# **APPENDIX 15: CLINICAL EVIDENCE -FOREST PLOTS**

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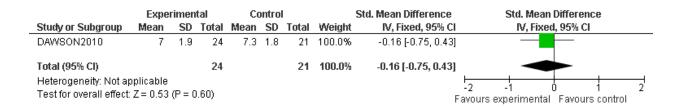
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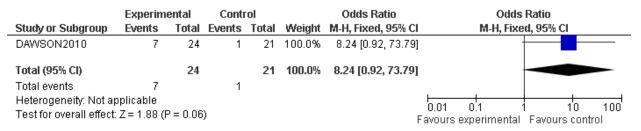
# 1.1.1 Behavioural interventions aimed at overall autistic behaviours as an indirect outcome

Early Start Denver Model versus treatment-as-usual for overall autistic behaviours as an indirect outcome

## Overall autistic behaviours (ADOS severity)

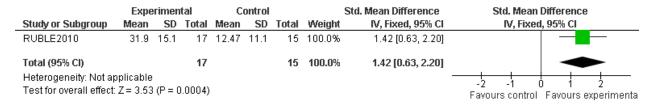


# Autism DSM-IV diagnosis (improvement in diagnosis from autistic disorder to PDD-NOS)

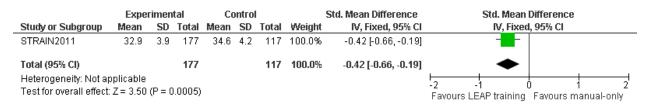


# 1.1.2 Educational interventions aimed at overall autistic behaviours as a direct outcome

# COMPASS versus treatment-as-usual for overall autistic behaviours as a direct outcome



# LEAP training versus manual-only control for overall autistic behaviours as a direct outcome



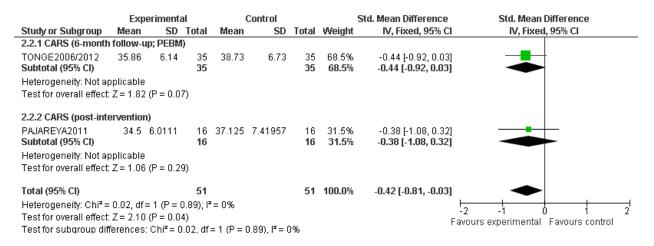
# 1.1.3 Parent training interventions aimed at overall autistic behaviours as a direct or indirect outcome

Parent training versus treatment-as-usual for overall autistic behaviours as an indirect outcome

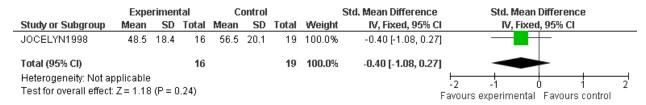
# Overall autistic behaviours (DBC-ASA; 6-month follow-up; PEC+PEBM combined)

|   |           | (        | Control |       |       | Std. Mean Difference | Std. Mean Difference |                     |                   |  |  |
|---|-----------|----------|---------|-------|-------|----------------------|----------------------|---------------------|-------------------|--|--|
| Study or Subgroup   | Mean      | SD       | Total   | Mean  | SD    | Total                | Weight               | IV, Fixed, 95% CI   | IV, Fixed, 95% CI |  |  |
| TONGE2006/2012  | 22.288971 | 8.662124 | 68      | 22.89 | 10.42 | 35                   | 100.0%               | -0.06 [-0.47, 0.34] | -                 |  |  |
| Total (95% CI)  |           |          | 68      |       |       | 35                   | 100.0%               | -0.06 [-0.47, 0.34] | •                 |  |  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.31 (P = 0.76) |           |          |         |       |       |                      |                      | F                   | -2 -1 0 1 2       |  |  |

### Overall autistic behaviours (CARS)

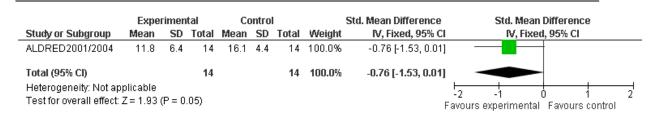


# Parent and day-care staff training versus standard day-care for overall autistic behaviours as a direct outcome



# 1.1.4 Social-communication interventions aimed at overall autistic behaviours as an indirect outcome

Child's Talk versus treatment-as-usual for overall autistic behaviours as an indirect outcome

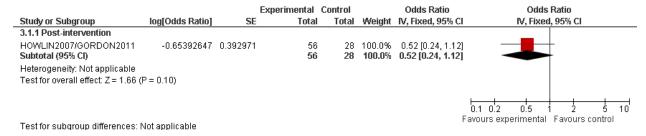


# 1.2 PSYCHOSOCIAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF IMPAIRED RECIPROCAL SOCIAL COMMUNICATION AND INTERACTION

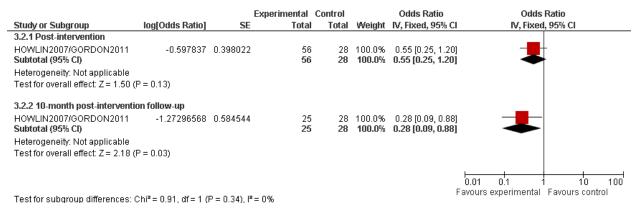
# 1.2.1 AAC intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

PECS training for teachers versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

# Communication (odds of being in a higher severity category on ADOS-G)



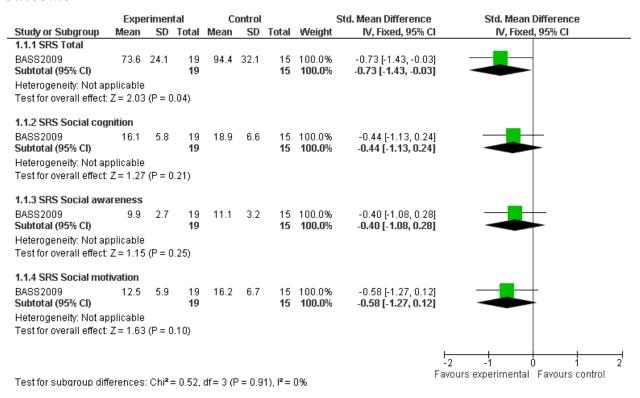
# Social interaction (odds of being in a higher severity category on ADOS-G)



Autism: the management and support of children and young people on the autism spectrum (March 2013)

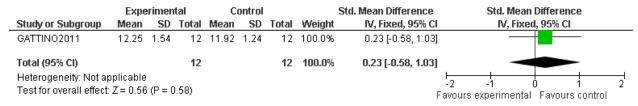
# 1.2.2 Animal-based intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Horseback riding versus waitlist control for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome



# 1.2.3 Arts-based intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

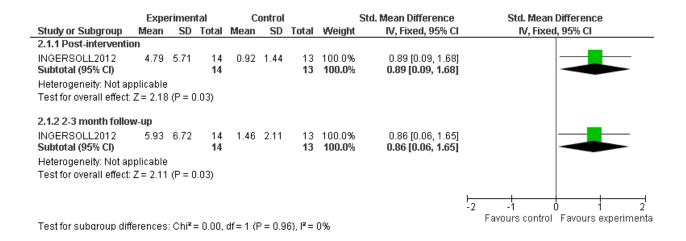
RMT versus waitlist control for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome



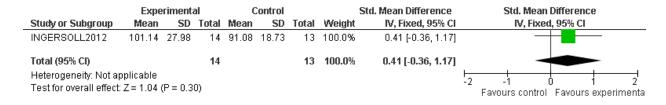
# 1.2.4 Behavioural intervention aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

RIT versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

# Examiner-child joint/shared attention (ESCS IJA)

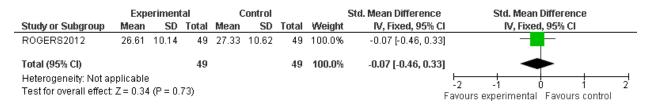


# Social and emotional development (Bayley-Social-emotional subscale)

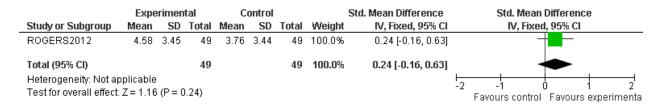


# P-ESDM versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

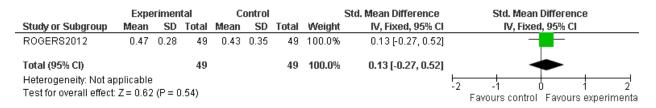
# Social affect (ADOS-T)



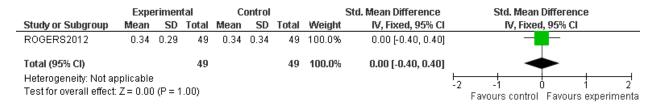
#### **Imitation**



# Orienting to social stimuli



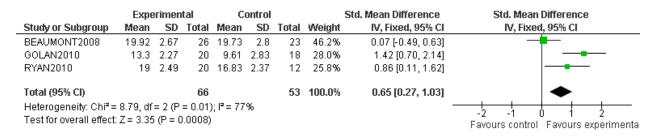
## Orienting to joint attention



# 1.2.5 Cognitive interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

ERT versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

# **Emotion recognition**



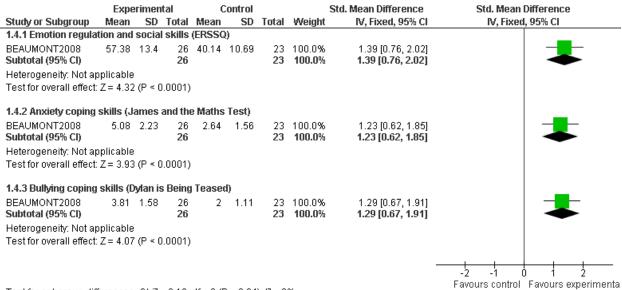
### Recognising emotion from posture

| Experimental                                      |       |      | C     | ontrol |      |       | Std. Mean Difference | Std. Mean Difference |  |  |  |
|---|-------|------|-------|--------|------|-------|----------------------|----------------------|--|--|--|
| Study or Subgroup                                 | Mean  | SD   | Total | Mean   | SD   | Total | Weight               | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |  |  |
| BEAUMONT2008                                      | 21.81 | 2.97 | 26    | 21.32  | 2.82 | 23    | 100.0%               | 0.17 [-0.40, 0.73]   | _  |  |  |
| Total (95% CI)                                    |       |      | 26    |        |      | 23    | 100.0%               | 0.17 [-0.40, 0.73]   | -  |  |  |
| Heterogeneity: Not ap<br>Test for overall effect: |       |      | ).56) |        |      |       |                      |                      | -2 -1 0 1 2<br>Favours control Favours experimenta |  |  |

