# Psychotropics in Learning Disabilities:

# Systematic reviews

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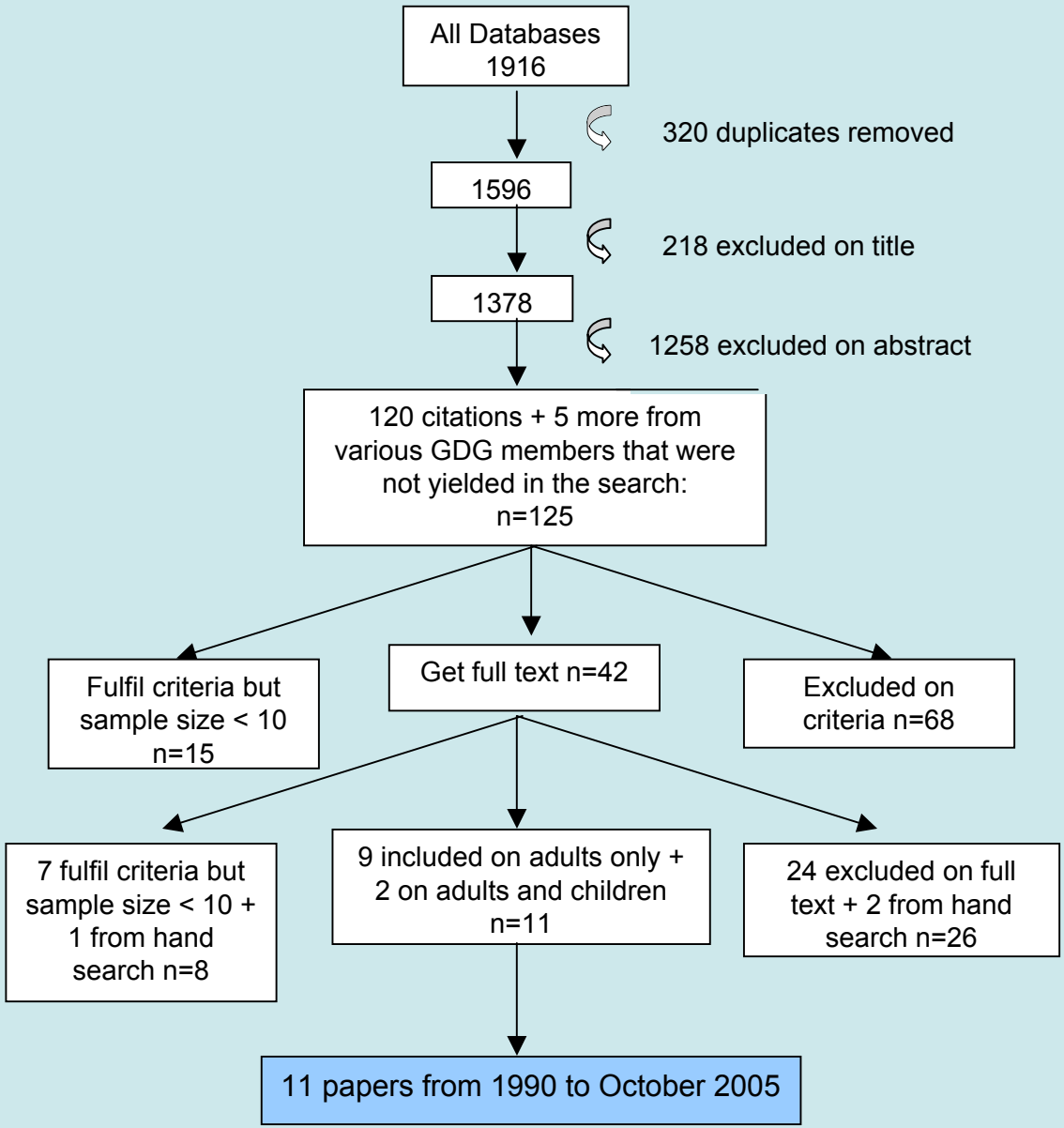
# HTA EVIDENCE CATEGORIES

- Type I: RCTs/ Meta analysis
- Type II: Other controlled studies
- Type III: Non-controlled studies
- Type IV:Expert reports/ consensus documents

# Electronic database search results (Antipsychotics)

| Database | Number of citations |
|---|---|
| PsycInfo | 187 |
| Medline | 291 |
| Embase | 1067 |
| Cinahl | 371 |


All Databases
1916
320 duplicates removed
1596
218 excluded on title
1378
1258 excluded on abstract
120 citations + 5 more from various GDG members that were not yielded in the search:
n=125
Fulfil criteria but sample size < 10
n=15
Get full text n=42
Excluded on criteria n=68
7 fulfil criteria but sample size < 10 + 1 from hand search n=8
9 included on adults only + 2 on adults and children
n=11
24 excluded on full text + 2 from hand search n=26
11 papers from 1990 to October 2005

