# QUESTION

| Should systemic pharmacotherapy (baclofen, tizanidine, gabapentin, dantrolene sodium, benzodiazepines, other) vs. no intervention be used for people with spasticity and spasms/cramps with Friedreich ataxia? | |
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| **POPULATION:** | people with spasticity and spasms/cramps with Friedreich ataxia |
| **INTERVENTION:** | systemic pharmacotherapy (baclofen, tizanidine, gabapentin, dantrolene sodium, benzodiazepines, other) |
| **COMPARISON:** | no intervention |
| **MAIN OUTCOMES:** | Mobility related to spasticity; Mobility related to spasticity; Mobility related to spasticity; Mobility related to spasticity; Frequency and severity of spasms; Frequency and severity of spasms; Pain; Pain; 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<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ 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. | The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic.<br><br>1/7 indicated spasticity and spasms were probably not serious, 2/7 indicated probably serious, 4/7 indicated serious. 3/7 indicated spasticity and spasms were probably not urgent, 2/7 indicated probably urgent, 2/7 indicated urgent. 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). |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Trivial<br>○ Small<br>● Moderate<br>○ Large<br>○ Varies<br>○ Don't know | | In clinical practice, beneficial effects have been seen for managing spasticity during the night, reducing sleep disturbance and reducing pain. There appears to be only small effects on mobility. |

| Outcomes | № of | Certainty of | Relative | Anticipated absolute effects* (95% CI) |
|---|---|---|---|---|

| | participants (studies) Follow up | the evidence (GRADE) | effect (95% CI) | Risk with no intervention | Risk difference with systemic pharmacotherapy (baclofen, tizanidine, gabapentin, dantrolene sodium, benzodiazepines, other) |
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| Mobility related to spasticity assessed with: Spastic Paraplegia Rating Scale Annex | 1 (1 observational study)[1] | ⨁◯◯◯ VERY LOW[a,b,c] | - | A 33-year old female with FA presented with lower limb spasticity and slow ambulation with single point stick. Provided with Idebenone, ubidecarenone, and baclofen combined therapy, SPRS score improved by 23/52 to 19/52. | |
| Mobility related to spasticity assessed with: Scale for the Assessment and Rating of Ataxia | 0 (1 observational study)[1] | ⨁◯◯◯ VERY LOW[a,b,c] | - | A 33 year old female with FA presented with lower limb spasticity and slow ambulation with single point stick. Provided with Idebenone, ubidecarone, and baclofen combined therapy, SPRS score improved from 23/52 to 19/52. | |
| Mobility related to spasticity assessed with: 10 Metre Walk | 0 (1 observational study)[2] | ⨁◯◯◯ VERY LOW[d,e,f] | - | 106 people with multiple sclerosis who underwent intrathecal baclofen therapy for MS-related spasticity were included in this 20 year prospective observational cohort study. Ambulatory status and 10m timed walk was collected for 8 ambulant patients. 5/8 subjects maintained their mobility after ITB pump implantation. 1/8 was unable to walk 1 year after pump insersion and 2/8 were unable to walk independently at 1.5 and 4 years respectively. (Sammaraiee et al 2019). | |
| Mobility related to spasticity assessed with: Timed 25-Foot | 0 (1 observational study)[3] | ⨁◯◯◯ VERY LOW[c,d,g] | - | 47 ambulant patients with multiple sclerosis who received ITB therapy were analysed retrospectively. The patients received 2 follow up visits at 6 months and 1 year after ITB therapy initiation. Repeated measures ANOVA tests were performed. There were no statistically | |