# Emotion understanding (EmoVoc)

|   | Experimental |      |        | Control |      |       |        | Std. Mean Difference | Std. Mean Difference                               |  |  |
|---|--------------|------|--------|---------|------|-------|--------|----------------------|--|--|--|
| Study or Subgroup                                 | Mean         | SD   | Total  | Mean    | SD   | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |  |  |
| GOLAN2010   | 12.5         | 3.09 | 20     | 9.11    | 3.45 | 18    | 100.0% | 1.02 [0.34, 1.70]    | —  |  |  |
| Total (95% CI)                                    |              |      | 20     |         |      | 18    | 100.0% | 1.02 [0.34, 1.70]    |  |  |  |
| Heterogeneity: Not ap<br>Test for overall effect: |              |      | ).003) |         |      |       |        |                      | -2 -1 0 1 2<br>Favours control Favours experimenta |  |  |

# **Emotion regulation**

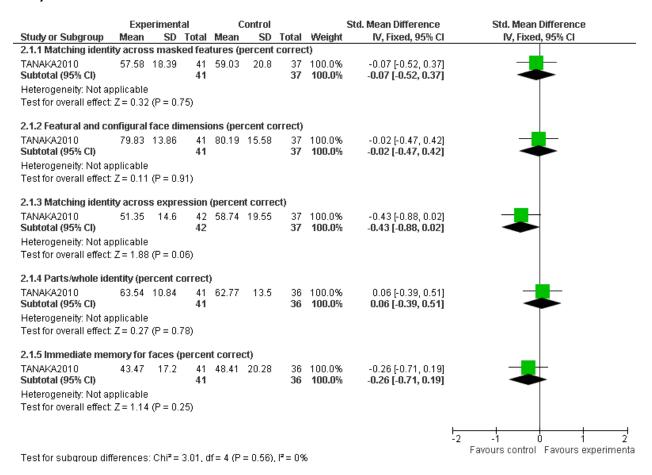


Test for subgroup differences:  $Chi^2 = 0.12$ , df = 2 (P = 0.94),  $I^2 = 0\%$ 

# Social skills (SSQ)

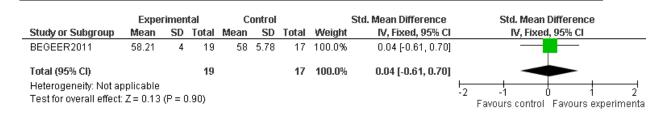
|  | Expe  | C    | ontrol |       |      | Std. Mean Difference | Std. Mean Difference |                   |                   |   |  |
|--|-------|------|--------|-------|------|----------------------|----------------------|-------------------|-------------------|---|--|
| Study or Subgroup  | Mean  | SD   | Total  | Mean  | SD   | Total                | Weight               | IV, Fixed, 95% CI | IV, Fixed, 95% CI |   |  |
| BEAUMONT2008   | 38.08 | 9.84 | 26     | 25.11 | 7.91 | 23                   | 100.0%               | 1.42 [0.79, 2.05] |                   | _ |  |
| Total (95% CI)   |       |      | 26     |       |      | 23                   | 100.0%               | 1.42 [0.79, 2.05] |                   | • |  |
| Heterogeneity: Not applicable Test for overall effect: Z = 4.40 (P < 0.0001)  Test for overall effect: Z = 4.40 (P < 0.0001) |       |      |        |       |      |                      |                      |                   |                   |   |  |

# FRT versus waitlist control for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

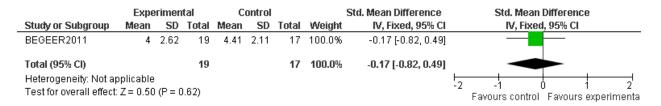


ToM versus waitlist control for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

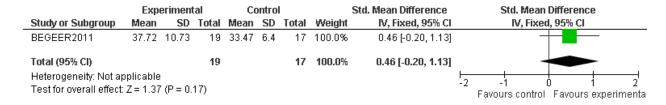
Theory of Mind (ToM test, total score)



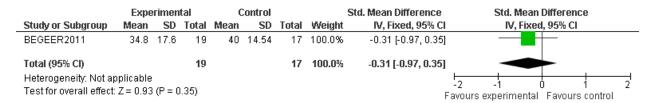
# **Empathy (Index of Empathy for Children and Adolescents)**



## **Emotional awareness (LEAS-C)**

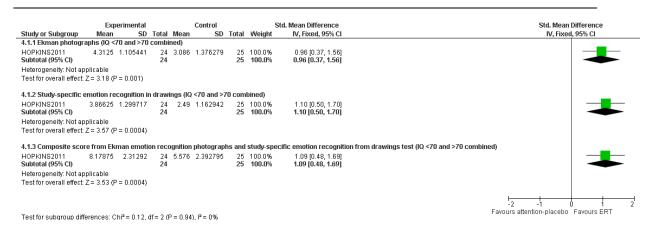


# Maladaptive social behaviour (CSBQ)

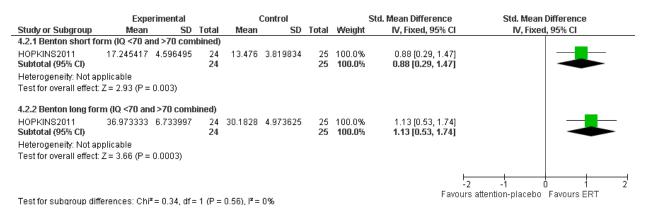


Computer-based ERT versus software training (attention-placebo) for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

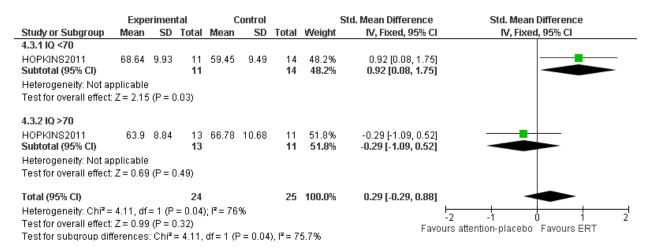
# **Emotion recognition**



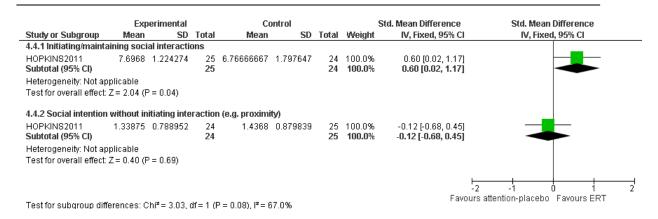
## **Face recognition**



# Social skills (SSRS standardised score)



# Positive social interaction (behavioural observation)

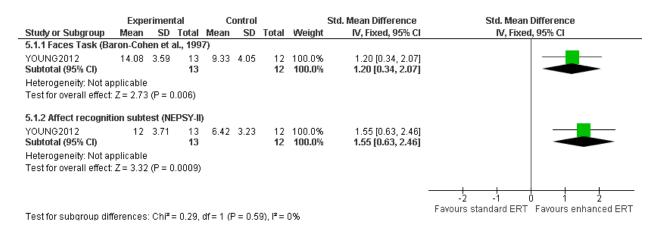


# Negative social interaction (behavioural observation)

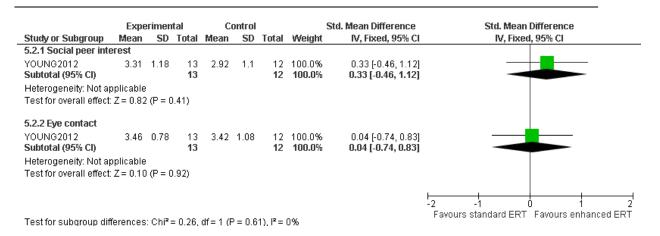
| Experimental             |         |          |       |        | Control  |       |             | Std. Mean Difference | Std. Mean Difference |  |  |  |
|--------------------------|---------|----------|-------|--------|----------|-------|-------------|----------------------|----------------------|--|--|--|
| Study or Subgroup        | Mean    | SD       | Total | Mean   | SD       | Total | Weight      | IV, Fixed, 95% CI    | IV, Fixed, 95% CI    |  |  |  |
| HOPKINS2011              | 0.63125 | 0.863339 | 24    | 1.5348 | 1.131922 | 25    | 100.0%      | -0.88 [-1.47, -0.29] | _                    |  |  |  |
| Total (95% CI)           |         |          | 24    |        |          | 25    | 100.0%      | -0.88 [-1.47, -0.29] |                      |  |  |  |
| Heterogeneity: Not as    |         |          |       |        |          |       | -2 -1       | <del>   </del>       |                      |  |  |  |
| Test for overall effect: |         |          |       |        |          |       | Favours ERT | Favours atte         | ntion-plac           |  |  |  |

