QUESTION

Should oral medication vs. none be used for patients with idiopathic RLS/PLMS with Friedreich ataxia?	
POPULATION:	patients with idiopathic RLS/PLMS with Friedreich ataxia
INTERVENTION:	oral medication
COMPARISON:	none
MAIN OUTCOMES:	Impact on sleep quality/ arousals; Impact on sleep quantity/ sleep benefit ; Impact on behaviour, cognition, mood; Degree of pain versus discomfort; HRQoL;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Data from the FA Clinical Outcome Measures (FA-COMS) registry (Lynch, 2017) found: 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). For individuals who reported sleep disturbance: 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).	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of restless legs. 2/7 indicated that the problem was serious, 4/7 indicated probably serious, 1/7 indicated probably not serious. 2/7 indicated that the problem was urgent, 4/7 indicated probably urgent, 1/7 indicated probably not urgent. 3/7 indicated that the problem was a priority, 3/7 indicated probably a priority, 1/7 indicated probably not 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	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.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	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.	

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	No published evidence.	

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)
Impact on sleep quality/ arousals - 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 versus discomfort - not measured	CRITICAL[b]	-
HRQoL - not measured	IMPORTANT[c]	-

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.
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.
c. Identified as critical (2/6) and important (4/6) 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	No published evidence.	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 oral medication for people with idiopathic Restless Leg Syndrome/Periodic Limb Movements of Sleep. Reflecting on the impact of **vitamins** on sleep quality/ arousals, 12.5% (3/24) clinical experts reported a benefit (large, moderate or small), 29.17% (7/24) reported no effect and, 0% (0/24) reported observing a harm (large, moderate or small). 14 clinicians could not provide any information on this outcome. Reflecting on the impact on s**leep quantity/ sleep benefit**, 16.67% (4/24) clinical experts reported a benefit, 25% (6/24) reported no effect and, 0% (0/24) reported observing a harm. 14 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **behaviour, cognition, mood**, 12.5% (3/24) clinical experts reported a benefit, 25% (6/24) reported no effect and, 0% (0/24) 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**, 12.5% (3/24) clinical experts reported a benefit, 29.17% (7/24) reported no effect and, 0% (0/24) reported observing a harm. 14 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **HRQOL**, 12.5% (3/24) clinical experts reported a benefit, 29.17%

		(7/24) reported no effect and, 0% (0/24) reported observing a harm. 14 expert clinicians could not provide any information on this outcome. Reflecting on the impact of **baclofen** on sleep quality/ arousals, 8.33% (2/24) clinical experts reported a benefit (large, moderate or small), 20.83% (5/24) reported no effect and, 4.17% (1/24) reported observing a harm (large, moderate or small). 16 clinicians could not provide any information on this outcome. Reflecting on the impact on **sleep quantity/ sleep benefit**, 4.17% (1/24) clinical experts reported a benefit, 25% (6/24) reported no effect and, 4.17% (1/24) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **behaviour, cognition, mood**, 0% (0/24) clinical experts reported a benefit, 25% (6/24) reported no effect and, 8.33% (2/24) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **Degree of pain versus discomfort**, 12.5% (3/24) clinical experts reported a benefit, 16.67% (4/24) reported no effect and, 4.17% (1/24) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **HRQOL**, 4.17% (1/24) clinical experts reported a benefit, 25% (6/24) reported no effect and, 4.17% (1/24) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact of **L-Dopa** on **sleep quality/ arousals**, 25% (6/24) clinical experts reported a benefit (large, moderate or small), 4.17% (1/24) reported no effect and, 4.17% (1/24) reported observing a harm (large, moderate or small). 16 clinicians could not provide any information on this outcome.Reflecting on the impact on **sleep quantity/ sleep benefit**, 25% (6/24) clinical experts reported a benefit, 4.17% (1/24) reported no effect and, 4.17% (1/24) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **behaviour, cognition, mood**, 20.83% (5/24) clinical experts reported a benefit, 8.33% (2/24) reported no effect and, 4.17% (1/24) reported observing a harm. 16 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, 4.17% (1/24) reported no effect and, 4.17% (1/24) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **HRQOL**, 25% (6/24) clinical experts reported a benefit, 4.17% (1/24) reported no effect and, 4.17% (1/24) reported observing a harm. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact of **Opioids** on **sleep quality/ arousals**, 13.04% (3/23) clinical experts reported a benefit (large, moderate or small), 4.35% (1/23) reported no effect and, 4.35%

