

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-Geier	Chez	Owley	Sandler	Carey	Kern	Levy	Molloy	Unis	Sponheim	Roberts	Corbett	Coniglio	Wray
Core features of autism	Yes	Yes	Yes	Yes				Yes	Yes		Yes	Yes	Yes	Yes
Communication	Yes		Yes			Yes	Yes	Yes			Yes	Yes	Yes	
Behaviour			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

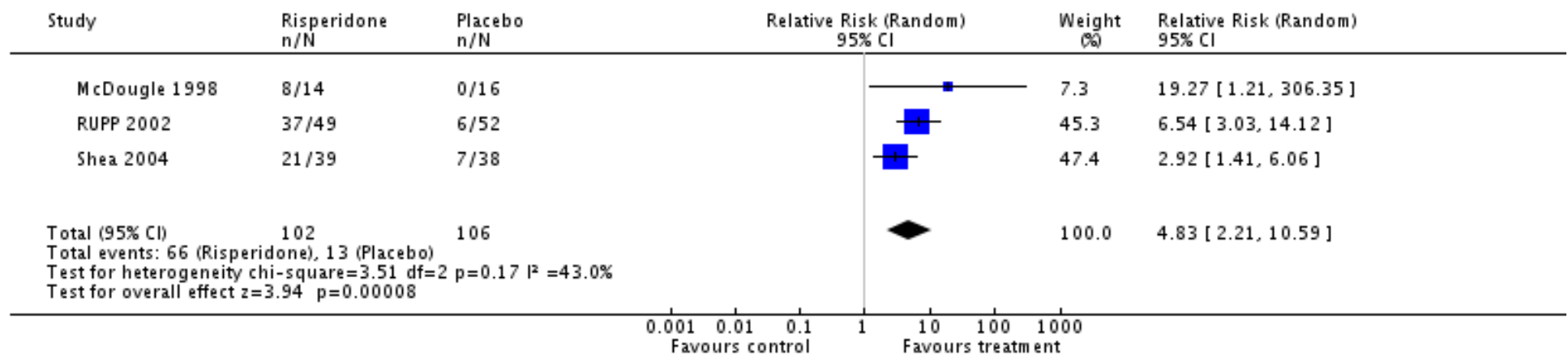
Cochrane reviews

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

Review: Risperidone for autism spectrum disorder
 Comparison: 01 Clinical global impression (CGI) (RR)
 Outcome: 01 Number of participants improved/very much improved



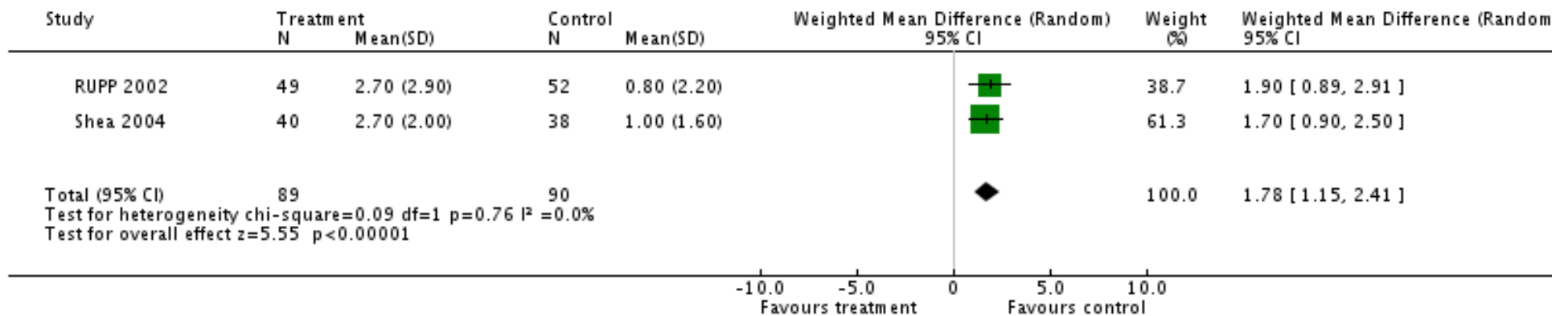
Risperidone: Aberrant Behavior Checklist