# Summary of types of studies

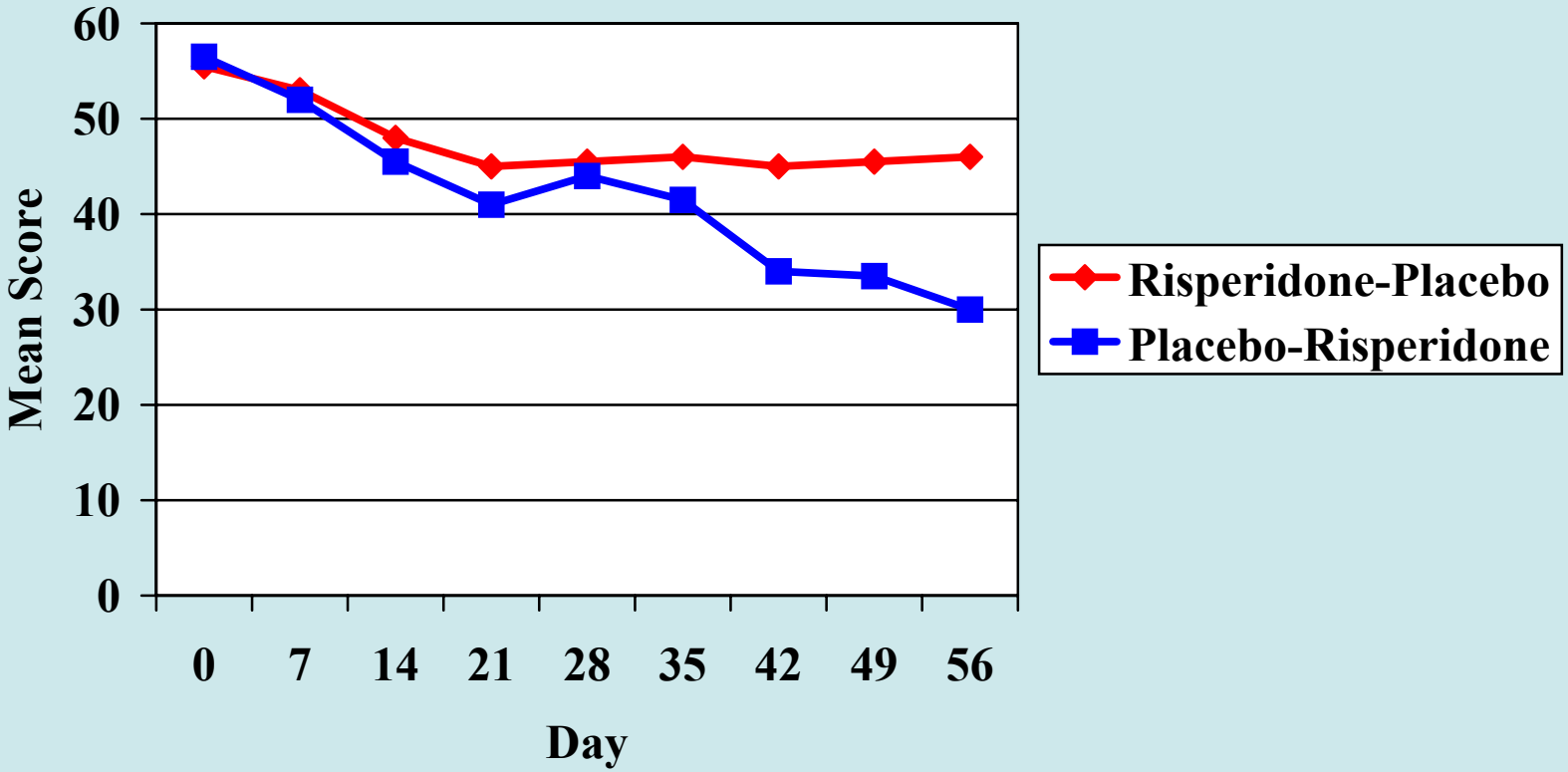
| Drug | n | RCT | Prospective | Retrospective |
|---|---|---|---|---|
| APT | 11 | 2 (39 vs. 38; 30) | 6 (15,15,18, 20,33,34) | 3 (17,20,24) |
| ATD | 10 | 1 (10) | 7 (10,14,15, 16,19,20,60) | 2 (14, 33) |
| AED | 4 | 1 (10) | 1 (28) | 2 (22,28) |
| Lithium | 3 | 2 (20 vs. 22; 52) | 0 | 1 (74) |

# Summary of types of studies

| Drug | n | RCT | Prospective | Retrospective |
|---|---|---|---|---|
| Naltrexone | 4 | 2 (33, 24) | 1 (15) | 1 (56) |
| Psychostimulants | 0 | 0 | 0 | 0 |
| Antianxiety Buspirone | 1 | 0 | 1 (26) | 0 |
| Diet/ vitamins | 1 | 1(Pica:128 control:30) | 0 | 0 |

