QUESTION

Should monitoring vs. no monitoring be used for restrictive lung disease in people with Friedreich ataxia?	
POPULATION:	restrictive lung disease in people with Friedreich ataxia
INTERVENTION:	monitoring
COMPARISON:	no monitoring
MAIN OUTCOMES:	Abnormal lung volumes; Impaired airway clearance; Excessive daytime sleepiness, fatigue;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There is a single case report (Botez et al, 1997) documenting a patient with severe FA and ”arduous” breathing and O2 desaturation together with sleep disordered breathing (SDB) at night. Preliminary data collected by one of the authors indicates decline in respiratory volumes in severe FA and also impaired cough mechanisms. There is a single case report (Botez et al, 1997) documenting a patient with severe FA and ”arduous” breathing and O2 desaturation together with SDB at night. In a study of 21 FA patients with abnormal scores on Epworth Sleepiness Scale (Corben et al, 2013), 17 had obstructive sleep apnea (SDB). Preliminary data collected by one of the authors indicates decline in respiratory volumes in severe FA and also impaired cough mechanisms. Also, in a web-based survey of FA patients presented at IARC (Patterson et al, 2018), 16.5% FA patients reported sleep apnea, correlated with higher age, longer duration and higher functional stage.	The Friedreich’s ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of pulmonary function. 6/7 indicated that the problem was serious, 1/7 indicated they didn’t know if serious. 6/7 indicated that the problem was urgent, 1/7 indicated they didn’t know if urgent. 6/7 indicated that the problem was a priority, 1/7 indicated they didn’t know if 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 28 October 2020. 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 28 October 2020. 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)
Abnormal lung volumes - not measured	CRITICAL[a]	-
Impaired airway clearance - not measured	CRITICAL[b]	-
Excessive daytime sleepiness, fatigue - not measured	IMPORTANT[c]	-

	a. Identified as critical (3/6), important (2/6) and low importance (1/6) by people with FA and important by experts on this topic. b. Identified as critical (3/6), important (1/6) and low importance (2/6) by people with FA and critical by experts on this topic. c. Identified as important (4/6) and low importance (2/6) by people with FA.	

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. Expert opinion: majority of experts had no opinion but among those that responded: • Majority favoured using respiratory symptom check list being of benefit for non-restorative sleep, dyspnea and orthopnea, quality of night time sleep, EDS and a more mixed benefit for ABG parameters and abnormal lung volumes. • Majority favoured sleep scales to manage restrictive lung disease and this could benefit non-restorative sleep, quality of night sleep, and EDS and a more mixed benefit for ABG, abnormal lung volumes. • Majority favoured PFT to benefit dyspnea, orthopnea, ABG, abnormal lung volumes, impaired airway clearance and mor mixed views on non-restorative sleep	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 using a **respiratory symptom check list** as a management strategy for people with **restrictive lung disease.** Reflecting on the impact of respiratory symptom check list on non-restorative sleep, 30.77% (8/26) clinical experts reported a benefit (large, moderate or small), and 0% (0/26) reported observing a harm (large, moderate or small). 18 clinicians could not provide any information on this outcome. Reflecting on the impact on dyspnea, orthopnea, 30.76% (8/26) clinical experts reported a benefit. 18 expert clinicians could not provide any information on this outcome. Reflecting on the impact on quality of night time sleep, 27% (7/26) clinical experts reported a benefit, 3.85% (1/26) reported no effect and, 0% (0/26) reported observing a harm. 18 expert clinicians could not provide any information on this outcome. Reflecting on the impact on blood gas parameters, 15.38% (4/26) clinical experts reported a benefit, 12% (3/26) reported no effect and, 0% (0/26) reported observing a harm. 19 expert clinicians could not provide any information on this outcome. Reflecting on the impact on excessive daytime sleepiness/fatigue, 35% (9/26) clinical experts reported a benefit. 17 expert clinicians could not provide any information on this outcome. Reflecting on the impact on abnormal lung volumes, 16% (4/25) clinical experts reported a benefit, 8% (2/25) reported no effect. 19 expert clinicians could not provide any information on this outcome. Reflecting on the impact on impaired airway clearance, 23.08% (6/26) clinical experts reported a benefit, 8% (2/26) reported no effect and, 0% (0/26) reported observing a harm. 18 expert clinicians could not provide

