# **Clinical Management Guidelines for Friedreich Ataxia**

# Chapter 7. Fatigue in Friedreich ataxia

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# 7. Fatigue in Friedreich ataxia

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This chapter describes the effects of Friedreich ataxia on fatigue, the functional consequences of these effects, and strategies for managing fatigue. In making recommendations for management of fatigue, the authors were tasked with answering the question:

# For individuals with Friedreich ataxia, what management strategies could be implemented for fatigue?

# 7.1 The effects of Friedreich ataxia on fatigue and functional consequences

Fatigue is characterized as a lack of physical or mental energy perceived by an individual (or caregiver) that interferes with usual and desired activity. Fatigue commonly includes an overwhelming sense of tiredness, lack of energy, and feeling exhausted. Fatigue can affect individuals with Friedreich ataxia (FRDA). In fact, it has been shown that fatigue, especially its physical component, is a major and frequent manifestation in FRDA and is associated with the severity and duration of the disease (1).

Fatigue can have an adverse impact on activities of daily living, ability to work, social life, mood, sleep, physical activity and quality of life. Many psychosocial factors can influence an individual's adjustment to fatigue, including family response, coping behaviors, psychological distress, and fatigue-related disability.

# 7.2 Management of fatigue

Although many individuals with FRDA report fatigue, there is little reported evidence regarding management strategies. However, the use of behavioral management, pharmacological intervention, alternative therapies and/or a specific diet have been reported in like conditions. These interventions are reviewed below.

# 7.2.1 Behavioral management

Due to a lack of studies, there is no direct evidence showing the benefits of behavioral management in individuals with FRDA. However, the clinical experience of the authors and published research in other neurological conditions, such as multiple sclerosis and neuromuscular diseases (2-9), favors (with low-level evidence) the consideration of using behavioral management for individuals who report fatigue with FRDA. This is because the overall benefit may be greater than not using behavioral management. Behavioral interventions include mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, cognitive behavioral therapy, relaxation, and avoiding multitasking.

# 7.2.2 Physical activity

Due to a lack of studies, there is no direct evidence showing the benefits of physical activity programs in individuals with FRDA experiencing fatigue. However, the clinical experience of the authors and published research in other neurological conditions such as multiple sclerosis (10-15) favors (with moderate certainty of evidence) the consideration of physical activity programs for individuals who report fatigue with FRDA.

# 7.2.3 Pharmacological intervention

There is very low certainty of evidence demonstrating small beneficial effects of pharmacological intervention (antioxidants, antidepressants, e.g., idebenone, citalopram) for individuals with FRDA reporting fatigue.

# 7.2.4 Alternative therapies/physical modalities

Due to a lack of studies, there is no direct evidence showing the benefits of alternative therapies/ physical modalities in individuals with FRDA. There is only very limited evidence of beneficial effects from using alternative therapies/physical modalities (i.e., light therapy, cooling therapy, pulsed electromagnetic devices, acupuncture) in published research in other neurological conditions such as multiple sclerosis (16, 17). Based on current research evidence no recommendation for alternative therapies/physical modalities can be made for individuals with FRDA reporting fatigue.

# 7.2.5 Specific diet

Due to a lack of studies, there is no direct evidence showing the benefits of a specific diet (i.e., vitamins, coffee, Mediterranean, ketogenic) in individuals with FRDA. There is only very low-level evidence of beneficial effects of applying a specific diet in published research in other neurological conditions such as multiple sclerosis (18-20). Therefore, no recommendation for a specific diet can be made at this time.

# Best practice statement

Sometimes it may be difficult for individuals with Friedreich ataxia to identify if they suffer from fatigue. In this case, they should be offered a detailed assessment of fatigue including administration of a standardized assessment such as the Modified Fatigue Impact Scale (21) and enquiry about the impact of fatigue on the capacity to participate in daily activities.

