

QUESTION

Should neuromodulation (broad - TMS, other) vs. no intervention be used for people with spasticity with Friedreich ataxia?

POPULATION:	people with spasticity with Friedreich ataxia
INTERVENTION:	neuromodulation (broad - TMS, other)
COMPARISON:	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; Severity of spasticity; Severity of spasticity; Severity of spasticity; Upper limb function;

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 type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<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.</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"> <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> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> <th>Risk with no intervention</th> <th>Risk difference with neuromodulation (broad - TMS, other)</th> </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 intervention	Risk difference with neuromodulation (broad - TMS, other)	<p>There are no studies examining the effects of neuromodulation on spasticity in individuals with FRDA; and the evidence for desirable effects in individuals with multiple sclerosis is variable. This may be due to low participant numbers and heterogeneity in neuromodulation approaches.</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 intervention	Risk difference with neuromodulation (broad - TMS, other)									

Mobility related to spasticity assessed with: Multiple Sclerosis Walking Scale	20 (1 RCT) ¹	⊕○○○ Very low ^{a,b,c,d}	-	20 people with multiple sclerosis were randomised to either anodal tDCS stimulation to the primary motor cortex of the more affected side for 20mins/day for 5 consecutive days (n=10) or sham tDCS stimulation (n=10). A mixed-model ANOVA did not show any significant interaction for the MSWS. One-way ANOVA did not show any significant change in MSWS for anodal tDCS or sham groups. There were no significant differences between the two groups at baseline and at 5 days. (Iodice et al 2015).
Frequency and severity of spasms - not measured	-	-	-	-
Pain	34 (1 RCT) ²	⊕○○○ Very low ^{a,b,c}	-	34 people with multiple sclerosis and lower spastic paraparesis were randomised to 3 groups: high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) (n=12), intermittent theta-burst stimulation (iTBS) (n=12), and sham stimulation (n=10). Patients were stimulation 1x/day for 5 consecutive days for 2 weeks. Effects of intervention on pain were compared using two-tailed Wilcoxon signed rank test. There was a significant reduction in the HF-rTMS group in the pain level after 10 sessions, this effect persisted for 2 weeks after the end of stimulation but by the end of the 12-week follow up, the pain level returned to the initial values. (Korzhova et al 2019).
Frequency and severity of cramps - not measured	-	-	-	-
Severity of spasticity assessed	71 (3 RCTs) ^{1,2,3}	⊕○○○ Very low ^{a,c,e,f}	-	20 people with multiple sclerosis were randomised to either anodal tDCS stimulation to the primary motor cortex of the more

	with: Modified Ashworth Scale				<p>affected side for 20mins/day for 5 consecutive days (n=10) or sham tDCS stimulation (n=10). A mixed-model ANOVA did not show any significant interaction for the MAS. One-way ANOVA did not show any significant change in MAS for anodal tDCS or sham groups. There were no significant differences between the two groups at baseline and at 5 days. (Iodice et al 2015). 34 people with multiple sclerosis and lower spastic paraparesis were randomised to 3 groups: high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) (n=12), intermittent theta-burst stimulation (iTBS) (n=12), and sham stimulation (n=10). Patients were stimulation 1x/day for 5 consecutive days for 2 weeks. Evaluations were performed at baseline (T0), after 2 weeks (T1), 2 weeks after that (T2) and 12 weeks later (T3). There was a significant reduction in MAS score in the HF-rTMS and iTBS groups at T1 ($p<0.001$). There were no changes in MAS in the sham control group. Kruskal-Wallis test showed MAS changes in the 3 groups were significantly different (between HF-rTMS and sham, iTBS and sham). (Korzhova et al 2018) 17 people with multiple sclerosis were randomised to receive real intermittent theta-burst stimulation (iTBS) or sham iTBS during the first half of a 5-week indoor rehab programme. Patients were stimulated once a day for 13 consecutive days. Spasticity was measured at Week 0, Week 3 (day after last session of iTBS) and Week 5 (end of rehab). An improvement in MAS scores was found in both groups. A two-way repeated-measures ANOVA (iTBS x time) identified no significant difference between groups. (Boutiere et al 2016).</p>	
	Severity of spasticity assessed with: Visual Analogue Scale	17 (1 RCT) ³	⊕○○○ Very low ^{a,b,c,d}	-	<p>17 people with multiple sclerosis were randomised to receive real intermittent theta-burst stimulation (iTBS) or sham iTBS during the first half of a 5-week indoor rehab programme. Patients were stimulated once a day for 13 consecutive days. Spasticity was measured at Week 0, Week 3 (day after last session of iTBS) and Week 5 (end of rehab). MAS scores decreased in both groups.</p>	

