QUESTION

Should alternative therapies/physical modalities (ie: light therapy, cooling therapy, pulsed electromagnetic devices, acupuncture) vs. no alternative therapies/physical modalities (ie: light therapy, cooling therapy, pulsed electromagnetic devices, acupuncture) be used for all individuals who report fatigue with Friedreich ataxia?

POPULATION:	all individuals who report fatigue with Friedreich ataxia
INTERVENTION:	alternative therapies/physical modalities (ie: light therapy, cooling therapy, pulsed electromagnetic devices, acupuncture)
COMPARISON:	no alternative therapies/physical modalities (ie: light therapy, cooling therapy, pulsed electromagnetic devices, acupuncture)
MAIN OUTCOMES:	Reported fatigue; Reported fatigue; Reported fatigue; Improved quality of life; Improved quality of life; Improved energy levels; Improved physical capacity; Improved capacity to participate in daily tasks; Reduced falls;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Fatigue may be a rather frequent and often under recognized feature in individuals with FRDA (da Silva et al, 2013).	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of fatigue. 4/7 indicated that the problem was serious, 3/7 indicated probably serious. 3/7 indicated that the problem was urgent, 2/7 indicated probably urgent, 2/7 indicated probably not urgent. 4/7 indicated that the problem was a priority, 3/7 indicated probably a priority. (Aug 2020)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		Literature predominantly reporting use of cooling vests in MS.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact

Reported fatigue assessed with: Fatigue Severity Scale	99 (2 RCTs)[1,2]	⊕◯◯◯ Very low[a,b,c,d]	2 groups of 24 patients with multiple sclerosis, a low fatigue (LF) and a high fatigue (HF) group, were exposed to 10x3 min session of whole-body cryostimulation (WBC), 1 exposure per day. Mann–Whitney U-test was used to investigate whether there were different kinds of changes between the two groups of patients with MS. The mean delta values were calculated with confidence intervals and changes adjusted for baseline values were evaluated using covariance analysis. Improvements in the FSS were found in both groups (p<0.001). (Miller et al 2016) 75 patients with multiple sclerosis were randomised to an experimental (cooling suit treatment, n=35) or control group (n=40) for 4 weeks. The independent samples t test was used to test the study hypotheses. At both the 4th-week follow-up (p=0.000 on the Fatigue Severity Scale) and at the last measurement (p<0.000), the experimental group reported significantly less fatigue on all measures than the control group. Thus, use of the cooling blanket was associated with lower fatigue levels. (Ozkan Tuncay et al 2017).	
Reported fatigue assessed with: Multidimensional Fatigue Inventory	18 (1 RCT)[3]	⊕◯◯◯ Very low[a,b,e]	18 patients with multiple sclerosis were randomly assigned to a cooling (wearing a cooling vest during a physical training program) or control group for 7 weeks. A Mann-Whitney U test was used to compare the changes (delta values), with their Confidence Intervals (CIs), obtained in the control group versus those obtained in the cooling group before and after the training program. There were significant decreases (p < 0.05) in general fatigue scores and changes in both groups. However, a significant decrease of physical fatigue is found only in the cooling group, whereas significant changes are observed between both groups. (Gonzales et al 2017).	
Reported fatigue assessed with: Fatigue Impact	75 (1 RCT)[2]	⊕◯◯◯ Very low[a,c,f]	75 patients with multiple sclerosis were randomised to an experimental (cooling suit treatment, n=35) or control group (n=40) for 4 weeks. The independent samples t test was	