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

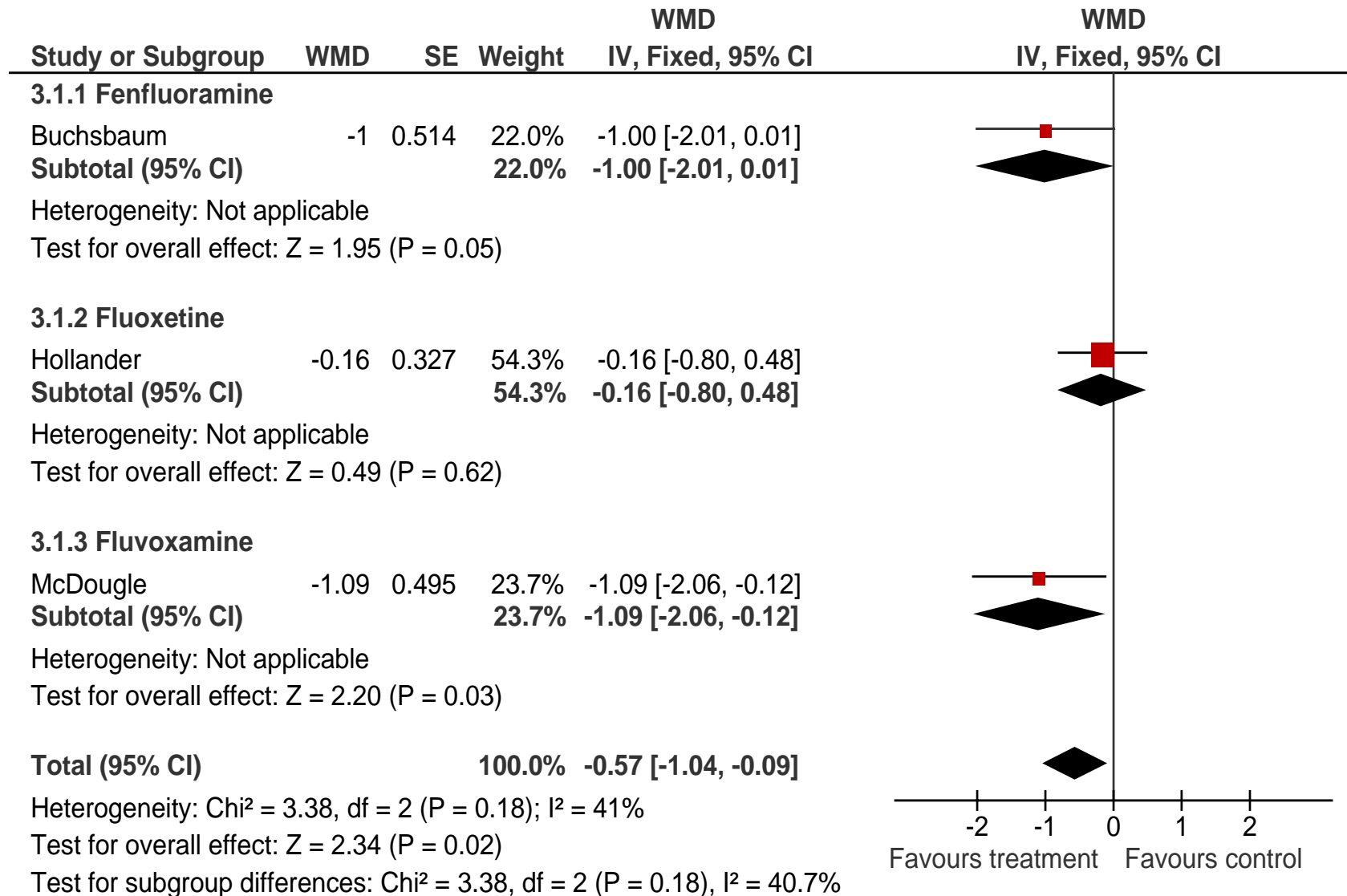
From two trials with a total of 178 participants