# 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             | $\uparrow\uparrow$ | High              | $\oplus \oplus \oplus \oplus$   |
| Conditional for intervention        | $\uparrow$         | Moderate          | $\oplus \oplus \oplus \bigcirc$ |
| Neither intervention nor comparison | _                  | Low               | $\Theta \Theta \odot \odot$     |

| Conditional against intervention | $\downarrow$            | Very low | 000 |
|----------------------------------|-------------------------|----------|-----|
| Strong against intervention      | $\checkmark \checkmark$ |          |     |

# **Behavioral management**

| Should behavioral management (mindfulness, energy conservation, use<br>of assistive devices, sleep hygiene, stress reduction, CBT, relaxation,<br>avoiding multitasking) versus no behavioral management be used for all<br>individuals who report fatigue with Friedreich ataxia? | Strength | Level of<br>evidence* |
|--|----------|-----------------------|
| We suggest behavioral management (mindfulness, energy conservation,<br>use of assistive devices, sleep hygiene, stress reduction, cognitive<br>behavioral therapy, relaxation, avoiding multitasking) may assist in<br>managing fatigue in individuals with Friedreich ataxia.     | 1        | ⊕⊕⊖⊖                  |
| Justification: There is low-level evidence indicating benefits in other diseases with similar characteristics to Friedreich ataxia.  |          |                       |
| <b>Subgroup considerations:</b> This recommendation is for individuals with Friedreich ataxia who report fatigue.  |          |                       |

#### **Physical activity**

| Should physical activity program (exercise such as aerobic exercise,<br>strengthening exercise, yoga, tai chi, dancing) versus no activity program<br>be used for all individuals who report fatigue with Friedreich ataxia?  | Strength  | Level of<br>evidence*                                 |
|---|---|---|
| We suggest a physical activity program be used to manage fatigue in individuals with Friedreich ataxia.   | 1   | ⊕⊕⊕⊖  |
| <b>Justification:</b> Most of the evidence reviewed for this recommendation was based on studies in multiple sclerosis. These studies indicate a favorable effect of physical activity programs on fatigue. The majority of expert authors surveyed consider a physical activity program to be of benefit for managing fatigue in individuals with Friedreich ataxia. |   |   |
| <b>Subgroup considerations:</b> This recommendation is for individuals with Frie<br>no medical contraindications to participating in a physical activity program<br>other medical comorbidities/contraindications for exercise should work wi<br>team to carefully consider the risks and benefits of an exercise program be  | dreich atax<br>. Those indi<br>th their hea<br>fore decidii | ia who have<br>viduals with<br>Ithcare<br>ng to begin |

# **Pharmacological interventions**

| Should pharmacological intervention (antioxidants, antidepressants, e.g.,<br>idebenone, citalopram) versus no pharmacological intervention be used<br>for people with Friedreich ataxia?  | Strength | Level of<br>evidence* |  |
|---|----------|-----------------------|--|
| We suggest some pharmacological intervention (antioxidants,<br>antidepressants) may have value in managing fatigue related to<br>Friedreich ataxia.   | 1        | <b>@@</b> OO          |  |
| <b>Justification:</b> Based on current small studies, there is only low certainty of evidence of small desirable effects of pharmacological intervention (antioxidants, antidepressants) for individuals with Friedreich ataxia reporting fatigue; thus, only a conditional recommendation can be made. |          |                       |  |

one.

Most studies of pharmacological interventions use clinical scales such as the ICARS/mFARS/SARA as outcome measures. Expert authors do not consider these scales to be sensitive enough to capture the extent and impact of fatigue. Indeed, in as yet unpublished evidence, one expert author found several patients reported that when they started using a wheelchair or a walker, their fatigue actually improved. So, although their ataxia severity score was likely to have got worse (reflected by moving to a wheelchair), their fatigue improved. Also, there is a lot of day to day fluctuation in fatigue, whereas there is unlikely to be comparable daily fluctuation in the ataxia severity score.

**Subgroup considerations:** This recommendation is for individuals with Friedreich ataxia who report fatigue.

#### Alternative therapies/physical modalities

| Should alternative therapies/physical modalities (i.e., light therapy, cooling therapy, pulsed electromagnetic devices, acupuncture) versus no alternative therapies/physical modalities be used for all individuals who report fatigue with Friedreich ataxia?                          | Strength | Level of<br>evidence* |
|--|----------|-----------------------|
| We cannot recommend either alternative therapies/physical modalities<br>(i.e., light therapy, cooling therapy, pulsed electromagnetic devices,<br>acupuncture) or no alternative therapies/physical modalities be used for<br>all individuals who report fatigue with Friedreich ataxia. | _        | 000                   |
| <b>Justification:</b> There is little evidence supporting the benefits of alternative therapies on fatigue in Friedreich ataxia. Undesirable effects are unclear; hence, we cannot make a recommendation either way.   |          |                       |
| <b>Subgroup considerations:</b> This recommendation is for individuals with Friedreich ataxia who report fatigue.  |          |                       |

# **Specific diet**

| Should a specific diet (i.e., vitamins, coffee, Mediterranean, ketogenic) versus usual diet be used for all individuals who report fatigue with Friedreich ataxia?         | Strength | Level of<br>evidence* |  |
|--|----------|-----------------------|--|
| We cannot recommend any specific diet over usual diet to assist in managing fatigue in individuals with Friedreich ataxia.   | —        | 0000                  |  |
| <b>Justification:</b> There is insufficient evidence and clinical experience to support the use of specific diets to manage fatigue in individuals with Friedreich ataxia. |          |                       |  |
| Subgroup considerations: This recommendation is for individuals with Friedreich ataxia who   |          |                       |  |

report fatigue.

