QUESTION

Should botulinum toxin injections of the ankle/foot musculature vs. no pharmacological intervention be used for ambulant people with ankle/foot spasticity with Friedreich ataxia?	
POPULATION:	ambulant people with ankle/foot spasticity with Friedreich ataxia
INTERVENTION:	botulinum toxin injections of the ankle/foot musculature
COMPARISON:	no pharmacological intervention
MAIN OUTCOMES:	Independence of ambulation; Balance; Falls; Walking capacity; Walking capacity; Walking capacity; Quality of life;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Gait instability is the most frequently reported initial symptom in individuals with FRDA, occurring as the first symptom in 76 - 88% of individuals (Reetz et al, 2015). Mobility typically declines, with loss of mobility for individuals with onset <15 years of age typically 11.5 years after first symptom onset; 18.3 years for individuals with onset 15-24 years of age and 23.5 years for individuals with onset >24 years (Rumney et al, 2020). 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 (Rumney et al, 2020). Seven out of 18 (39%) of ambulant individuals had muscle length shortening indicative of contracture (Rumney et al, 2020). In the same study, reduced muscle length and worsening spasticity of the calf musculature was significantly associated with decreased ability to ambulate or 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 the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably serious, 5/7 indicated serious, 1/7 indicated didn't know if serious. 1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably not urgent, 1/7 indicated probably urgent, 5/7 indicated urgent. 1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably a priority, 6/7 indicated priority. (Aug 2020). In a public forum entitled "Voice of the patient", held on 2 June 2017 in the USA to inform the United States Food and Drug Administration approximately 400 attendees (in-person and online) were asked to choose top three symptoms that would be most meaningful to treat. 55% of people chose improving balance or improved walking as two of their top symptoms (weblink: http://curefa.org/pdf/news/FA-Voice-of-the-Patient.pdf).

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 pharmacological intervention	Risk difference with botulinum toxin injections of the ankle/foot musculature
Independence of ambulation assessed with: Walking Handicap Scale	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified an increase in WHS score (p=0.0084) between baseline and 3 months.	
Balance assessed with: Timed Up and Go Test follow-up: mean 18 weeks	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified an reduction in TUG score (p=0.0364) between baseline and 3 months.	
Falls - not measured	-	-	-	-	-
Walking capacity assessed with: 10 Metre Walk Test	0 (2 observational studies)[1,2]	⨁◯◯◯ Very low[a,c,d,e]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months	

There are no studies specifically examining the effects of botulinum toxin injections for individuals with FRDA who are able to ambulate. Studies in hereditary spastic paraplegia (HSP) suggest botulinum toxin injection is effective in improving walking independence, gait speed, balance and quality of life. However, the clinical differences between FRDA and HSP limit the extrapolation of these findings to individuals with FRDA.

	follow-up: mean 18 weeks				post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified an reduction in 10MWT (p=0.0012) between baseline and 3 months. (Paparella et al 2020). 15 people with hereditary spastic paraplegia received BoNT-A injections followed by twice daily stretching exercises for 18 weeks. One-way ANOVA for repeated measures was used to test the 10MWT for time effects (baseline, T1 - 4 weeks after treatment, and T2 - 18 weeks after treatment). The 10MWT showed a main effect of time (p<0.001), consisting of a 9% increase from baseline at T1 (p=0.006) and a 12% increase from baseline at T2 (p=0.002). (de Niet et al 2014).
	Walking capacity assessed with: Timed Up and Go Test	0 (2 observational studies)[1,2]	⨁◯◯◯ Very low[a,c,d,e]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified a reduction in the TUG (p=0.0364) between baseline and 3 months. (Paparella et al 2020). 15 people with hereditary spastic paraplegia received BoNT-A injections followed by twice daily stretching exercises for 18 weeks. One-way ANOVA for repeated measures was used to test the TUG for time effects (baseline, T1 - 4 weeks after treatment, and T2 - 18 weeks after treatment). The TUG did not show any time effects (p=0.118). (de Niet et al 2014).
	Walking capacity assessed with:	0 (1 observational	⨁◯◯◯ Very low[a,b,c,d]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective

2 Minute Walking Test	study)[1]			observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified a reduction in the 2MWT (p=0.008) between baseline and 1 months and between baseline and 3 months (p=0.0012). (Paparella et al 2020).
Quality of life assessed with: Visual Analogue Scale	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified a reduction in the VAS (p=0.0084) between baseline and 3 months. (Paparella et al 2020).