Risperidone: Weight Gain

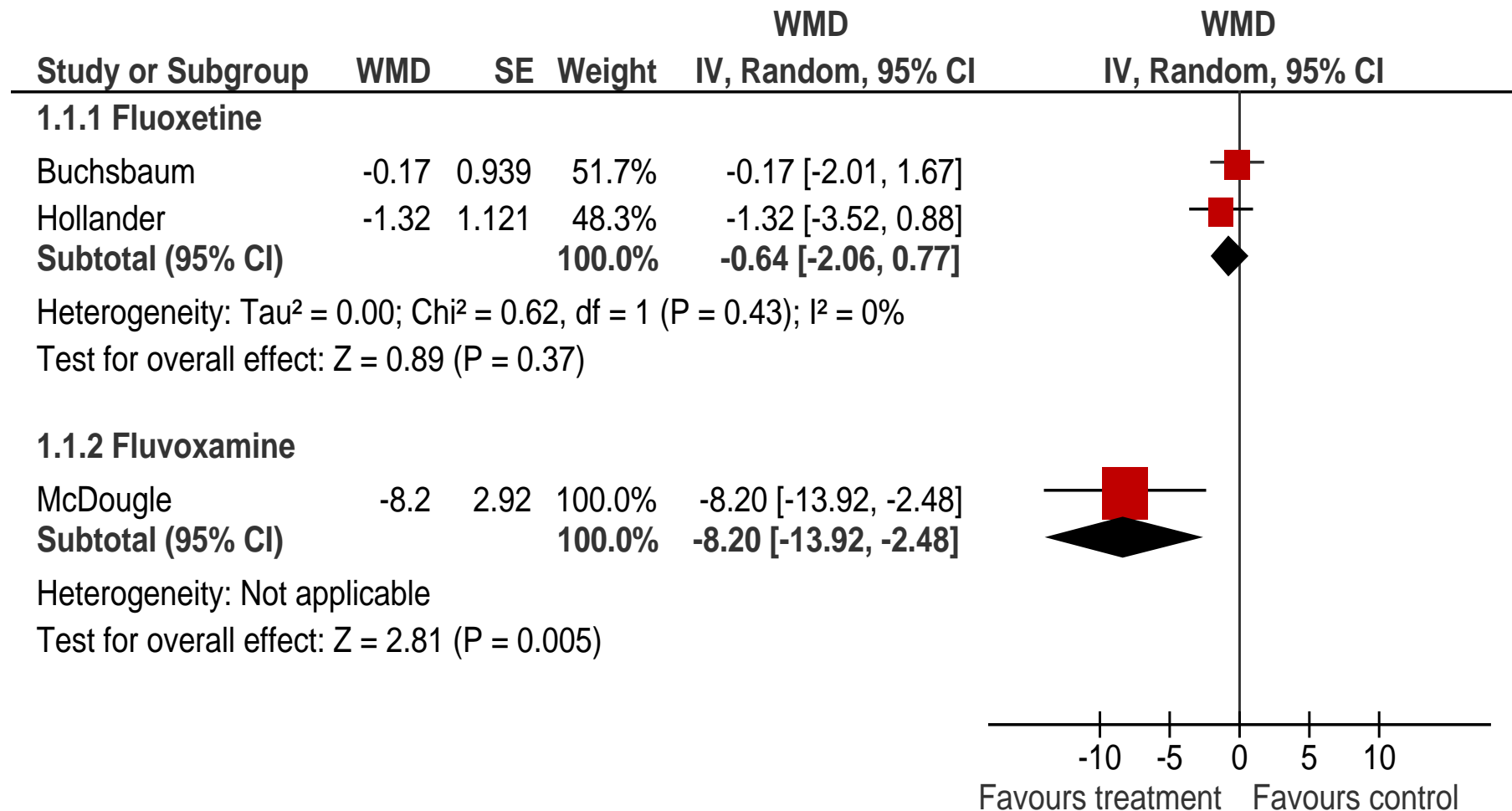
Review: Risperidone for autism spectrum disorder
 Comparison: 03 Adverse events
 Outcome: 01 Weight gain