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| Walk | | | | significant differences between baseline and follow up visits ($p$=0.28) in the T25FW. |
| Frequency and severity of spasms assessed with: Penn Spasm Frequency Scale | 0 (3 observational studies)[2,4,5] | ⊕◯◯◯ VERY LOW[e,f,h,i] | - | 106 people with multiple sclerosis who underwent intrathecal baclofen therapy for MS-related spasticity were included in this 20 year prospective observational cohort study. Mean Penn score at baseline across both legs was 3.50 (0-4) which had improved to 1.00 (0-4) following ITB therapy ($p$<0.0001). Change in Penn scores remained significant for 5 years after pump implantation (mean 2.2, $p$<0.002). In subjects with pumps for 6-10 years, significant change in Penn scores from baseline were sustained (mean 1.67, $p$=0.001). (Sammaraiee et al 2019). 28 people with multiple sclerosis were followed up for mean 74 months to determine long-term response to intrathecal baclofen therapy. They were evaluated at baseline, immediately after ITB, 2 months post implant and regular follow ups of at least every 180 days for at least 1 year. Mean Penn score decreased from 1.52 pre-ITB to 0..64 ($p$<0.005) for upper extremities and from 2.78 to 0.78 ($p$<0.001) for lower extremities. (Natale et al 2016). 5 patients with SCA (n=3), FRDA (n=1), spastic ataxia (n=1) who received intrathecal baclofen were assessed for its effectiveness. The patients were assessed as baseline and 1 year after treatment. Penn score was at level 3-4 prior to ITB treatment, and reduced to 0 for all patients. (Berntsson et al 2019). |
| Frequency and severity of spasms assessed with: Spasm Frequency Scale | 0 (2 observational studies)[3,6] | ⊕◯◯◯ VERY LOW[d,e,i] | - | 47 ambulant patients with multiple sclerosis who received ITB therapy were analysed retrospectively. The patients received 2 follow up visits at 6 months and 1 year after ITB therapy initiation. For spasm frequency, Fisher's exact tests were used to compare proportion of patients at each time point. Prior to ITB therapy, 45.7% reported a spasm frequency of >=1 event/hr and 15.6% and 4.3% reported the same at 6 months and 1 year. The |

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| | | | | proportion of patients reporting spasm frequencies >=1/hr decreased from baseline to 6 months ($p$=0.0029) and from baseline to 1 year ($p$<0.0001). (Lee et al 2018). 256 ambulatory patients with multiple sclerosis underwent intrathecal baclofen therapy. A mixed effects model identified a statistically significant reduction in spasm frequency at 6 months ($p$<0.001) and was maintained through the 5-year follow up period ($p$<0.001). (Abbatemarco et al 2020). |
| Pain assessed with: Brief Pain Inventory | 0 (1 observational study)[4] | ⨁◯◯◯ VERY LOW[d,i,j] | - | 5 patients with SCA (n=3), FRDA (n=1), spastic ataxia (n=1) who received intrathecal baclofen were assessed for its effectiveness. The patients were assessed as baseline and 1 year after treatment. Before ITB, the mean BPI scale score was 7.5 (pain at its worst) which had decreased to 3.0 after ITB. (Berntsson et al 2019). |
| Pain assessed with: Numeric Rating Scale | 0 (2 observational studies)[2,3,6] | ⨁◯◯◯ VERY LOW[d,e,i] | - | 47 ambulant patients with multiple sclerosis who received ITB therapy were analysed retrospectively. The patients received 2 follow up visits at 6 months and 1 year after ITB therapy initiation. A repeated measures ANOVA identified a decrease in Numeric Pain Rating Scale scores (4.4 ± 0.5 before ITB, 2.8 ± 0.5 at 6 months, and 2.4 ± 0.4 at 1 year [p < 0.05]) (Lee et al 2018). 56 ambulatory patients with multiple sclerosis underwent intrathecal baclofen therapy. Pain scores were significantly reduced, from 4.4 ± 0.6 before ITB therapy to 2.8 ± 0.5 at 6 months post-ITB (p < 0.05) and 2.4 ± 0.5 at 1 year post-ITB (p < 0.005) (overall repeated-measures ANOVA significance, p = 0.0028). (Abbatemarco et al 2020). 106 people with multiple sclerosis who underwent intrathecal baclofen therapy for MS-related spasticity were included in this 20 year prospective observational cohort study. Mean NRS pain score was 5.4 (0-10) at baseline. Following ITB trial, NRS pain score improved (mean 1.91 (0-8)). Changes were also significant from baseline for NRS Pain |

