Clinical Management Guidelines for Friedreich Ataxia

Chapter 8. Pain in Friedreich ataxia

Contents

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Funding

The authors of this document gratefully acknowledge the support of the Friedreich Ataxia Research Alliance (**FARA)**. The views and opinions expressed in the Guidelines are solely those of the authors and do not necessarily reflect the official policy or position of FARA.

8. Pain in Friedreich ataxia

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This chapter describes the effects of Friedreich ataxia on pain, the functional consequences of these effects, and strategies for managing pain related to neuropathy as well as non-neuropathic pain. In making recommendations for management of pain, the authors were tasked with answering the following questions:

For individuals with Friedreich ataxia, what management strategies could be implemented for neuropathy-related pain? (see 8.2)

For individuals with Friedreich ataxia, what management strategies could be implemented for pain other than that related to neuropathy? (see 8.3)

8.1 Overview of pain in Friedreich ataxia

The authors acknowledge Kelly Sullivan for the use of some content from the previous version of the guidelines (2014).

Individuals with Friedreich ataxia (FRDA) can experience pain from a variety of disease-related symptoms including neuropathy, spasms, and cardiac and orthopedic issues. When measured using a validated scale, pain has a significant impact on the quality of life of people with FRDA (1).

There are no systematic evaluations of the prevalence, severity or management of pain associated with FRDA and few case reports. Often, pain relief is achieved through treatment of the underlying cause; for example, treatment of orthopedic issues or muscle spasms. Cardiomyopathy is common in people with FRDA and chest pain can occur due to abnormal coronary vasculature (2). Chest pain as the first symptom of FRDA has also been reported in a 9-year-old child diagnosed with FRDA six years later (3). Spasticity can contribute to pain in individuals with FRDA. Even without clinical signs of spasticity, one individual was reported to have frequent painful extensor and flexor spasms that severely interfered with quality of life (4). These spasms persisted despite oral baclofen treatment but responded to intrathecal baclofen. Two other more recent case studies suggest Intrathecal baclofen may be of benefit to individuals with painful spasms (5, 6).

See Chapter 4 for further details on cardiac issues.

See Chapter 3.4 for further details on treatment of pain related to spasticity.

8.2 Pain related to neuropathy

The authors acknowledge Marios Hadjivassiliou for the use of some content from the previous version of the guidelines (2014).

8.2.1 Neuropathy in Friedreich ataxia

Peripheral neuropathy occurs in FRDA due to dysfunction in the central somatosensory pathways and dorsal root ganglia (7, 8). The exact incidence and prevalence of painful peripheral neuropathy in FRDA is unknown, but treatment of neuropathy-related pain appears to be an unmet need. In 2020, the Friedreich's Ataxia Clinical Management Guideline Patient and Parent Advisory Panel was interviewed on the consequences, urgency and priority of neuropathic pain, among other disease symptoms. More than half the respondents thought that painful neuropathy in FRDA was, or

probably was a serious issue in this population, and many respondents thought that treatment of painful neuropathy in FRDA was a 'priority'.

8.2.2 Management of painful neuropathy

There is a lack of studies regarding treatment of painful peripheral neuropathy in FRDA. However, there is considerable published research related to the treatment of neuropathic pain in other conditions, including diabetic peripheral neuropathy, chemotherapy-induced peripheral neuropathy, and HIV-related neuropathy (9). Clinical guidelines based on randomized controlled trials (RCTs) in these conditions recommend several medications that could be considered to treat neuropathy related to FRDA, including pregabalin, venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids, and topical lidocaine and capsaicin (9). The use of these agents must be balanced against potential untoward side effects. Like all other aspects of FRDA, the neuropathy is best managed by a suitably trained health care professional who is familiar with the condition and the management of peripheral neuropathy (8).