		(1/23) reported observing a harm (large, moderate or small). 18 clinicians could not provide any information on this outcome. Reflecting on the impact on **sleep quantity/ sleep benefit**, 13.05% (3/23) clinical experts reported a benefit, 4.35% (1/23) reported no effect and, 4.35% (1/23) reported observing a harm. 18 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **behaviour, cognition, mood**, 4.35% (1/23) clinical experts reported a benefit, 4.35% (1/23) reported no effect and, 17.39% (4/23) reported observing a harm. 17 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **Degree of pain versus discomfort**, 13.04% (3/23) clinical experts reported a benefit, 8.7% (2/23) reported no effect and, 4.35% (1/23) reported observing a harm. 17 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **HRQOL**, 13.05% (3/23) clinical experts reported a benefit, 8.7% (2/23) reported no effect and, 4.35% (1/23) reported observing a harm. 17 expert clinicians could not provide any information on this outcome. Reflecting on the impact of **other medication** (to those listed above) on **sleep quality/ arousals**, 18.19% (4/22) clinical experts reported a benefit (large, moderate or small), 4.55% (1/22) reported no effect and, 0% (0/22) reported observing a harm (large, moderate or small). 17 clinicians could not provide any information on this outcome. Reflecting on the impact on **sleep quantity/ sleep benefit**, 18.19% (4/22) clinical experts reported a benefit, 4.55% (1/22) reported no effect and, 0% (0/22) reported observing a harm. 17 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **behaviour, cognition, mood**, 13.64% (3/22) clinical experts reported a benefit, 9.09% (2/22) reported no effect and, 0% (0/22) reported observing a harm. 17 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **Degree of pain versus discomfort**, 18.19% (4/22) clinical experts reported a benefit, 4.55% (1/22) reported no effect and, 0% (0/22) reported observing a harm. 17 expert clinicians could not provide any information on this outcome. Reflecting on the impact on **HRQOL**, 18.19% (4/22) clinical experts reported a benefit, 4.55% (1/22) reported no effect and, 0% (0/22) reported observing a harm. 17 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 oral medication in people with restless leg syndrome was acceptable (weighing up the balance between benefits, harms and costs). 2/3 indicated the intervention was probably acceptable, 1/3 indicated more information on the benefits and potential harms was required. (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 conditionally recommend medication for individuals with Friedreich ataxia with RLS which interferes with sleep (with or without associated PLMS) over no medication.

Gabapentin and pregabalin are the preferred choice of pharmacological treatment of RLS in FRDA as they are as effective as levodopa but do not have the same side-effects. The dopamine agonists pramipexole and ropinirole may be helpful but should be used with caution in FRDA due to the risk of augmentation of RLS symptoms. If PLMS is present it should be treated if the individual has disabling symptoms. Levodopa may be used intermittently when disabling RLS/PLMS symptoms are present since augmentation of RLS occurs only with long-term use. Given that levodopa alleviates symptoms of RLS rapidly, a 'test dose' of levodopa may be used to confirm a diagnosis of RLS in an individual with Friedreich ataxia.

Justification

RLS is a significant problem affecting 44.8% of adults with FRDA. However, there is uncertainty or variability in the opinion expressed about the value of medication to treat RLS. There are no RCTs addressing the impact of vitamins, baclofen, opioids or dopaminergic drugs, L-Dopa on sleep quantity/sleep benefit, impact on behaviour, cognition, mood, degree of pain versus discomfort, or HRQOL in FRDA patients with RLS.

A survey of experts in FRDA, showed that the majority, 16 out of 24 clinicians, had no opinion or expertise in using these medications. Of those who had, 6 out of 8 clinicians, found that L-dopa had a modest effect on RLS. However, L-dopa can cause the undesirable side effect of augmentation which is where there is an increase in severity of RLS, faster onset of symptoms at rest, earlier onset of symptoms during the day, the symptoms spread to the upper limbs and trunk and shortened duration of treatment effect. Vitamin supplementation, baclofen and opioids and other dopaminergic drugs are of limited value in the treatment of restless legs in FRDA.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia with symptoms of RLS/PLMS. There is greater clinical experience with using medication for RLS in adults than children; therefore, even more caution needs to be exercised when prescribing medication for children.

Implementation considerations

Research priorities

Systematic clinical studies of the impact of medication on symptomatic RLS to assess side-effects and determine benefits versus risks are highly warranted.

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.