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| | | | | scores (p < 0.05) for subjects with pumps in situ for 6-10 years. (Sammaraiee et al 2019). | |
| Pain assessed with: Visual Analog Scale | 0 (2 observational studies)[2,5] | ⨁◯◯◯ VERY LOW[d,e,f] | - | 106 people with multiple sclerosis who underwent intrathecal baclofen therapy for MS-related spasticity were included in this 20 year prospective observational cohort study. VAS mean scores improved post-trial compared with baseline (p < 0.001). (Sammaraiee et al 2019). 28 people with multiple sclerosis were followed up for mean 74 months to determine long-term response to intrathecal baclofen therapy. They were evaluated at baseline, immediately after ITB, 2 months post implant and regular follow ups of at least every 180 days for at least 1 year. The mean pain VAS score decreased from 5.18 at baseline to 0.89 at last available follow up (*p*<0.005). (Natale et al 2016). | |
| Frequency and severity of cramps - not measured | - | - | - | - | - |
| Severity of spasticity assessed with: Modified Ashworth Scale | 0 (5 observational studies)[2,3,4,5,6] | ⨁◯◯◯ VERY LOW[k,l] | - | 106 people with multiple sclerosis who underwent intrathecal baclofen therapy for MS-related spasticity were included in this 20 year prospective observational cohort study. Mean Ashworth score across all recorded muscle groups was 1.57 (0–3.5). Following ITB trial, mean Ashworth score was 0.34 (0-2.25), *p*<0.0001). Changes from baseline remained significant for Ashworth scores (mean 0.62, *p*<0.001) for 5 years following pump implantation and sustained in those with pump in situ 6-10 years (mean 0.78, *p*=0.002). (Sammaraiee et al 2019). 47 ambulant patients with multiple sclerosis who received ITB therapy were analysed retrospectively. The patients received 2 follow up visits at 6 months and 1 year after ITB therapy initiation. Repeated measures ANOVA tests were | |

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| | | | | | performed. There was a statistically significant reduction in aggregate lower-extremity Modified Ashworth Scale scores (from 14.8 ± 1.0 before ITB therapy to 5.8 ± 0.8 at 6 months post treatment and 6.4 ± 0.9 at 1 year [$p < 0.05$]). (Lee et al 2018). 28 people with multiple sclerosis were followed up for mean 74 months to determine long-term response to intrathecal baclofen therapy. They were evaluated at baseline, immediately after ITB, 2 months post implant and regular follow ups of at least every 180 days for at least 1 year. During follow up the mean MAS score for upper extremities decreased from 2.32 to 1.11, and for lower extremities decreased from 3.96 to 1.61. The changes from baseline to 6, 12, and 24 months are all statistically significant ($p < 0.005$). Also for lower extremities, the decreases from baseline to every 6 month interval are statistically significant ($p <0.005$) up to 36 months. (Natale et al 2016). 56 ambulatory patients with multiple sclerosis underwent intrathecal baclofen therapy. Random intercept linear model with repeated time points was performed for statistical comparison between baseline and each follow-up time point after ITB implantation. Aggregate Modified Ashworth Scale (MAS) scores for the ambulatory ITB cohort decreased from 13.5±6.96 to 4.54±4.18 at 5years ($p<0.001$) (Abbatemarco et al 2020).<br><br>5 patients with SCA (n=3), FRDA (n=1), spastic ataxia (n=1) who received intrathecal baclofen were assessed for its effectiveness. The patients were assessed as baseline and 1 year after treatment. A mild increase was found in muscle tone, graded as 1+ for 3 patients before ITB treatment and afterward a reduction to 0 was observed (i.e., no increase in muscle tone). As for 2 other patients, the muscle tone was graded as 3–4 before ITB treatment and afterward the muscle tone was almost normal (1–0) (Berntsson et al 2019). |

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| Severity of spasticity assessed with: Spastic Paraplegia Rating Scale Annex 1 | 0 (1 observational study)[1] | ⨁◯◯◯ VERY LOW[b] | - | A 33-year old female with FA presented with lower limb spasticity and slow ambulation with single point stick. Provided with Idebenone, ubidecarenone, and baclofen combined therapy, SPRS score improved by 23/52 to 19/52. | |
| Upper limb function - not measured | - | - | - | - | - |


