

## QUESTION

### Should antidepressant medication vs. none be used for depressed patients with Friedreich ataxia?

|                |   |
|----------------|---|
| POPULATION:    | depressed patients with Friedreich ataxia                                 |
| INTERVENTION:  | antidepressant medication   |
| COMPARISON:    | none  |
| MAIN OUTCOMES: | Less depression; Side effect frequency; Reduced vegetative symptoms; QOL; |

## ASSESSMENT

### Problem

Is the problem a priority?

| JUDGEMENT   | RESEARCH EVIDENCE  | ADDITIONAL CONSIDERATIONS  |
|---|--|--|
| <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul> | <p>Depressive symptoms higher than expected in FRDA, but often individuals with FRDA do not present as depressed.</p> <p>In a cohort of 62 individuals with FA the mean BDI score was 15.32 (SD=10.33). Minimal depressive symptoms were observed in 50% of participants, 23% of participants scored in the “mild” range, 23% had moderate depressive symptoms, and 5% scored in the “severe” range (Perez-Flores et al 2020). In a cohort of 57 adults with FA the mean BDI score for FRDA patients was 13.62 (SD = 9.52) which is significantly higher than the mean score in the general population (<math>t(56) = 3.15, p &lt; .01</math>), according to populations norms (Neito et al 2018),</p> <p>Depression varies: one study using the Beck Depression Inventory (BDI-II) showed the following frequencies for each level of depression: 0–9 (score normal) 21/33 patients, 63.6%; 10–18: mild depression 6/33 patients, 18.2%; 19–29: moderate depression 5/33 patients, 15.1%; 30–63: severe depression 1/33 patient, 3% (Alexandra Durr, personal communication, 2021).</p> | <p>The Friedreich’s ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of depression.</p> <p>5/6 indicated that the problem was serious, 1/6 indicated they didn’t know if serious.</p> <p>4/6 indicated that the problem was urgent, 1/6 indicated probably urgent, 1/6 indicated probably not urgent.</p> <p>4/6 indicated that the problem was a priority, 2/6 indicated probably 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"> <li><input type="radio"/> Trivial</li> <li><input type="radio"/> Small</li> </ul> | <p>A search of five databases (CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 29 July 2020. No</p> |                           |

|   |   |  |
|---|---|--|
| <ul style="list-style-type: none"> <li>○ Moderate</li> <li>● Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul> | <p>further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p> |  |
|---|---|--|

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT   | RESEARCH EVIDENCE  | ADDITIONAL CONSIDERATIONS   |
|---|--|---|
| <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>● Varies</li> <li>○ Don't know</li> </ul> | <p>A search of five databases (CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 29 July 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p> | <p>Clinical experience of suicide, withdrawal from physical therapy.</p> <p>Side effects of antidepressants may be undesirable such as dizziness, reduced balance and mobility</p> <p>Side effect of improvement in dysarthria may be reported.</p> <p>Response can vary from person to person.</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"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>● No included studies</li> </ul> | <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"> <li>○ Important uncertainty or variability</li> <li>● Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> </ul> |                   | <p>Clinical experience that individuals with FA may not put great emphasis on main outcomes.</p> <p>Need further research.</p> |

|   |  |                        |  |  |
|---|--|------------------------|--|--|
| <input type="radio"/> No important uncertainty or variability   | <b>Outcomes</b>                            | <b>Importance</b>      | <b>Certainty of the evidence (GRADE)</b> |  |
|   | Less depression - not measured             | IMPORTANT <sup>a</sup> | -  |  |
|   | Side effect frequency - not measured       | IMPORTANT <sup>b</sup> | -  |  |
|   | Reduced vegetative symptoms - not measured | CRITICAL <sup>c</sup>  | -  |  |
|   | QOL - not measured                         | CRITICAL <sup>d</sup>  | -  |  |
| <p>a. 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.</p> <p>b. Identified as critical (1/6), important (2/6), low importance (2/6) and requiring more information (1/6) by people with FA and important by expert authors on this topic.</p> <p>c. 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.</p> <p>d. Identified as critical (3/6) and important (3/6) by people with FA and important by expert authors on this topic.</p> |  |                        |  |  |