Absence of distal sensation may make the individual more prone to the development of foot trauma leading to ulceration. The most common mechanism of injury is unperceived, excessive and repetitive pressure on plantar bony prominences. Foot deformities, which are very common in FRDA (10), may contribute to increased focal pressure, making ulceration more likely. Meticulous foot care is important and the input of a podiatrist may be required. This is even more important in those patients with FRDA who also have diabetes mellitus.

Neuropathic pain due to sensory neuropathy may be a significant feature in FRDA that can be treated in the same way as neuropathic pain due to any other cause. This includes the use of several antiepileptic drugs, such as gabapentin, pregabalin, and lamotrigine; tricyclic anti-depressant medication, such as amitriptyline; and the serotonin re-uptake inhibitor duloxetine (9, 11, 12)

Reduced mobility and weakness as well as the presence of a sensory neuropathy make FRDA patients more susceptible to focal neuropathies. If such mononeuropathies are clinically suspected, a neurophysiological assessment can help to confirm the diagnosis. If bothersome to the patient, such entrapment neuropathies can be alleviated by review of activities of daily living and wheelchair positioning, splinting or surgical release.

See Chapters 3.2 and 3.3 for further details on mobility issues.

See Chapter 9 for further details on surgical treatments.

Best practice statements

Neuropathic pain may be treated with gabapentin, pregabalin, lamotrigine, amitriptyline or duloxetine.
A detailed sensory assessment and examination by a clinician familiar with the peripheral neuropathy related to Friedreich ataxia will establish the extent of neuropathy.
Protective foot care is important.
Preventative measures such as review of daily activities, transfers and wheelchair positioning may reduce the incidence of focal neuropathies.

Recommendations

Grading for strength of recommendation and level of evidence

For the rating of the **strength** of the recommendation, in addition to evidence from studies in FRDA, evidence from like conditions, clinical experience and expert consensus are taken into account when published evidence is not available.

The **level of evidence** is based on published evidence from studies in FRDA. If there is no published evidence in FRDA, evidence from other like conditions or clinical expertise may have been used to make the recommendation – this is graded as 'very low' or in some cases 'low' level evidence. See the table below for an explanation of the symbols used to grade recommendations.

Strength of recommendation	Symbol	Level of evidence	Symbol
Strong for intervention	↑↑	High	⊕⊕⊕⊕
Conditional for intervention	↑	Moderate	⊕⊕⊕◯
Neither intervention nor comparison	—	Low	⊕⊕◯◯
Conditional against intervention	↓	Very low	⊕◯◯◯
Strong against intervention	↓↓		

Oral medication

Should oral medication versus none be used for painful neuropathy patients with Friedreich ataxia?	**Strength**	**Level of evidence**
We suggest the use of oral medication over no medication in individuals with Friedreich ataxia who have painful neuropathy.	↑	⊕⊕◯◯
Justification: There is good research on the treatment of neuropathic pain in other conditions, such as diabetic peripheral neuropathy, peripheral neuropathy from chemotherapy, and HIV-related neuropathy (9). Clinical guidelines based on randomized controlled trials (RCTs) in the above-mentioned conditions recommend medications that might help painful neuropathy, including pregabalin, venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids, and topical lidocaine and capsaicin (9).		
Subgroup considerations: When individuals with Friedreich ataxia and painful neuropathy are treated with medication, the risk of possible side effects that derive from other aspects of Friedreich ataxia, such as heart involvement, should be considered and monitoring for such side effects should be done.		

Oral supplements

Should oral supplements versus none be used for peripheral neuropathy patients with Friedreich ataxia?	**Strength**	**Level of evidence**
We suggest that clinicians should *not* consider the use of oral supplements to manage neuropathic pain in individuals with Friedreich ataxia.	↓	⊕◯◯◯

Justification: There is no evidence to support the use of oral supplements to manage neuropathic pain in individuals with Friedreich ataxia.
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia with peripheral neuropathy.