1. Tessa A., Fiorillo C.,De Grandis D.,et al. Friedreich's Ataxia Presenting as Isolated Spastic Paraparesis. . Can. J. Neurol. Sci.; 2014.
2. Sammaraiee Y, Yardley M,Keenan L,Buchanan K,Stevenson V,Farrell R.. Intrathecal baclofen for multiple sclerosis related spasticity: A twenty year experience. . Mult Scler Relat Disord. ; 2019.
3. Lee BS, Jones J,Lang M,et al.. Early outcomes after intrathecal baclofen therapy in ambulatory patients with multiple sclerosis. . J Neurosurg.; 2018.
4. Berntsson S.G., Gauffin H.,Melberg A.,Holtz A.,Landtblom A.M.. Inherited Ataxia and Intrathecal Baclofen for the Treatment of Spasticity and Painful Spasms. . Stereotactic Funct. Neurosurg; 2019.
5. 7. Natale M, D'Oria S,Nero VV,Squillante E,Gentile M,Rotondo M.. Long-term effects of intrathecal baclofen in multiple sclerosis. . Clin Neurol Neurosurg. ; 2016.
6. Abbatemarco J.R., Griffin A.,Jones N.G.,et al. Long-term outcomes of intrathecal baclofen in ambulatory multiple sclerosis patients: A single-center experience. . Mult. Scler. J.; 2020.


a. Baclofen prescribed in combination with Idebenone and Coenzyme Q10. No comparator examined
b. Single case study only
c. No confidence interval reported with a low absolute number of participants and events.
d. All participants have a diagnosis of multiple sclerosis (not FRDA).
e. Confidence intervals not reported.
f. No specific eligibility criteria except for multiple sclerosis diagnosis.
g. Retrospective cohort study.
h. Only one participant with a diagnosis of FRDA (total participants n=139 with majority having a diagnosis of multiple sclerosis n=134).
i. Consecutive recruitment for all studies.
j. Case series of five participants (n=5).
k. Only one participant with a diagnosis of FRDA (total participants n=242 with majority having a diagnosis of multiple sclerosis n=237).
l. Confidence intervals not reported for most studies.

## Undesirable Effects

How substantial are the undesirable anticipated effects?

**JUDGEMENT**

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

**RESEARCH EVIDENCE**

| 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 systemic pharmacotherapy (baclofen, tizanidine, gabapentin, dantrolene sodium, benzodiazepines, other) |
| Mobility related to spasticity assessed with: Spastic Paraplegia Rating Scale Annex | 1 (1 observational study)[1] | ⨁◯◯◯ VERY LOW[a,b,c] | - | A 33-year old female with FA presented with lower limb spasticity and slow ambulation with single point stick. Provided with Idebenone, ubidecarenone, and baclofen combined therapy, SPRS score improved by 23/52 to 19/52. | |
| Mobility related to spasticity assessed with: Scale for the Assessment and Rating of Ataxia | 0 (1 observational study)[1] | ⨁◯◯◯ VERY LOW[a,b,c] | - | A 33 year old female with FA presented with lower limb spasticity and slow ambulation with single point stick. Provided with Idebenone, ubidecarone, and baclofen combined therapy, SPRS score improved from 23/52 to 19/52. | |
| Mobility related to spasticity assessed with: 10 Metre Walk | 0 (1 observational study)[2] | ⨁◯◯◯ VERY LOW[d,e,f] | - | 106 people with multiple sclerosis who underwent intrathecal baclofen therapy for MS-related spasticity were included in this 20 year prospective observational cohort study. Ambulatory status and 10m timed walk was collected for 8 ambulant patients. 5/8 subjects maintained their mobility after ITB pump implantation, 1/8 was unable to | |

**ADDITIONAL CONSIDERATIONS**

Clinical observations indicate a possible detrimental impact on capacity to stand during transfer, sleepiness, drowsiness and confusion for some individuals.

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| | | | | walk 1 year after pump insersion and 2/8 were unable to walk independently at 1.5 and 4 years respectively. (Sammaraiee et al 2019). |
| Mobility related to spasticity assessed with: Timed 25-Foot Walk | 0 (1 observational study)[3] | ⨁◯◯◯ VERY LOW[c,d,g] | - | 47 ambulant patients with multiple sclerosis who received ITB therapy were analysed retrospectively. The patients received 2 follow up visits at 6 months and 1 year after ITB therapy initiation. Repeated measures ANOVA tests were performed. There were no statistically significant differences between baseline and follow up visits ($p$=0.28) in the T25FW. |
| Frequency and severity of spasms assessed with: Penn Spasm Frequency Scale | 0 (3 observational studies)[2,4,5] | ⨁◯◯◯ VERY LOW[e,f,h,i] | - | 106 people with multiple sclerosis who underwent intrathecal baclofen therapy for MS-related spasticity were included in this 20 year prospective observational cohort study. Mean Penn score at baseline across both legs was 3.50 (0-4) which had improved to 1.00 (0-4) following ITB therapy ($p$<0.0001). Change in Penn scores remained significant for 5 years after pump implantation (mean 2.2, $p$<0.002). In subjects with pumps for 6-10 years, significant change in Penn scores from baseline were sustained (mean 1.67, $p$=0.001). (Sammaraiee et al 2019). 28 people with multiple sclerosis were followed up for mean 74 months to determine long-term response to intrathecal baclofen therapy. They were evaluated at baseline, immediately after ITB, 2 months post implant and regular follow ups of at least every 180 days for at least 1 year. Mean Penn score decreased from 1.52 pre-ITB to 0..64 ($p$<0.005) for upper extremities and from 2.78 to 0.78 ($p$<0.001) for lower extremities. (Natale et al 2016). 5 patients with SCA (n=3), FRDA (n=1), spastic ataxia (n=1) who received intrathecal baclofen were assessed for its effectiveness. The patients were assessed as baseline and 1 year after treatment. Penn score was at level 3-4 prior to ITB treatment, and reduced to 0 for all |