Scale			used to test the study hypotheses. At both the 4th-week follow-up (p=0.005 on the Fatigue Impact Scale General) and at the last measurement (p=0.000), the experimental group reported significantly less fatigue on all measures than the control group. Thus, use of the cooling blanket was associated with lower fatigue levels. (Ozkan Tuncay et al 2017).
Improved quality of life assessed with: Multiple Sclerosis Impact Scale	0 cases 0 controls (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d,e]	2 groups of 24 patients with multiple sclerosis, a low fatigue (LF) and a high fatigue (HF) group, were exposed to 10x3 min session of whole-body cryostimulation (WBC), 1 exposure per day. Mann–Whitney U-test was used to investigate whether there were different kinds of changes between the two groups of patients with MS. The mean delta values were calculated with confidence intervals and changes adjusted for baseline values were evaluated using covariance analysis. Improvements in the MSIS-29-PHYS and MSIS-29-PSYCH were found in both groups (p<0.001). WBC induced larger changes in the HF than in the LF group in both MSIS-29-PHYS and MSIS-29-PSYCH. (Miller et al 2016)
Improved quality of life assessed with: SEP-59	18 (1 RCT)[3]	⨁◯◯◯ Very low[a,b,e]	18 patients with multiple sclerosis were randomly assigned to a cooling (wearing a cooling vest during a physical training program) or control group for 7 weeks. A Mann-Whitney U test was used to compare the changes (delta values), with their Confidence Intervals (CIs), obtained in the control group versus those obtained in the cooling group before and after the training program. The SEP-59 indicates that the cooling group experienced significant (p < 0.05) increases in emotional well-being and cognitive function and changes between both groups are significant (p < 0.05). There is no significant difference between the 2 groups regarding other domains. (Gonzales et al 2017).
Improved energy levels - not measured	-	-	

Improved physical capacity assessed with: 6-minute walk test	18 (1 RCT)[3]	⨁◯◯◯ Very low[a,b,e]	18 patients with multiple sclerosis were randomly assigned to a cooling (wearing a cooling vest during a physical training program) or control group for 7 weeks. A Mann-Whitney U test was used to compare the changes (delta values), with their Confidence Intervals (CIs), obtained in the control group versus those obtained in the cooling group before and after the training program. Both groups show a significant increase in walking distance ($p < 0.05$; 28 ± 14 m and 61 ± 31 m in the control and cooling groups, respectively). (Gonzales et al 2017).
Improved capacity to participate in daily tasks assessed with: Modified Barthel Index	75 (1 RCT)[2]	⨁◯◯◯ Very low[a,c,f]	75 patients with multiple sclerosis were randomised to an experimental (cooling suit treatment, n=35) or control group (n=40) for 4 weeks. The independent samples t test was used to test the study hypotheses. At the 4th-week measurement, the experimental group scored significantly better on the Modified Barthel Index than the control group (p=0.034). At final follow-up, the experimental group's mean scores increased over the 4th-week measurement while the scores of the control group exhibited no change from baseline at either the 4th-week or the final measurement periods. (Ozkan Tuncay et al 2017)
Reduced falls - not measured	-	-	

1. 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 Neurologica Scandinavica; 2016.
2. Ozkan Tuncay F, Mollaoglu M. Effect of the cooling suit method applied to individuals with multiple sclerosis on fatigue and activities of daily living. Journal of Clinical Nursing; 2017.
3. Gonzales B, Chopard G Charry B 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. European Neurology; 2017.

a. Participants with multiple sclerosis (no participants with a diagnosis of FRDA).
b. No confidence intervals reported with low absolute numbers of participants

and events.
c. Allocation concealment not reported or allocation not concealed from enrolling investigator.
d. ≥20% participant drop out in one study.
e. Small sample size and single study published.
f. Confidence intervals not reported.

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)	Impact
Reported fatigue assessed with: Fatigue Severity Scale	99 (2 RCTs)[1,2]	⨁◯◯◯ Very low[a,b,c,d]	2 groups of 24 patients with multiple sclerosis, a low fatigue (LF) and a high fatigue (HF) group, were exposed to 10x3 min session of whole-body cryostimulation (WBC), 1 exposure per day. Mann–Whitney U-test was used to investigate whether there were different kinds of changes between the two groups of patients with MS. The mean delta values were calculated with confidence intervals and changes adjusted for baseline values were evaluated using covariance analysis. Improvements in the FSS were found in both groups (p<0.001). (Miller et al 2016) 75 patients with multiple sclerosis were randomised to an experimental (cooling suit treatment, n=35) or control group (n=40) for 4 weeks. The independent samples t test was used to test the study hypotheses. At both the 4th-week follow-up (p=0.000 on the Fatigue Severity Scale) and at the last measurement (p<0.000), the experimental group reported significantly less fatigue on all measures than

ADDITIONAL CONSIDERATIONS

No undesirable effects reported in literature.