# ANTIPSYCHOTICS

# Mean Score on the ABC for 2 Subgroups During the Eight Weeks of Observation (van Den Borre et al, 1993)

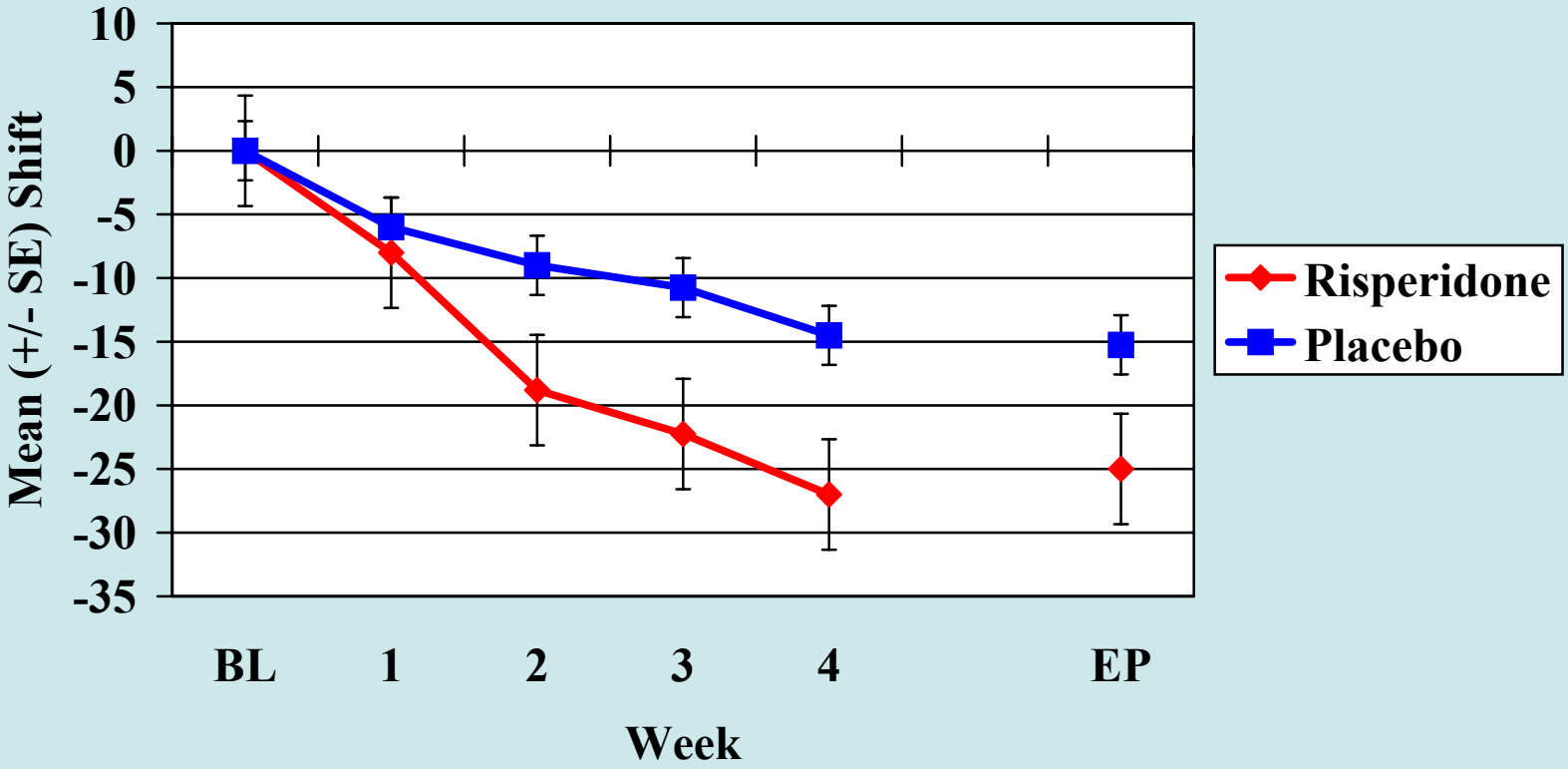


# van Den Borre, Acta Psychiatrica Scandi, 1993

- **Participants:** 37 adults (15-58 years); ID + ? psychiatric disorders. AGG, SIB, agitation, hyperactivity, irritability.
- **Intervention:** Risperidone (n=30 after 7 drop outs) 4-12 mgs/ day add-on.
- **Methods:** RCT Crossover.
- **Follow up:** 1 week wash out-3 weeks RCT-1 week wash out-3 weeks crossover RCT.
- **Outcomes:** Primary outcome = ABC total score; CGI + VAS (target behaviours); Extrapyramidal symptoms: ESRS: Blood tests, ECG, Wt..
- **Results:** 1st phase Ris: 16% & placebo: 15% drop in the ABC score; 2nd phase Ris: 27% & placebo: 0% drop. CGI: week 1: <0.05, week 3: <0.01 (both phases). VAS: no change. ESRS & ECG: no change. Ris: sedation: 10 times, drowsiness: 6 times; placebo: 0%. Blood & ECG: NAD.
- **Comments:** Risperidone is found to be superior. Conflicting results in two phases of the study. Conflicting results according to different outcome measures. Very short wash out period (chance of contamination with withdrawal symptoms). Short follow up period. Not known how many were on risperidone and how many were on placebo. The method of randomisation and blinding are not described. The IQ level or gender ratio was not specified.

# Aberrant Behaviour Checklist Total Scores (Gagiano et al, 2005)

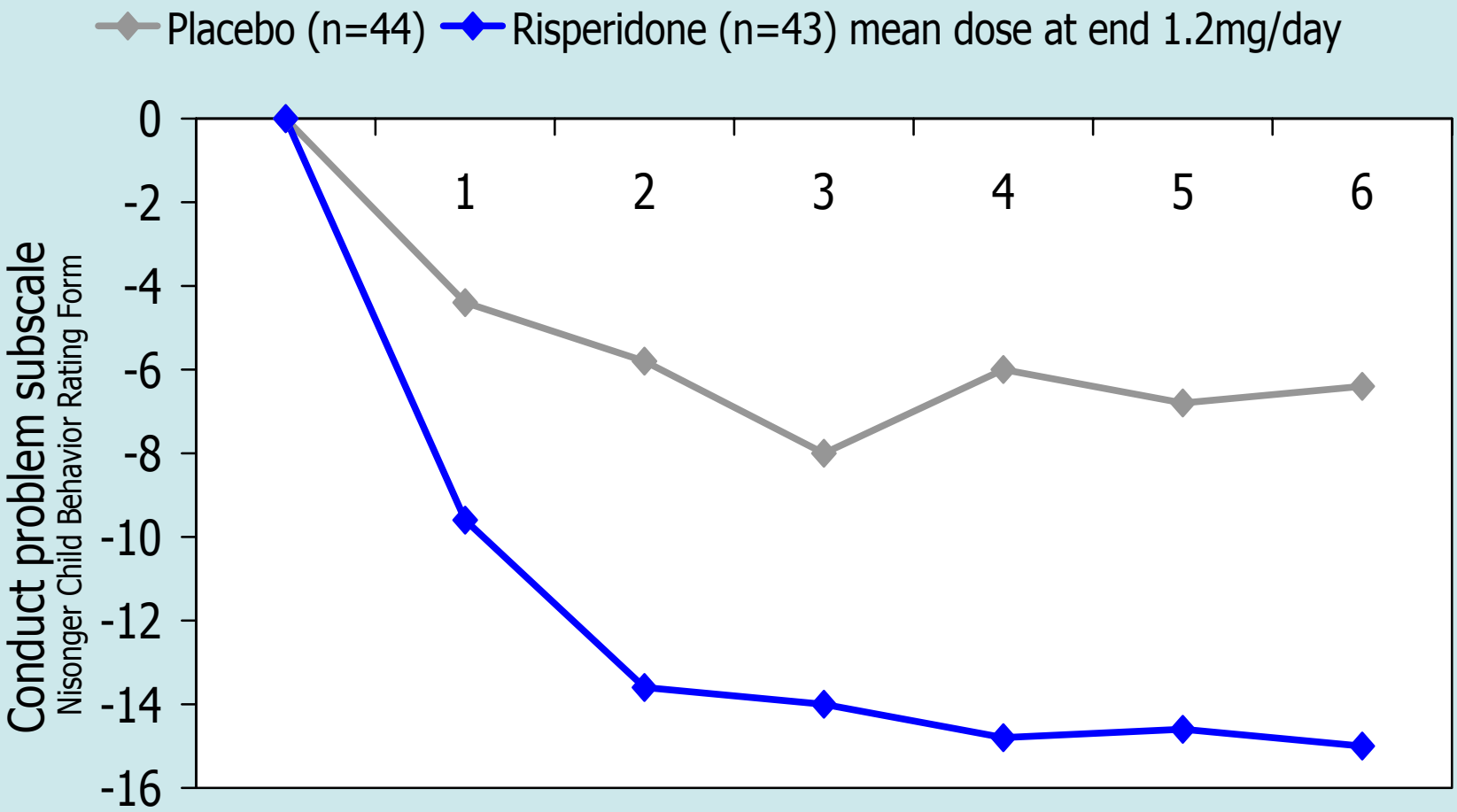
BL Baseline; EP End Point- Last Observation Carried Forward