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| | | | | patients. (Berntsson et al 2019). |
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| Pain assessed with: Brief Pain Inventory | 0 (1 observational study)[4] | ⨁◯◯◯ VERY LOW[d,i,j] | - | 5 patients with SCA (n=3), FRDA (n=1), spastic ataxia (n=1) who received intrathecal baclofen were assessed for its effectiveness. The patients were assessed as baseline and 1 year after treatment. Before ITB, the mean BPI scale score was 7.5 (pain at its worst) which had decreased to 3.0 after ITB. (Berntsson et al 2019). |
| Pain assessed with: Numeric Rating Scale | 0 (2 observational studies)[2,3,6] | ⨁◯◯◯ VERY LOW[d,e,i] | - | 47 ambulant patients with multiple sclerosis who received ITB therapy were analysed retrospectively. The patients received 2 follow up visits at 6 months and 1 year after ITB therapy initiation. A repeated measures ANOVA identified a decrease in Numeric Pain Rating Scale scores (4.4 ± 0.5 before ITB, 2.8 ± 0.5 at 6 months, and 2.4 ± 0.4 at 1 year [p < 0.05]) (Lee et al 2018). 56 ambulatory patients with multiple sclerosis underwent intrathecal baclofen therapy. Pain scores |

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| | | | | were significantly reduced, from 4.4 ± 0.6 before ITB therapy to 2.8 ± 0.5 at 6 months post-ITB ($p < 0.05$) and 2.4 ± 0.5 at 1 year post-ITB ($p < 0.005$) (overall repeated-measures ANOVA significance, $p = 0.0028$). (Abbatemarco et al 2020). 106 people with multiple sclerosis who underwent intrathecal baclofen therapy for MS-related spasticity were included in this 20 year prospective observational cohort study. Mean NRS pain score was 5.4 (0-10) at baseline. Following ITB trial, NRS pain score improved (mean 1.91 (0-8)). Changes were also significant from baseline for NRS Pain scores ($p < 0.05$) for subjects with pumps in situ for 6-10 years. (Sammaraiee et al 2019). | |
| Pain assessed with: Visual Analog Scale | 0 (2 observational studies)[2,5] | ⨁◯◯◯ VERY LOW[d,e,f] | - | 106 people with multiple sclerosis who underwent intrathecal baclofen therapy for MS-related spasticity were included in this 20 year prospective observational cohort study. VAS mean scores improved post-trial compared with baseline ($p < 0.001$). (Sammaraiee et al 2019). 28 people with multiple sclerosis were followed up for mean 74 months to determine long-term response to intrathecal baclofen therapy. They were evaluated at baseline, immediately after ITB, 2 months post implant and regular follow ups of at least every 180 days for at least 1 year. The mean pain VAS score decreased from 5.18 at baseline to 0.89 at last available follow up ($p<0.005$). (Natale et al 2016). | |
| Frequency and severity of cramps - not measured | - | - | - | - | - |
| Severity of spasticity assessed with: Modified | 0 (5 observational studies)[2,3,4,5,6] | ⨁◯◯◯ VERY LOW[k,l] | - | 106 people with multiple sclerosis who underwent intrathecal baclofen therapy for MS-related spasticity were included in this 20 year prospective observational cohort study. Mean Ashworth score across all | |

