A randomised placebo-controlled trial to determine if fluoxetine is effective for improving autistic behaviours

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Background

- Restricted and repetitive behaviours are a core feature of the autism spectrum disorders
- They interfere with function and quality of life

Background

- More than half of children and adolescents with ASD are prescribed medication
- 21% to 32% receive Selective Serotonin Receptor Inhibitors (SSRIs)
- Efficacy remains inconclusive

Cochrane Review - 2013

- Nine randomised trials with a total of 320 participants
- Fluoxetine, fluvoxamine, fenfluramine and citalopram
- Five studies included only children / four included only adults
- 18 different outcome measures reported
- The largest RCT involving 149 children showed no evidence of a positive effect of citalopram compared with placebo
- The authors concluded there is no evidence of effectiveness of SSRIs for ASD in children

Aim of study

To determine the effectiveness and tolerability of low dose fluoxetine for reducing the frequency and severity of restricted, repetitive and stereotypic behaviours – the Fluoxetine for Autistic Behaviours Study (FAB study)

Methods

Multi-centre randomised placebo-controlled trial

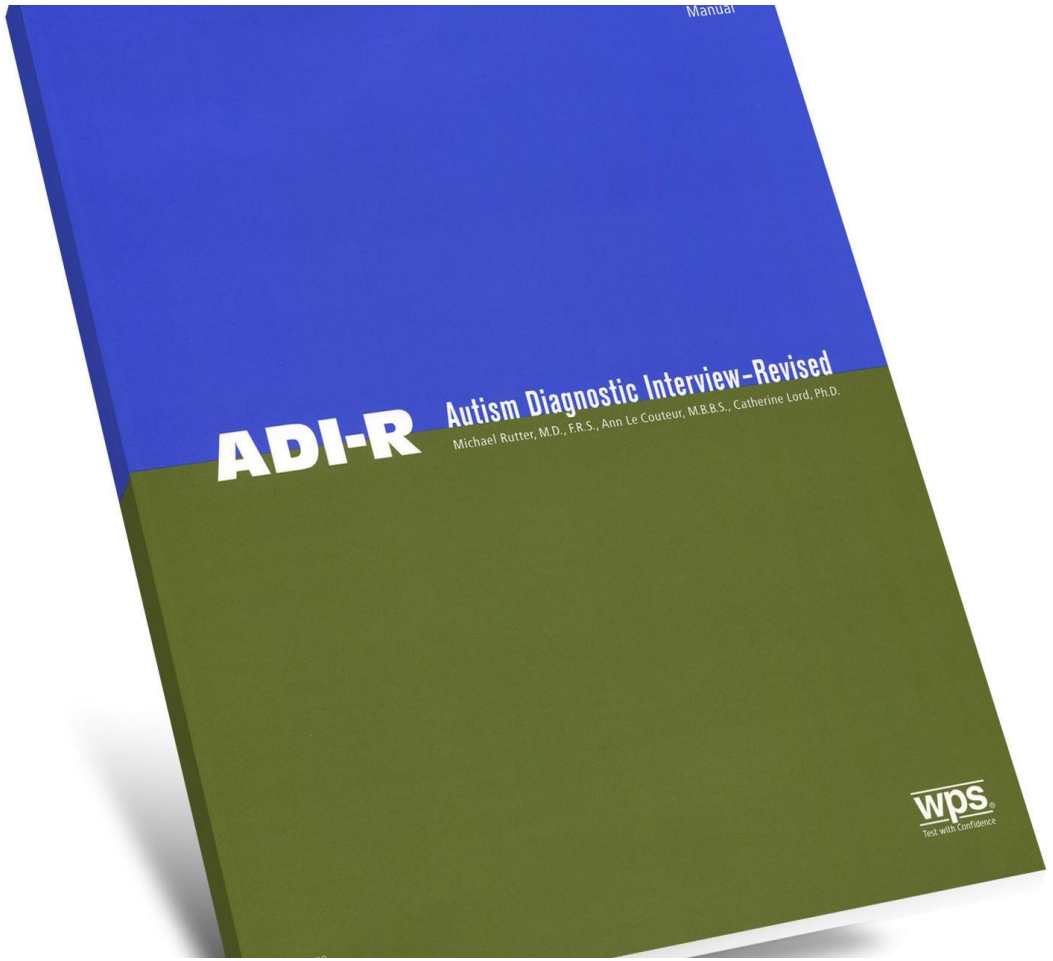
Three Australian sites:

- Royal Children's Hospital, Melbourne
- Sydney Children's Hospitals Network
- State Child Development Centre, Perth.

Methods – inclusion criteria

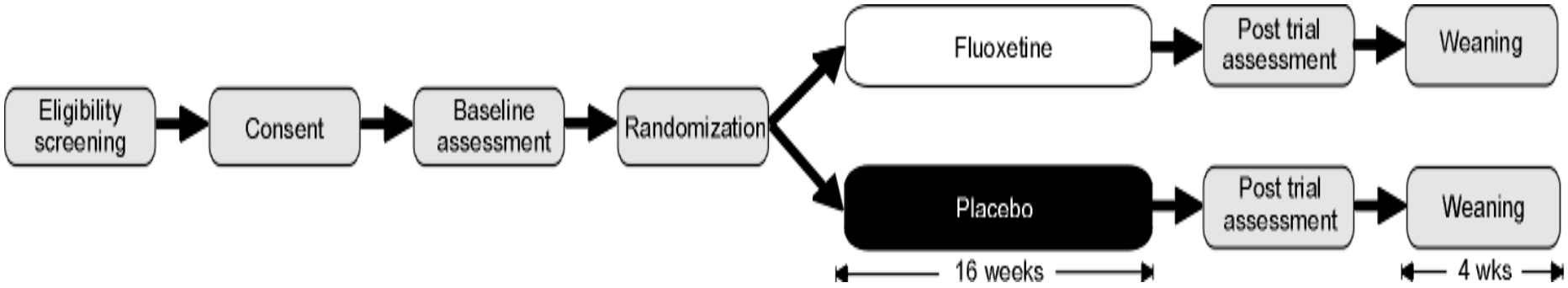
- Children and adolescents aged 7.5 - 18 years with ASD based on the Autism Diagnostic Interview

- Total score of ≥ 6 on the Children's Yale-Brown Obsessive-Compulsive Scale – modified for pervasive developmental disorders (CYBOCS-PDD)



Methods - dosage

- Randomised, fluoxetine commenced at 4 or 8mg/day for the first week (4mg if <40Kg; 8mg if ≥40Kg)
- Titrated up to a maximum dose of 20mg/day for participants <40kg and 30mg/day for participants ≥40kg, over 4 weeks
- Participants remained on the medication for 16 weeks



Outcome measures

Primary outcome

Total score on the Children's Yale-Brown Obsessive Compulsion Scale – Modified for Pervasive Developmental Disorders (CYBOCS-PDD) at 16 weeks

- Detailed symptom checklist of possible obsessions and compulsions
- Rated from zero to four across five items
- Time spent on obsessions, interference, distress, resistance, and degree of control
- Total scores range from 0 – 20 with higher scores indicating higher levels of maladaptive behaviour

Secondary outcomes – all measured at 16 weeks

- Repetitive Behaviours Scale – Revised (RBS-R)
- Spence Children's Anxiety Scale (SCAS)
- Aberrant Behaviour Checklist (ABC) – Community Version

Clinical Global Impressions Scale (CGI)

Sample size

- Based on the study investigators' clinical experience, a difference of 2 on the CYBOCS represented a clinically important improvement in repetitive behaviours.
- Study powered to find an effect size of 0·5 (corresponding to a difference of 2 on the CYBOCS based on a SD = 3·9).
- With 80% power and two-sided alpha of 0·05, a sample size of 64 per treatment group was required.
- We allowed for a 15% drop-out rate
- Therefore needed to recruit 73 participants per treatment group, 146 participants in total.