# Enhanced ERT versus standard ERT for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

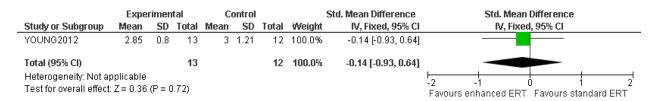
### **Emotion recognition**



#### Positive social behaviours

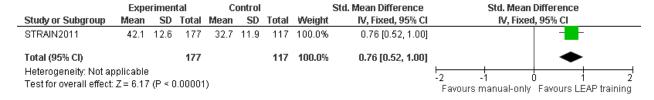


#### Gaze aversion

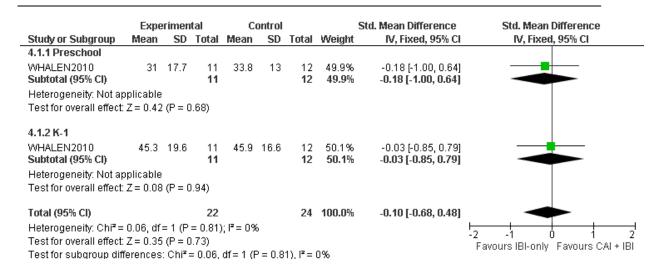


# 1.2.6 Educational interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

LEAP training versus manual-only control for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome



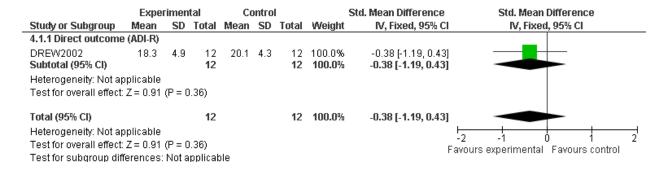
Combined TeachTown and IBI versus IBI-only for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome



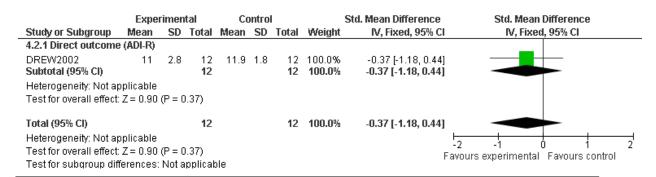
# 1.2.7 Parent training interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

Parent training versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

# Reciprocal social interaction

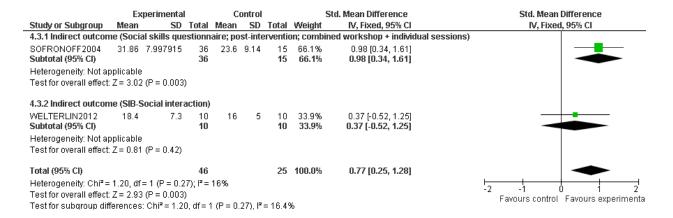


#### Nonverbal communication



Autism: the management and support of children and young people on the autism spectrum (March 2013)

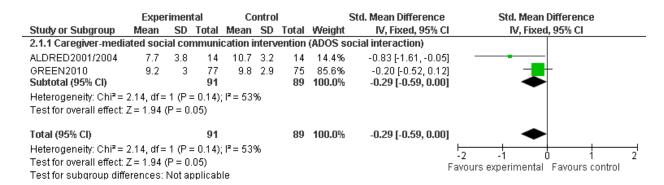
# Parent training versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome



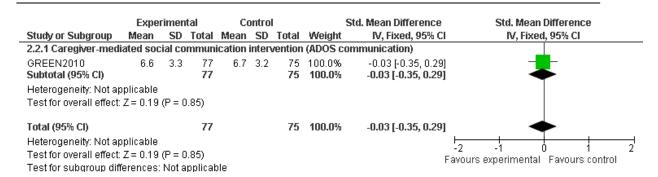
# 1.2.8 Social-communication interventions aimed at the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Caregiver- or preschool-teacher- mediated social-communication interventions versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

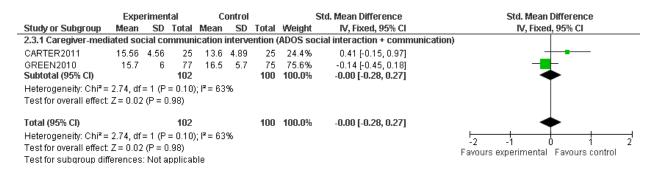
### Social interaction



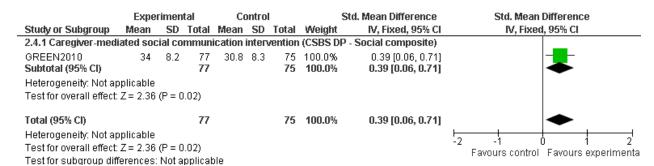
#### Communication



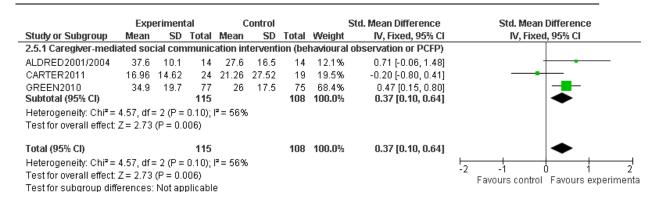
### Social interaction and communication



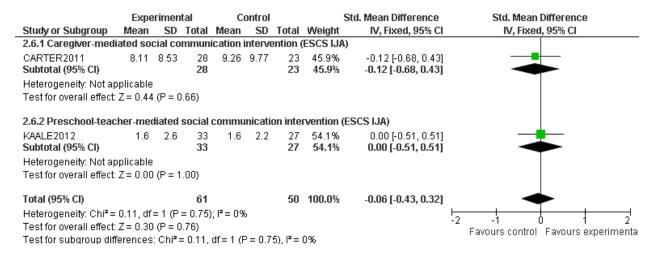
#### Parent-rated social-communication



#### Communication acts



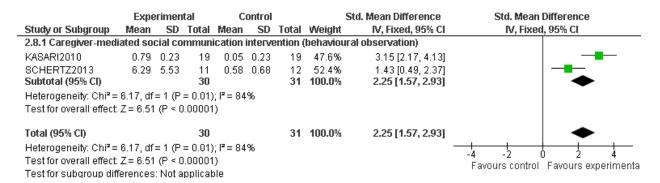
# Examiner-child joint/shared attention



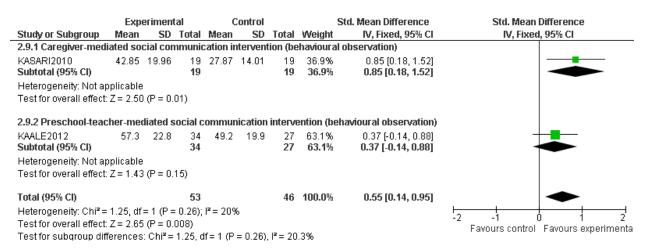
### Parent-child joint/shared attention

|  | Expe                                    | erimen                    | tal                                       | C            | ontrol         |                  | S                             | td. Mean Difference   | Std. Mean Difference                          |
|--|---|---------------------------|---|--------------|----------------|------------------|-------------------------------|---|---|
| Study or Subgroup  | Mean                                    | SD                        | Total                                     | Mean         | SD             | Total            | Weight                        | IV, Fixed, 95% CI   | IV, Fixed, 95% CI                             |
| 2.7.1 Caregiver-med  | liated soc                              | ial co                    | nmuni                                     | cation i     | nterve         | ntion (l         | pehavioura                    | l observation)  |   |
| ALDRED2001/2004  | 77.6                                    | 17.8                      | 14  | 62.6         | 32.7           | 14               | 9.1%                          | 0.55 [-0.20, 1.31]  | <del>  -</del>                                |
| GREEN2010  | 64                                      | 25.7                      | 77  | 55.6         | 25.7           | 75               | 50.9%                         | 0.33 [0.01, 0.65]   | <del></del>                                   |
| KASARI2010   | 3.11                                    | 3.41                      | 19  | 3.77         | 3.76           | 19               | 12.9%                         | -0.18 [-0.82, 0.46]   |   |
| SCHERTZ2013<br>Subtotal (95% CI)   | 3.27                                    | 3.17                      | 11<br><b>121</b>                          | 0.86         | 0.77           | 12<br><b>120</b> | 6.7%<br><b>79.6</b> %         | 1.03 [0.15, 1.91]<br><b>0.33 [0.07, 0.59]</b>                       | •   |
| Test for overall effect<br>2.7.2 Preschool-tead  |   | `                         | ,   |              |                |                  |                               |   |   |
| 2.7.2 Preschool-tead   | cher-med                                | liotod (                  |   |              |                |                  |                               |   |   |
| KAALE2012  | 2.4                                     |                           |   |              |                |                  | ,                             | ehavioural observation)<br>0.17 (-0.33, 0.68)                       |   |
| KAALE2012<br>Subtotal (95% CI)   | 2.4                                     |                           | 34<br>34<br>34                            | commu<br>1.8 | nicatio<br>3.2 |                  | vention (b)<br>20.4%<br>20.4% | ehavioural observation)<br>0.17 [-0.33, 0.68]<br>0.17 [-0.33, 0.68] | -   |
| Subtotal (95% CI)  |   |                           | 34  |              |                | 27               | 20.4%                         | 0.17 [-0.33, 0.68]  | <del>-</del>                                  |
| <b>Subtotal (95% CI)</b><br>Heterogeneity: Not a                                       | pplicable                               | 3.6                       | 34<br><b>34</b>                           |              |                | 27               | 20.4%                         | 0.17 [-0.33, 0.68]  | -   |
| Subtotal (95% CI)<br>Heterogeneity: Not a<br>Test for overall effect                   | pplicable                               | 3.6                       | 34<br><b>34</b>                           |              |                | 27               | 20.4%<br><b>20.</b> 4%        | 0.17 [-0.33, 0.68]  | •   |
| Subtotal (95% CI)<br>Heterogeneity: Not a<br>Test for overall effect<br>Total (95% CI) | pplicable<br>:: Z = 0.67                | 3.6<br>(P = 0             | 34<br><b>34</b><br>.50)<br><b>155</b>     | 1.8          | 3.2            | 27<br><b>27</b>  | 20.4%<br><b>20.</b> 4%        | 0.17 [-0.33, 0.68]<br><b>0.17 [-0.33, 0.68]</b>                     |   |
|  | pplicable<br>:: Z = 0.67<br>= 5.51, df= | 3.6<br>(P = 0<br>= 4 (P : | 34<br>34<br>.50)<br><b>155</b><br>= 0.24) | 1.8          | 3.2            | 27<br><b>27</b>  | 20.4%<br><b>20.</b> 4%        | 0.17 [-0.33, 0.68]<br><b>0.17 [-0.33, 0.68]</b>                     | -2 -1 0 1 2 Favours control Favours experimen |