# Lay summary

#### Lay summary of clinical recommendations for fatigue in Friedreich ataxia

Individuals with Friedreich ataxia often experience fatigue, which can have widespread effects on many domains of a person's life. Fatigue can hamper participating in leisure, society, employment, physical activity and daily activities.

#### Why these recommendations?

There is a range of strategies that have been suggested as being helpful in managing fatigue, but due to a lack of studies in people with Friedreich ataxia, it is not yet known which strategies give the most benefit.

#### Behavioral management

Behavioral management techniques to manage fatigue include mindfulness, energy conservation, use of assistive devices, sleep hygiene, stress reduction, cognitive behavioural therapy (CBT), relaxation, and avoiding multitasking. While there is little published evidence that these techniques help to treat fatigue in individuals with Friedreich ataxia, the clinical experience of the authors and published research in other neurological conditions, such as multiple sclerosis and neuromuscular diseases, suggest the use of behavioural management techniques may also give individuals with Friedreich ataxia some relief from fatigue.

#### Physical activity

Due to a lack of studies, there is no direct evidence showing the benefits of physical activity programs in individuals with Friedreich ataxia experiencing fatigue. However, the clinical experience of the authors and published research in other neurological conditions, such as multiple sclerosis, suggests that physical activity programs for individuals with Friedreich ataxia who report fatigue could be considered.

# Medication

Due to the small and diverse nature of current research studies, there is only low-level evidence that medicines (antioxidants, antidepressants) may be of small benefit for managing fatigue in individuals with Friedreich ataxia.

# Alternative therapies/physical modalities

Alternative therapies/physical modalities (light therapy, cooling therapy, pulsed electromagnetic devices, acupuncture) have been suggested as helpful for managing fatigue, but no studies have been done in individuals with Friedreich ataxia. There is some low-level evidence that these techniques may be of benefit in other neurological conditions such as multiple sclerosis. Based on current research, we cannot recommend the use of alternative therapies/physical modalities for individuals with Friedreich ataxia experiencing fatigue.

#### Specific diet

It has been suggested that specific diets (including vitamins, coffee, Mediterranean, ketogenic) may be helpful for fatigue. This has not been studied in individuals with Friedreich ataxia. There is some low-level evidence showing some benefit from specific diets in other neurological conditions such as multiple sclerosis. Based on current research, we cannot recommend specific diets for individuals with Friedreich ataxia experiencing fatigue.

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

If you are suffering from fatigue, which is frequent in patients with Friedreich ataxia, it might be important for you to talk to your allied health care provider and doctor to see if behavioural management, physical activity or in some cases, medicines may be appropriate for you.

## Who are these recommendations specifically for?

These recommendations are relevant to all individuals with Friedreich ataxia experiencing fatigue.

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# References

- 1. da Silva CB, Chevis CF, D'Abreu A, Lopes-Cendes I, Franca MC, Jr. Fatigue is frequent and multifactorial in Friedreich's ataxia. Parkinsonism Relat Disord. 2013;19(8):766-7.
- Bogosian A, Chadwick P, Windgassen S, Norton S, McCrone P, Mosweu I, et al. Distress improves after mindfulness training for progressive MS: A pilot randomised trial. Mult Scler. 2015;21(9):1184-94.
- Cavalera C, Rovaris M, Mendozzi L, Pugnetti L, Garegnani M, Castelnuovo G, et al. Online meditation training for people with multiple sclerosis: A randomized controlled trial. Mult Scler. 2019;25(4):610-7.
- 4. Hoogerwerf AEW, Bol Y, Lobbestael J, Hupperts R, van Heugten CM. Mindfulness-based cognitive therapy for severely fatigued multiple sclerosis patients: A waiting list controlled study. J Rehabil Med. 2017;49(6):497-504.
- Levin AB, Hadgkiss EJ, Weiland TJ, Marck CH, van der Meer DM, Pereira NG, et al. Can meditation influence quality of life, depression, and disease outcome in multiple sclerosis? Findings from a large international web-based study. Behav Neurol. 2014;2014:916519.
- Okkersen K, Jimenez-Moreno C, Wenninger S, Daidj F, Glennon J, Cumming S, et al. Cognitive behavioural therapy with optional graded exercise therapy in patients with severe fatigue with myotonic dystrophy type 1: a multicentre, single-blind, randomised trial. Lancet Neurol. 2018;17(8):671-80.
- 7. Pilutti LA, Dlugonski D, Sandroff BM, Klaren R, Motl RW. Randomized controlled trial of a behavioral intervention targeting symptoms and physical activity in multiple sclerosis. Mult Scler. 2014;20(5):594-601.
- 8. van den Akker LE, Beckerman H, Collette EH, Knoop H, Bleijenberg G, Twisk JW, et al. Cognitive behavioural therapy for MS-related fatigue explained: A longitudinal mediation analysis. J Psychosom Res. 2018;106:13-24.