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| | Ashworth Scale | | | | recorded muscle groups was 1.57 (0–3.5). Following ITB trial, mean Ashworth score was 0.34 (0-2.25), *p*<0.0001). Changes from baseline remained significant for Ashworth scores (mean 0.62, *p*<0.001) for 5 years following pump implantation and sustained in those with pump in situ 6-10 years (mean 0.78, *p*=0.002). (Sammaraiee et al 2019). 47 ambulant patients with multiple sclerosis who received ITB therapy were analysed retrospectively. The patients received 2 follow up visits at 6 months and 1 year after ITB therapy initiation. Repeated measures ANOVA tests were performed. There was a statistically significant reduction in aggregate lower-extremity Modified Ashworth Scale scores (from 14.8 ± 1.0 before ITB therapy to 5.8 ± 0.8 at 6 months post treatment and 6.4 ± 0.9 at 1 year [p < 0.05]). (Lee et al 2018). 28 people with multiple sclerosis were followed up for mean 74 months to determine long-term response to intrathecal baclofen therapy. They were evaluated at baseline, immediately after ITB, 2 months post implant and regular follow ups of at least every 180 days for at least 1 year. During follow up the mean MAS score for upper extremities decreased from 2.32 to 1.11, and for lower extremities decreased from 3.96 to 1.61. The changes from baseline to 6, 12, and 24 months are all statistically significant (p < 0.005). Also for lower extremities, the decreases from baseline to every 6 month interval are statistically significant (p <0.005) up to 36 months. (Natale et al 2016). 56 ambulatory patients with multiple sclerosis underwent intrathecal baclofen therapy. Random intercept linear model with repeated time points was performed for statistical comparison between baseline and each follow-up time point after ITB implantation. Aggregate Modified Ashworth Scale (MAS) scores for the ambulatory ITB cohort decreased from 13.5±6.96 to 4.54±4.18 at 5years (p<0.001) (Abbatemarco et al 2020). | |

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| | | | | 5 patients with SCA (n=3), FRDA (n=1), spastic ataxia (n=1) who received intrathecal baclofen were assessed for its effectiveness. The patients were assessed as baseline and 1 year after treatment. A mild increase was found in muscle tone, graded as 1+ for 3 patients before ITB treatment and afterward a reduction to 0 was observed (i.e., no increase in muscle tone). As for 2 other patients, the muscle tone was graded as 3–4 before ITB treatment and afterward the muscle tone was almost normal (1–0) (Berntsson et al 2019). | |
| Severity of spasticity assessed with: Spastic Paraplegia Rating Scale Annex 1 | 0 (1 observational study)[1] | ⊕◯◯◯ VERY LOW[b] | - | A 33-year old female with FA presented with lower limb spasticity and slow ambulation with single point stick. Provided with Idebenone, ubidecarenone, and baclofen combined therapy, SPRS score improved by 23/52 to 19/52. | |
| Upper limb function - not measured | - | - | - | - | - |


1. Tessa A., Fiorillo C.,De Grandis D.,et al. Friedreich's Ataxia Presenting as Isolated Spastic Paraparesis. . Can. J. Neurol. Sci.; 2014.
2. Sammaraiee Y, Yardley M,Keenan L,Buchanan K,Stevenson V,Farrell R.. Intrathecal baclofen for multiple sclerosis related spasticity: A twenty year experience. . Mult Scler Relat Disord. ; 2019.
3. Lee BS, Jones J,Lang M,et al.. Early outcomes after intrathecal baclofen therapy in ambulatory patients with multiple sclerosis. . J Neurosurg.; 2018.
4. Berntsson S.G., Gauffin H.,Melberg A.,Holtz A.,Landtblom A.M.. Inherited Ataxia and Intrathecal Baclofen for the Treatment of Spasticity and Painful Spasms. . Stereotactic Funct. Neurosurg; 2019.
5. 7. Natale M, D'Oria S,Nero VV,Squillante E,Gentile M,Rotondo M.. Long-term effects of intrathecal baclofen in multiple sclerosis. . Clin Neurol Neurosurg. ; 2016.
6. Abbatemarco J.R., Griffin A.,Jones N.G.,et al. Long-term outcomes of intrathecal baclofen in ambulatory multiple sclerosis patients: A single-center experience. . Mult. Scler. J.; 2020.


a. Baclofen prescribed in combination with Idebenone and Coenzyme Q10. No comparator examined

