

QUESTION

Should iron supplementation vs. no supplementation be used for patients with RLS symptoms and serum ferritin <50mcg.ml with Friedreich ataxia?

POPULATION:	patients with RLS symptoms and serum ferritin <50mcg.ml with Friedreich ataxia
INTERVENTION:	iron supplementation
COMPARISON:	no supplementation
MAIN OUTCOMES:	Impact on sleep quality/ arousal; Impact on sleep quantity/ sleep benefit; Impact on behaviour, cognition, mood; Degree of pain vs discomfort;

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 (Lynch, 2017) found:</p> <p>44.8% (312/696) of adults and 34.9% (110/315) of children reported restless legs; 75.0% (522/696) of adults and 55.6% (175/315) of children reported leg spasms. By comparison, restless legs affect between 4% and 14% of the general population (Ohayon et al, 2012).</p> <p>For individuals who reported sleep disturbance:</p> <p>Restless legs were present in 46.3% (229/495) of adults and 32.9% (53/161) of children, and leg cramps in 58.6% (290/495) adults and 44.7% (72/161) of children (Lynch, 2017).</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of restless legs.</p> <p>2/7 indicated that the problem was serious, 4/7 indicated probably serious, 1/7 indicated probably not serious.</p> <p>2/7 indicated that the problem was urgent, 4/7 indicated probably urgent, 1/7 indicated probably not urgent.</p> <p>3/7 indicated that the problem was a priority, 3/7 indicated probably a priority, 1/7 indicated probably not a 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 checked="" type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 30 October. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know 	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 30 October. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	

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>No published evidence.</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;"> <thead> <tr> <th style="width: 50%;">Outcomes</th> <th style="width: 20%;">Importance</th> <th style="width: 30%;">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Impact on sleep quality/ arousal - not measured</td> <td>IMPORTANT^a</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Impact on sleep quantity/ sleep benefit - not measured</td> <td>IMPORTANT^a</td> <td style="text-align: center;">-</td> </tr> </tbody> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)	Impact on sleep quality/ arousal - not measured	IMPORTANT ^a	-	Impact on sleep quantity/ sleep benefit - not measured	IMPORTANT ^a	-	
Outcomes	Importance	Certainty of the evidence (GRADE)									
Impact on sleep quality/ arousal - not measured	IMPORTANT ^a	-									
Impact on sleep quantity/ sleep benefit - not measured	IMPORTANT ^a	-									

	Impact on behaviour, cognition, mood - not measured	IMPORTANT ^a	-
	Degree of pain vs discomfort - not measured	CRITICAL ^b	-
<p>a. Identified as critical (1/6), important (4/6) and low importance (1/6) by people with FA and important by expert authors on this topic</p> <p>b. 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</p>			

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>No published evidence.</p>	<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 iron supplementation for people with Friedreich ataxia with Restless Leg Syndrome and ferritin <50 mg/dl.</p> <p>Reflecting on the impact of on Impact on sleep quality/arousal, 33.34% (8/24) clinical experts reported a benefit (large, moderate or small), 0% (0/24) reported no effect and, 4.17% (1/24) reported observing a harm (large, moderate or small). 15 clinicians could not provide any information on this outcome. Reflecting on the impact on sleep quantity/sleep benefit, 33.34% (8/24) clinical experts reported a benefit, 0% (0/24) reported no effect and, 4.17% (1/24) reported observing a harm. 15 expert clinicians could not provide any information on this outcome. Reflecting on the impact on behaviour, cognition, mood, 25% (6/24) clinical experts reported a benefit, 8.33% (2/24) reported no effect and, 4.17% (1/24) reported observing a harm. 15 expert clinicians could not provide any information on this outcome. Reflecting on the impact on Degree of pain versus discomfort, 25% (6/24) clinical experts reported a benefit, 8.33% (2/24) reported no effect and, 4.17% (1/24) reported observing a harm. 15 expert clinicians could not provide any information on this outcome.</p>

Acceptability

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	No published evidence.	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using iron supplementation in people with restless legs syndrome was acceptable (weighing up the balance between benefits, harms and costs).</p> <p>3/3 indicated more information on the benefits and potential harms was required. (Aug 2020).</p>

SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	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 <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input checked="" type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
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CONCLUSIONS

Recommendation

We suggest iron supplementation could be trialed for treatment of RLS in individuals with Friedreich ataxia and serum ferritin <50 mcg/ml, but only if other treatments have been tried and are not effective. Clinicians should only consider a trial of iron supplements if serum ferritin is <50 mcg/ml and no acute or chronic inflammation is present, with close monitoring and a review to assess any adverse effects on ataxia after 3 to 6 months.

If an individual has RLS and serum ferritin >75 mcg/ml, they should not be given iron supplements.

Justification

RLS is a significant problem affecting 44.8% of adults with FRDA. Internationally, the recommendation for the treatment of RLS in the general population is to give iron supplements if ferritin is below 50-75 mcg/ml. However, in FRDA, the pathophysiology of iron is not clear with iron overload in the mitochondria of cells and iron deficiency in the cytoplasm. Although there is currently no strong evidence, it is thought that iron supplementation may make ataxia worse. Therefore, we recommend that alternative treatments be given before iron is used to treat RLS.

There have been no RCTs of iron supplementation to treat RLS in those with FRDA. A survey on iron supplementation in RLS from expert clinicians involved in the care of those with FRDA could not reach a consensus on this question. From the survey of 24 clinicians, 15 could not provide any information, one reported that iron did harm and six reported a small benefit. Therefore, the benefits of iron supplementation in the case of true iron deficiency with symptoms need to be considered against the side effects of iron supplementation. Due to the possibility of pathophysiological iron overload in the mitochondria in FRDA, excess iron should be avoided.

As RLS can interfere with the quality of sleep, it is an important symptom and effective treatment is desirable. However, the theoretical possibility of making ataxia worse in people with FRDA is an important consideration.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia with symptoms of RLS. Restless legs are more common in those who have sleep disturbances.

Implementation considerations

Not relevant

Research priorities

Further research in this area is needed. An RCT using iron supplementation in those with FRDA and serum ferritin < 50 mcg/ml would be very useful to guide clinical recommendations for treatment of RLS.

References

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

Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. *Sleep Med Rev.* 2012;16(4):283-95.