

Tricyclic Antidepressants for Autism

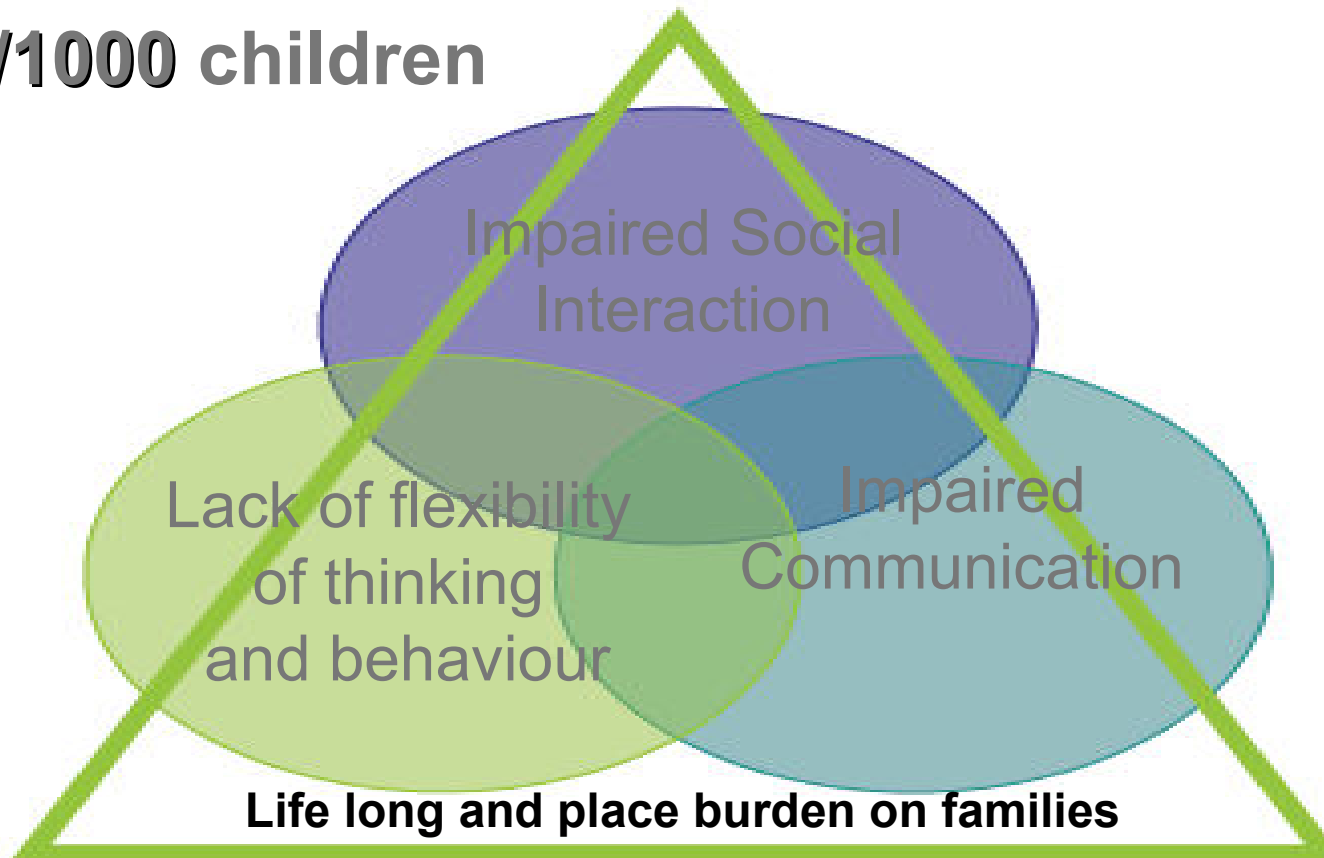
A Cochrane Review

Review team:

Dr Romy Hurwitz ; Dr Roger Blackmore; Dr Sue Woolfenden
Assoc Prof Katrina Williams; Prof Phil Hazel; Ms Danielle Wheeler

Autism Spectrum Disorder

3- 6/1000 children



DSM IV - Autistic Disorder, Asperger Syndrome, Pervasive Developmental Disorder Not Otherwise Specified

ICD10 – Childhood Autism, Atypical Autism

Current Treatment

- Behavioural and Educational Interventions
 - = main focus
- Pharmacological
 - = adjunct
 - Assist with problematic symptoms and comorbidities

Search Results

Show Results in:
Cochrane Reviews [11] | [Other Reviews \[18\]](#) | [Clinical Trials \[334\]](#) | [Methods Studies \[6\]](#) | [Technology A](#)
There are 11 results out of 5821 records for: "autism in Title, Abstract or Keywords in Cochrane Database"

View: 1-11

[Export All Results](#)