SSRIs: Clinical Global Impression



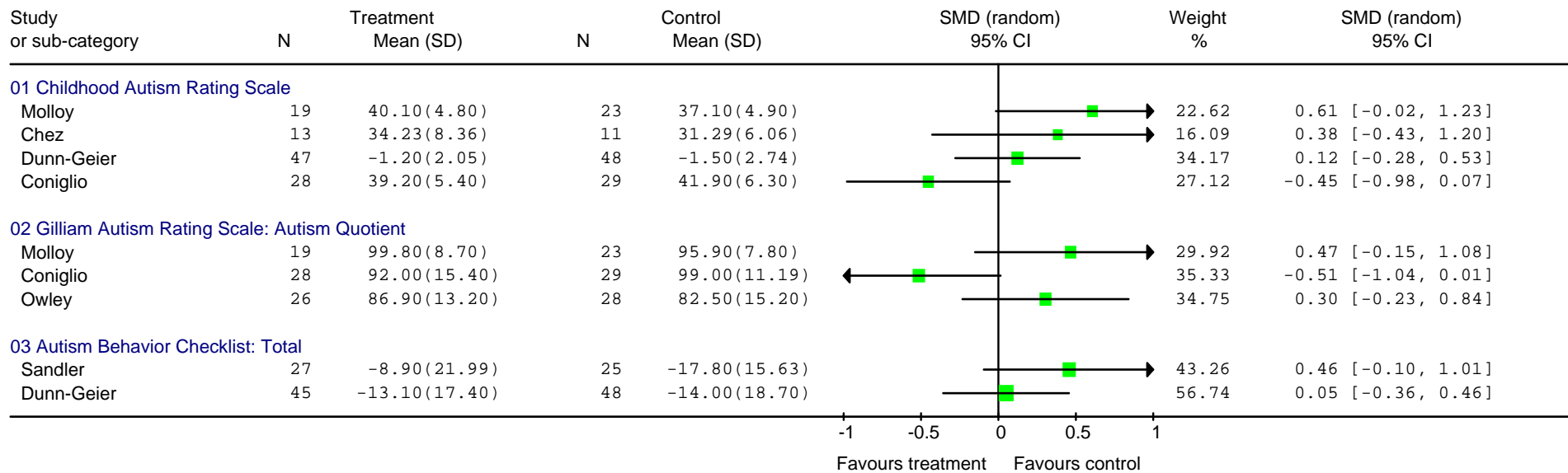
SSRIs: Obsessive Compulsive Behaviour



Secretin

Diagnostic features of autism

Review: Intravenous secretin for autism spectrum disorder (reanalysed)
 Comparison: 04 Core features of autism
 Outcome: 02 Core features of autism, total scores



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

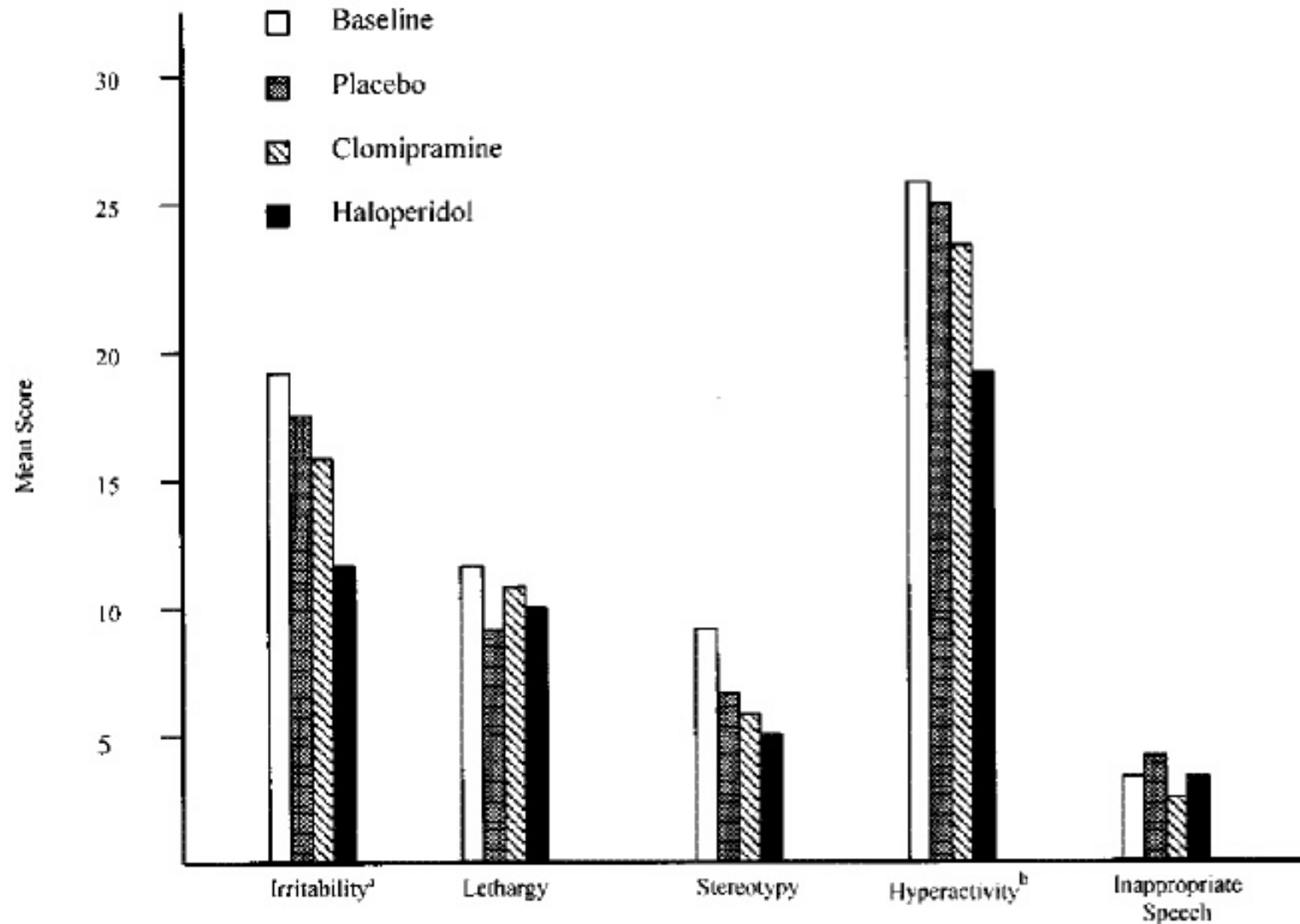
^aCARS, Childhood Autism Rating Scale; ESRS, Extrapyramidal Symptom Rating Scale; DOTES, Dosage Treatment Emergent Symptom Scale.

