT03090789</a>.</p> <p>There are a number of publications that report the incidence of spasticity or hypertonia in individuals with FRDA (1-4) which ranges between 12.2 and 15% in individuals with typical onset FRDA and 33% to 40% in individuals with late onset FRDA (LOFA). However, these studies did not define spasticity or indicate if the spasticity was localised or global.</p> <p>A 2016 cross-sectional study of 31 people with FRDA (typical onset n=23 and LOFA n=8) in Australia used the Modified Tardieu Scale to describe the incidence of focal gastrocnemius and soleus spasticity. This study found 100% of participants had spasticity present in at least one of the calf muscles (5). Seven out of 18 (39%) ambulant and nine out of 13 (69%) non-ambulant individuals had muscle length shortening indicative of contracture (5). 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 study did not present any data on spasticity in other lower limb muscles.</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 spasticity and spasms were probably not serious, 2/7 indicated probably serious, 4/7 indicated serious.</p> <p>3/7 indicated spasticity and spasms were probably not urgent, 2/7 indicated probably urgent, 2/7 indicated urgent.</p> <p>1/7 indicated spasticity and spasms were not a priority, 2/7 indicated probably not a priority, 1/7 indicated probably a priority, 3/7 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"> <li>○ Trivial</li> <li>○ Small</li> <li>● Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies 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.</p>	<p>Clinical expert observation (from 12 clinicians as below) suggest some benefit on mobility related to spasticity, spasms &amp; cramps, pain. There was less certainty on the effect on upper limb function.</p> <p>Anecdotal evidence also suggests focal spasticity management may have positive effects on pressure care management when orthotics are required to assist weight-bearing.</p> <p>Clinical experience indicates local pharmacological treatment is useful for patients with severe cramps in the hip.</p>

## Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>● Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies 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.</p>	<p>Clinical expert observation (from 12 clinicians as below) does not suggest any harm from focal spasticity management; however, there are negative side-effects such as over-weakness of targeted muscles and fatigue. This may be more relevant in ambulant individuals where anti-gravity muscles are required for upright stance and gait. Treatment should be undertaken after a thorough and individualised assessment to determine the risks and benefits of the intervention.</p> <p>Expert panel discussed undesirable effects may include possible decline of ambulation/increase in pain, systemic effects of botulinum toxicity and possible allergic reaction.</p> <p>Requirement to consider expertise of person injecting, the amount injected and the individualised treatment approach.</p> <p>It was noted that the effect does wear off, including any undesirable effects. This is worthy of consideration.</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"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>● No included studies</li> </ul>	<p>No published evidence.</p>	
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## 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"> <li>○ Important uncertainty or variability</li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>● No important uncertainty or variability</li> </ul>	<table border="1" data-bbox="518 662 1423 1170"> <thead> <tr> <th>Outcomes</th> <th>Importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Mobility related to spasticity - not measured</td> <td>IMPORTANT<sup>a</sup></td> <td>-</td> </tr> <tr> <td>Frequency and severity of spasms - not measured</td> <td>IMPORTANT<sup>b</sup></td> <td>-</td> </tr> <tr> <td>Pain - not measured</td> <td>CRITICAL<sup>c</sup></td> <td>-</td> </tr> <tr> <td>Frequency and severity of cramps - not measured</td> <td>IMPORTANT<sup>d</sup></td> <td>-</td> </tr> <tr> <td>Severity of spasticity - not measured</td> <td>CRITICAL<sup>e</sup></td> <td>-</td> </tr> <tr> <td>UL function - not measured</td> <td>CRITICAL<sup>f</sup></td> <td>-</td> </tr> </tbody> </table> <p data-bbox="562 1214 1402 1490">           a. Identified as important (5/6) and low importance (1/6) by people with FA and critical by expert authors on this topic            b. 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            c. 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            d. Identified as critical (1/6) and important (5/6) by people with FA and critical by expert authors on this topic            e. 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            f. Identified as critical (3/6) and important (3/6) by people with FA and         </p>	Outcomes	Importance	Certainty of the evidence (GRADE)	Mobility related to spasticity - not measured	IMPORTANT <sup>a</sup>	-	Frequency and severity of spasms - not measured	IMPORTANT <sup>b</sup>	-	Pain - not measured	CRITICAL <sup>c</sup>	-	Frequency and severity of cramps - not measured	IMPORTANT <sup>d</sup>	-	Severity of spasticity - not measured	CRITICAL <sup>e</sup>	-	UL function - not measured	CRITICAL <sup>f</sup>	-	
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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"><li>○ Favors the comparison</li><li>○ Probably favors the comparison</li><li>○ Does not favor either the intervention or the comparison</li><li>● Probably favors the intervention</li><li>○ Favors the intervention</li><li>○ Varies</li><li>○ Don't know</li></ul>	<p>No published evidence.</p>	<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 local pharmacotherapy as a management strategy for people who have focal spasticity and this is impacting on function or pain.</p> <p>Reflecting on the impact of local pharmacotherapy on Mobility related to spasticity, 38.46% (10/26) clinical experts reported a benefit (large, moderate or small), 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm (large, moderate or small). 14 clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Frequency &amp; severity of spasms, 42.3% (11/26) clinical experts reported a benefit, 3.85% (1/26) reported no effect and, 0% (0/26) reported observing a harm. 14 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Pain, 42.31% (11/26) clinical experts reported a benefit, 3.85% (1/26) reported no effect and, 0% (0/26) reported observing a harm. 14 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Frequency &amp; severity of cramps, 38.46% (10/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 14 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Severity of spasticity, 42.31% (11/26) clinical experts reported a benefit, 3.85% (1/26) reported no effect and, 0% (0/26) reported observing a harm. 14 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on UL function, 26.93% (7/26) clinical experts reported a benefit, 11.54% (3/26) reported no effect and, 0% (0/26) reported observing a harm. 16 expert clinicians</p>

