

The evidence for (or against) therapies in autism

With thanks to Danielle Wheeler
and other systematic reviewers

Many different “popular” “biomedical interventions”

Drug-based
Complementary medicine

Cochrane Systematic reviews

- Risperidone
- SSRIs – not yet published
- Tricyclic antidepressants – in development
- Secretin
- Gluten/casein diet
- Vit B6/Magnesium
- Free fatty acids – in development

Validity and applicability of existing evidence

- Outcomes
 - multiple
 - may not be sensitive to change
- Low numbers
 - low precision
 - clinical subgroups not investigated
- Variable
 - diagnostic inclusions
 - age groups
 - therapy
- Short follow-up
- Risk-benefit (side effects and cost)

Secretin Multiple outcomes Outcomes might not be sensitive to change

Outcome measure	Dunn-Geiler	Chez	Owley	Sandler	Carey	Kern	Levy	Molloy	Uhlis	Spethheim	Roberts	Corbett	Caviglio	Way
Core features of autism	Yes	Yes	Yes	Yes				Yes	Yes		Yes	Yes	Yes	Yes
Communication	Yes		Yes			Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes
Behaviour			Yes	Yes	Yes	Yes	Yes		Yes	Yes		Yes		
Visio-spatial skills			Yes					Yes				Yes		
Adverse events				Yes										

25 different outcome measures were used

Low numbers, Variable ages

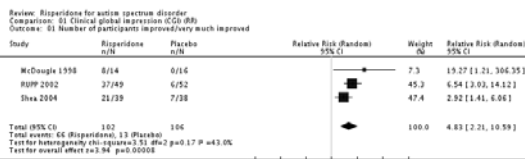
Title	Study sample size range	Age
Intravenous secretin	6-95	2-18 yrs
Risperidone	31-101	5-43 yrs
Vitamin B6-Mg	12-15	3-18 yrs
Gluten and casein free diet	15-20	2-16 yrs

Cochrane reviews

Quality of studies in Cochrane reviews

	Number of trials	Allocation concealment adequate	Blinding of outcome assessors
Secretin	14	6	7
Vitamin B6 & Mg	3	0	3
Risperidone	3	0	3
Gluten & casein free diet	2	2	2

Risperidone: Clinical Global Impression Scale

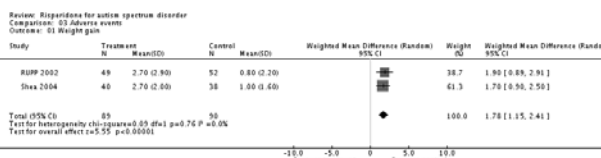


Risperidone: Aberrant Behavior Checklist

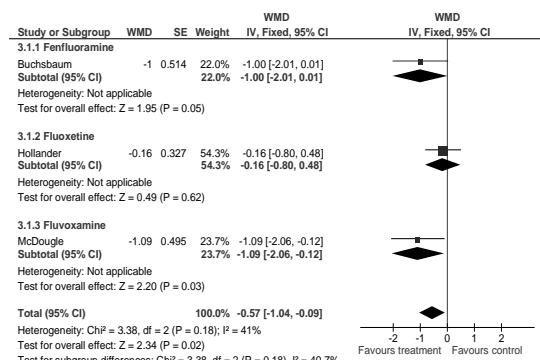
Subgroups of Aberrant Behavior Checklist	Measure of treatment effect (95% CI)	Quality of evidence
Irritability	-8.09 (-12.99, -3.19)	low, I ² =77.75
Social withdrawal/lethargy	-3.00 (-5.03, 0.97)	low
Hyperactivity	-8.98 (-12.01, -5.94)	low
Stereotypy	-1.71 (-2.97, -0.45)	low
Inappropriate speech	-1.93 (-3.79, -0.07)	low

From two trials with a total of 178 participants

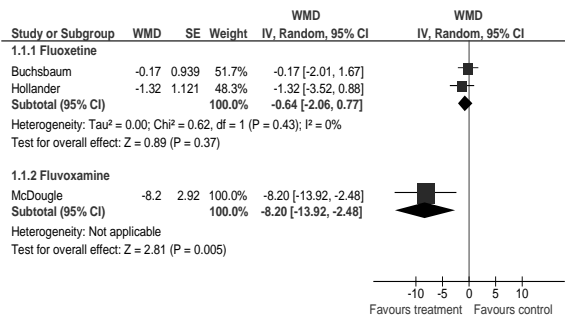
Risperidone: Weight Gain



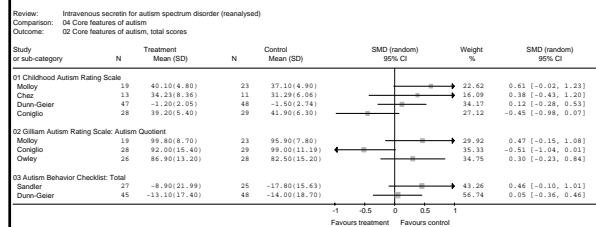
SSRIs: Clinical Global Impression



SSRIs: Obsessive Compulsive Behaviour



Secretin Diagnostic features of autism



Gluten and casein free diet, Vitamin B6-Mg

- No meta-analyses possible:
 - results only available for one study
 - diversity of participants and clinical populations
- Some individual studies reported some statistically significant positive effects