1. Paparella G., Vavla M.,Bernardi L.,Girardi G.,Stefan C.,Martinuzzi A.. Efficacy of a Combined Treatment of Botulinum Toxin and Intensive Physiotherapy in Hereditary Spastic Paraplegia. . Front. Neurosci.; 2020.
2. de Niet M, de Bot ST,van de Warrenburg BPC,Weerdesteyn V,Geurts AC. Functional effects of botulinum toxin type-A treatment and subsequent stretching of spastic calf muscles: A study in patients with hereditary spastic paraplegia. Journal of Rehabilitation Medicine; 2015.

a. All participants had a diagnosis of hereditary spastic paraparesis (not FRDA).
b. Intervention botulinum toxin injections plus physiotherapy intervention.
c. Small sample sze.
d. Confidence intervals not reported.
e. Intervention included physiotherapy or home stretching (not botulinum toxin injections alone).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		In clinical practice, there are variable effects from botulinum toxin as a treatment approach for ankle and foot spasticity in ambulant individuals with FRDA. Balancing the potential negative effects, such as muscle weakness and an inability to use effective (although often compensatory) antagonist-agonist co-contraction to stabilise over the foot during gait, with the potential beneficial effects is difficult to gauge prior to injecting.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no pharmacological intervention	Risk difference with botulinum toxin injections of the ankle/foot musculature
Independence of ambulation assessed with: Walking Handicap Scale	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified an increase in WHS score (p=0.0084) between baseline and 3 months.	
Balance assessed with: Timed Up and Go Test follow-up: mean 18 weeks	0 (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified an reduction in TUG score (p=0.0364) between baseline and 3 months.	
Falls - not measured	-	-	-	-	-

Walking capacity assessed with: 10 Metre Walk Test follow-up: mean 18 weeks	0 (2 observational studies)[1,2]	⊕◯◯◯ Very low[a,c,d,e]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified an reduction in 10MWT (p=0.0012) between baseline and 3 months. (Paparella et al 2020). 15 people with hereditary spastic paraplegia received BoNT-A injections followed by twice daily stretching exercises for 18 weeks. One-way ANOVA for repeated measures was used to test the 10MWT for time effects (baseline, T1 - 4 weeks after treatment, and T2 - 18 weeks after treatment). The 10MWT showed a main effect of time (p<0.001), consisting of a 9% increase from baseline at T1 (p=0.006) and a 12% increase from baseline at T2 (p=0.002). (de Niet et al 2014).	
Walking capacity assessed with: Timed Up and Go Test	0 (2 observational studies)[1,2]	⊕◯◯◯ Very low[a,c,d,e]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified a reduction in the TUG (p=0.0364) between baseline and 3 months. (Paparella et al 2020). 15 people with hereditary spastic paraplegia received BoNT-A injections followed by twice daily stretching exercises for 18 weeks. One-way ANOVA for repeated measures was used to test the TUG for time effects (baseline, T1 - 4 weeks after treatment, and T2 - 18 weeks after treatment). The TUG did not show any time effects (p=0.118). (de Niet et al	

				2014).
Walking capacity assessed with: 2 Minute Walking Test	0 (1 observational study)[1]	⊕◯◯◯ Very low[a,b,c,d]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified a reduction in the 2MWT (p=0.008) between baseline and 1 months and between baseline and 3 months (p=0.0012). (Paparella et al 2020).
Quality of life assessed with: Visual Analogue Scale	0 (1 observational study)[1]	⊕◯◯◯ Very low[a,b,c,d]	-	18 people with hereditary spastic paraplegia treated with BoNT-A injections were recruited to this retrospective observational cohort study. Assessments occurred at baseline, 1 and 3 months post injection. Linear mixed models were used to determine the relationship between the WHS at the three time points, considering the subject as a random effect. Post-hoc comparisons identified a reduction in the VAS (p=0.0084) between baseline and 3 months. (Paparella et al 2020).

1. Paparella G, Vavla M,Bernardi L,Girardi G,Stefan C,Martinuzzi A. Efficacy of a Combined Treatment of Botulinum Toxin and Intensive Physiotherapy in Hereditary Spastic Paraplegia. Frontiers in Neuroscience; 2020.
2. de Niet M, de Bot ST,van de Warrenburg BPC,Weerdesteyn V,Geurts AC. Functional effects of botulinum toxin type-A treatment and subsequent stretching of spastic calf muscles: A study in patients with hereditary spastic paraplegia. Journal of Rehabilitation Medicine; 2015.

a. All participants had a diagnosis of hereditary spastic paraparesis (not FRDA).
b. Intervention botulinum toxin injections plus physiotherapy intervention.
c. Small sample sze.
d. Confidence intervals not reported.
e. Intervention included physiotherapy or home stretching (not botulinum toxin injections alone).