		<p>could not provide any information on this outcome.</p> <p>Although there are no studies that have examined focal spasticity management for spasticity in individuals with FRDA, it is used, although not commonly, in clinical practice. The Ataxia UK Medical Guidelines (9) recommends:</p> <p><i>· To treat focal spasticity, particularly in small muscles, refer to a specialised clinic for treatment with intramuscular botulinum toxin injections, followed by physiotherapy.</i></p> <p>This is a good practice point, based on clinical expertise.</p> <p>Use of local pharmacotherapy requires individualised assessment of the benefits and risks as in some individuals or at particular stages of the disease, this treatment may not be beneficial.</p>
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## Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input checked="" type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>Data from all individuals with FRDA (with and without spasm/cramps) in the FA Clinical Outcome Measures (FA-COMS) registry found 2.4% (20/847) adults and 0.2% (1/454) children had received at one or more botulinum injections. <a href="https://clinicaltrials.gov/ct2/show/NCT03090789">https://clinicaltrials.gov/ct2/show/NCT03090789</a></p>	<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 local pharmacotherapy was probably reasonable, 1/5 indicated reasonable, 1/5 indicated varied or sometimes reasonable, 1/5 indicated they didn't know. (Aug 2020).</p>

## SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	<b>Moderate</b>	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	<b>Small</b>	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			<b>No included studies</b>
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	<b>No important uncertainty or variability</b>			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the	<b>Probably favors the intervention</b>	Favors the intervention	Varies	Don't know

JUDGEMENT							
			comparison				
ACCEPTABILITY	No	Probably no	<b>Probably yes</b>	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 ○	<b>Conditional recommendation for the intervention</b> ●	Strong recommendation for the intervention ○
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## CONCLUSIONS

### Recommendation

We suggest local pharmacological (i.e. injection of botulinum toxin) management of spasticity for individuals with Friedreich ataxia over no local spasticity management in the following circumstances: a thorough assessment is conducted to weigh up the negative and positive effects of this intervention; spasticity is significantly affecting mobility, function, pain or positioning, and conservative treatment options (such as physiotherapy) are no longer effective.

### Justification

There are no published studies in FRDA; however clinical expert observations in clinical practice suggests this may be a beneficial approach. Expert opinion suggests pharmacological intervention should be coupled with physiotherapy interventions (refer to other recommendations in this topic). This recommendation is supported by a similar recommendation from the Ataxia UK Medical Guidelines (de Silva et al, 2019).

### Subgroup considerations

This treatment for spasticity may pose greater risks to mobility in ambulant individuals as compared to individuals who are no longer ambulant. However, this is not substantiated with published evidence.

## Research priorities

There is a need to evaluate the effects of focal spasticity management on ambulant and non-ambulant individuals with FRDA, to ensure appropriately targeted therapy.

### References

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de Silva RN, Greenfield J, Cook A, Bonney H, Vallortigara J, Hunt B, et al. Guidelines on the diagnosis and management of progressive ataxia in adults. *Orphanet J Rare Dis*. 2019;14:51.

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