# Gagiano et al, Psychopharmacology, 2005

- **Participants:** 77 adults (18-57 years); ID + no psychiatric disorders.
- **Intervention:** Risperidone (n=39); Placebo (n=38). RCT. Open label with Risperidone (n=58) 1-4 mgs/ day (mean dose 1.8 mgs/ day) add-on.
- **Methods:** RCT + Open label.
- **Follow up:** RCT 4 weeks; open label 48 weeks.
- **Outcomes:** Primary outcome = ABC total score; BPI + CGI-S + VAS (target behaviours); Cognitive outcome: CPT + MV-CVLT; Extrapyramidal symptoms: ESRS.
- **Results:** ANCOVA (ITT): Least square means. Ris = 52% improved; Placebo = 31% improved (NNT = 5). ABC: $p=0.036$; CGI: $p<0.05$. Somnolence = 23-41%; Wt. Gain = 3.8+/-0.6. QTc = OK; ESRS = OK.
- **Comments:** Good quality study and supports the use of risperidone among adults, reasonable number in cohort; good design; good outcome measure; good stats. Short period of follow up in the RCT part (4 weeks), under powered, not one target behaviour.

# Double-blind Study of Risperidone in Children with Sub-Average Intelligence



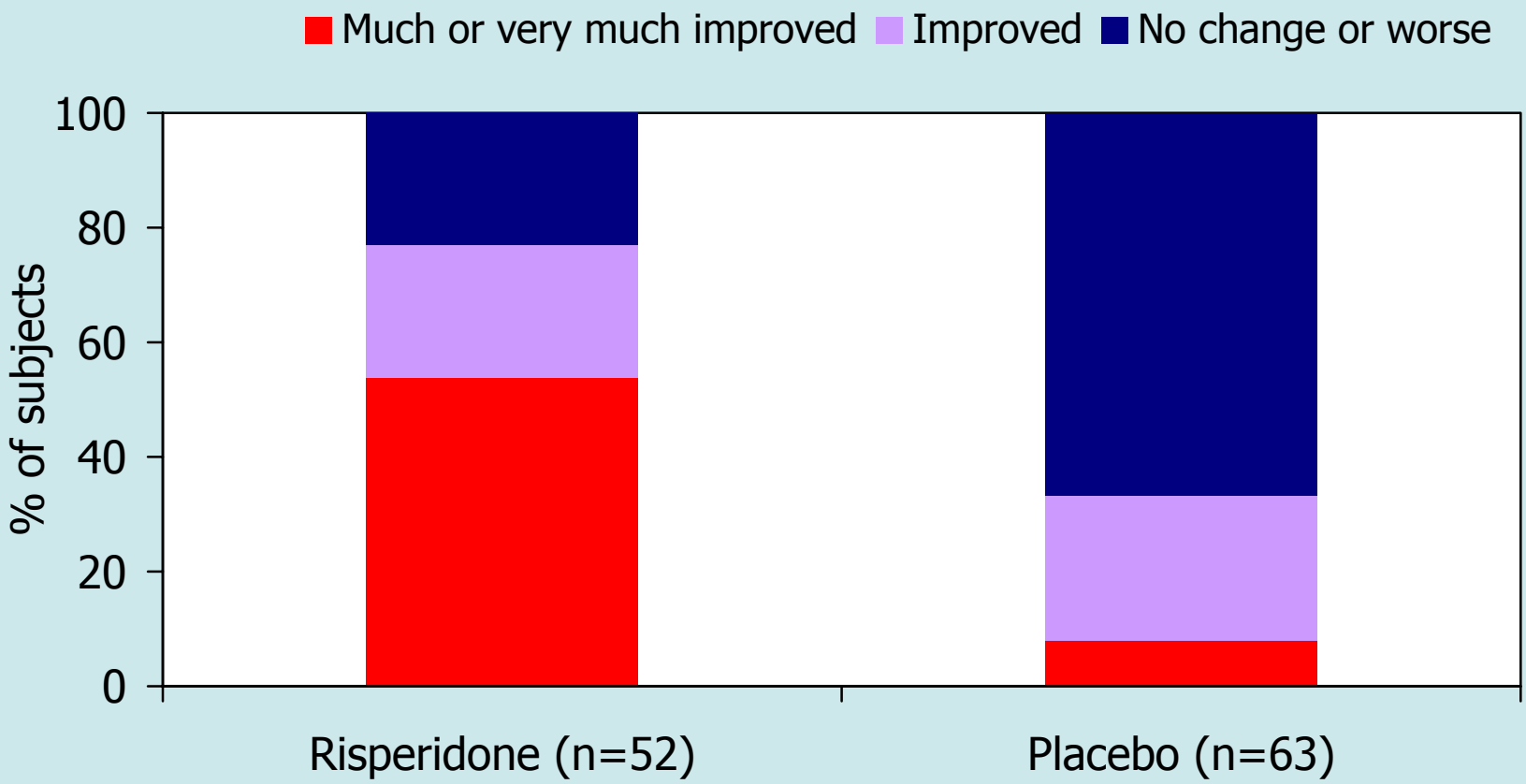

LOCF, Significant difference by week 1 (p=0.007)