		any information on this outcome. Reflecting on the impact on excessive daytime sleepiness/fatigue, 35% (9/26) clinical experts reported a benefit. 17 expert clinicians could not provide any information on this outcome. Clinical experts were asked to consider the harms/benefits of using a **sleep scale** as a management strategy for people with **restrictive lung disease**. Reflecting on the impact of sleep scale on non-restorative sleep, 28% (7/25) clinical experts reported a benefit (large, moderate or small), and 0% (0/25) reported observing a harm (large, moderate or small). 18 clinicians could not provide any information on this outcome. Reflecting on the impact on dyspnea, orthopnea, 16% (4/25) clinical experts reported a benefit, 8% (2/25) reported no effect. 19 expert clinicians could not provide any information on this outcome. Reflecting on the impact on quality of night time sleep, 24% (6/25) clinical experts reported a benefit, 4% (1/25) reported no effect. 18 expert clinicians could not provide any information on this outcome. Reflecting on the impact on blood gas parameters, 12% (3/25) clinical experts reported a benefit, 8% (2/25) reported no effect. 20 expert clinicians could not provide any information on this outcome. Reflecting on the impact on excessive daytime sleepiness/fatigue, 24% (6/25) clinical experts reported a benefit, 4% (1/25) reported no effect. 18 expert clinicians could not provide any information on this outcome. Reflecting on the impact on abnormal lung volumes, 12% (3/25) clinical experts reported a benefit, 8% (2/25) reported no effect. 20 expert clinicians could not provide any information on this outcome. Reflecting on the impact on impaired airway clearance, 16% (4/25) clinical experts reported a benefit, 8% (2/25) reported no effect. 19 expert clinicians could not provide any information on this outcome. Reflecting on the impact on excessive daytime sleepiness/fatigue, 24% (6/25) clinical experts reported a benefit, 4% (1/25) reported no effect. 18 expert clinicians could not provide any information on this outcome. Clinical experts were asked to consider the harms/benefits of using a **pulmonary function test** as a management strategy for people with restrictive lung disease. Reflecting on the impact of pulmonary function test on non-restorative sleep, 20% (5/25) clinical experts reported a benefit (large, moderate or small), 16% (4/25) reported no effect and, 0% (0/25) reported observing a harm (large, moderate or small). 16 clinicians could not provide any information on this outcome. Reflecting on the impact on dyspnea, orthopnea, 32% (8/25) clinical experts reported a benefit, 8% (2/25) reported no effect. 15 expert clinicians could not provide any information on this outcome. Reflecting on the

		impact on quality of night time sleep, 20% (5/25) clinical experts reported a benefit, 16% (4/25) reported no effect. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on blood gas parameters, 28% (7/25) clinical experts reported a benefit, 8% (2/25) reported no effect. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on excessive daytime sleepiness/fatigue, 24% (6/25) clinical experts reported a benefit, 12% (3/25) reported no effect. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on abnormal lung volumes, 28% (7/25) clinical experts reported a benefit, 8% (2/25) reported no effect. 16 expert clinicians could not provide any information on this outcome. Reflecting on the impact on impaired airway clearance, 32% (8/25) clinical experts reported a benefit, 8% (2/25) reported no effect. 15 expert clinicians could not provide any information on this outcome. Reflecting on the impact on excessive daytime sleepiness/fatigue, 20% (5/25) clinical experts reported a benefit, 12% (3/25) reported no effect. 17 expert clinicians could not provide any information on this outcome. Clinical experts were asked to consider the harms/benefits of a **sleep scale** as a management strategy for people with **sleep disordered breathing**. Reflecting on the impact of on non-restorative sleep, 24% (6/25) clinical experts reported a benefit (large, moderate or small), 4% (1/25) reported no effect and, 0% (0/25) reported observing a harm (large, moderate or small). 18 clinicians could not provide any information on this outcome. Reflecting on the impact on dyspnea, orthopnea, 12% (3/25) clinical experts reported a benefit, 16% (4/25) reported no effect and, 0% (0/25) reported observing a harm. 18 expert clinicians could not provide any information on this outcome. Reflecting on the impact on quality of night time sleep, 24% (6/25) clinical experts reported a benefit, 4% (1/25) reported no effect and, 0% (0/25) reported observing a harm. 18 expert clinicians could not provide any information on this outcome. Reflecting on the impact on blood gas parameters, 4% (1/25) clinical experts reported a benefit, 16% (4/25) reported no effect and, 0% (0/25) reported observing a harm. 20 expert clinicians could not provide any information on this outcome. Reflecting on the impact on excessive daytime sleepiness, fatigue, 24% (6/25) clinical experts reported a benefit, 4% (1/25)