			the control group. Thus, use of the cooling blanket was associated with lower fatigue levels. (Ozkan Tuncay et al 2017).
Reported fatigue assessed with: Multidimensional Fatigue Inventory	18 (1 RCT)[3]	⨁◯◯◯ Very low[a,b,e]	18 patients with multiple sclerosis were randomly assigned to a cooling (wearing a cooling vest during a physical training program) or control group for 7 weeks. A Mann-Whitney U test was used to compare the changes (delta values), with their Confidence Intervals (CIs), obtained in the control group versus those obtained in the cooling group before and after the training program. There were significant decreases ($p < 0.05$) in general fatigue scores and changes in both groups. However, a significant decrease of physical fatigue is found only in the cooling group, whereas significant changes are observed between both groups. (Gonzales et al 2017).
Reported fatigue assessed with: Fatigue Impact Scale	75 (1 RCT)[2]	⨁◯◯◯ Very low[a,c,f]	75 patients with multiple sclerosis were randomised to an experimental (cooling suit treatment, n=35) or control group (n=40) for 4 weeks. The independent samples t test was used to test the study hypotheses. At both the 4th-week follow-up (p=0.005 on the Fatigue Impact Scale General) and at the last measurement (p=0.000), the experimental group reported significantly less fatigue on all measures than the control group. Thus, use of the cooling blanket was associated with lower fatigue levels. (Ozkan Tuncay et al 2017).
Improved quality of life assessed with: Multiple Sclerosis Impact Scale	0 cases 0 controls (1 observational study)[1]	⨁◯◯◯ Very low[a,b,c,d,e]	2 groups of 24 patients with multiple sclerosis, a low fatigue (LF) and a high fatigue (HF) group, were exposed to 10x3 min session of whole-body cryostimulation (WBC), 1 exposure per day. Mann–Whitney U-test was used to investigate whether there were different kinds of changes between the two groups of patients with MS. The mean delta values were calculated with confidence intervals and changes adjusted for baseline values were evaluated using covariance analysis. Improvements in the MSIS-29-PHYS and MSIS-29-PSYCH were found in both

			groups (p<0.001). WBC induced larger changes in the HF than in the LF group in both MSIS-29-PHYS and MSIS-29-PSYCH. (Miller et al 2016)
Improved quality of life assessed with: SEP-59	18 (1 RCT)[3]	⨁◯◯◯ Very low[a,b,e]	18 patients with multiple sclerosis were randomly assigned to a cooling (wearing a cooling vest during a physical training program) or control group for 7 weeks. A Mann-Whitney U test was used to compare the changes (delta values), with their Confidence Intervals (CIs), obtained in the control group versus those obtained in the cooling group before and after the training program. The SEP-59 indicates that the cooling group experienced significant (p < 0.05) increases in emotional well-being and cognitive function and changes between both groups are significant (p < 0.05). There is no significant difference between the 2 groups regarding other domains. (Gonzales et al 2017).
Improved energy levels - not measured	-	-	
Improved physical capacity assessed with: 6-minute walk test	18 (1 RCT)[3]	⨁◯◯◯ Very low[a,b,e]	18 patients with multiple sclerosis were randomly assigned to a cooling (wearing a cooling vest during a physical training program) or control group for 7 weeks. A Mann-Whitney U test was used to compare the changes (delta values), with their Confidence Intervals (CIs), obtained in the control group versus those obtained in the cooling group before and after the training program. Both groups show a significant increase in walking distance (p < 0.05; 28 ± 14 m and 61 ± 31 m in the control and cooling groups, respectively). (Gonzales et al 2017).
Improved capacity to participate in daily tasks assessed with: Modified Barthel Index	75 (1 RCT)[2]	⨁◯◯◯ Very low[a,c,f]	75 patients with multiple sclerosis were randomised to an experimental (cooling suit treatment, n=35) or control group (n=40) for 4 weeks. The independent samples t test was used to test the study hypotheses. At the 4th-week measurement, the experimental group scored significantly better on the Modified

			Barthel Index than the control group (p=0.034). At final follow-up, the experimental group's mean scores increased over the 4th-week measurement while the scores of the control group exhibited no change from baseline at either the 4th-week or the final measurement periods. (Ozkan Tuncay et al 2017)
Reduced falls - not measured	-	-	