				($p=0.0003$). A two-way repeated-measures ANOVA (iTBS x time) identified a difference between both groups ($p=0.013$) with the real iTBS group experiencing greater improvement of spasticity compared to the sham group at Week 3 (Wilcoxon: $p=0.026$). (Boutiere et al 2016).
Severity of spasticity assessed with: Multiple Sclerosis Spasticity Scale	20 (1 RCT) ¹	⊖ _{a,b,c}	-	20 people with multiple sclerosis were randomised to either anodal tDCS stimulation to the primary motor cortex of the more affected side for 20mins/day for 5 consecutive days (n=10) or sham tDCS stimulation (n=10). A mixed-model ANOVA did not show any significant interaction for the MSSS-88. One-way ANOVA did not show any significant change in MSSS-88 for anodal tDCS or sham groups. There were no significant differences between the two groups at baseline and at 5 days. (Iodice et al 2015).
Severity of spasticity assessed with: Subjective Evaluating Spasticity Scale	34 (1 RCT) ²	⊕○○○ Very low ^{a,b,c}	-	34 people with multiple sclerosis and lower spastic paraparesis were randomised to 3 groups: high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) (n=12), intermittent theta-burst stimulation (iTBS) (n=12), and sham stimulation (n=10). Patients were stimulation 1x/day for 5 consecutive days for 2 weeks. Effects of intervention on spasticity measured by the SESS were compared using two-tailed Wilcoxon signed rank test. There was a significant reduction in the HF-rTMS group in the spasticity level measured by the SESS after 10 sessions. In the iTBS group, there was a significant reduction in spasticity assessed by the SESS immediately after stimulation and the effect persisted for 12 weeks. I(Korzhova et al 2019).
Severity of spasticity assessed with: Numerical Analogue Scale	34 (1 RCT) ²	⊕○○○ Very low ^{a,b,c}	-	34 people with multiple sclerosis and lower spastic paraparesis were randomised to 3 groups: high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) (n=12), intermittent theta-burst stimulation (iTBS) (n=12), and sham stimulation (n=10). Patients were stimulation 1x/day for 5 consecutive days for 2 weeks. Effects of intervention on