# Parent-child joint attention responses



# Parent-child joint engagement



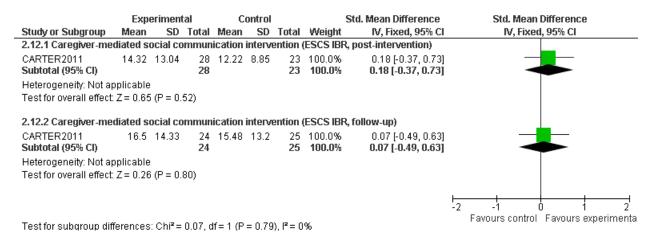
# Teacher-child joint/shared attention

|  | Ехрег     | imen   | tal             | Co     | ontrol | ı               |                          | Std. Mean Difference                          | Std. Mean Difference                            |
|--|-----------|--------|-----------------|--------|--------|-----------------|--------------------------|---|---|
| Study or Subgroup  | Mean      | SD     | Total           | Mean   | SD     | Total           | Weight                   | IV, Fixed, 95% CI                             | IV, Fixed, 95% CI                               |
| 2.10.1 Preschool-teac  | her-med   | diated | l socia         | l comm | unic   | ation in        | terventio                | n (behavioural observation)                   |   |
| KAALE2012<br>Subtotal (95% CI)   | 1.8       | 3.2    | 34<br><b>34</b> | 0.4    | 0.7    | 27<br><b>27</b> | 100.0%<br><b>100.0</b> % | 0.57 [0.05, 1.08]<br><b>0.57 [0.05, 1.08]</b> |   |
| Heterogeneity: Not app<br>Test for overall effect: 2                                     |           | (P = 0 | .03)            |        |        |                 |                          |   |   |
| Total (95% CI) Heterogeneity: Not app Test for overall effect: 2 Test for subgroup diffe | z= 2.15 ( | •      |                 | nle    |        | 27              | 100.0%                   | 0.57 [0.05, 1.08]                             | -2 -1 0 1 2 Favours control Favours experimenta |

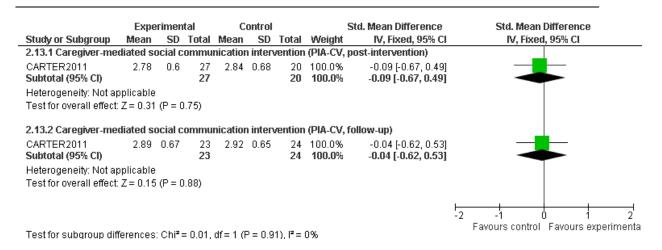
# Teacher-child joint engagement

|   | Expe    | rimen  | tal             | С      | ontrol |                 |                          | Std. Mean Difference                               | Std. Mean Difference                            |
|---|---------|--------|-----------------|--------|--------|-----------------|--------------------------|--|---|
| Study or Subgroup   | Mean    | SD     | Total           | Mean   | SD     | Total           | Weight                   | IV, Fixed, 95% CI                                  | IV, Fixed, 95% CI                               |
| 2.11.1 Preschool-tea  | cher-me | ediate | d socia         | l comm | nunica | tion int        | ervention                | (behavioural observation)                          |   |
| KAALE2012<br>Subtotal (95% CI)  | 56      | 22.2   | 34<br><b>34</b> | 62.7   | 20.9   | 27<br><b>27</b> | 100.0%<br><b>100.0</b> % | -0.31 [-0.81, 0.20]<br>- <b>0.31 [-0.81, 0.20]</b> | -   |
| Heterogeneity: Not ap<br>Test for overall effect:   | •       |        | 0.24)           |        |        |                 |                          |  |   |
| Total (95% CI)<br>Heterogeneity: Not ap<br>Test for overall effect<br>Test for subgroup dif | Z=1.18  | (P = 0 |                 | ole    |        | 27              | 100.0%                   | -0.31 [-0.81, 0.20]                                | -2 -1 0 1 2 Favours control Favours experimenta |

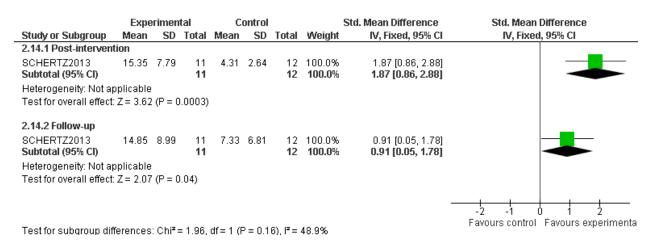
# **Behaviour requests**



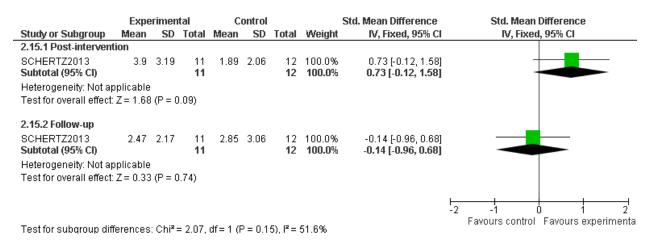
# Non-verbal communication



# Focusing on faces (behavioural observation; caregiver-mediated)



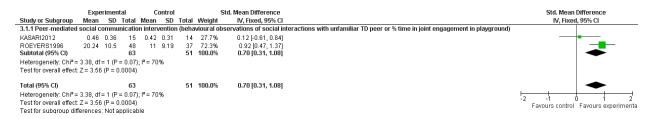
# Turn-taking (behavioural observation; caregiver-mediated)



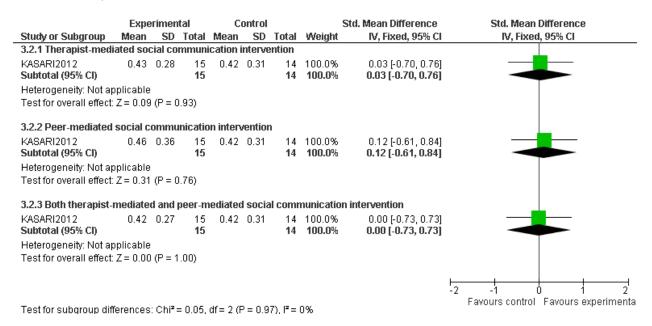
Autism: the management and support of children and young people on the autism spectrum (March 2013)

Peer-mediated (and/or therapist-mediated) social-communication interventions versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

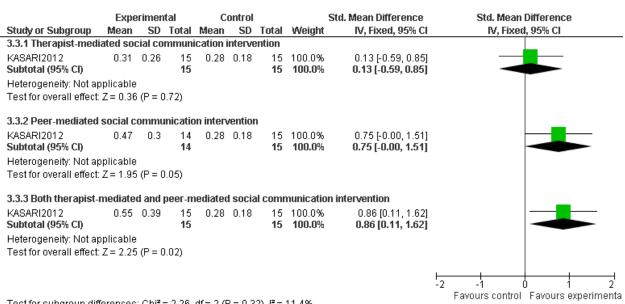
## Peer-child joint engagement



# Percentage of time jointly engaged during playground observations (post-intervention)

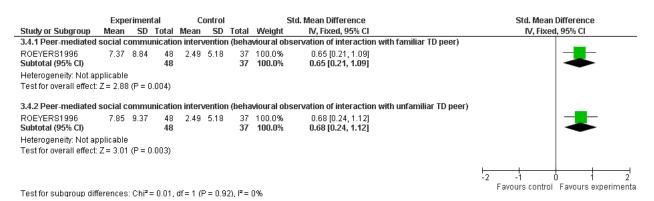


Percentage of time jointly engaged during playground observations (follow-up)

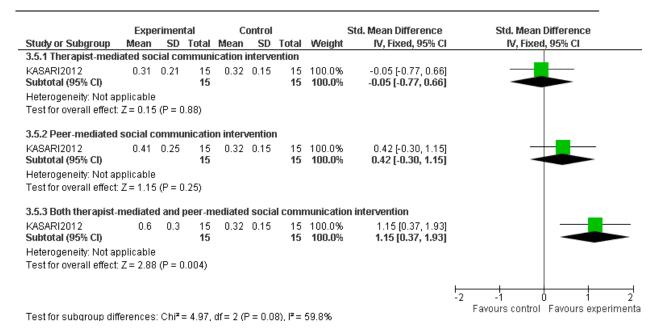


Test for subgroup differences:  $Chi^2 = 2.26$ , df = 2 (P = 0.32),  $I^2 = 11.4\%$ 

