QUESTION

Should anti-psychotic medication vs. none be used for psychosis patients with Friedreich ataxia ?	
POPULATION:	psychosis patients with Friedreich ataxia
INTERVENTION:	anti-psychotic medication
COMPARISON:	none
MAIN OUTCOMES:	Less psychosis; Side effect frequency; QOL;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of psychosis. 3/6 indicated that the problem was serious, 1/6 indicated probably serious, 2/6 indicated they didn't know if serious. 2/6 indicated that the problem was urgent, 1/6 indicated probably urgent, 1/6 indicated probably not urgent, 2/6 indicated they didn't know if urgent. 2/6 indicated that the problem was a priority, 2/6 indicated probably a priority, 1/6 indicated probably not a priority, 2/6 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		Psychosis is more likely to be in end-stage patients rather than earlier stage FRDA, so it may be hard to judge the efficacy of medication, particularly if severe dysarthria is present. Patients may stop attending clinical services at end-stage FRDA, hence the beginnings of psychosis may not be apparent. The incidence of the first episode of schizophrenia may occur in young people or be related to hypoxia. It is important to exclude other sources of psychosis (recreational drugs, hypoxia due to SDB or schizophrenia) in those with non-advanced FRDA.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with none	Risk difference with anti-psychotic medication

	Less psychosis - not measured	-	-	-		Antipsychotics should work as well in people with FRDA as in those without FRDA; however, it is hard to judge as patients often cannot communicate or are lost to follow-up. It is important that primary health care providers are alert to and consider psychosis in individuals with advanced FRDA. The effects of antipsychotics vary by how interactive the patient is.
	Side effect frequency assessed with: Self report	0 (1 observational study)[1]	⨁◯◯◯ VERY LOW[a]	-	A 29-year old man with Friedreich ataxia presented with a 1 week history of irritability, dysphoria, perseverations, derailment, paranoid delusions, auditory hallucinations, and somatic sensations shortly after administration of IV amiodarone. He was initially treated with aripiprazole, followed by risperidone and subsequently added its long-acting metabolite, PP, albeit withoutpersistent symptom remission. The severe sedative side effects of the neuroleptic medication, in addition to recurrent psychotic episodes, further complicated the course of the disorder. The patient passed away a few months after with exact cause of death remaining unclear.	
	QOL - not measured	-	-	-	-	-

1. Ganos C., Schottle D.,Zuhlke C.,Munchau A.. Psychosis Complicating Friedreich Ataxia. . Mov. Disord. Clin. Pract.; 2015.

a. Single case study.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
● Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with none	Risk difference with anti-psychotic medication
Less psychosis - not measured	-	-	-		
Side effect frequency assessed with: Self report	0 (1 observational study)[1]	⨁◯◯◯ VERY LOW[a]	-	A 29-year old man with Friedreich ataxia presented with a 1 week history of irritability, dysphoria, perseverations, derailment, paranoid delusions, auditory hallucinations, and somatic sensations shortly after administration of IV amiodarone. He was initially treated with aripiprazole, followed by risperidone and subsequently added its long-acting metabolite, PP, albeit withoutpersistent symptom remission. The severe sedative side effects of the neuroleptic medication, in addition to recurrent psychotic episodes, further complicated the course of the disorder. The patient passed away a few months after with exact cause of death remaining unclear.	
QOL - not measured	-	-	-	-	-

1. Ganos C., Schottle D.,Zuhlke C.,Munchau A.. Psychosis Complicating Friedreich Ataxia. . Mov. Disord. Clin. Pract.; 2015.

a. Single case study.

In end-stage disease, medication can reduce respiration. It may affect heart function and speech. Medical fragility in FRDA patients is a consideration.

Shapiro et al (2006) published a paper on psychosis in Late Onset Tay Sachs (LOTS) and concluded the following: “Notwithstanding the limitations of a retrospective study, our data support reports of neurologic worsening in patients with LOTS exposed to certain psychotropic medications, notably haloperidol. Our data also implicate risperidone and chlorpromazine in neurologic worsening and support the use of lorazepam, clonazepam, and carbamazepine in patients with LOTS".

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 of evidence 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	<table><tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Less psychosis - not measured</td><td>IMPORTANT[a]</td><td>-</td></tr><tr><td>Side effect frequency assessed with: Self report</td><td>IMPORTANT[b]</td><td>⨁◯◯◯ VERY LOW[c]</td></tr><tr><td>QOL - not measured</td><td>CRITICAL[d]</td><td>-</td></tr></table> a. Identified as critical (2/6), low importance (2/6) and requiring more information about the outcome (2/6) by people with FA and important by expert authors on this topic b. Identified as low importance (2/4), important (2/4) by people with FA and important by expert authors on this topic c. Single case study. d. Identified as important (3/6), critical (3/6) by people with FA and important by expert authors on this topic	Self-report difficult – value of treating, compliance

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	No published evidence.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if antipsychotic medication use in people with psychosis was acceptable (weighing up the balance between benefits, harms and costs). 2/4 indicated the intervention was acceptable, 2/4 indicated they didn't know if 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**			
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 the use of antipsychotic medication in individuals with Friedreich ataxia with confirmed episodes of psychosis.

Justification

Antipsychotics should work as well in individuals with FRDA as in those without FRDA. It is important for the primary healthcare provider to be alert to and consider psychosis in individuals with advanced FRDA.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia and a confirmed diagnosis of psychosis. Individuals who have severe dysarthria require careful screening to ensure accurate diagnosis.

Research priorities

More research is required regarding both the incidence and mechanism of psychosis in individuals with FRDA.

Reference

Shapiro BE, Hatters-Friedman S, Fernandes-Filho JA, Anthony K, Natowicz MR. Late-onset Tay-Sachs disease: adverse effects of medications and implications for treatment. Neurology. 2006 Sep 12;67(5):875-7.