Topical agents

Should topical agents versus none be used for peripheral neuropathy patients with Friedreich ataxia?	**Strength**	**Level of evidence**
We suggest the use of topical agents over no treatment in the management of neuropathic pain in Friedreich ataxia.	↑	⊕◯◯◯
Justification: There is no evidence to support the use of topical agents in Friedreich ataxia; however, some studies in neuropathic pain related to other conditions indicate, on balance, small beneficial effects versus side effects (9). The cardiovascular and renal risk from nonsteroidal anti-inflammatory drugs, and issues with opioids, have resulted in increasing demand and attention to non-systemic topical alternatives. In the light of the necessity of treatment, topical treatments (such as lidocaine) may be used by individuals with Friedreich ataxia despite of lack of direct evidence.		
Subgroup considerations: Individuals with Friedreich ataxia with painful neuropathy may benefit from topical agents; however, based on clinical judgement, most of these patients would be managed with oral medicines instead. Topical agents might not be appropriate for patients with skin problems. On the other hand, topical agents might be useful in those who can't tolerate oral medication.		

Lay summary

Lay summary of clinical recommendations for neuropathic pain in Friedreich ataxia

Peripheral neuropathy occurs in Friedreich ataxia due to damage in sensory pathways and nerves. It is not known how many individuals with Friedreich ataxia experience painful peripheral neuropathy, but treatment of pain related to neuropathy appears to be an unmet need, as indicated by patients and parents. The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel was interviewed on the consequences, urgency and priority of neuropathic pain, among other disease symptoms in 2020. More than half the respondents thought that painful neuropathy in Friedreich ataxia was, or probably was a serious issue in this population, and many respondents thought that treatment of painful neuropathy in Friedreich ataxia was a priority.

Why these recommendations?

There is a lack of studies about treatment of painful peripheral neuropathy in Friedreich ataxia. However, there is good research about treatment of neuropathic pain in other conditions, including diabetic peripheral neuropathy, peripheral neuropathy from chemotherapy, and HIV-related neuropathy. Clinical guidelines from randomized controlled trials (RCTs) in these conditions recommend that several medications might help painful neuropathy, including pregabalin, venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids, and topical (applied to the skin) lidocaine and capsaicin. The use of these medicines must be balanced against potential side effects, and this should be discussed with your healthcare provider.

It is important that your healthcare provider takes a detailed history and carries out a clinical examination if you experience pain and numbness in the lower part of your limbs, particularly to

rule out other causes of painful limbs or numbness that could be confused with painful neuropathy, such as a vascular condition, a metabolic condition, or an injury. It is important that you let your healthcare provider know how long you have experienced a painful neuropathy and if it affects your quality of life, such as sleeping or walking.

Peripheral neuropathy can be a consequence of Friedreich ataxia. However, there is as yet no published research or specific guidelines to help people with Friedreich ataxia manage painful peripheral neuropathy.

We suggest that you and your medical team explore management strategies to reduce painful neuropathy if it affects your quality of life.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It is important for you to speak with your Friedreich ataxia healthcare provider if you are experiencing painful neuropathy that adversely affects your quality of life.

Who is this recommendation specifically for?

People with Friedreich ataxia who are experiencing painful peripheral neuropathy.

8.3 Pain not related to neuropathy

8.3.1 Non-neuropathic pain in Friedreich ataxia

There is little published data about non-neuropathic pain in FRDA, and the prevalence of non-neuropathic pain in FRDA patients is unknown. Individuals with FRDA appear to suffer from pain, as indicated by symptom-specific scales (1, 13, 14). Specifically, non-neuropathic pain may originate from spasticity, cramping, musculoskeletal and orthopedic issues, scoliosis, injury, and chest pain due to cardiac dysfunction. Osteoarticular problems with associated inflammation may also contribute to non-neuropathic pain.