		reported no effect and, 0% (0/25) reported observing a harm. 18 expert clinicians could not provide any information on this outcome. Reflecting on the impact on abnormal lung volumes, 4% (1/25) clinical experts reported a benefit, 16% (4/25) reported no effect and, 0% (0/25) reported observing a harm. 20 expert clinicians could not provide any information on this outcome. Reflecting on the impact on impaired airway clearance, 12% (3/25) clinical experts reported a benefit, 16% (4/25) reported no effect and, 0% (0/25) reported observing a harm. 18 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 monitoring for restrictive lung disease was acceptable (weighing up the balance between benefits, harms and costs). 1/3 indicated the intervention was acceptable, 2/3 indicated probably 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			

	JUDGEMENT						
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 that individuals with advanced Friedreich ataxia be monitored* at least annually for restrictive lung disease and sleep disordered breathing (SDB).

*Monitoring should include a respiratory symptom check list (dyspnea, orthopnea, episodes of apnea during night, poor sleep, morning headache, decreased concentration and attention, fatigue, treated chest infection within the past few months), a sleepiness questionnaire and a fatigue scale. Annual (or more frequent) pulmonary function testing should be performed to include forced vital capacity (FVC), maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP), peak expiratory cough flow (PECF), SpO2 and partial pressure of end tidal CO2 (PetCO2).

Justification

There are no published data. Expert opinion and limited unpublished data suggest that restrictive lung disease and SDB can occur in advanced FRDA. Monitoring will be of benefit. Methods for monitoring include using a respiratory symptom check list (Boentert et al, 2020), sleepiness and fatigue scales and pulmonary function tests.

Restrictive lung disease and SDB can lead to abnormal blood gases and symptoms that impair quality of life. Detecting these and providing appropriate intervention will be of benefit.

Subgroup considerations

Monitoring is recommended for individuals with Friedreich ataxia with advanced disease.

Research priorities

Further research is required to establish the efficacy of monitoring for restrictive lung disease/SDB/sleep apnoea to identify non-restorative sleep; dyspnea, orthopnea; quality of night time sleep; blood gas parameters; excessive daytime sleepiness and fatigue in individuals with Friedreich ataxia.

References

Boentert M, Cao M, Mass D, De Mattia E, Falcier E, Goncalves M, et al. Consensus-based care recommendations for pulmonologists treating adults with myotonic dystrophy type 1. Respiration. 2020;99(4):360-8.

Botez MI, Mayer P, Bellemare F, Couture J. Can we treat respiratory failure in Friedreich ataxia? Archives of Neurology. 1997;54(8):1030-3.

Corben LA, Ho M, Copland J, Tai G, Delatycki MB. Increased prevalence of sleep-disordered breathing in Friedreich ataxia. Neurology. 2013;81(1):46-51.

Patterson A, Almeida L, Monari E, et al. Sleep and fatigue in Friedreich ataxia. IARC Meeting; Pisa, Italy 2018.