	<table border="1"> <tr> <td data-bbox="514 105 640 487"></td> <td data-bbox="640 105 766 487"></td> <td data-bbox="766 105 892 487"></td> <td data-bbox="892 105 997 487"></td> <td data-bbox="997 105 1423 487"> <p>NAS were compared using two-tailed Wilcoxon signed rank test. There was a significant reduction in the HF-rTMS group in the spasticity measured by the NAS immediately after therapy. This effect persisted for 2 weeks after the end of stimulation but by the end of the 12-week follow up, the spasticity level returned to the initial values. There was a slight decrease in spasticity in the iTBS group post-intervention and at the 2-week follow up. (Korzhova et al 2019).</p> </td> </tr> <tr> <td data-bbox="514 487 640 641">Upper limb function - not measured</td> <td data-bbox="640 487 766 641">-</td> <td data-bbox="766 487 892 641">-</td> <td data-bbox="892 487 997 641">-</td> <td data-bbox="997 487 1423 641">-</td> </tr> </table> <p>1. Iodice R, Dubbioso R, Ruggiero L, Santoro L, Manganelli F. Anodal transcranial direct current stimulation of motor cortex does not ameliorate spasticity in multiple sclerosis. <i>Restorative Neurology and Neuroscience</i>; 2015.</p> <p>2. Korzhova J, Bakulin I, Sinityn D et al. High-frequency repetitive transcranial magnetic stimulation and intermittent theta-burst stimulation for spasticity management in secondary progressive multiple sclerosis. <i>European Journal of Neurology</i>; 2019.</p> <p>3. Boutiere C., Rey C., Zaaraoui W. et al. Improvement of spasticity following intermittent theta burst stimulation in multiple sclerosis is associated with modulation of resting-state functional connectivity of the primary motor cortices. <i>Multiple Sclerosis</i>; 2017.</p> <p>a. Participants with multiple sclerosis (no FRDA) b. One study with small sample size published. c. Small sample size d. Allocation concealment not reported. e. Exploratory RCTs with small sample sizes. f. Allocation concealment not reported in two of the studies.</p>					<p>NAS were compared using two-tailed Wilcoxon signed rank test. There was a significant reduction in the HF-rTMS group in the spasticity measured by the NAS immediately after therapy. This effect persisted for 2 weeks after the end of stimulation but by the end of the 12-week follow up, the spasticity level returned to the initial values. There was a slight decrease in spasticity in the iTBS group post-intervention and at the 2-week follow up. (Korzhova et al 2019).</p>	Upper limb function - not measured	-	-	-	-	
				<p>NAS were compared using two-tailed Wilcoxon signed rank test. There was a significant reduction in the HF-rTMS group in the spasticity measured by the NAS immediately after therapy. This effect persisted for 2 weeks after the end of stimulation but by the end of the 12-week follow up, the spasticity level returned to the initial values. There was a slight decrease in spasticity in the iTBS group post-intervention and at the 2-week follow up. (Korzhova et al 2019).</p>								
Upper limb function - not measured	-	-	-	-								

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT


RESEARCH EVIDENCE

ADDITIONAL CONSIDERATIONS

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

Outcomes	No 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 neuromodulation (broad - TMS, other)
Mobility related to spasticity assessed with: Multiple Sclerosis Walking Scale	20 (1 RCT) ¹	⊕○○○ Very low ^{a,b,c,d}	-	20 people with multiple sclerosis were randomised to either anodal tDCS stimulation to the primary motor cortex of the more affected side for 20mins/day for 5 consecutive days (n=10) or sham tDCS stimulation (n=10). A mixed-model ANOVA did not show any significant interaction for the MSWS. One-way ANOVA did not show any significant change in MSWS for anodal tDCS or sham groups. There were no significant differences between the two groups at baseline and at 5 days. (Iodice et al 2015).	
Frequency and severity of spasms - not measured	-	-	-	-	-
Pain	34 (1 RCT) ²	⊕○○○ Very low ^{a,b,c}	-	34 people with multiple sclerosis and lower spastic paraparesis were randomised to 3 groups: high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) (n=12), intermittent theta-burst stimulation (iTBS) (n=12), and sham stimulation (n=10). Patients were stimulation 1x/day for 5 consecutive days for 2 weeks. Effects of intervention on pain were compared using two-tailed Wilcoxon signed rank test. There was a significant reduction in the HF-rTMS group in the pain level after 10 sessions, this effect persisted for 2 weeks after the end of stimulation but by the end of the 12-week follow up, the pain level returned to the initial values. (Korzhova et al 2019).	

There are no studies examining the effects of neuromodulation on spasticity in individuals with FRDA; and the evidence for desirable effects in individuals with multiple sclerosis is variable. This may be due to low participant numbers and heterogeneity in neuromodulation approaches.