## Balance of effects

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

| JUDGEMENT   | RESEARCH EVIDENCE      | ADDITIONAL CONSIDERATIONS   |
|---|------------------------|---|
| <input type="radio"/> Favors the comparison<br><input type="radio"/> Probably favors the comparison<br><input type="radio"/> Does not favor either the intervention or the comparison<br><input type="radio"/> Probably favors the intervention<br><input checked="" type="radio"/> Favors the intervention<br><input type="radio"/> Varies<br><input type="radio"/> Don't know | No published evidence. | Clinical experience is that if person accepts medication they are grateful to have the intervention.<br><br>Variability and uncertainty does not detract from need to trial the intervention because of possible benefit to patient.<br><br>Clinicians need to be aware of side effects in ataxic patients. |

## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|-----------|-------------------|---------------------------|
|           |                   |                           |

|   |                        |   |
|---|------------------------|---|
| <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input checked="" type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul> | No published evidence. | <p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if antidepressant medication use in depression was acceptable (weighing up the balance between benefits, harms and costs).</p> <p>1/4 indicated that the intervention was acceptable, 2/4 indicated probably acceptable, 1/4 indicated probably not acceptable. (Aug 2020).</p> |
|---|------------------------|---|

## 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 | <b>Possibly important uncertainty or variability</b> | 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        | <b>Favors the intervention</b> | Varies | Don't know          |
| ACCEPTABILITY         | No                                   | Probably no  | Probably yes   | Yes                                     |                                | Varies | Don't know          |

## TYPE OF RECOMMENDATION

|   |  |   |   |   |
|---|--|---|---|---|
| Strong recommendation against the intervention<br><input type="radio"/> | Conditional recommendation against the intervention<br><input type="radio"/> | Conditional recommendation for either the intervention or the comparison<br><input type="radio"/> | Conditional recommendation for the intervention<br><input checked="" type="radio"/> | Strong recommendation for the intervention<br><input type="radio"/> |
|---|--|---|---|---|

## CONCLUSIONS

Recommendation

We conditionally recommend the use of antidepressant medication in individuals with Friedreich ataxia who present with symptoms of depression.

## Justification

Cohort studies indicate that the presence of depressive symptoms may be greater in individuals with FRDA than those without FRDA. Whilst there is no published evidence in FRDA, if treatment is efficacious then the desirable effect on individuals who are depressed would be large. Clinical experience of the authors indicates there is no difference in response rate in individuals with FRDA compared to those without FRDA, when they accept use of medication. Individuals with FRDA less likely to accept a diagnosis of depression; however, there is no reason why they would not respond to treatment after accepting that treatment may be of benefit. For this reason, it is important to make sure individuals with FRDA are screened and clinicians are alert to the possibility of depression.

Note, the consequences of depression are major (suicidal, hospitalisation) and the experience of the expert authors indicate individuals with FRDA may not recognise depressive symptoms. Clinicians need to be very careful in considering both the degree of depression and the possibility of masking of symptoms. As such, careful assessment of severity of depression is warranted.

## Subgroup considerations

This recommendation is for individuals with Friedreich ataxia and depression and should be implemented according to an assessment of the severity of depression. Balance of side effects versus efficacy needs to be taken into account when considering treatment options.

## Research priorities

Further research to both confirm the prevalence and explore efficacy of treatment options for depressive symptoms is required.

### References

Nieto A, Hernández-Torres A, Pérez-Flores J, Montón F. Depressive symptoms in Friedreich ataxia. *Int J Clin Health Psychol*. 2018;18(1):18-26.

Pérez-Flores J, Hernández-Torres A, Montón F, et al. Health-related quality of life and depressive symptoms in Friedreich ataxia. *Qual Life Res* 2020;29(2):413–420.