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| | b. Single case study only<br>c. No confidence interval reported with a low absolute number of participants and events.<br>d. All participants have a diagnosis of multiple sclerosis (not FRDA).<br>e. Confidence intervals not reported.<br>f. No specific eligibility criteria except for multiple sclerosis diagnosis.<br>g. Retrospective cohort study.<br>h. Only one participant with a diagnosis of FRDA (total participants n=139 with majority having a diagnosis of multiple sclerosis n=134).<br>i. Consecutive recruitment for all studies.<br>j. Case series of five participants (n=5).<br>k. Only one participant with a diagnosis of FRDA (total participants n=242 with majority having a diagnosis of multiple sclerosis n=237).<br>l. Confidence intervals not reported for most studies. | |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ 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<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>● No important uncertainty or variability | | |

| Outcomes | Importance | Certainty of the evidence (GRADE) |
|---|---|---|

| | | |
|---|---|---|
| Mobility related to spasticity<br>assessed with: Spastic Paraplegia Rating Scale Annex | IMPORTANT[a] | ⨁◯◯◯<br>VERY LOW[b,c,d] |
| Mobility related to spasticity<br>assessed with: Scale for the Assessment and Rating of Ataxia | IMPORTANT[a] | ⨁◯◯◯<br>VERY LOW[b,c,d] |
| Mobility related to spasticity<br>assessed with: 10 Metre Walk | IMPORTANT[a] | ⨁◯◯◯<br>VERY LOW[e,f,g] |
| Mobility related to spasticity<br>assessed with: Timed 25-Foot Walk | IMPORTANT[a] | ⨁◯◯◯<br>VERY LOW[d,e,h] |
| Frequency and severity of spasms<br>assessed with: Penn Spasm Frequency Scale | CRITICAL[i] | ⨁◯◯◯<br>VERY LOW[f,g,j,k] |
| Frequency and severity of spasms<br>assessed with: Spasm Frequency Scale | CRITICAL[i] | ⨁◯◯◯<br>VERY LOW[e,f,k] |
| Pain<br>assessed with: Brief Pain Inventory | IMPORTANT[l] | ⨁◯◯◯<br>VERY LOW[e,k,m] |
| Pain<br>assessed with: Numeric Rating Scale | IMPORTANT[l] | ⨁◯◯◯<br>VERY LOW[e,f,k] |
| Pain<br>assessed with: Visual Analog Scale | IMPORTANT[l] | ⨁◯◯◯<br>VERY LOW[e,f,g] |
| Frequency and severity of cramps - not measured | IMPORTANT[n] | - |
| Severity of spasticity<br>assessed with: Modified Ashworth Scale | CRITICAL[o] | ⨁◯◯◯<br>VERY LOW[p,q] |
| Severity of spasticity<br>assessed with: Spastic Paraplegia Rating Scale Annex 1 | CRITICAL[o] | ⨁◯◯◯<br>VERY LOW[c] |
| Upper limb function - not measured | CRITICAL[r] | - |

a. Identified as important (5/6) and low importance (1/6) by people with FA

| | | |
|---|---|---|
| | and critical by expert authors on this topic<br>b. Baclofen prescribed in combination with Idebenone and Coenzyme Q10. No comparator examined<br>c. Single case study only<br>d. No confidence interval reported with a low absolute number of participants and events.<br>e. All participants have a diagnosis of multiple sclerosis (not FRDA).<br>f. Confidence intervals not reported.<br>g. No specific eligibility criteria except for multiple sclerosis diagnosis.<br>h. Retrospective cohort study.<br>i. 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<br>j. Only one participant with a diagnosis of FRDA (total participants n=139 with majority having a diagnosis of multiple sclerosis n=134).<br>k. Consecutive recruitment for all studies.<br>l. 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<br>m. Case series of five participants (n=5).<br>n. Identified as critical (1/6) and important (5/6) by people with FA and critical by expert authors on this topic<br>o. 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<br>p. Only one participant with a diagnosis of FRDA (total participants n=242 with majority having a diagnosis of multiple sclerosis n=237).<br>q. Confidence intervals not reported for most studies.<br>r. 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<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>● Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ 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 systemic pharmacotherapy (Baclofen, Tizanidine, gabapentin, Dantrolene sodium, Benzodiazepines, other) as a management strategy for individuals with spasticity and spasms/cramps.<br><br>Reflecting on the impact of systemic pharmacotherapy (Baclofen, Tizanidine, gabapentin, Dantrolene sodium, Benzodiazepines, other) on Mobility related to spasticity, 46.15% (12/26) clinical experts reported a benefit (large, moderate or small), 7.69% (2/26) reported no effect and, 3.85% (1/26) reported observing a |