*(Aman et al 2002)*

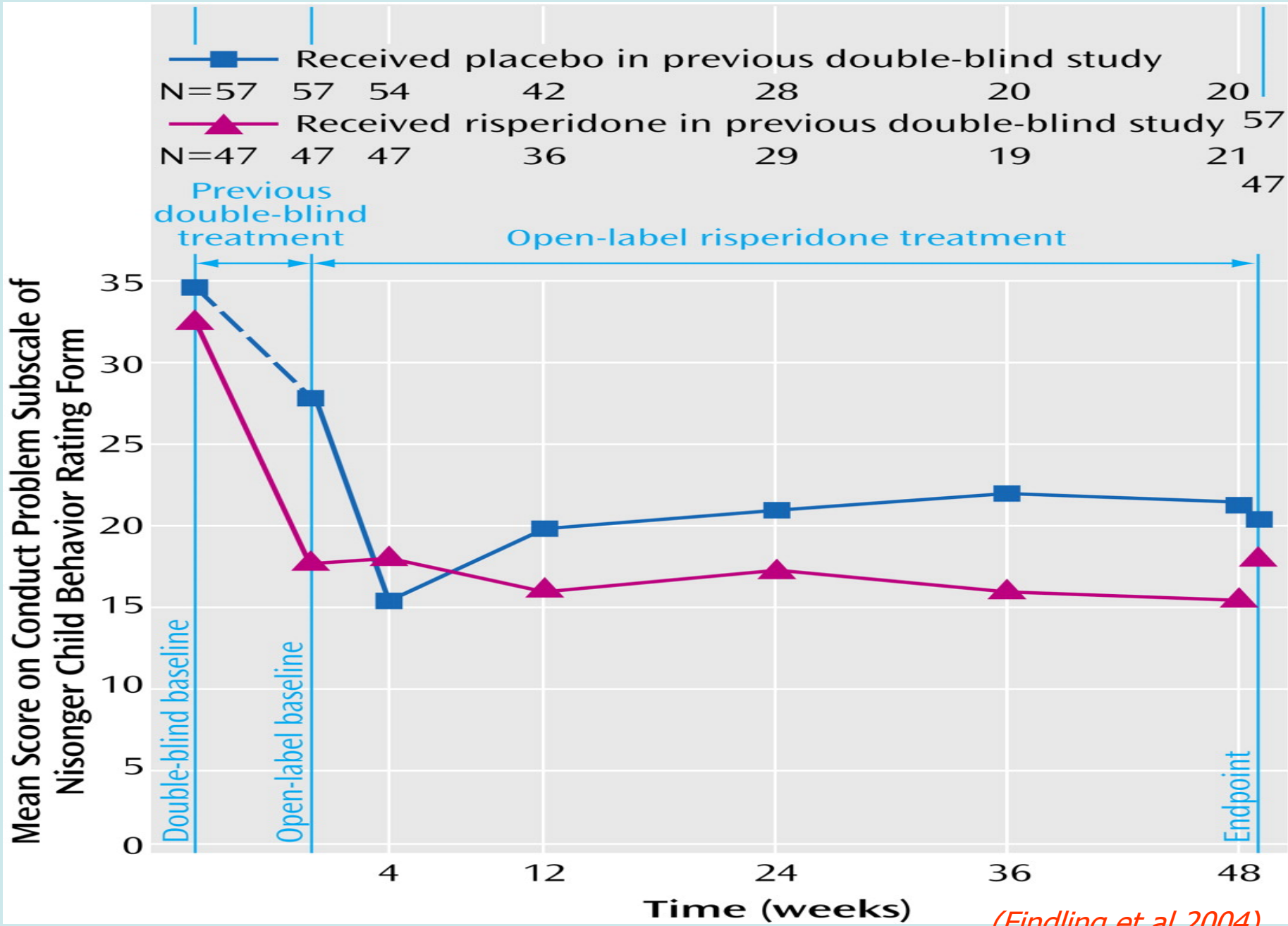
# Aman et al, AJP, 2002

- **Participants:** 115 children (5-12 years); IQ 36-48.
- **Intervention:** Risperidone 0.02-0.06 mg/ kg/ day vs. placebo.
- **Methods:** Multi centre, RCT (parallel design).
- **Follow up:** 6 weeks.
- **Outcomes:** Nisonger Child Behaviour Rating form (conduct problem subscale) + ABC subscales, BPI, VAS, CGI.
- **Results:** Risperidone –15.2 vs. placebo –6.2; significant improvement according to all subscales + ABC-irritability/ hyperactivity subscales, BPI-aggressive/ destructive behaviour subscales, CGI and VAS. Adverse effects: headache and somnolence (not extrapyramidal symptoms). Weight gain Risperidone 2.2 kg vs. placebo 0.9 kg.
- **Comments:** Good quality study and supports the use of risperidone among children. Slightly low powered and the method of randomisation and concealment are not well (CONSORT) described, short period of follow up.