Frequency and severity of cramps - not measured	-	-	-	-	-
Severity of spasticity assessed with: Modified Ashworth Scale	71 (3 RCTs) ^{1,2,3}	 Very low ^{a,c,e,f}	-		<p>20 people with multiple sclerosis were randomised to either anodal tDCS stimulation to the primary motor cortex of the more affected side for 20mins/day for 5 consecutive days (n=10) or sham tDCS stimulation (n=10). A mixed-model ANOVA did not show any significant interaction for the MAS. One-way ANOVA did not show any significant change in MAS for anodal tDCS or sham groups. There were no significant differences between the two groups at baseline and at 5 days. (Iodice et al 2015). 34 people with multiple sclerosis and lower spastic paraparesis were randomised to 3 groups: high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) (n=12), intermittent theta-burst stimulation (iTBS) (n=12), and sham stimulation (n=10). Patients were stimulation 1x/day for 5 consecutive days for 2 weeks. Evaluations were performed at baseline (T0), after 2 weeks (T1), 2 weeks after that (T2) and 12 weeks later (T3). There was a significant reduction in MAS score in the HF-rTMS and iTBS groups at T1 ($p < 0.001$). There were no changes in MAS in the sham control group. Kruskal-Wallis test showed MAS changes in the 3 groups were significantly different (between HF-rTMS and sham, iTBS and sham). (Korzhova et al 2018) 17 people with multiple sclerosis were randomised to receive real intermittent theta-burst stimulation (iTBS) or sham iTBS during the first half of a 5-week indoor rehab programme. Patients were stimulated once a day for 13 consecutive days. Spasticity was measured at Week 0, Week 3 (day after last session of iTBS) and Week 5 (end of rehab). An improvement in MAS scores was found in both groups. A two-way repeated-measures ANOVA (iTBS x time) identified no significant difference between groups. (Boutiere et al 2016).</p>

	Severity of spasticity assessed with: Visual Analogue Scale	17 (1 RCT) ³	⊕○○○ Very low ^{a,b,c,d}	-	17 people with multiple sclerosis were randomised to receive real intermittent theta-burst stimulation (iTBS) or sham iTBS during the first half of a 5-week indoor rehab programme. Patients were stimulated once a day for 13 consecutive days. Spasticity was measured at Week 0, Week 3 (day after last session of iTBS) and Week 5 (end of rehab). VAS scores decreased in both groups ($p=0.0003$). A two-way repeated-measures ANOVA (iTBS x time) identified a difference between both groups ($p=0.013$) with the real iTBS group experiencing greater improvement of spasticity compared to the sham group at Week 3 (Wilcoxon: $p=0.026$). (Boutiere et al 2016).	
	Severity of spasticity assessed with: Multiple Sclerosis Spasticity Scale	20 (1 RCT) ¹	-a,b,c	-	20 people with multiple sclerosis were randomised to either anodal tDCS stimulation to the primary motor cortex of the more affected side for 20mins/day for 5 consecutive days (n=10) or sham tDCS stimulation (n=10). A mixed-model ANOVA did not show any significant interaction for the MSSS-88. One-way ANOVA did not show any significant change in MSSS-88 for anodal tDCS or sham groups. There were no significant differences between the two groups at baseline and at 5 days. (Iodice et al 2015).	
	Severity of spasticity assessed with: Subjective Evaluating Spasticity Scale	34 (1 RCT) ²	⊕○○○ Very low ^{a,b,c}	-	34 people with multiple sclerosis and lower spastic paraparesis were randomised to 3 groups: high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) (n=12), intermittent theta-burst stimulation (iTBS) (n=12), and sham stimulation (n=10). Patients were stimulation 1x/day for 5 consecutive days for 2 weeks. Effects of intervention on spasticity measured by the SESS were compared using two-tailed Wilcoxon signed rank test. There was a significant reduction in the HF-rTMS group in the spasticity level measured by the SESS after 10 sessions. In the iTBS group, there was a significant reduction in spasticity assessed by the SESS immediately after stimulation and the effect persisted for 12 weeks. I(Korzhova et al 2019).	

Severity of spasticity assessed with: Numerical Analogue Scale	34 (1 RCT) ²	⊕○○○ Very low ^{a,b,c}	-	34 people with multiple sclerosis and lower spastic paraparesis were randomised to 3 groups: high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) (n=12), intermittent theta-burst stimulation (iTBS) (n=12), and sham stimulation (n=10). Patients were stimulation 1x/day for 5 consecutive days for 2 weeks. Effects of intervention on NAS were compared using two-tailed Wilcoxon signed rank test. There was a significant reduction in the HF-rTMS group in the spasticity measured by the NAS immediately after therapy. This effect persisted for 2 weeks after the end of stimulation but by the end of the 12-week follow up, the spasticity level returned to the initial values. There was a slight decrease in spasticity in the iTBS group post-intervention and at the 2-week follow up. (Korzhova et al 2019).
Upper limb function - not measured	-	-	-	-