| | | |
|---|---|---|
| | | harm (large, moderate or small). 11 clinicians could not provide any information on this outcome.<br><br>Reflecting on the impact on Frequency & severity of spasms, 57.69% (15/26) clinical experts reported a benefit, 0% (0/26) reported no effect and, 0% (0/26) reported observing a harm. 11 expert clinicians could not provide any information on this outcome.<br><br>Reflecting on the impact on Pain, 57.7% (15/26) clinical experts reported a benefit, 0% (0/26) reported no effect and, 0% (0/26) reported observing a harm. 11 expert clinicians could not provide any information on this outcome.<br><br>Reflecting on the impact on Frequency & severity of cramps, 57.69% (15/26) clinical experts reported a benefit, 0% (0/26) reported no effect and, 0% (0/26) reported observing a harm. 11 expert clinicians could not provide any information on this outcome.<br><br>Reflecting on the impact on Severity of spasticity, 53.84% (14/26) clinical experts reported a benefit, 3.85% (1/26) reported no effect and, 0% (0/26) reported observing a harm. 11 expert clinicians could not provide any information on this outcome.<br><br>Reflecting on the impact on UL function, 34.62% (9/26) clinical experts reported a benefit, 19.23% (5/26) reported no effect and, 0% (0/26) reported observing a harm. 12 expert clinicians could not provide any information on this outcome.<br><br>In clinical practice expert opinion report beneficial effect from systemic pharmacotherapy, however the effects of intrathecal baclofen are varied in this population. There are regional differences regarding the availability of intrathecal baclofen which may influence expert opinion. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Data from the FA Clinical Outcome Measures (FA-COMS) registry found 7.5% (58/774) of all individuals still ambulating (with and without spasm/cramps) were taking baclofen and 5.8% (45/774) were taking gabapentin. In individuals no longer ambulating, 32.2% (183/568) were taking baclofen and 14.4% (82/568) were taking gabapentin. Benzodiazepines were taken by 7.5% (58/774) of all ambulant individuals with FRDA (with and without spasm/cramps) and 14.3% (81/568) of all non-ambulant individuals. Cyclobenzaprine was taken by 1.0% (8/774) ambulant and 2.5% (14/568) non-ambulant individuals. Tizanidine and Clonidine were taken by 1.2% (9/774) and 0.5% (4/777) ambulant individuals and 5.1% (29/568) and 0.7% (4/568) non-ambulant individuals, respectively. For medications with multiple indications, the data did not discern the primary reason for prescription. | 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).<br><br>1/5 indicated systemic pharmacotherapy was probably reasonable, 2/5 indicated reasonable, 1/5 indicated varied/sometimes reasonable, 1/5 indicated they didn't know if reasonable. (Aug 2020). |

| | | |
|---|---|---|
| | https://clinicaltrials.gov/ct2/show/NCT03090789 | |

## 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 offering systemic pharmacotherapy (baclofen, tizanidine, gabapentin, dantrolene sodium, benzodiazepines, other) for the management of generalized spasticity and spasms in individuals with Friedreich ataxia, with a view to reducing the severity of spasticity and the frequency of spasms and cramps, which may improve mobility and upper limb function and reduce pain.

## Justification

The studies on systematic pharmacological treatment for spasticity and spasm in Friedreich ataxia are small and only oral or intrathecal baclofen has been studied. Most evidence is derived from studies of spasticity in multiple sclerosis which show evidence of efficacy, although with varying quality of evidence. However, clinical expert observations in clinical practice suggests this can be a beneficial approach in Friedreich ataxia.

## Subgroup considerations

This recommendation is for individuals with Friedreich ataxia with spasticity and spasms/cramps.

## Research priorities

There is a need to evaluate in greater detail and with high quality studies the effectiveness and side effects of systemic pharmacotherapy versus no intervention, as well as the relative benefits and side effects of different agents, in treating spasticity and spasms in Friedreich ataxia to determine the most effective and best tolerated treatments.