- Record Information**
- Intravenous secretin for autism spectrum disorder**
Katrina J Williams, John J Wray, Danielle M Wheeler
Year: 2005
[Record](#) [Review](#)
 - Gluten- and casein-free diets for autistic spectrum disorder**
Claire Millward, Michael Ferriter, Sarah J Calver, Graham G Connell-Jones
Year: 2008
[Record](#) [Review](#)
 - Combined vitamin B6-magnesium treatment in autism spectrum disorder**
Chad Nye, Alejandro Brice
Year: 2005
[Record](#) [Review](#)
 - Risperidone for autism spectrum disorder**
Ora S Jesner, Mehmoosh Aref-Adib, Esther Coren
Year: 2007
[Record](#) [Review](#)
 - Auditory integration training and other sound therapies for autism spectrum**
Yashwant Sinha, Natalie Silove, Danielle M Wheeler, Katrina J Williams
Year: 2004
[Record](#) [Review](#)
 - Parent-mediated early intervention for young children with autism spectrum**
Tim T J Diggle, Helen H R McConachie
Year: 2002
[Record](#) [Review](#)
 - Selective serotonin reuptake inhibitors for the treatment of autism spectrum**
Danielle M Wheeler, Philip Hazell, Natalie Silove, Katrina Williams
Year: 2004
[Record](#) [Protocol](#)
 - Risperidone for attention deficit hyperactivity disorder in people with intellectual disabilities**

Risperidone
Secretin
Gluten/casein diet
Vit B6/Magnesium
In development (Protocol)
SSRIs
Tricyclic antidepressants
Free fatty acids

This Cochrane Review: TCA's for ASD

- Intervention review
- Review current best evidence regarding the potential benefits and safety of TCA use in individuals with ASD

Tricyclic Antidepressants

- Block noradrenaline and serotonin reuptake at pre-synaptic neurons
- Increased availability in CNS
- Chronic use - up-regulate post-synaptic serotonin receptors

NB Limited use in children - narrow therapeutic index and high toxicity profile

- Potent membrane stabiliser \Rightarrow cardiac conduction abnormalities, lower seizure thresholds

The theory

- Serotonin (5-hydroxytryptamine) - inhibitory neurotransmitter in CNS
 - Regulates multiple functions eg mood, emotions, sleep, aggression and O-C behaviours
- High levels whole blood and platelet serotonin in patients with ASD
- Acute dietary depletion of precursor associated with exacerbation of behavioural symptoms
- ?reduced central responsivity to serotonin
- Pharmacological interventions targeting serotonin may impact core symptoms or co-morbidities

Objectives

To evaluate the experience of using TCAs in people with ASD

Determine if TCAs:

1. Improve core features
2. Improve non-core features
3. Improve co-morbid states
4. Cause adverse effects

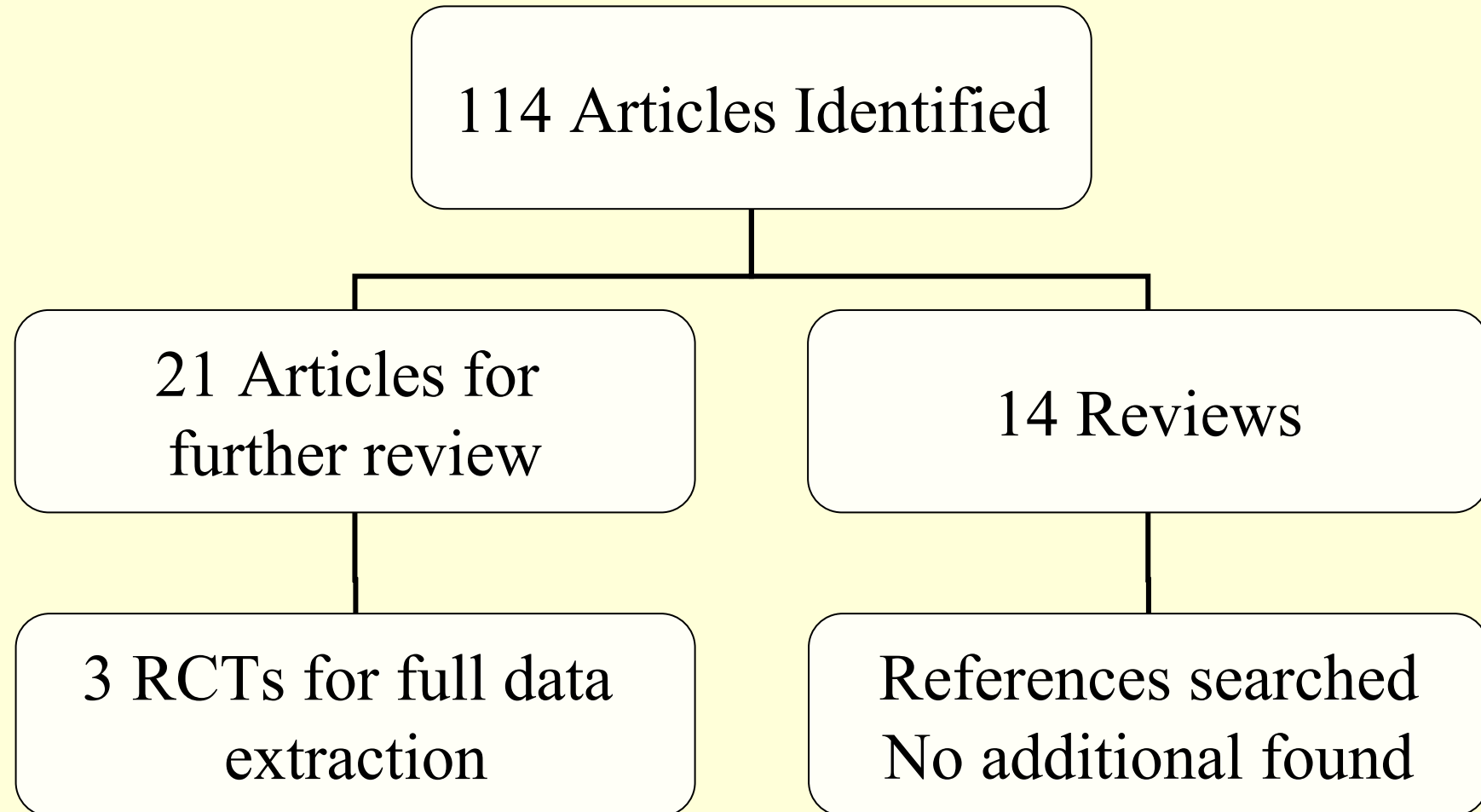
Methods

- Searching Electronic databases & contact with trialists
- Study types: Randomised controlled trials
- Participants: Diagnosis of ASD using standardised diagnostic instrument or criteria
 - PDD excluding Rett syndrome and Childhood Disintegrative Disorder
- Intervention: Oral TCA compared with placebo
- Outcomes: 1. Core symptoms of autism
 - 2. Non-core symptoms- challenging behaviours, sleep disturbance, aggression
 - 3. Co-morbidities - e.g. depression, anxiety
 - 4. Adverse effects
 - 5. Other - parental, child or family quality of life, family stress

Inclusion Criteria

- Randomised Control Trial
- Oral Tricyclic Antidepressants
- At least one standardised outcome measure
- Subjects diagnosed with ASD/Autistic disorder or PDD, excluding Rett Syndrome and Childhood Disintegrative Disorder
- Placebo Controlled

Results of Search



Included Articles

Study	n	Crossover study	TCA	Age	Duration
Niederhofer, 2003	12	√	Tianeptine	4-15yrs	6 weeks
Gordon, 1993	14	√	Clomipramine	7-15yrs	5 weeks
Remington, 2001	36	√	Clomipramine	10-36yrs	7 weeks

Small numbers, short durations, short washout times

Risk of Bias Table

	Gordon	Niederhofer	Remington
Random Sequence Generation	Yes	Unclear	Yes
Allocation Concealment	Yes	Yes	Yes
Blinding			
-Participants	Yes	Yes	Yes
-Personnel	Yes	Yes	Yes
-Assessors	Unclear	Yes	Unclear
Incomplete Data Addressed	Yes	Yes	Unclear
No Selective Reporting	Yes	Unclear	Yes
Overall Risk of Bias	Low	Unclear	Low

Statistical Significance of Clinical Outcomes

<i>Outcomes: P values</i>	<i>Autistic Symptoms</i>	<i>Anger/Irritability</i>	<i>Hyperactivity</i>	<i>Stereotypy</i>	<i>Abnormal Eye Contact</i>	<i>Inappropriate Speech</i>	<i>OCD Symptoms</i>	<i>Clinical Global Impression Scale</i>
Gordon, 1993 (clomipramine)	0.0001	0.0001	0.001	-	-	Not Significant	0.001	0.0001
Neiderhofer, 2003 (tianeptine)	-	0.047	0.035	-	0.041	0.042	-	-
Remington, 2001 (clomipramine)	0.02	0.04	Not significant	0.001	-	Not significant	-	-

Side Effects on TCAs

Trails of Clomipramine

- Fatigue/lethargy
- Tremors/twitches
- Tachycardia
- Insomnia
- Anticholinergic (constipation, dry mouth, flush)

Overall: No statistical significance between clomipramine and placebo

- *Gordon – 1 prolonged QT interval, 1 tachycardia*
- *Remington – no significant changes in cardiac conduction, no arrhythmias*

Side Effects Continued

Tianeptine (*Niederhofer*)

- Significant increase in drowsiness and reduction in activity at 6 weeks
- By 12 weeks, no significant difference between tianeptine and placebo

Conclusion

TCAAs are antidepressants which are used in individuals with ASD.

There appears to be some evidence of effectiveness in impacting autistic symptoms and comorbidities.

BUT Small numbers, short durations, short washout times, quality of studies

When completed, this review will analyse and summarise the existing evidence base about their use.

Intervention Protocol – published in Issue 2, January 2010

*Cochrane Database of Systematic Reviews 2010, Issue 2. Art.
No:CD008372.DOI:10.1002/14651858.CD008372*

With thanks to

- Dr Katrina Williams
- Dr Roger Blackmore
- Dr Sue Woolfenden
- Dr Phil Hazell
- Danielle Wheeler
- Cochrane Collaboration

And to Archie.....

- Archie Cochrane

“It is truly a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials” (1979)

“Help make well-informed decisions about health-care by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions”