1. Iodice R, Dubbioso R, Ruggiero L, Santoro L, Manganelli F. Anodal transcranial direct current stimulation of motor cortex does not ameliorate spasticity in multiple sclerosis. *Restorative Neurology and Neuroscience*; 2015.
 2. Korzhova J, Bakulin I, Sinityn D et al. High-frequency repetitive transcranial magnetic stimulation and intermittent theta-burst stimulation for spasticity management in secondary progressive multiple sclerosis. *European Journal of Neurology*; 2019.
 3. Boutiere C., Rey C. Zaaraoui W. et al. Improvement of spasticity following intermittent theta burst stimulation in multiple sclerosis is associated with modulation of resting-state functional connectivity of the primary motor cortices. *Multiple Sclerosis*; 2017.
- a. Participants with multiple sclerosis (no FRDA)
 - b. One study with small sample size published.
 - c. Small sample size
 - d. Allocation concealment not reported.
 - e. Exploratory RCTs with small sample sizes.
 - f. Allocation concealment not reported in two of the studies.

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>Very low certainty of evidence as per the evidence profile table.</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" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr style="background-color: #f2f2f2;"> <th data-bbox="518 800 1026 883">Outcomes</th> <th data-bbox="1033 800 1171 883">Importance</th> <th data-bbox="1178 800 1423 883">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td data-bbox="518 888 1026 987"> Mobility related to spasticity assessed with: Multiple Sclerosis Walking Scale </td> <td data-bbox="1033 888 1171 987">IMPORTANT^a</td> <td data-bbox="1178 888 1423 987"> ⊕○○○ VERY LOW^{b,c,d,e} </td> </tr> <tr> <td data-bbox="518 992 1026 1057"> Frequency and severity of spasms - not measured </td> <td data-bbox="1033 992 1171 1057">IMPORTANT^f</td> <td data-bbox="1178 992 1423 1057">-</td> </tr> <tr> <td data-bbox="518 1062 1026 1161"> Pain </td> <td data-bbox="1033 1062 1171 1161">IMPORTANT^g</td> <td data-bbox="1178 1062 1423 1161"> ⊕○○○ VERY LOW^{b,c,d} </td> </tr> <tr> <td data-bbox="518 1166 1026 1230"> Frequency and severity of cramps - not measured </td> <td data-bbox="1033 1166 1171 1230">IMPORTANT^h</td> <td data-bbox="1178 1166 1423 1230">-</td> </tr> <tr> <td data-bbox="518 1235 1026 1334"> Severity of spasticity assessed with: Modified Ashworth Scale </td> <td data-bbox="1033 1235 1171 1334">CRITICALⁱ</td> <td data-bbox="1178 1235 1423 1334"> ⊕○○○ VERY LOW^{b,d,j,k} </td> </tr> <tr> <td data-bbox="518 1339 1026 1438"> Severity of spasticity assessed with: Visual Analogue Scale </td> <td data-bbox="1033 1339 1171 1438">CRITICALⁱ</td> <td data-bbox="1178 1339 1423 1438"> ⊕○○○ VERY LOW^{b,c,d,e} </td> </tr> </tbody> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)	Mobility related to spasticity assessed with: Multiple Sclerosis Walking Scale	IMPORTANT ^a	⊕○○○ VERY LOW ^{b,c,d,e}	Frequency and severity of spasms - not measured	IMPORTANT ^f	-	Pain	IMPORTANT ^g	⊕○○○ VERY LOW ^{b,c,d}	Frequency and severity of cramps - not measured	IMPORTANT ^h	-	Severity of spasticity assessed with: Modified Ashworth Scale	CRITICAL ⁱ	⊕○○○ VERY LOW ^{b,d,j,k}	Severity of spasticity assessed with: Visual Analogue Scale	CRITICAL ⁱ	⊕○○○ VERY LOW ^{b,c,d,e}	
Outcomes	Importance	Certainty of the evidence (GRADE)																					
Mobility related to spasticity assessed with: Multiple Sclerosis Walking Scale	IMPORTANT ^a	⊕○○○ VERY LOW ^{b,c,d,e}																					
Frequency and severity of spasms - not measured	IMPORTANT ^f	-																					
Pain	IMPORTANT ^g	⊕○○○ VERY LOW ^{b,c,d}																					
Frequency and severity of cramps - not measured	IMPORTANT ^h	-																					
Severity of spasticity assessed with: Modified Ashworth Scale	CRITICAL ⁱ	⊕○○○ VERY LOW ^{b,d,j,k}																					
Severity of spasticity assessed with: Visual Analogue Scale	CRITICAL ⁱ	⊕○○○ VERY LOW ^{b,c,d,e}																					