- 9. Veenhuizen Y, Cup EHC, Jonker MA, Voet NBM, van Keulen BJ, Maas DM, et al. Selfmanagement program improves participation in patients with neuromuscular disease: A randomized controlled trial. Neurology. 2019;93(18):e1720-e31.
- 10. Bulguroglu I, Guclu-Gunduz A, Yazici G, Ozkul C, Irkec C, Nazliel B, et al. The effects of mat pilates and reformer pilates in patients with multiple sclerosis: A randomized controlled study. NeuroRehabilitation. 2017;41(2):413-22.
- Burschka JM, Keune PM, Oy UH, Oschmann P, Kuhn P. Mindfulness-based interventions in multiple sclerosis: beneficial effects of Tai Chi on balance, coordination, fatigue and depression. BMC Neurol. 2014;14:165.
- 12. Carter A, Daley A, Humphreys L, Snowdon N, Woodroofe N, Petty J, et al. Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes in people with multiple sclerosis: a randomised controlled trial. Mult Scler. 2014;20(8):1112-22.
- 13. Hasanpour Dehkordi A. Influence of yoga and aerobics exercise on fatigue, pain and psychosocial status in patients with multiple sclerosis: a randomized trial. J Sports Med Phys Fitness. 2016;56(11):1417-22.
- 14. Sangelaji B, Nabavi SM, Estebsari F, Banshi MR, Rashidian H, Jamshidi E, et al. Effect of combination exercise therapy on walking distance, postural balance, fatigue and quality of life in multiple sclerosis patients: a clinical trial study. Iran Red Crescent Med J. 2014;16(6):e17173.
- 15. Gervasoni E, Cattaneo D, Bertoni R, Grosso C, Bisio A, Rovaris M, et al. Effect of arm cycling and task-oriented exercises on fatigue and upper limb performance in multiple sclerosis: a randomized crossover study. Int J Rehabil Res. 2019;42(4):300-8.
- 16. Gonzales B, Chopard G, Charry B, Berger E, Tripard J, Magnin E, et al. Effects of a training program involving body cooling on physical and cognitive capacities and quality of life in multiple sclerosis patients: A pilot study. Eur Neurol. 2017;78(1-2):71-7.
- 17. Miller E, Kostka J, Wlodarczyk T, Dugue B. Whole-body cryostimulation (cryotherapy) provides benefits for fatigue and functional status in multiple sclerosis patients. A case-control study. Acta Neurol Scand. 2016;134(6):420-6.
- Bitarafan S, Harirchian MH, Nafissi S, Sahraian MA, Togha M, Siassi F, et al. Dietary intake of nutrients and its correlation with fatigue in multiple sclerosis patients. Iran J Neurol. 2014;13(1):28-32.
- 19. Coe S, Axelsson E, Murphy V, Santos M, Collett J, Clegg M, et al. Flavonoid rich dark cocoa may improve fatigue in people with multiple sclerosis, yet has no effect on glycaemic response: An exploratory trial. Clin Nutr ESPEN. 2017;21:20-5.
- 20. Katz Sand I, Benn EKT, Fabian M, Fitzgerald KC, Digga E, Deshpande R, et al. Randomizedcontrolled trial of a modified Mediterranean dietary program for multiple sclerosis: A pilot study. Mult Scler Relat Disord. 2019;36:101403.
- 21. Larson RD. Psychometric properties of the modified fatigue impact scale. Int J MS Care. 2013;15(1):15-20.