8.3.2 Management of non-neuropathic pain

The effect of non-neuropathic pain on individuals with FRDA appears to be under recognized and underreported. There is currently no cure for FRDA, and treatment remains symptomatic. Pain relief in neurological diseases may be accomplished by pharmacological therapy, focal injections of botulinum toxin for musculoskeletal issues, nerve blocks, physical therapy, spinal stimulators, and surgery for orthopedic issues. The efficacy of these treatments has not been reported extensively in rigorous studies.

Despite this, and as with neuropathic pain, non-neuropathic pain that interferes with a person's quality of life should be addressed and alleviated. Each treatment, from pharmacological to invasive, should be weighed according to risks and benefits. Caution should be exercised when using agents with potential cardiac side effects in the FRDA population. Although the recommendations for pain treatment in FRDA are cautious, this is due to a paucity of data rather than evidence that interventions are not efficacious. More research is needed to examine the role of pain in FRDA and the efficacy of various treatments.

Recommendations

Oral medications

Should oral medications versus none be used for pain with Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend the use of oral medication over no medication to manage pain in individuals with Friedreich ataxia.	↑	⊕◯◯◯
Justification: Despite there being no published evidence directly related to the use of medication for pain management in Friedreich ataxia, the expert authors agree that the negative effects of pain on quality of life, mobility and participation in daily activities support proactive management of pain by medication. Consideration needs to be given to side-effects of pain medication that may exacerbate existing issues, such as reduced balance, poor mobility, falls risk and increased fatigue, and people with Friedreich ataxia taking medication should be monitored for possible adverse effects.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia who report pain.		

Physical therapy

Should physical therapy versus no intervention or versus medications be used for musculoskeletal pain with Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend the use of physical therapy in the first instance, over no physical therapy or medication to manage pain in individuals with Friedreich ataxia. If physical therapy is not effective, as per the previous recommendation we conditionally recommend the use of oral medication over no medication.	↑	⊕◯◯◯
Justification: Despite there being no published evidence directly related to the use of physical therapy for pain management in Friedreich ataxia, the expert authors agree that the negative effects of pain on quality of life, mobility and participation in daily activities support proactive management of pain by physical therapy. Clinical experience in both individuals with and without Friedreich ataxia suggests that physical therapy is a low-risk intervention that may be effective and might limit the reliance on medication.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia who report pain. Some individuals may have significant limitations to the type and extent of physical therapy they can do due to their neurological and possibly cardiac disease manifestations.		

Focal injection

Should focal injections (e.g., spine or joint injection or nerve block) versus medication be used for pain with Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend that injections for musculoskeletal pain can be tried in individuals with Friedreich ataxia when medications are not tolerated or are insufficiently effective.	↑	⊕◯◯◯
Justification: Clinical experience in other populations suggests that injections can be used for treatment of musculoskeletal pain that is poorly responsive to medications, with variable effectiveness. There is no reason to believe that individuals with Friedreich ataxia would respond substantially differently to other people.		

Subgroup considerations: This recommendation is for individuals with Friedreich ataxia with severe pain that is not alleviated by other treatments.

Implanted devices

Should implanted devices (spinal stimulator or pain pump) versus oral medication be used for pain with Friedreich ataxia?	**Strength**	**Level of evidence**
We cannot recommend the use of implanted devices (spinal stimulator or pain pump) over oral medication for pain in individuals with Friedreich ataxia. Clinicians may consider implanted devices in individuals with severe symptoms in whom less invasive treatments have proven insufficiently effective.	—	⊕◯◯◯
Justification: There are only three reported case studies to guide the suitability of implanted devices for pain control in individuals with Friedreich ataxia (4-6). Based on other patient populations, adverse events can be severe. In summary, even though the problem of pain is considered to be important and the case studies reported improvement in pain after intervention with implanted devices, more evidence is needed on acceptability and efficacy of implanted devices before they could be recommended as a treatment.		
Subgroup considerations: An implanted device should only be considered for individuals with Friedreich ataxia experiencing severe pain that has not been helped with other treatments.		