Results - Demographics

	Fluoxetine (N = 75)	Placebo (N = 71)	Overall (N = 146)
Sex (Male)	69 (92%)	56 (78%)	124 (86%)
Mean Age	11.3 years	11.0 years	11.2 years
Intellectual disability present	23 (31%)	21 (30%)	44 (30%)

Primary outcome - CYBOCS

	Fluoxetine		Placebo		Analysis[2]		
CYBOS-PDD 16 weeks	N	Mean[1]	N	Mean[1]	MD	95% CI	p-value
	75	8·84	71	10·68	-1·62	(-3·57; 0·33)	0·10

[1] Mean scores presented following multiple imputation for the missing data. Given this there is no corresponding standard deviation

[2] Linear regression model - adjusted for the stratification factors (site, age and intellectual disability), sex, verbal vs non-verbal, CYBOS-PDD at baseline, and variables that were found to be imbalanced at baseline: total RBS items, total RBS score and total score on ABC 11-lethargy.

Secondary outcomes

	Fluoxetine		Placebo		Statistical analysis		
	N	Mean (SD)	N	Mean (SD)	MD	95% CI	p-value
RBS - Total Items	75	16·71	71	21·47	-2·93	(-6·81; 0·95)	0.137
RBS - Total Score	75	26.05	71	35·17	-4·48	(-12·11; 3·16)	0.248
Spence Children's Anxiety TOTAL	75	21.70	71	24·54	-3·00	(-8·42 ; 2·41)	0·274
ABC I - Irritability	75	12.19	71	13·65	-2·23	(-5·88 ; 1·42)	0.228
ABC II - Lethargy	75	9.54	71	14·23	-2·97	(-6·15 ; 0·21)	0.067
ABC III - Stereotypy	75	5.10	71	5·35	0·18	(-1·49 ; 1·84)	0.833
ABC IV - Hyperactivity	75	16.29	71	18·06	-2·12	(-6·23 ; 1·98)	0.306
ABC V - Inappropriate speech	75	3.82	71	3·87	0·28	(-0·89 ; 1·45)	0.636

Adverse events

	Fluoxetine N= 75	Placebo N = 71	Overall N = 146
Patients with at least one AE	34 (45%)	30 (42·3%)	64 (44%)

Conclusions

- This was the largest study of the effectiveness of fluoxetine for treating ASD to date
- Little evidence that low dose fluoxetine reduced the restricted and repetitive behaviours associated with ASD compared with placebo
- Cannot exclude the possibility that SSRIs may help children with anxiety or aggression

How will this information be used?

- Will the information be translated into practice with reduced use of SSRIs for the treatment of restricted and repetitive behaviour?
- What will be the best way to transmit this message and how can patient groups be advised about it?
  - Parents should be informed about lack of efficacy
  - Potential risks
  - Alternate treatments should be considered

Limitations

- Very difficult to recruit participants – took > 7 years, involving extra $$$
- Retention in study also difficult but missing data unlikely to have affected outcome – multiple imputation analysis
- More consumer involvement in study may have been beneficial

Future directions

1. Investigation of subgroups that may be more responsive to SSRIs

Serotonin transporter gene has a more common 16 repeat long allele (L), and a less common 14 repeat short allele (S)

Those with two long alleles (L/L genotypes) rate more severely on the ‘stereotyped and repetitive motor mannerisms’ domain of the ADIR

Correlation between response to fluvoxamine and the serotonin transporter gene has been described – more effective in those with an L/L or L/S genotype compared to the S/S genotype

2. Further investigation of the role of SSRIs for anxiety and / or aggression

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Thank you to the participants, their families and all the investigators on the team

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