# Double-Blind Study of Risperidone in Children with Sub-Average Intelligence

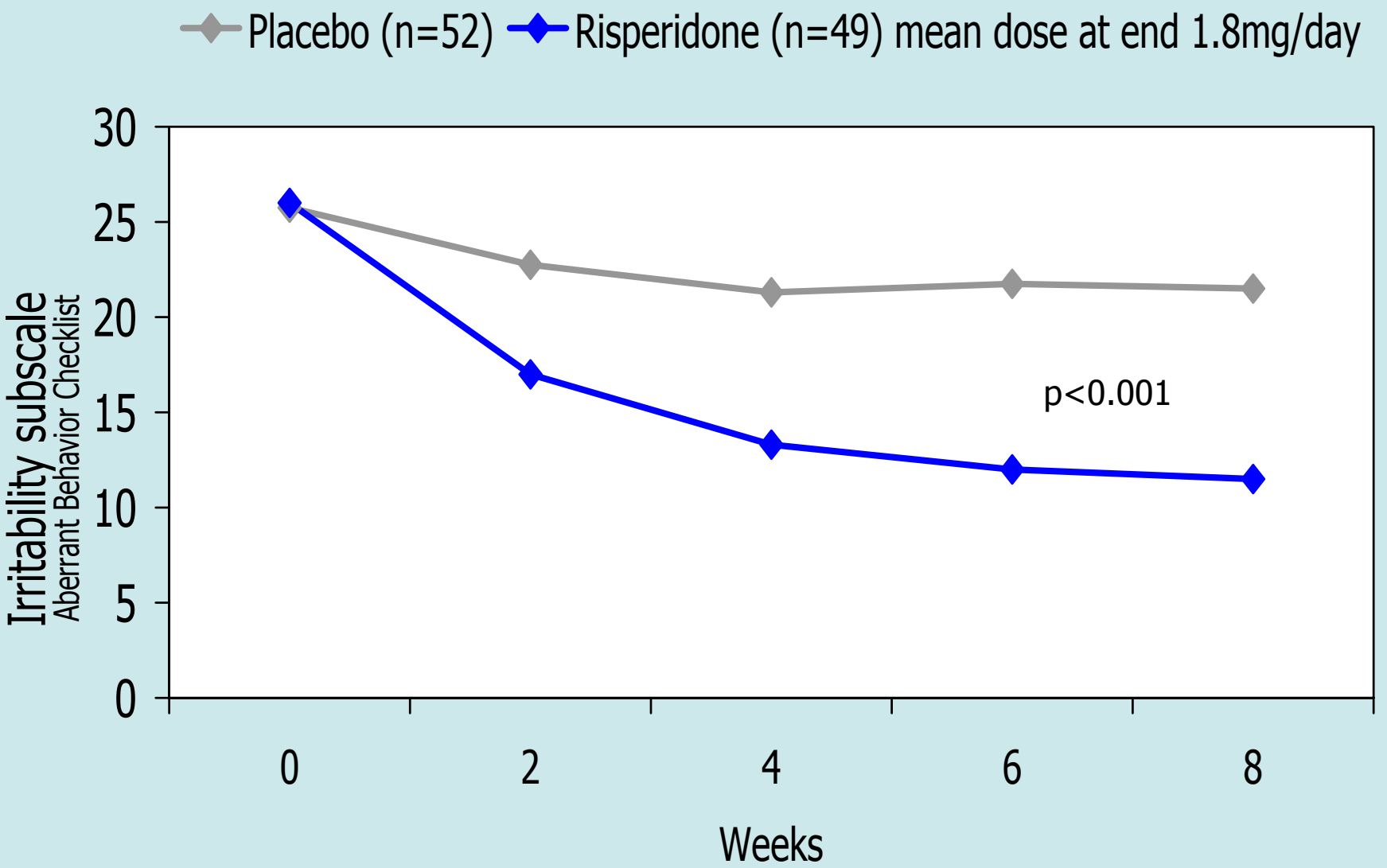



CGI change score: improvement significantly greater in risperidone group, $p<0.001$




*(Findling et al 2004)*

# DOUBLE-BLIND STUDY OF RISPERIDONE IN CHILDREN WITH AUTISM AND SERIOUS BEHAVIOURAL PROBLEMS




*Research Units on Pediatric Psychopharmacology of Autism 2002*

# Research Units on Pediatric Psychopharmacology Autism Network; NEJM, 2002

- **Participants:** 101 children (5-17 years) autism; 74 ID + 12 Borderline IQ.
- **Intervention:** Risperidone 0.5-3.5 mg/ day (n=49) vs. placebo (n=52).
- **Methods:** Multi-centre, RCT (parallel design).
- **Follow up:** 8 weeks.
- **Outcomes:** ABC irritability subscale, CGI-I.
- **Results:** Risperidone 56.9% reduction in score vs. placebo 14.1% ($p<0.001$); CGI much or very much improved: Risperidone 69% vs. placebo 12% ($p<0.001$). Average weight gain Risperidone $2.7\pm2.9$ kg vs. placebo $0.8\pm2.2$ kg ($p<0.001$). Increased appetite, fatigue, drowsiness, dizziness, drooling more common in Risp. ($p<0.05$). 2/3rd with positive response in 8 weeks maintained at 6 months.
- **Comments:** Good quality study and supports use of risperidone among children. Slightly low powered and the method of randomisation and concealment are not well described, short period of follow up.