Lay summary

Lay summary of clinical recommendations for pain not related to neuropathy in Friedreich ataxia

Why these recommendations?

Individuals with Friedreich ataxia may experience pain that is not related to neuropathy. This may be due to causes such as pain from spasticity, cramping, musculoskeletal and orthopedic issues, scoliosis, injury, and chest pain due to heart problems. In addition, bone and joint problems with associated inflammation may cause pain. However, there is little published research on either the proportion of people with Friedreich ataxia who experience pain, or the cause of pain in these individuals.

The following points summarize the best ways to manage pain in individuals with Friedreich ataxia that is not due to neuropathy.

- Some oral medications may be used rather than no medication for non-neuropathic pain with Friedreich ataxia.
- Physical therapy may assist in treating pain in Friedreich ataxia. However, there is no evidence as to whether physical therapy is more effective than medication for musculoskeletal pain with Friedreich ataxia.
- There is no evidence to show whether focal injections (e.g., spine or joint injection or nerve block) or implanted devices (spinal stimulator or pain pump) are more effective than medication to treat pain with Friedreich ataxia.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It is important for you to speak with your Friedreich ataxia healthcare provider if you are experiencing pain of any type that negatively affects your quality of life.

Who is this recommendation specifically for?

People with Friedreich ataxia who are experiencing pain from any cause other than peripheral neuropathy.

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References

1. Perez-Flores J, Hernandez-Torres A, Monton F, Nieto A. Health-related quality of life and depressive symptoms in Friedreich ataxia. Qual Life Res. 2020;29(2):413-20.
2. Giugliano GR, Sethi PS. Friedreich's ataxia as a cause of premature coronary artery disease. Tex Heart Inst J. 2007;34(2):214-7.
3. Ferres-Sanchez P, Subirana-Domenech M, Torner-Soler M. Chest pain during exercise as first manifestation of Friedreich's ataxia. Br Heart J. 1995;74(4):464-7.
4. Ben Smail D, Jacq C, Denys P, Bussel B. Intrathecal baclofen in the treatment of painful, disabling spasms in Friedreich's ataxia. Mov Disord. 2005;20(6):758-9.
5. Berntsson SG, Gauffin H, Melberg A, Holtz A, Landtblom AM. Inherited ataxia and intrathecal baclofen for the treatment of spasticity and painful spasms. Stereotact Funct Neurosurg. 2019;97(1):18-23.
6. Kalyvas AV, Drosos E, Korfias S, Gatzonis S, Themistocleous M, Sakas DE. Intrathecal baclofen therapy for painful muscle spasms in a patient with Friedreich's ataxia. Stereotact Funct Neurosurg. 2018;96(2):127-30.
7. Koeppen AH, Mazurkiewicz JE. Friedreich ataxia: neuropathology revised. J Neuropathol Exp Neurol. 2013;72(2):78-90.
8. Lynch DR, Schadt K, Kichula E, McCormack S, Lin KY. Friedreich ataxia: Multidisciplinary clinical care. J Multidiscip Healthc. 2021;14:1645-58.
9. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17(9):1113-e88.
10. Reetz K, Dogan I, Hohenfeld C, Didszun C, Giunti P, Mariotti C, et al. Nonataxia symptoms in Friedreich Ataxia: Report from the Registry of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS). Neurology. 2018;91(10):e917-e30.

11. Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: a review. J Clin Pharmacol. 2012;52(1):6-17.
12. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162-73.
13. Epstein E, Farmer JM, Tsou A, Perlman S, Subramony SH, Gomez CM, et al. Health related quality of life measures in Friedreich Ataxia. J Neurol Sci. 2008;272(1-2):123-8.
14. Xiong E, Lynch AE, Corben LA, Delatycki MB, Subramony SH, Bushara K, et al. Health related quality of life in Friedreich Ataxia in a large heterogeneous cohort. J Neurol Sci. 2020;410:116642.