^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 (\pm SD) on the Aberrant Behavior Checklist at Baseline and 6 Weeks

	Fish Oil ($n = 7$)			Placebo ($n = 5$)			Comparison	
	Baseline	6 Weeks	Change	Baseline	6 Weeks	Change	Difference in Change	Effect Size (Glass' δ)
Irritability	29.3 (\pm 9.2)	24.6 (\pm 8.7)	4.7 (\pm 3.5)	26.4 (\pm 5.7)	21.8 (\pm 2.8)	4.6 (\pm 7.5)	.1	.02
Social Withdrawal	24.4 (\pm 12.0)	18.9 (\pm 13.3)	5.6 (\pm 8.1)	25.6 (\pm 4.4)	21.0 (\pm 2.0)	4.6 (\pm 5.6)	1.0	.17
Stereotypy	14.4 (\pm 5.1)	13.0 (\pm 5.2)	1.4 (\pm 2.2)	7.8 (\pm 6.4)	8.8 (\pm 4.1)	-1.0 (\pm 3.4)	2.4	.72
Hyperactivity	33.3 (\pm 4.8)	29.3 (\pm 5.7)	4.0 (\pm 2.4)	24.6 (\pm 5.5)	27.6 (\pm 5.9)	-3.0 (\pm 9.9)	7.0	.71
Inappropriate Speech	8.3 (\pm 4.0)	7.6 (\pm 4.0)	.7 (\pm 3.0)	9.0 (\pm 1.6)	9.4 (\pm 2.9)	-.4 (\pm 2.9)	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

- Wheeler DM, Hazell P, Silove N, Williams K. Selective serotonin reuptake inhibitors for the treatment of autism spectrum disorders. Cochrane Database of Systematic Reviews: Protocols 2004 Issue 1 John Wiley & Sons, Ltd Chichester, UK
- Millward C, Ferriter M, Calver S, Connell-Jones G. Gluten- and casein-free diets for autistic spectrum disorder. Cochrane Database of Systematic Reviews: Reviews 2004 Issue 2 John Wiley & Sons, Ltd Chichester, UK
- Nye C, Brice A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. Cochrane Database of Systematic Reviews: Reviews 2005 Issue 4 John Wiley & Sons, Ltd Chichester, UK
- Williams K, Wray JJ, Wheeler DM. Intravenous secretin for autism spectrum disorder. Cochrane Database of Systematic Reviews: Reviews 2005 Issue 3 John Wiley & Sons, Ltd Chichester, UK
- Jesner OS, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. Cochrane Database of Systematic Reviews: Reviews 2007 Issue 1 John Wiley & Sons, Ltd Chichester, UK