# Research Units on Pediatric Psychopharmacology Autism Network; AJP, 2005 (Continuation study)

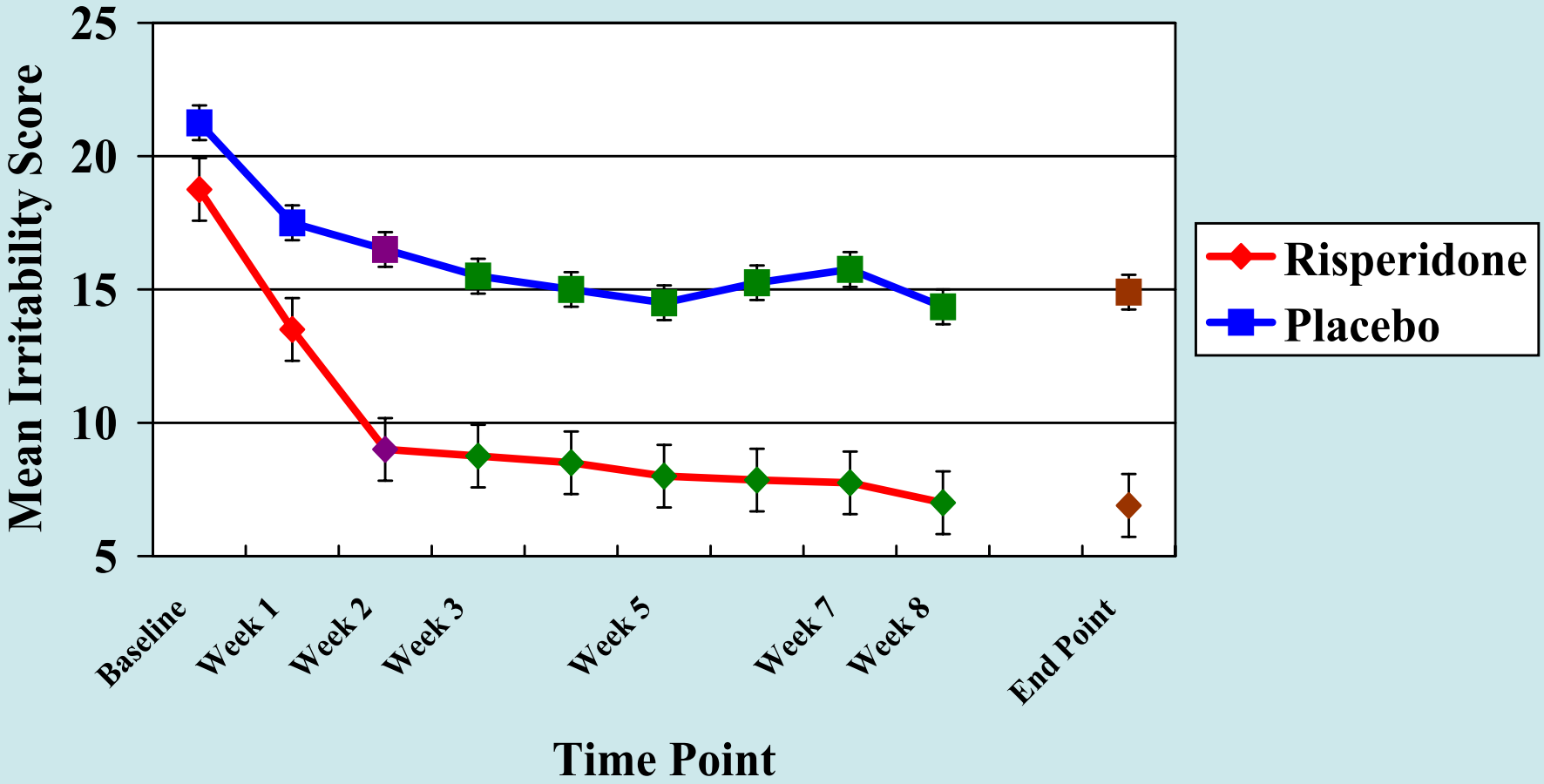
- **Participants:** Phase I: 63 children (5-17 years) autism; 53 ID + 7 Borderline IQ. Phase II: 38 children autism; 31 ID + 5 Borderline IQ.
- **Intervention:** Risperidone mean dose 1.96 mg/ day.
- **Methods:** Multi-centre, Follow up from the RCT.
- **Follow up:** Phase I: 4 months open label continuation with risperidone. Phase II: 8 weeks double blind placebo controlled withdrawal vs. continuation with risperidone.
- **Outcomes:** ABC irritability subscale.
- **Results:** Phase I: Change in ABC subscale small and non-significant. Average weight gain 5.1 kg ($p<0.001$). Phase II: Relapse in 63% gradual placebo substitution vs. 13% for continued risperidone.
- **Comments:** Risperidone showed persistent efficacy and good tolerability for intermediate length treatment of children with autism and ID. Somnolence disappeared after a few weeks but weight gain persisted. Did authors take into account the behavioural adverse effect of withdrawal?

# Irritability Subscale of ABC (Shea et al,2004)

P<0.05 for between-group comparison of change from baseline.

P<0.01 for between-group comparison of change from baseline.

P<0.001 for between-group comparison of change from baseline.



# Shea et al, Pediatrics, 2004

- **Participants:** 79 children (5-12 years) PDD; 42 ID + 10 Borderline IQ.
- **Intervention:** Risperidone mean dose 1.17 mg/ day (n=40) vs. placebo (n=39).
- **Methods:** Multi-centre, RCT (parallel design).
- **Follow up:** 8 weeks.
- **Outcomes:** ABC, Nisonger Child Behaviour Rating form; VAS, CGI-C + safety measures.
- **Results:** ABC-irritability subscale Risperidone 64% improvement vs. placebo 31% ($p<0.01$) + significant improvement according to all ABC subscales, NCBR subscales and VAS, CGI global improvement Risperidone 87% vs. placebo 40% ($p<0.001$). Adverse effects: extrapyramidal symptoms comparable between two groups, weight gain Risperidone 2.7 kg vs. placebo 1 kg, somnolence 78% vs. 8%.
- **Comments:** Good quality study and supports use of risperidone among children. Possibly low powered, no CONSORT, methods of randomisation and concealment are not well described, short period of follow up. Children were excluded if did not respond to risperidone previously. No correction for multiple testing (Type I error).

# Snyder et al, JAACAP, 2002

- **Participants:** 110 children (5-12 years) 52% ID, 48% Borderline IQ.
- **Intervention:** Risperidone mean dose mean 0.98 (range 0.4-3.8) mg/day (n = 53) vs. placebo (n = 57).
- **Methods:** RCT (parallel design).
- **Follow up:** 6 weeks.
- **Outcomes:** Nisonger Child Behaviour Rating form-conduct behaviour subscale; ABC, BPI. VAS, CGI + cognitive measures.
- **Results:** NCBR-F subscale Risperidone 47% reduction vs. placebo 21% ($p<0.001$) + significant improvement according to all ABC subscales, BPI ($p<0.01$), VAS ($p<0.001$), CGI ($p=0.001$). Risperidone common adverse effects: weight gain 2 kg ($p<0.001$), somnolence, headache, appetite increase and dyspepsia. Extrapyramidal symptoms: 13% in risperidone group vs. 5% in placebo ($p=0.25$).
- **Comments:** Good quality study and supports use of risperidone among children. Possibly under powered, short period of follow up.

# Turgay et al, Pediatrics, 2002 (continuation study)

- **Participants:** 77 children (5-12 years) ID + Borderline IQ.
- **Intervention:** Risperidone average 1.38 mg/ day.
- **Methods:** Follow up from the Snyder et al RCT.
- **Follow up:** 48 weeks open label of risperidone.
- **Outcomes:** Assessment of adverse events.
- **Results:** Somnolence (52%), headache (38%), weight gain (36%) (mean gain 7.1 kg), increased appetite (27%) (50% showed weight gain + 20 others with wt. gain). Prolactin level peaked at 4 weeks and then came down to normal. EPS (26%) (mild/ moderate) ESRS score 0.4 at baseline and 0.5 at end point. No change in cognitive measures, haematology, vital signs and ECG. Improvement in behaviour was maintained.
- **Comments:** Risperidone showed persistent efficacy and good tolerability for intermediate length treatment of children with ID. Somnolence and weight gain are the common adverse effects. Authors did not check for lipid profile and glucose intolerance.

