

QUESTION

Should commencing a course of natural estrogen vs. no treatment be used for sexually active females with inadequate vaginal lubrication with Friedreich ataxia?

POPULATION:	sexually active females with inadequate vaginal lubrication with Friedreich ataxia
INTERVENTION:	commencing a course of natural estrogen
COMPARISON:	no treatment
MAIN OUTCOMES:	Adequate vaginal lubrication; Improved self-esteem; Improved intimate relationships; Improved sexual quality of life;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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).</p> <p>Sexual functioning, sexual satisfaction and the capacity to form intimate relationships is impacted by FA as evident by: inadequate vaginal lubrication interfering with sexual responsiveness in 57.7% (26/45) of females. (Corben et al, 2021)</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic.</p> <p>3/7 indicated disturbance of sexual function was probably not serious, 3/7 indicated probably serious, 1/7 indicated didn't know if serious.</p> <p>4/7 indicated disturbance of sexual function was probably not urgent, 1/7 indicated probably urgent, 2/7 indicated didn't know if urgent.</p> <p>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).</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 15 October 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	<p>Given findings of one study identifying inadequate vaginal lubrication in over half the female responders with FA the desirable anticipated effects of enquiry about sexual dysfunction is moderate.</p>

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know 	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 15 October 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	<p>The use of these agents would require a risk assessment, particularly in terms of the individual's risk for developing breast/uterine cancer.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	<p>No published evidence.</p>	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS									
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability 	<table border="1"> <thead> <tr> <th>Outcomes</th> <th>Importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Adequate vaginal lubrication - not measured</td> <td>IMPORTANT^a</td> <td>-</td> </tr> <tr> <td>Improved self-esteem - not measured</td> <td>IMPORTANT^b</td> <td>-</td> </tr> </tbody> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)	Adequate vaginal lubrication - not measured	IMPORTANT ^a	-	Improved self-esteem - not measured	IMPORTANT ^b	-	
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	<table border="1"> <tr> <td>Improved intimate relationships - not measured</td> <td>IMPORTANT^c</td> <td>-</td> </tr> <tr> <td>Improved sexual quality of life - not measured</td> <td>IMPORTANT^d</td> <td>-</td> </tr> </table>	Improved intimate relationships - not measured	IMPORTANT ^c	-	Improved sexual quality of life - not measured	IMPORTANT ^d	-	
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Improved sexual quality of life - not measured	IMPORTANT ^d	-						
	<p>a. Identified as important (3/6), low important (2/6) and requiring more information (1/6) by people with FA and important by expert authors on this topic</p> <p>b. Identified as critical (2/6), important (3/6) and requiring more information (1/6) by people with FA and important by expert authors on the topic.</p> <p>c. 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.</p> <p>d. 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.</p>							

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● 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.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know 	No data on oestradiol-releasing vaginal ring, oestrogen-based vaginal creams, pessaries containing oestriol or a slow-release 17 β -oestradiol tablet was found in the FA Clinical Outcome Measures (FA-COMS) registry.	<p>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).</p> <p>2/5 indicated commencing a course of natural estrogen for sexually active females with inadequate vaginal lubrication was probably reasonable, 3/5 indicated more information on the</p>

		benefits and potential harms required. (Aug 2020).
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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 ○
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CONCLUSIONS

Recommendation

We recommend not commencing a course of natural estrogen in sexually active females with inadequate vaginal lubrication with Friedreich ataxia.

Justification

While high rates of poor vaginal lubrication are documented in women with FRDA, there is no evidence for use of estrogen creams in FRDA. Moreover, the use of these agents would depend upon a risk assessment, particularly in terms of the individual's risk for developing breast/uterine cancer. Vaginal lubricants (aqueous/oil-based/silicone) are generally the first-line option for managing poor vaginal lubrication.

Subgroup considerations

This recommendation is for sexually active females with Friedreich ataxia with poor vaginal lubrication.

Research priorities

Further research is required on the use of estradiol-releasing vaginal ring, oestrogen-based vaginal creams, pessaries containing estriol or a slow-release 17 β -estradiol tablet in females with Friedreich ataxia who report inadequate vaginal lubrication.

Reference

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>]