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 evidence as per the 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 of ambulation assessed with: Walking Handicap Scale	IMPORTANT[a]	⨁◯◯◯ VERY LOW[b,c,d,e]
Balance assessed with: Timed Up and Go Test follow up: mean 18 weeks	IMPORTANT[f]	⨁◯◯◯ VERY LOW[b,c,d,e]

Falls - not measured	CRITICAL[g]	-
Walking capacity assessed with: 10 Metre Walk Test follow up: mean 18 weeks	IMPORTANT[h]	⨁◯◯◯ VERY LOW[b,d,e,i]
Walking capacity assessed with: Timed Up and Go Test	IMPORTANT[h]	⨁◯◯◯ VERY LOW[b,d,e,i]
Walking capacity assessed with: 2 Minute Walking Test	IMPORTANT[h]	⨁◯◯◯ VERY LOW[b,c,d,e]
Quality of life assessed with: Visual Analogue Scale	CRITICAL[j]	⨁◯◯◯ VERY LOW[b,c,d,e]

a. Identified as critical (1/6), important (3/6), and low importance (2/6) by people with FA and critical by expert authors on this topic
b. All participants had a diagnosis of hereditary spastic paraparesis (not FRDA).
c. Intervention botulinum toxin injections plus physiotherapy intervention.
d. Small sample sze.
e. Confidence intervals not reported.
f. Identified as critical (2/5) and important (3/5) by people with FA and important by expert authors on this topic
g. Identified as critical (3/5) and important (2/5) by people with FA and important by expert authors on this topic.
h. Identified as critical (2/6), important (3/6) and low importance (1/6) by people with FA and important by expert authors on this topic
i. Intervention included physiotherapy or home stretching (not botulinum toxin injections alone).
j. 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		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 Botulinum toxin injections of the ankle/foot musculature as a management strategy for Ambulant people with ankle/foot spasticity. Reflecting on the impact of Botulinum toxin injections of the ankle/foot musculature on Independence of ambulation, 34.62% (9/26) clinical experts reported a benefit (large, moderate or small), 11.54% (3/26) 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. Reflecting on the impact on Balance, 23.08% (6/26) clinical experts reported a benefit, 23.08% (6/26) reported no effect and, 3.85% (1/26) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Falls, 26.92% (7/26) clinical experts reported a benefit, 19.23% (5/26) reported no effect and, 0% (0/26) reported observing a harm. 14 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Walking capacity, 38.47% (10/26) clinical experts reported a benefit, 3.85% (1/26) reported no effect and, 3.85% (1/26) reported observing a harm. 14 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Quality of life, 38.47% (10/26) clinical experts reported a benefit, 3.85% (1/26) reported no effect and, 3.85% (1/26) reported observing a harm. 14 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Independence of ambulation, 38.47% (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. For individuals with ataxia (including people with FRDA) the Ataxia UK Medical Guidelines (de Silva et al, 2019) also recommends: • Careful assessment by a neurologist, with advice from a physiotherapist, is required to decide on the type of treatment of spasticity. • 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 and do not provide separate recommendations based on ability to ambulate (3).

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). 2/4 indicated botulinum toxin injections of the ankle/foot musculature for people who are walking and have ankle and/or foot spasticity were probably reasonable, 1/4 indicated reasonable, 1/4 indicated that 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**	Probably favors the intervention	Favors the intervention	Varies	Don't know

	JUDGEMENT						
			comparison				
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 cannot recommend either botulinum toxin injection or no pharmacological therapy for ambulant individuals with Friedreich ataxia with ankle or foot spasticity. In selected cases, botulinum toxin injection could be considered after weighing up the potential benefits and harms related to ambulation and dynamic standing balance and therapy-based treatments (such as physiotherapy) have been tried but have not been completely effective. Clinicians should discuss potential negative effects and ensure the individual is aware of the risks prior to this treatment.

Justification

There are no publications examining the effectiveness of botulinum toxin injections in the ankle or foot muscles in individuals with FRDA who are ambulant. Clinical experience indicates some beneficial effects from this treatment, although there are not consistent observations of benefit.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia who are ambulant.

Research priorities

There is an urgent need to evaluate the effects of focal spasticity management on individuals with FRDA to ensure the detrimental effects of spasticity do not impact on function. Identifying the most appropriate individuals for this management strategy is important to ensure appropriately targeted therapy.

References

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. See: https://www.ataxia.org.uk/healthcare-professionals/resources-for-healthcare-professionals/medical-guidelines/ for the full guidelines.

Reetz K, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. Lancet Neurol. 2015;14(2):174-82.

Rummey C, Farmer JM, Lynch DR. Predictors of loss of ambulation in Friedreich's ataxia. EClinicalMedicine. 2020;18:100213.