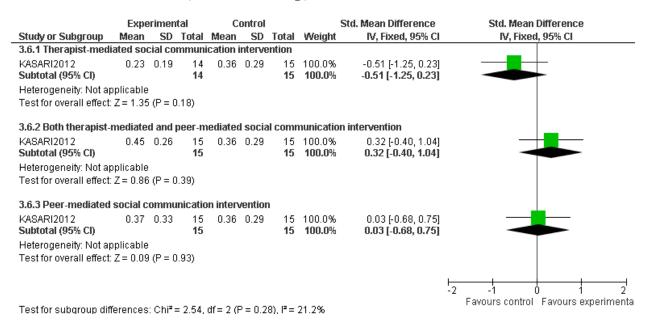
#### Child-initiated social interactions



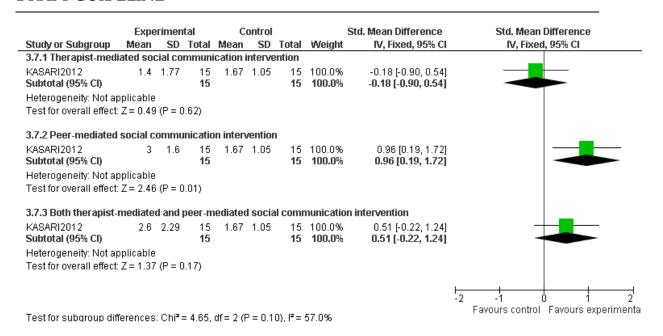
Social network salience (SNS; post-intervention)



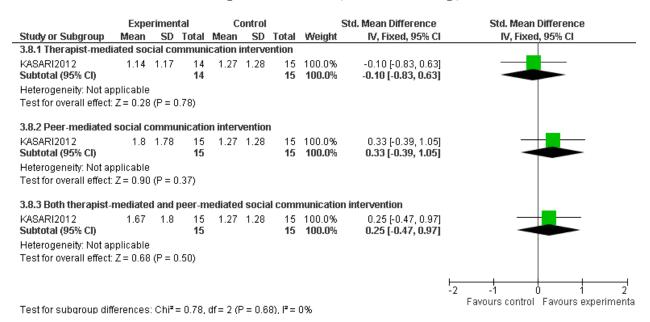
# Social network salience (SNS; follow-up)



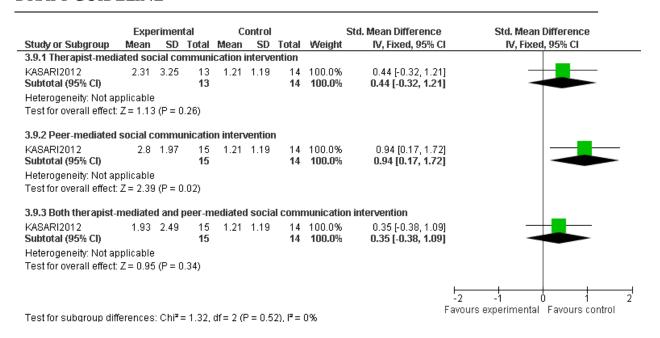
# Number of received friendship nominations (SNS; post-intervention)



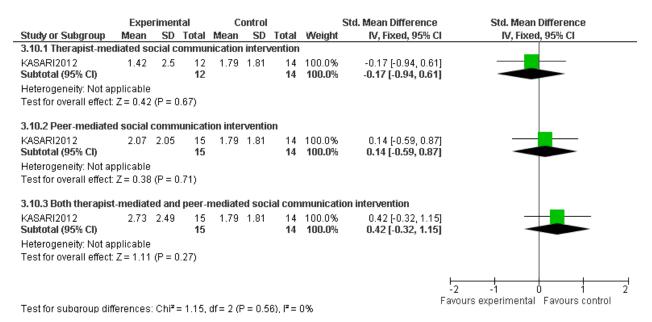
# Number of received friendship nominations (SNS; follow-up)



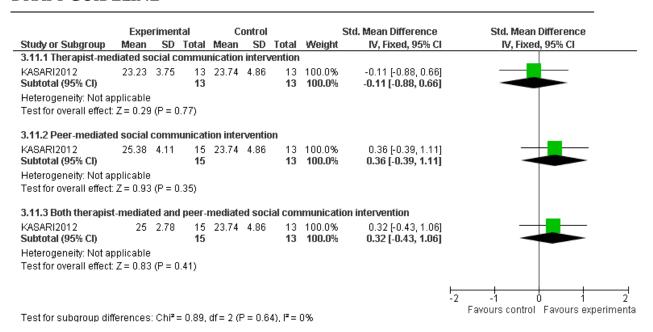
Number of times child identified as someone other children don't like to 'hang out with' (SNS; post-intervention)



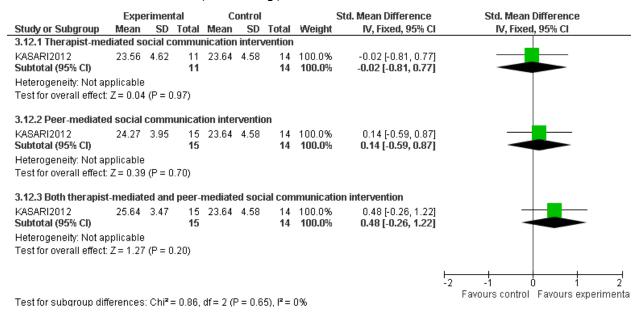
# Number of times child identified as someone other children don't like to 'hang out with' (SNS; follow-up)



# Teacher-rated social skills (post-intervention)



# Teacher-rated social skills (follow-up)



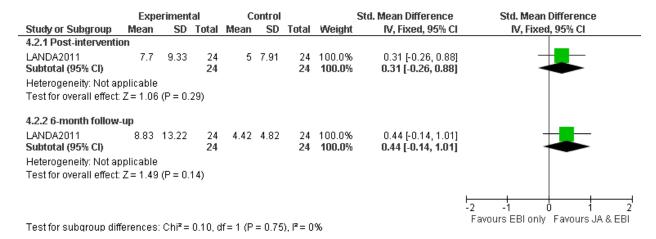
Joint attention training and EBI/EIBI versus EBI/EIBI only for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Examiner-child joint attention - Child-initiated JA (EScs, post-intervention)

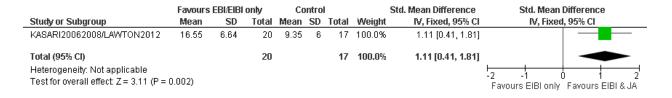
|   | Favours | EBI/EIBI | only            | C     | ontrol |                 |                          | Std. Mean Difference                                | Std. Mean Difference |
|---|---------|----------|-----------------|-------|--------|-----------------|--------------------------|---|----------------------|
| Study or Subgroup   | Mean    | SD       | Total           | Mean  | SD     | Total           | Weight                   | IV, Fixed, 95% CI                                   | IV, Fixed, 95% CI    |
| I.1.1 Coordinated JA looks  |         |          |                 |       |        |                 |                          |   |                      |
| KASARI20062008/LAWTON2012<br>Subtotal (95% CI)                              | 9.55    | 7.88     | 20<br><b>20</b> | 10.35 | 9.74   | 17<br><b>17</b> | 100.0%<br><b>100.0</b> % | -0.09 [-0.74, 0.56]<br>- <b>0.09 [-0.74, 0.56</b> ] | <u> </u>             |
| Heterogeneity: Not applicable<br>Fest for overall effect: Z = 0.27 (P = 0.1 | 79)     |          |                 |       |        |                 |                          |   |                      |
| I.1.2 Showing   |         |          |                 |       |        |                 |                          |   |                      |
| KASARI20062008/LAWTON2012<br>Subtotal (95% Cl)                              | 0.7     | 1.19     | 20<br><b>20</b> | 0.17  | 0.53   | 17<br><b>17</b> | 100.0%<br><b>100.0</b> % | 0.55 [-0.11, 1.21]<br><b>0.55 [-0.11, 1.21]</b>     | -                    |
| Heterogeneity: Not applicable<br>Fest for overall effect: Z = 1.63 (P = 0.  | 10)     |          |                 |       |        |                 |                          |   |                      |
| J.1.3 Pointing  |         |          |                 |       |        |                 |                          |   |                      |
| KASAR120062008/LAWTON2012<br>Subtotal (95% CI)                              | 14.65   | 15.6     | 20<br><b>20</b> | 5.76  | 7.57   | 17<br><b>17</b> | 100.0%<br><b>100.0</b> % | 0.69 [0.02, 1.36]<br><b>0.69 [0.02, 1.36</b> ]      |                      |
| Heterogeneity: Not applicable<br>Fest for overall effect: Z = 2.03 (P = 0.1 | 04)     |          |                 |       |        |                 |                          |   |                      |
| I.1.4 Givina  |         |          |                 |       |        |                 |                          |   |                      |
| (ASARI20062008/LAWTON2012<br>Subtotal (95% Cl)                              | 5.1     | 3.54     | 20<br><b>20</b> | 3.59  | 2.4    | 17<br><b>17</b> | 100.0%<br><b>100.0</b> % | 0.48 [-0.18, 1.14]<br><b>0.48 [-0.18, 1.14</b> ]    |                      |
| Heterogeneity: Not applicable<br>Fest for overall effect: Z = 1.44 (P = 0.1 | 15)     |          |                 |       |        |                 |                          |   |                      |
|   |         |          |                 |       |        |                 |                          |   |                      |
|   |         |          |                 |       |        |                 |                          |   | -2 -1 1 1            |