# Risperidone

| Behaviour | Study | N/ duration | Outcome | Result |
|---|---|---|---|---|
| AGG | Prospective uncontrolled | 18/ 3 months | HBS, PIMRA, CGI | Improvement |
| AGG, SIB | Prospective uncontrolled | 33/ 6 months | Frequency of target behaviour | Improved 61-85% |
| AGG, SIB | RCT crossover | 22/ 22 weeks | ABC, NCBR, CGI, SIB-Q | Mixed result between high and low dose |

# Clozapine (2) + Olanzapine + Quetiapine

| Behaviour | Study | N/ duration | Outcome | Result |
|---|---|---|---|---|
| AGG, SIB + Psychosis | Retrospective uncontrolled | 24 | CGI, OAS | 92% better |
| AGG, SIB + Psychosis | Retrospective uncontrolled | 17 | Clinical rating | 76% better<br>24% worse |
| AGG, SIB | Retrospective uncontrolled | 20 | Clinical rating | 93% AGG<br>86% SIB better |
| AGG, SIB | Prospective uncontrolled | 15/ 6 months | HBS | Improvement in HBS score |

# ANTIPSYCHOTICS

- Adequate good quality evidence based on studies on adults but mainly children with LD (with or without autism) that risperidone is effective in the management of behaviour problems
- Concern about adverse effects such as somnolence and weight gain (not much evidence available on other adverse effects such as metabolic and cardiac)
- Long term follow up studies among children are reassuring as for the adverse effects

# ANTIDEPRESSANTS

# Fluoxetine (20-40 mgs add-on)

| Behaviour | Study | N/ duration | Outcome | Result |
|---|---|---|---|---|
| AGG + EP | Prospective uncontrolled | 19/ 36 weeks | MOAS | 11% better<br>47% worse |
| AGG, SIB, OCB | Prospective uncontrolled | 16/ 4 months | unspecified | 44% responders |
| AGG, SIB | Prospective uncontrolled | 15/ 7-467 days | CGI | 60% improved |
| AGG, SIB, OCB + PI | Prospective uncontrolled | 20/ 3 months | Caretaker observation | 60% marked improvement |

# Paroxetine (20-40 mgs add-on)

| Behaviour | Study | N/ duration | Outcome | Result |
|---|---|---|---|---|
| AGG, SIB | Retrospective uncontrolled | 14/ 6 months | In house rating scale | SIB better AGG not |
| Rituals, AGG, SIB | Retrospective uncontrolled | 33 | CGI | 36% improved |
| Rituals, SIB | Prospective uncontrolled | 10/ 4 months | Observation | Improved severity not frequency |

# Fluvoxamine (2) + Clomipramine

| Behaviour | Study | N/ duration | Outcome | Result |
|---|---|---|---|---|
| AGG | Prospective uncontrolled | 60/ 6 weeks | HBS | Severity decreased |
| AGG, SIB | Prospective uncontrolled | 14/ 6 weeks | CGI, PIMRA, DASH | Improved subjectively |
| Stereotypy, SIB | RCT crossover | 10/ 19 weeks | ABC, 5-point Likert scale | Improvement in some stereotypy |

# ANTIDEPRESSANTS

- Equivocal evidence primarily based on prospective and retrospective case studies
- On average less than half of the cohort showed improvement in behaviour
- The rest either didn't improve or deteriorated
- Most pronounced effect in the presence of anxiety or OCD symptoms
- Concern regarding adverse effects (sometimes making behaviour worse)

# MOOD STABILISERS

| Author | Drug | Target Behaviour | Type of study | No | Response Rate % |
|---|---|---|---|---|---|
| Langee 1990 | Lithium | SIB AGG HYP | Retrospective Uncontrolled | 66 | 47 |
| Tyrer 1993 | Lithium | AGG SIB | RCT crossover | 52 | 56 |
| Craft 1987 | Lithium | AGG SIB | RCT | 22 (20) | 73 (30) |
| Verhoeven 2001 | VPA | AGG SIB (EP 29%) | Prospective Uncontrolled | 28 | 68 |
| Reudrich 1999 | VPA | SIB AGG (EP 43%) | Retrospective Uncontrolled | 28 | 71 |
| Reid 1981 | CBZ | Overactivity (EP 50%) | RCT crossover | 10 | 40 |
| Janowsky 2003 | TPM | AGG SIB (EP 41%) | Retrospective Uncontrolled | 22 | 41-50 |

# MOOD STABILISERS

- Some evidence to support the use of lithium (however the outcome measures are of questionable validity)
- Primarily small case study (prospective and retrospective) based evidence to support the use of sodium valproate

# OPIOID ANTAGONIST

| Author | Drug | Target Behaviour | Type of study | No | Response Rate |
|---|---|---|---|---|---|
| Williamsen-Swinkels 1995 | Naltrexone | SIB ASD | RCT crossover | 33 | No effect |
| Sandman 1993 | Naltrexone | SIB | RCT crossover | 24 | NTX 50% |
| Sandman 2000 | Naltrexone | SIB | Continuation | 15 | Mixed result |
| Cassner 1996 | Naltrexone | SIB | Retrospective Uncontrolled | 56 | 50% |

# OPIOID ANTAGONISTS

- Equivocal evidence
- Some showed better results on a lower dose but others showed a better result on a higher dose

# ANTIANXIETY DRUGS

| Author | Drug | Target Behaviour | Type of study | No | Response Rate |
|---|---|---|---|---|---|
| King 1996 | Buspirone | SIB AGG | Open Prospective | 26 | No diff |

# ANTIANXIETY DRUGS

- No evidence is currently available
- Absence of evidence is not evidence of absence

# WITHDRAWAL STUDIES

- Ahmed et al
- Branford

- 1/3rd total withdrawal
- 1/3rd some reduction in dose
- 1/3rd no reduction in dose

- Factors influencing withdrawal

# Systematic reviews on non-medication management

- Corrigan, 1991
- Scotti et al, 1991
- Didden et al, 1997
- Carr et al, 1999 (Positive Behavioural Support)

# PROBLEMS

- Lack of RCTs (CONSORT, ITT, NNT)
- Predominantly case reports
- Small numbers (problem with power)
- Non-validated outcome measures
- Lack of full assessment of behaviour
- Confounding from other medication
- Confounding from other interventions
- Effect on OCD, anxiety, ADHD etc.