QUESTION

Should oral supplements vs. none be used for peripheral neuropathy patients with Friedreich ataxia?	
POPULATION:	peripheral neuropathy patients with Friedreich ataxia
INTERVENTION:	oral supplements
COMPARISON:	none
MAIN OUTCOMES:	Reduction in pain; QOL; ADLs; Ambulation;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of neuropathic pain. 4/7 indicated that the problem was serious, 2/7 indicated probably serious, 1/7 indicated they didn't know if serious. 2/7 indicated that the problem was urgent, 2/7 indicated probably urgent, 2/7 indicated probably not urgent, 1/7 indicated they didn't know if urgent. 2/7 indicated that the problem was a priority, 3/7 indicated probably a priority, 1/7 indicated probably not a priority, 1/7 indicated they didn't know if 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		

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with none	Risk difference with oral supplements

Reduction in pain assessed with: Visual Analog Pain Scale	25 (1 observational study)[1]	⊕◯◯◯ Very low[a,b]	-	25 patients with chemotherapy-induced peripheral neuropathy (CIPN) were administered a new dietary supplement (OPERA) to determine its safety and efficacy in managing CIPN. Assessments were administered every 3 weeks for 12 weeks. Analysis of VAS data showed a progressive reduction in pain perceived by enrolled patients during study period. At enrollment (T0), 12% of patients signaled pain G0, 40% pain G1, 44% pain G2 and 4% pain G3, while at the last assessment (T4) the percentage of pain G0 increased to 32% and G1 and G2 pain percentage decreased, respectively, to 36 and 32%. No G3 pain toxicity was found at last evaluation: The only patients that showed pain G3 at first assessment reported a reduction in pain relief to grade G2 after 6 weeks from first assumption of OPERA. (Desideri et al 2017).	
QOL - not measured	-	-	-	-	-
ADLs - not measured	-	-	-	-	-
Ambulation - not measured	-	-	-	-	-

1. Desideri I., Francolini G. Becherini C. et al. Use of an alpha lipoic, methylsulfonylmethane and bromelain dietary supplement (Opera) for chemotherapy-induced peripheral neuropathy management, a prospective study. Med. Oncol; 2017.

a. No participants had a diagnosis of FRDA (all participants had chemotherapy-induced peripheral neuropathy).
b. No confidence intervals reported with low absolute numbers of participants and events.

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 none	Risk difference with oral supplements
Reduction in pain assessed with: Visual Analog Pain Scale	25 (1 observational study)[1]	⨁◯◯◯ Very low[a,b]	-	25 patients with chemotherapy-induced peripheral neuropathy (CIPN) were administered a new dietary supplement (OPERA) to determine its safety and efficacy in managing CIPN. Assessments were administered every 3 weeks for 12 weeks. Analysis of VAS data showed a progressive reduction in pain perceived by enrolled patients during study period. At enrollment (T0), 12% of patients signaled pain G0, 40% pain G1, 44% pain G2 and 4% pain G3, while at the last assessment (T4) the percentage of pain G0 increased to 32% and G1 and G2 pain percentage decreased, respectively, to 36 and 32%. No G3 pain toxicity was found at last evaluation: The only patients that showed pain G3 at first assessment reported a reduction in pain relief to grade G2 after 6 weeks from first assumption of OPERA. (Desideri et al 2017).	
QOL - not measured	-	-	-	-	-
ADLs - not measured	-	-	-	-	-
Ambulation - not measured	-	-	-	-	-

1. Desideri I., Francolini G. Becherini C. et al. Use of an alpha lipoic,

ADDITIONAL CONSIDERATIONS

	methylsulfonylmethane and bromelain dietary supplement (Opera) for chemotherapy-induced peripheral neuropathy management, a prospective study. Med. Oncol; 2017. a. No participants had a diagnosis of FRDA (all participants had chemotherapy-induced peripheral neuropathy). b. No confidence intervals reported with low absolute numbers of participants and events.	

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	The is very low certainty of 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)
Reduction in pain assessed with: Visual Analog Pain Scale	IMPORTANT[a]	⨁◯◯◯ VERY LOW[b,c]
QOL - not measured	IMPORTANT[d]	-
ADLs - not measured	IMPORTANT[d]	-

Ambulation - not measured	IMPORTANT[e]	-

a. Identified as critical (1/6), important (3/6) and low importance (2/6) by people with FA and important by expert authors on this topic.
b. No participants had a diagnosis of FRDA (all participants had chemotherapy-induced peripheral neuropathy).
c. No confidence intervals reported with low absolute numbers of participants and events.
d. Identified as critical (3/6) and important (3/6) by people with FA and important by expert authors on this topic.
e. Identified as critical (2/6), important (3/6) and low importance (1/6) by people with FA and important 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		

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 oral medication in people with pain related to peripheral neuropathy was acceptable (weighing up the balance between benefits, harms and costs). 2/4 indicated the intervention was acceptable, 1/4 indicated probably acceptable, 1/4 indicated probably not acceptable. (Aug 2020).

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 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.

Research priorities

Further research is required to establish if oral supplements shown to be effective in neuropathic pain secondary to other conditions (such as chemotherapy) are effective in managing neuropathic pain related to Friedreich ataxia.