Test for subgroup differences:  $\mathrm{Chi}^{\mathbf{z}} = 3.18$ ,  $\mathrm{df} = 3$  (P = 0.37),  $\mathrm{I}^{\mathbf{z}} = 5.6\%$ 

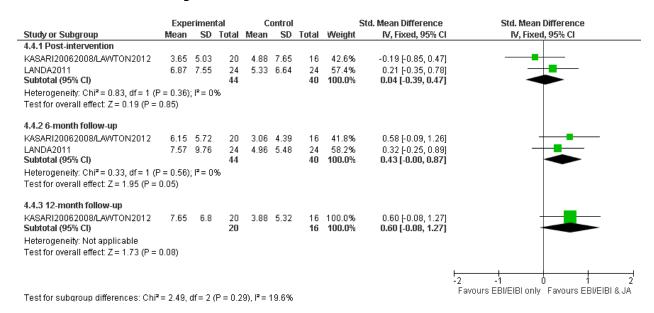
# Examiner-child joint attention- Child-initiated JA (CSBSDP)



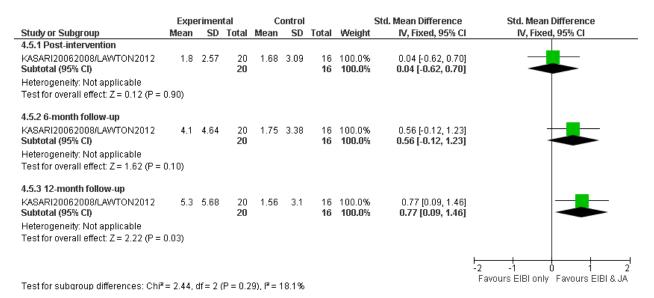
# Examiner-child joint attention - Child responding to JA (EScs, post-intervention)



### Examiner-child shared positive affect



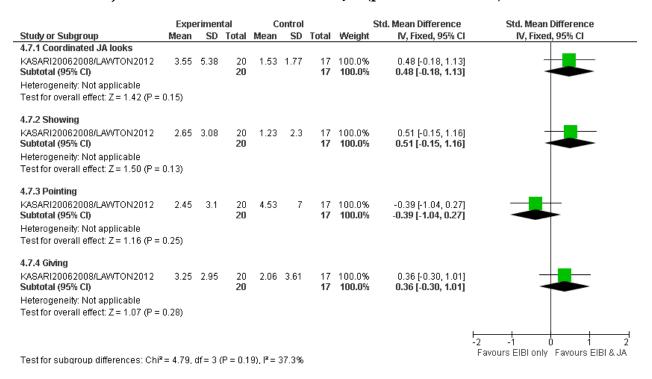
## Examiner-child joint attention, shared positive affect & utterance (EScs)



# Examiner-child socially engaged imitation (SEI)

|                          | Expe     | rimen   | tal  | C         | ontrol            |                   | !      | Std. Mean Difference |                                  |
|--------------------------|----------|---------|--|-----------|-------------------|-------------------|--------|----------------------|----------------------------------|
| Study or Subgroup        | Mean     | SD      | SD Total Mean SD Total Weight IV, Fixed, 95% |           | IV, Fixed, 95% CI | IV, Fixed, 95% CI |        |                      |                                  |
| 4.6.1 Post-intervention  | on       |         |  |           |                   |                   |        |                      |                                  |
| LANDA2011                | 0.42     | 0.24    | 24   | 0.35      | 0.23              | 24                | 100.0% | 0.29 [-0.28, 0.86]   | <del></del>                      |
| Subtotal (95% CI)        |          |         | 24   |           |                   | 24                | 100.0% | 0.29 [-0.28, 0.86]   | <del></del>                      |
| Heterogeneity: Not ap    | plicable |         |  |           |                   |                   |        |                      |                                  |
| Test for overall effect: | Z = 1.01 | (P = 0) | .31)   |           |                   |                   |        |                      |                                  |
| 4.0.0.0                  |          |         |  |           |                   |                   |        |                      |                                  |
| 4.6.2 6-month follow-    | up       |         |  |           |                   |                   |        |                      |                                  |
| LANDA2011                | 0.44     | 0.22    | 24   | 0.28      | 0.21              | 24                | 100.0% | 0.73 [0.15, 1.32]    | <del>-   -  </del>               |
| Subtotal (95% CI)        |          |         | 24   |           |                   | 24                | 100.0% | 0.73 [0.15, 1.32]    |                                  |
| Heterogeneity: Not ap    | plicable |         |  |           |                   |                   |        |                      |                                  |
| Test for overall effect: | Z= 2.45  | (P = 0) | .01)   |           |                   |                   |        |                      |                                  |
|                          |          | •       | •  |           |                   |                   |        |                      |                                  |
|                          |          |         |  |           |                   |                   |        |                      | + <del></del>                    |
|                          |          |         |  |           |                   |                   |        |                      | -2 -1 0 1                        |
| Test for subgroup diff   |          | · ONE-  | - 1 11                                       | AF _ 1 /0 |                   | 03 13 -           | 0.00/  |                      | Favours EBI only Favours JA & EB |

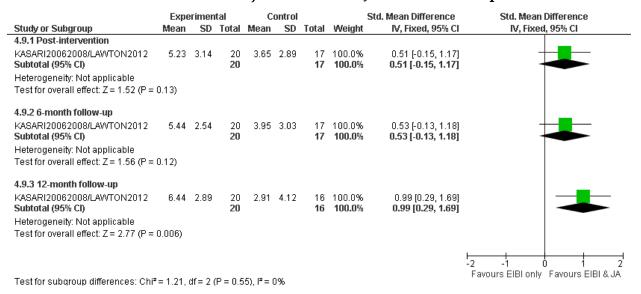
# Mother-child joint attention - Child-initiated JA (post-intervention)



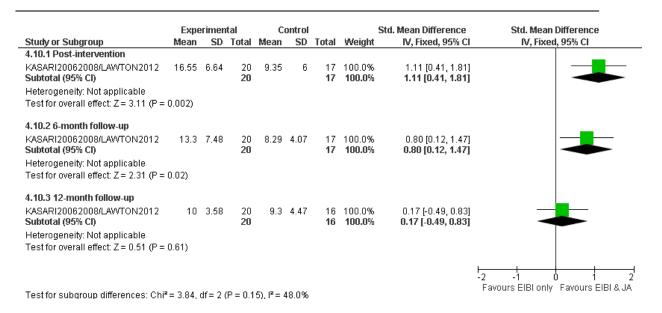
## Mother-child joint attention: Child-initiated JA (duration in seconds)

|   | Expo        | erimenta   | ıl    | 0      | ontrol |       | 9      | Std. Mean Difference | Std. Mean Difference   |
|---|-------------|------------|-------|--------|--------|-------|--------|----------------------|--|
| Study or Subgroup                               | Mean        | SD         | Total | Mean   | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI  |
| 4.8.1 Post-intervention                         |             |            |       |        |        |       |        |                      |  |
| KASARI20062008/LAWTON2012                       | 299         | 237        | 20    | 128    | 188    | 17    | 100.0% | 0.77 [0.10, 1.45]    | <del>-     -     -     -     -     -     -       -</del> |
| Subtotal (95% CI)                               |             |            | 20    |        |        | 17    | 100.0% | 0.77 [0.10, 1.45]    | -  |
| Heterogeneity: Not applicable                   |             |            |       |        |        |       |        |                      |  |
| Test for overall effect: Z = 2.26 (P =          | 0.02)       |            |       |        |        |       |        |                      |  |
| 4.8.2 6-month follow-up                         |             |            |       |        |        |       |        |                      |  |
| KASARI20062008/LAWTON2012                       | 244.9       | 188.87     | 20    | 197.06 | 310.13 | 17    | 100.0% | 0.19 [-0.46, 0.83]   |  |
| Subtotal (95% CI)                               |             |            | 20    |        |        | 17    | 100.0% | 0.19 [-0.46, 0.83]   |  |
| Heterogeneity: Not applicable                   |             |            |       |        |        |       |        |                      |  |
| Test for overall effect: Z = 0.56 (P =          | 0.57)       |            |       |        |        |       |        |                      |  |
| 4.8.3 12-month follow-up                        |             |            |       |        |        |       |        |                      |  |
| KASARI20062008/LAWTON2012                       | 363.55      | 316.58     | 20    | 129.4  | 228.69 | 16    | 100.0% | 0.81 [0.13, 1.50]    | <del>-     -     -     -     -       -  </del>   |
| Subtotal (95% CI)                               |             |            | 20    |        |        | 16    | 100.0% | 0.81 [0.13, 1.50]    | -  |
| Heterogeneity: Not applicable                   |             |            |       |        |        |       |        |                      |  |
| Test for overall effect: Z = 2.32 (P =          | 0.02)       |            |       |        |        |       |        |                      |  |
|   |             |            |       |        |        |       |        |                      |  |
|   |             |            |       |        |        |       |        |                      | -2 -1 0 1  |
| Test for subgroup differences: Chi <sup>2</sup> | '= 2.19. dt | f = 2 (P = | 0.33) | r=8.6% |        |       |        |                      | Favours EIBI only Favours EIBI &   |

