QUESTION

Should commencing a phosphodiesterase-5 inhibitor vs. no treatment be used for sexually active males with erectile dysfunction with Friedreich ataxia?	
POPULATION:	sexually active males with erectile dysfunction with Friedreich ataxia
INTERVENTION:	commencing a phosphodiesterase-5 inhibitor
COMPARISON:	no treatment
MAIN OUTCOMES:	Erectile function; Sexual quality of life; Improved intimate relationships;

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 found 3.3% (15/456) females and 6.8% (30/439) males reported sexual dysfunction (Lynch, 2017). Sexual functioning, sexual satisfaction and the capacity to form intimate relationships is impacted by FA as evident by: erectile dysfunction reported in 57% (20/35) of males, and reduced genital sensation in 47% (51/107) of people with Friedreich ataxia (Corben et al, 2021)	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic. 3/7 indicated disturbance of sexual function was probably not serious, 3/7 indicated probably serious, 1/7 indicated didn't know if serious. 4/7 indicated disturbance of sexual function was probably not urgent, 1/7 indicated probably urgent, 2/7 indicated didn't know if urgent. 3/7 indicated disturbance of sexual function was probably not a priority, 1/7 indicated probably a priority, 2/7 indicated didn't know if a priority, 1/7 indicated varies/sometimes 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		Over half of male responders (20/35) with FA reported erectile dysfunction potentially amenable to phosphodiesterase-5 inhibitor (Corben et al 2019).

Outcomes	№ of	Certainty of	Relative	Anticipated absolute effects* (95% CI)

	participants (studies) Follow-up	the evidence (GRADE)	effect (95% CI)	Risk with no treatment	Risk difference with commencing a phosphodiesterase-5 inhibitor
Erectile function assessed with: International Index of Erectile Function	24 (1 RCT)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	24 patients with erectile disease (n=12 with Parkinson's disease, n=12 with multiple system atrophy) were recruited in a randomised crossover study of sildenafil, starting at 50mg (titrated up to 100mg or down to 25 mg depending on efficacy and tolerability) over 24 weeks. For items 3 (ability to obtain erection) and 4 (ability to maintain erection adequate for intercourse) on the IIEF, there was a significant improvement over placebo (p=0.0095 and p=0.0041 respectively). (Hussain et al 2001).	
Sexual quality of life assessed with: Quality of life	24 (1 RCT)[1]	⨁◯◯◯ Very low[a,b,c,d,e]	-	24 patients with erectile disease (n=12 with Parkinson's disease, n=12 with multiple system atrophy) were recruited in a randomised crossover study of sildenafil, starting at 50mg (titrated up to 100mg or down to 25 mg depending on efficacy and tolerability) over 24 weeks. There was a significant improvement in the sex life component of the quality of life questionnaire (p=0.0073) after taking sildenafil when compared to placebo. (Hussain et al 2001).	
Improved intimate relationships - not measured	-	-	-	-	-

1. Hussain IF, Brady CM,Swinn MJ,Mathias CJ,Fowler CJ. Treatment of erectile dysfunction with sildenafil citrate (Viagra) in parkinsonism due to Parkinson's disease or multiple system atrophy with observations on orthostatic hypotension. Journal of neurology, neurosurgery, and psychiatry; 2001.

a. All participants had a diagnosis Parkinson’s disease (not FRDA).
b. Small sample size (n=12)
c. Confidence intervals not reported.
d. Withdrawal (n=3)

e. Use of an un-validated outcome measure (Quality of Life survey).