Severity of spasticity assessed with: Multiple Sclerosis Spasticity Scale	CRITICAL ^l	_b,c,d
Severity of spasticity assessed with: Subjective Evaluating Spasticity Scale	CRITICAL ^l	⊕○○○ VERY LOW ^{b,c,d}
Severity of spasticity assessed with: Numerical Analogue Scale	CRITICAL ^l	⊕○○○ VERY LOW ^{b,c,d}
Upper limb function - not measured	CRITICAL ^l	-

- a. Identified as important (5/6) and low importance (1/6) by people with FA and critical by expert authors on this topic
- b. Participants with multiple sclerosis (no FRDA)
- c. One study with small sample size published.
- d. Small sample size
- e. Allocation concealment not reported.
- f. 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
- g. 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
- h. Identified as critical (1/6) and important (5/6) by people with FA and critical by expert authors on this topic
- i. 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
- j. Exploratory RCTs with small sample sizes.
- k. Allocation concealment not reported in two of the studies.
- l. 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

<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 Neuromodulation (broad – TMS, other) as a management strategy for People with spasticity.</p> <p>Reflecting on the impact of Neuromodulation (broad – TMS, other) on Mobility related to spasticity, 11.54% (3/26) 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). 21 clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Frequency & severity of spasms, 7.7% (2/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 22 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Pain, 7.69% (2/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 22 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Frequency & severity of cramps, 7.7% (2/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 22 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on Severity of spasticity, 7.69% (2/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 22 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on UL function, 11.54% (3/26) clinical experts reported a benefit, 7.69% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 21 expert clinicians could not provide any information on this outcome.</p>
--	--	---

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes 	<p>No published evidence.</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</p>

<ul style="list-style-type: none"> ○ Varies ● Don't know 		<p>and costs).</p> <p>1/4 indicated neuromodulation was reasonable, 3/4 didn't know if 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 ○	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 conditionally recommend against the use of neuromodulation for the treatment of spasticity in individuals with Friedreich ataxia.

Justification

There is no published evidence of the effects of neuromodulation for spasticity management in individuals with FRDA. Benussi and colleagues (2020) reviewed 10 published studies (n=116) which confirmed the favourable effect of tDCS on a range of motor domains including gait, balance and upper limb function in neurodegenerative ataxias, but did not report effects on spasticity.

A review specifically examining the effect of repetitive transcranial magnetic stimulation or transcranial direct current stimulation on spasticity of the limbs found 30 randomised controlled trials, with the majority of the studies including participants post-stroke or with multiple sclerosis (Leo et al, 2017). The findings suggest neuromodulation is useful in reducing spasticity, but its effects depend on the applied hemisphere and the underlying pathology. Furthermore, they recommended neuromodulation should be applied as a pre-cursor to other medical and/or physical therapy.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia with spasticity.

Research priorities

Given the preliminary positive effects on spasticity in multiple sclerosis, this may be a treatment approach worth evaluating further. We suggest consideration of future research studies trialling neuromodulation for the treatment of spasticity in individuals with FRDA.

References

Benussi A, Pascual-Leone A, Borroni B. Non-invasive cerebellar stimulation in neurodegenerative ataxia: A literature review. *Int J Mol Sci.* 2020;21(6).

Leo A, Naro A, Molonia F, Tomasello P, Saccà I, Bramanti A, et al. Spasticity management: The current state of transcranial neuromodulation. *PM R.* 2017;9(10):1020-9.

Lynch D. FA Clinical Outcome Measures (FA-COMS) Registry (unpublished data): clinicaltrials.gov; 2017 [Available from: <https://clinicaltrials.gov/ct2/show/NCT03090789>