### Examiner-child and mother-child joint attention: JA initiation composite

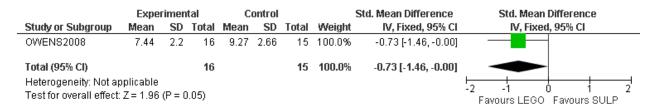


# Examiner-child and mother-child joint attention: JA responses composite

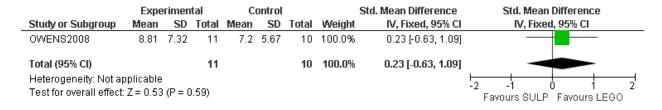


## LEGO® therapy versus SULP for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

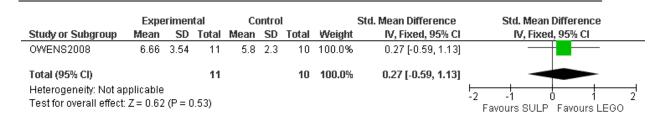
### Social interaction (GARS)



## Frequency of child-initiated social interactions with TD peers (behavioural observation)



### Duration of all social interactions with TD peers (behavioural observation)

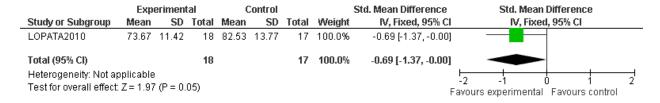


Social skills group versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

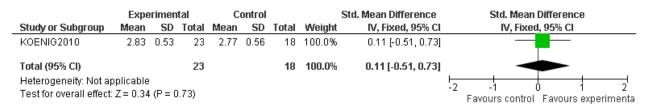
### Social skills (SSRS Assertion/Social skills standardized score or BASC-2-PRS)

|                         | Expe       | rimen  | tal     | C     | ontrol |       |        | Std. Mean Difference | Std. M      | ean Difference            |
|-------------------------|------------|--------|---------|-------|--------|-------|--------|----------------------|-------------|---------------------------|
| Study or Subgroup       | Mean       | SD     | Total   | Mean  | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, F       | Fixed, 95% CI             |
| FRANKEL2010             | 11.8       | 3.2    | 35      | 10.5  | 3.2    | 33    | 51.3%  | 0.40 [-0.08, 0.88]   |             | <del></del>               |
| LAUGESON2009            | 89.7       | 12.1   | 17      | 79.8  | 11.7   | 16    | 23.3%  | 0.81 [0.10, 1.52]    |             | <del></del>               |
| LOPATA2010              | 41.39      | 7.27   | 18      | 35.11 | 7.65   | 18    | 25.4%  | 0.82 [0.14, 1.51]    |             | -                         |
| Total (95% CI)          |            |        | 70      |       |        | 67    | 100.0% | 0.60 [0.26, 0.95]    |             | •                         |
| Heterogeneity: Chi²=    |            | •      |         |       | 6      |       |        |                      | -2 -1       |                           |
| Test for overall effect | : Z = 3.44 | (P = 0 | 1.0006) |       |        |       |        |                      | Favours cor | ntrol Favours experimenta |

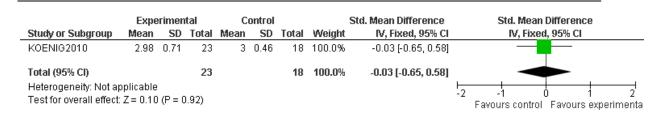
### Social impairment (SRS total)



### Adaptive social behaviour (SCI Pro-social index)



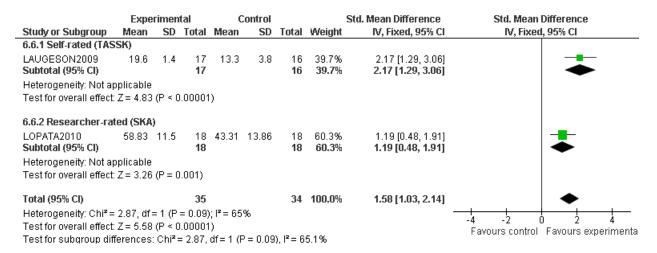
### Capacity for social interactions (SCI Social initiation index)



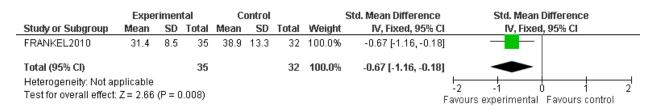
### Study-specific targeted social skills (ASC)

|   | Expe   | riment   | al    | C      | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                               |
|---|--------|----------|-------|--------|--------|-------|--------|----------------------|--|
| Study or Subgroup                                 | Mean   | SD       | Total | Mean   | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |
| LOPATA2010  | 119.56 | 17.13    | 18    | 103.72 | 17.23  | 18    | 100.0% | 0.90 [0.21, 1.59]    |  |
| Total (95% CI)                                    |        |          | 18    |        |        | 18    | 100.0% | 0.90 [0.21, 1.59]    |  |
| Heterogeneity: Not ap<br>Test for overall effect: | •      | (P = 0.0 | 1)    |        |        |       |        |                      | -2 -1 0 1 2<br>Favours control Favours experimenta |

### Social skills knowledge



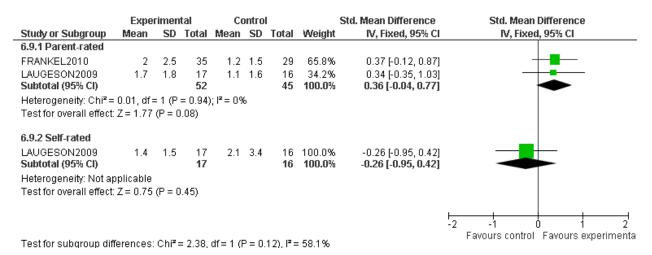
### Feelings of loneliness (Loneliness Scale)



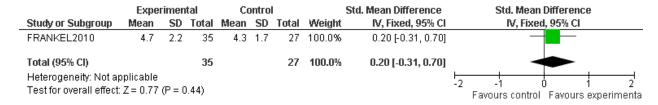
### Popularity (self-rated PHS popularity)

|   | Expe | rimen | tal   | Co   | ontro | l     |        | Std. Mean Difference | Std. Mean Difference                               |
|---|------|-------|-------|------|-------|-------|--------|----------------------|--|
| Study or Subgroup                                 | Mean | SD    | Total | Mean | SD    | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |
| FRANKEL2010                                       | 8    | 2.8   | 35    | 6.4  | 2.9   | 33    | 100.0% | 0.56 [0.07, 1.04]    |  |
| Total (95% CI)                                    |      |       | 35    |      |       | 33    | 100.0% | 0.56 [0.07, 1.04]    | -  |
| Heterogeneity: Not ap<br>Test for overall effect: | •    |       | 1.02) |      |       |       |        |                      | -2 -1 0 1 2<br>Favours control Favours experimenta |

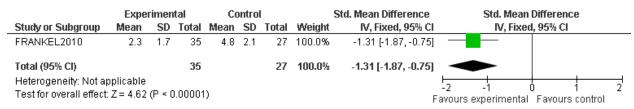
### Number of times child invited to a play date (QPQ Guest)



### Time spent in interactive activities (QPQ Engage)



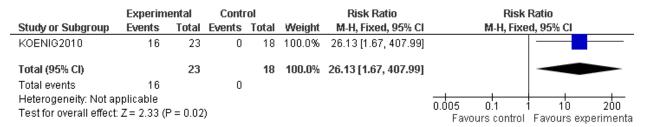
### Time spent in minimally interactive activities (QPQ Disengage)



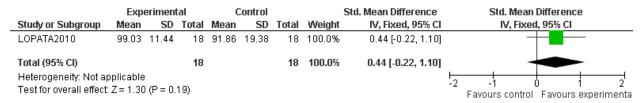
### Quality of friendships (self-rated FQS)

|   | Exper | rimen | tal   | Co   | ontro | ı     |        | Std. Mean Difference |    | Std. Mean Diff             | егепсе          |              |
|---|-------|-------|-------|------|-------|-------|--------|----------------------|----|----------------------------|-----------------|--------------|
| Study or Subgroup                                 | Mean  | SD    | Total | Mean | SD    | Total | Weight | IV, Fixed, 95% CI    |    | IV, Fixed, 95              | % CI            |              |
| LAUGESON2009                                      | 17.2  | 4     | 17    | 16.6 | 4.6   | 16    | 100.0% | 0.14 [-0.55, 0.82]   |    |                            |                 |              |
| Total (95% CI)                                    |       |       | 17    |      |       | 16    | 100.0% | 0.14 [-0.55, 0.82]   |    |                            | -               |              |
| Heterogeneity: Not ap<br>Test for overall effect: | •     |       | ).70) |      |       |       |        |                      | -2 | -1 0<br>Favours control Fa | 1<br>vours expe | 2<br>rimenta |

### Positive treatment response ('much improved/very improved' on CGI-improvement)

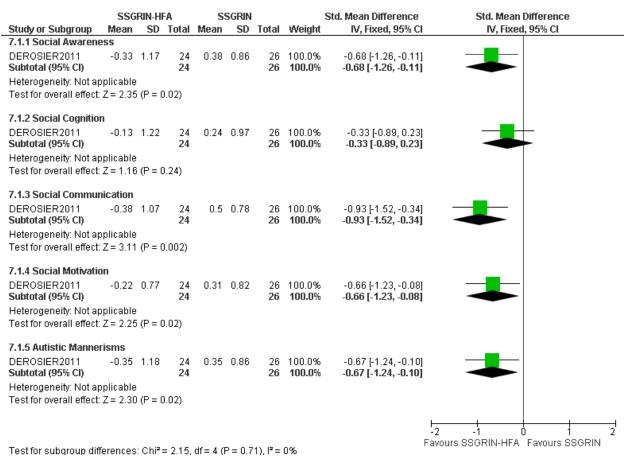


### **Emotion recognition (DANVA2)**

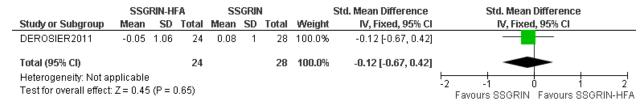


Social skills group modified for autism versus standard social skills group for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