1. 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 Neurologica Scandinavica; 2016.
2. Ozkan Tuncay F, Mollaoglu M. Effect of the cooling suit method applied to individuals with multiple sclerosis on fatigue and activities of daily living. Journal of Clinical Nursing; 2017.
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a. Participants with multiple sclerosis (no participants with a diagnosis of FRDA).
b. No confidence intervals reported with low absolute numbers of participants and events.
c. Allocation concealment not reported or allocation not concealed from enrolling investigator.
d. ≥20% participant drop out in one study.
e. Small sample size and single study published.
f. Confidence intervals not reported.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	Very low evidence of effects 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 ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability		

Outcomes	Importance	Certainty of the evidence (GRADE)
Reported fatigue assessed with: Fatigue Severity Scale	IMPORTANT[a]	⨁◯◯◯ VERY LOW[b,c,d,e]
Reported fatigue assessed with: Multidimensional Fatigue Inventory	IMPORTANT[a]	⨁◯◯◯ VERY LOW[b,c,f]
Reported fatigue assessed with: Fatigue Impact Scale	IMPORTANT[a]	⨁◯◯◯ VERY LOW[b,d,g]
Improved quality of life assessed with: Multiple Sclerosis Impact Scale	IMPORTANT[h]	⨁◯◯◯ VERY LOW[b,c,d,e,f]
Improved quality of life assessed with: SEP-59	IMPORTANT[h]	⨁◯◯◯ VERY LOW[b,c,f]
Improved energy levels - not measured	IMPORTANT[i]	-
Improved physical capacity assessed with: 6-minute walk test	IMPORTANT[i]	⨁◯◯◯ VERY LOW[b,c,f]

Improved capacity to participate in daily tasks assessed with: Modified Barthel Index	IMPORTANT[a]	⨁◯◯◯ VERY LOW[b,d,g]
Reduced falls - not measured	CRITICAL[j]	-

a. Identified as important (6/6) by people with FA and critical by expert authors on this topic.
b. Participants with multiple sclerosis (no participants with a diagnosis of FRDA).
c. No confidence intervals reported with low absolute numbers of participants and events.
d. Allocation concealment not reported or allocation not concealed from enrolling investigator.
e. ≥20% participant drop out in one study.
f. Small sample size and single study published.
g. Confidence intervals not reported.
h. Identified as critical (1/6) and important (5/6) by people with FA and important by expert authors on this topic.
i. Identified as important (6/6) by people with FA and important by expert authors on this topic.
j. 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 ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● 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 Alternative therapies/physical modalities (ie:light therapy, cooling therapy, pulsed electromagnetic devices, acupuncture) as a management strategy for all individuals who report fatigue. Reflecting on the impact of Alternative therapies/physical modalities (ie:light therapy, cooling therapy, pulsed electromagnetic devices, acupuncture) on reported fatigue, 13.64% (3/22) clinical experts reported a benefit (large, moderate or small), 13.64% (3/22) reported no effect and, 0% (0/22) reported observing a harm (large, moderate or small). 16

		clinicians could not provide any information on this outcome. Reflecting on the impact on quality of life, 13.04% (3/23) clinical experts reported a benefit, 17.39% (4/23) reported no effect and, 0% (0/23) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on energy levels, 4.35% (1/23) clinical experts reported a benefit, 26.09% (6/23) reported no effect and, 0% (0/23) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on physical capacity, 4.35% (1/23) clinical experts reported a benefit, 26.09% (6/23) reported no effect and, 0% (0/23) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on capacity to participate in daily tasks, 8.7% (2/23) clinical experts reported a benefit, 21.74% (5/23) reported no effect and, 0% (0/23) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on falls, 0% (0/22) clinical experts reported a benefit, 31.82% (7/22) reported no effect and, 0% (0/22) reported observing a harm. 15 expert clinicians could not provide any information on this outcome.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No published evidence.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using alternative therapies in people who report fatigue was acceptable (weighing up the balance between benefits, harms and costs). 1/4 indicated the intervention was acceptable, 2/4 indicated probably not acceptable, 1/4 indicated they didn't know if acceptable. (Aug 2020).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
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 cannot recommend either alternative therapies/physical modalities (i.e., light therapy, cooling therapy, pulsed electromagnetic devices, acupuncture) or no alternative therapies/physical modalities be used for all individuals who report fatigue with Friedreich ataxia.

Justification

There is little evidence supporting the benefits of alternative therapies on fatigue in FRDA. Undesirable effects are unclear; hence, we cannot make a recommendation either way.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia who report fatigue.

Research priorities

Reference

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.