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 no treatment	Risk difference with commencing a phosphodiesterase-5 inhibitor
Erectile function assessed with: International Index of Erectile Function	24 (1 RCT)[1]	⨁◯◯◯ Very low[a,b,c,d]	-	24 patients with erectile disease (n=12 with Parkinson's disease, n=12 with multiple system atrophy) were recruited in a randomised crossover study of sildenafil, starting at 50mg (titrated up to 100mg or down to 25 mg depending on efficacy and tolerability) over 24 weeks. For items 3 (ability to obtain erection) and 4 (ability to maintain erection adequate for intercourse) on the IIEF, there was a significant improvement over placebo (p=0.0095 and p=0.0041 respectively). (Hussain et al 2001).	
Sexual quality of life assessed with: Quality of life	24 (1 RCT)[1]	⨁◯◯◯ Very low[a,b,c,d,e]	-	24 patients with erectile disease (n=12 with Parkinson's disease, n=12 with multiple system atrophy) were recruited in a randomised crossover study of sildenafil, starting at 50mg (titrated up to 100mg or down to 25 mg depending on efficacy and tolerability) over 24 weeks. There was a significant improvement in the sex life component of the quality of life questionnaire (p=0.0073) after taking sildenafil when compared to placebo. (Hussain et al 2001).	

ADDITIONAL CONSIDERATIONS

Improved intimate relationships - not measured	-	-	-	-	-	

1. Hussain IF, Brady CM,Swinn MJ,Mathias CJ,Fowler CJ. Treatment of erectile dysfunction with sildenafil citrate (Viagra) in parkinsonism due to Parkinson's disease or multiple system atrophy with observations on orthostatic hypotension. Journal of neurology, neurosurgery, and psychiatry; 2001.

a. All participants had a diagnosis Parkinson's disease (not FRDA).
b. Small sample size (n=12)
c. Confidence intervals not reported.
d. Withdrawal (n=3)
e. Use of an un-validated outcome measure (Quality of Life survey).

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 certainty 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)
Erectile function assessed with: International Index of Erectile Function	IMPORTANT[a]	⨁◯◯◯ Very low[b,c,d,e]
Sexual quality of life assessed with: Quality of life	IMPORTANT[f]	⨁◯◯◯ Very low[b,c,d,e,g]
Improved intimate relationships - not measured	IMPORTANT[h]	-

a. Identified as important (4/6), low importance (1/6) and requiring more information (1/6) by people with FA and important by expert authors on the topic.
b. All participants had a diagnosis Parkinson's disease (not FRDA).
c. Small sample size (n=12)
d. Confidence intervals not reported.
e. Withdrawal (n=3)
f. Identified as critical (3/6), important (2/6) and requiring more information (1/6) by people with FA and important by expert authors on the topic.
g. Use of an un-validated outcome measure (Quality of Life survey).
h. Identified as critical (2/6), important (2/6), low importance (1/6) and requiring more information (1/6) by people with FA and important by expert authors on the 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	The FA Clinical Outcome Measures (FA-COMS) registry found 1.2% (5/424) adults had been administered Sildenafil since their last visit; 0.7% (3/424) had been administered Cialis, and 0.5% (2/424) had been administered Tadalafil. The presence, or not, of erectile function in this cohort was not identified. https://clinicaltrials.gov/ct2/show/NCT03090789	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if the intervention was acceptable (weighing up the balance between benefits, harms and costs). 1/5 indicated commencing a phosphodiesterase-5 inhibitor for sexually active males with erectile dysfunction was probably reasonable, 4/5 indicated didn't know if reasonable. (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 recommend commencing a phosphodiesterase-5 inhibitor in males with Friedreich ataxia who report erectile dysfunction.

Justification

There is little evidence regarding the benefits of commencing a phosphodiesterase-5 inhibitor in males with Friedreich ataxia who report erectile dysfunction; however, there is sufficient evidence to indicate erectile dysfunction may be a problem and evidence in other neurological conditions that phosphodiesterase-5 inhibitor therapy can be of benefit in this setting.

Subgroup considerations

This recommendation is for sexually active males with Friedreich ataxia who report erectile dysfunction and who are not taking nitrates for coexistent angina.

Research priorities

Further research in sexually active males with Friedreich ataxia is required to confirm the efficacy of commencing a phosphodiesterase-5 inhibitor for males with Friedreich ataxia in alleviating erectile dysfunction.

References

Corben LA, Hermans MM, Marks A, Crowe LM, Delatycki MB. Sexual function, intimate relationships and Friedreich ataxia. J Neurol. 2021;268(3):1088-95.

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