Cochrane reviews in development

Tricyclic antidepressants

Clomipramine Versus Haloperidol in the Treatment of Autistic Disorder: A Double-Blind, Placebo-Controlled, Crossover Study
Remington et al. J Clin Psychopharmacol, Volume 21(4);2001:440-444

- 36 Individuals with a DSM-IV diagnosis of autistic disorder
- Mean age 16.3 years; range, 10–36 years
- Randomly assigned
- 7-week trials
- Clomipramine comparable to haloperidol for completed therapy
- Fewer individuals receiving clomipramine versus haloperidol completed the trial (37.5% vs. 69.7%, respectively)
 - side effects
 - efficacy
 - behavior problems.
- In the intent-to-treat sample only haloperidol proved superior to baseline
 - global measure of autistic symptom severity
 - measures for irritability and hyperactivity

Tricyclic antidepressants and Haloperidol

Measure	Baseline	Placebo	Clomipramine	Haloperidol	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
CARS	41.8 (7.1)	39.4 (7.0)	37.8 (8.7)	36.7 (6.1)	0.05 ^a
ESRS	6.6 (6.7)	7.9 (7.1)	10.3 (7.3)	7.8 (5.8)	0.35 ^b
DOTES	0.6 (2.2)	0.8 (1.7)	2.0 (2.9)	2.3 (3.3)	0.07 ^c

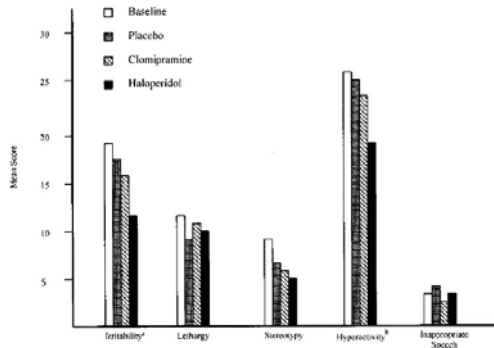
^aCARS, Childhood Autism Rating Scale; ESRS, Extrapyramidal Symptom Rating Scale; DOTES, Dosage/Treatment Emergent Symptom Scale

^bHaloperidol versus baseline (p < 0.05).

^cResults reported for Parkinsonism score, but nonsignificant for all ESRS measures.

^dResults for Behavioral Toxicity subscale, but nonsignificant for all subscales.

Tricyclic antidepressants and Haloperidol



Fatty Acids

Angley M et al.
**Children and autism—
 Part 2—management with
 complementary
 medicines and dietary
 interventions.**
 Aust Fam Physician.
 2007;36(10):827-30.

Omega-3 and omega-6 fatty acids

Omega-3 and omega-6 fatty acids, recognised as vital building blocks for developing neurological systems, are also claimed to have beneficial effects in children with autism. These essential fatty acids (EFAs) are present in fish oils, evening primrose oil and linseed (flaxseed) oil.²⁰ One case report²¹ and one comparative study (interrupted time series) without concurrent controls²² have reported benefits of essential fatty acid use in autism. Gastrointestinal side effects are reported with EFAs including: nausea, diarrhoea, increased belching, acid/reflux/heartburn/indigestion, abdominal bloating, and abdominal pain. Fishy aftertaste is commonly experienced and rare reports of skin rash have occurred.²³

Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study.

Amminger GP et al. Biol Psychiatry. 2007;61:551-3.

- Randomized, double-blind, placebo-controlled 6-week pilot trial
- 1.5 g/d of omega-3 fatty acids
- 13 children (aged 5 to 17 years)
- Autistic disorders accompanied by severe tantrums, aggression, or self-injurious behaviour.
- Outcome measure was the Aberrant Behavior Checklist (ABC)
- Omega-3 fatty acids more effective v placebo
 - Hyperactivity
 - stereotypy
- No clinically relevant adverse effects were elicited in either group.

Omega-3 Fatty Acid supplementation

Table 1. Mean Scores (± SD) on the Aberrant Behavior Checklist at Baseline and 6 Weeks

	Fish-Oil (n = 7)			Placebo (n = 6)			Comparison	
	Baseline	6 Weeks	Change	Baseline	6 Weeks	Change	Difference in Change	Effect Size (Cohen's d)
Irritability	29.3 (±9.2)	24.6 (±8.7)	4.7 (±3.5)	26.4 (±5.7)	21.8 (±2.8)	4.6 (±7.5)	.1	.02
Social Withdrawal	24.4 (±12.0)	18.9 (±13.5)	5.6 (±9.3)	25.4 (±4.4)	21.0 (±2.0)	4.6 (±5.4)	1.0	.37
Stereotypy	14.4 (±5.1)	13.0 (±5.2)	1.4 (±2.2)	7.8 (±6.4)	8.8 (±4.1)	-1.0 (±3.4)	2.4	.72
Hyperactivity	31.3 (±4.8)	29.3 (±5.7)	2.0 (±2.4)	24.6 (±5.5)	27.6 (±5.8)	-3.0 (±9.8)	7.0	.21
Inappropriate Speech	8.3 (±4.0)	7.6 (±4.0)	.7 (±3.8)	9.0 (±1.6)	9.4 (±2.8)	-4 (±2.8)	1.1	.39

What we know.....

Not as much as we should!

What needs to be done before we can make clinical decisions....

- All studies to follow CONSORT guidelines
- Multi-centre studies if one site studies can not recruit sufficient sample size
- Engagement with consumers so we measure important outcomes that will change practice (or not)
- **Pragmatic studies** that answer the clinical question for the clinical context

Cochrane review references

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