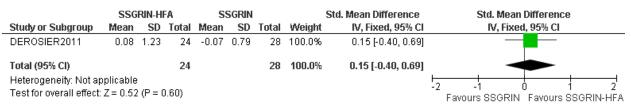
Social skills (SRS standardized change score)



### Social self-efficacy (self-rated Social Self-efficacy Scale; standardized change score)



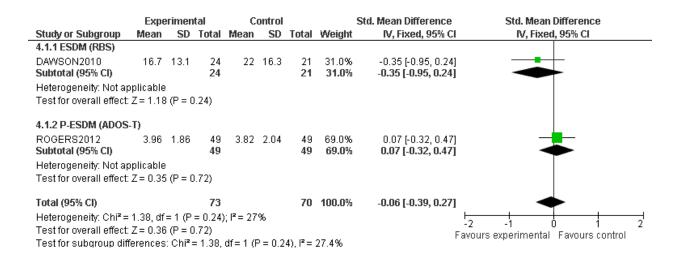
### Feelings of loneliness (Social Dissatisfaction Questionnaire; standardized change score)



# 1.3 PSYCHOSOCIAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF RESTRICTED INTERESTS AND RIGID AND REPETITIVE BEHAVIOURS

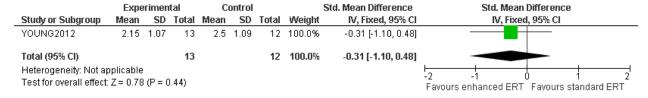
1.3.1 Behavioural interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

ESDM or P-ESDM versus treatment-as-usual for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



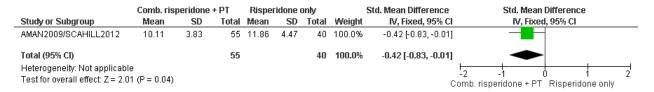
# 1.3.2 Cognitive intervention aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Enhanced ERT versus standard ERT for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



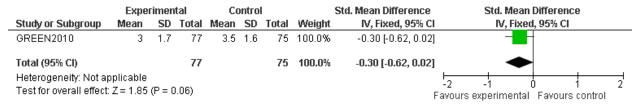
# 1.3.3 Parent training intervention aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Combined parent training and antipsychotic versus antipsychotic-only for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



# 1.3.4 Social-communication intervention aimed at the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

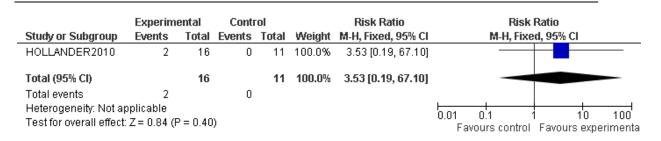
Caregiver-mediated social-communication intervention (PACT) versus treatment-as-usual for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



# 1.4 PHARMACOLOGICAL INTERVENTIONS AIMED AT CORE FEATURES OF AUTISM (OVERALL AUTISTIC BEHAVIOURS)

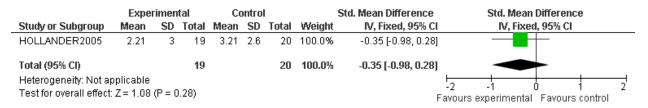
# 1.4.1 Anticonvulsants for overall autistic behaviours as an indirect outcome

Divalproex sodium versus placebo for overall autistic behaviours as an indirect outcome



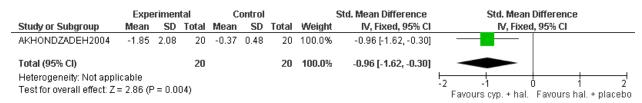
# 1.4.2 Antidepressants for overall autistic behaviours as an indirect outcome

Fluoxetine versus placebo for overall autistic behaviours as an indirect outcome



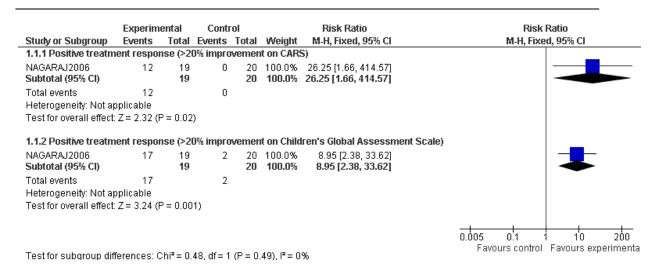
# 1.4.3 Antihistamines for overall autistic behaviours as an indirect outcome

Cyproheptadine and haloperidol versus placebo and haloperidol for overall autistic behaviours as an indirect outcome

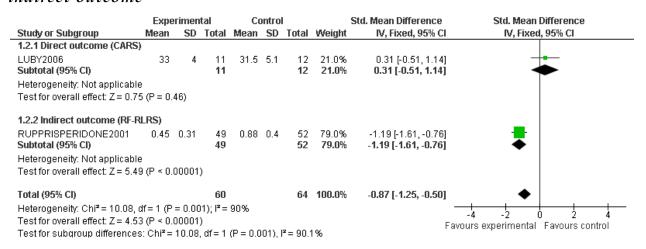


# 1.4.4 Antipsychotics for overall autistic behaviours as a direct or indirect outcome

Risperidone versus placebo for overall autistic behaviours as a direct outcome

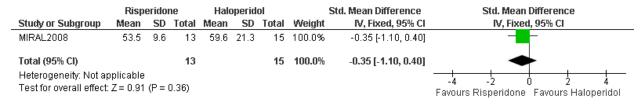


### Risperidone versus placebo for overall autistic behaviours as a direct or indirect outcome

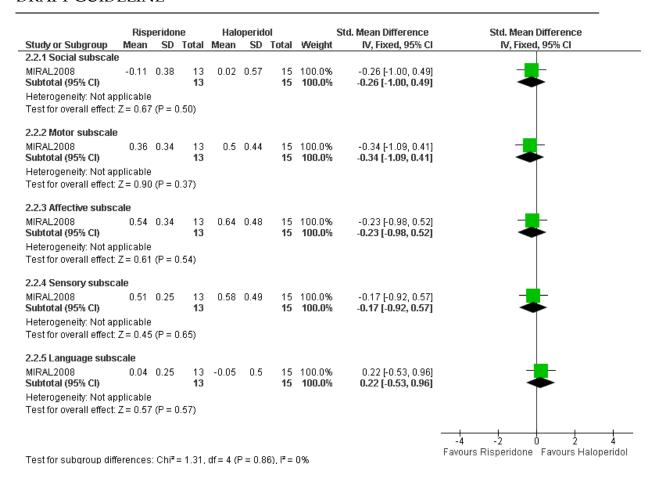


### Risperidone versus haloperidol for overall autistic behaviours as a direct outcome

### Overall autistic behaviours (Turgay DSM-IV PDD Rating Scale)

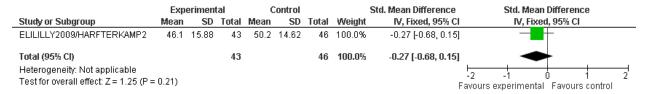


### Overall autistic behaviours (RF-RLRS)



### 1.4.5 SNRIs for overall autistic behaviours as an indirect outcome

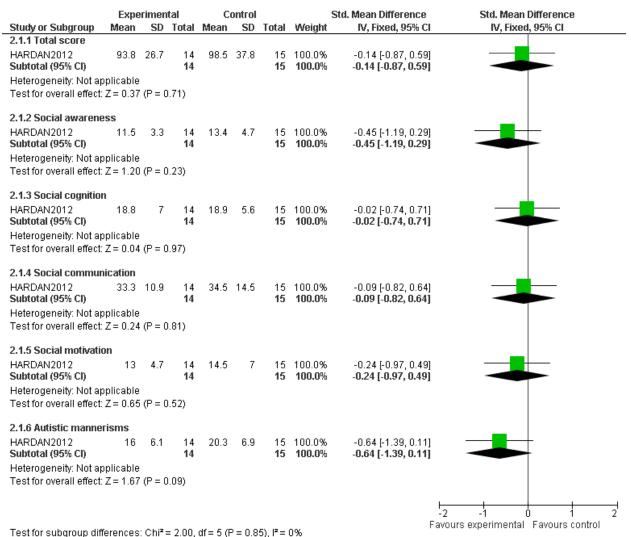
Atomoxetine versus placebo for overall autistic behaviours as an indirect outcome



# 1.5 PHARMACOLOGICAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF IMPAIRED RECIPROCAL SOCIAL COMMUNICATION AND INTERACTION

# 1.5.1 Antioxidants for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

N-acetylcysteine versus placebo for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

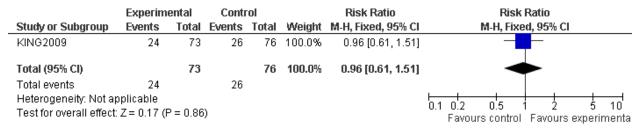


# 1.6 PHARMACOLOGICAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF RESTRICTED INTERESTS AND RIGID AND REPETITIVE BEHAVIOURS

# 1.6.1 Antidepressants for the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome

SSRIs versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome

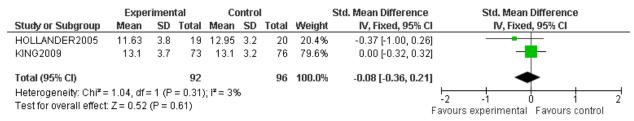
## Global positive treatment response ('much improved/very improved' on CGI-improvement)



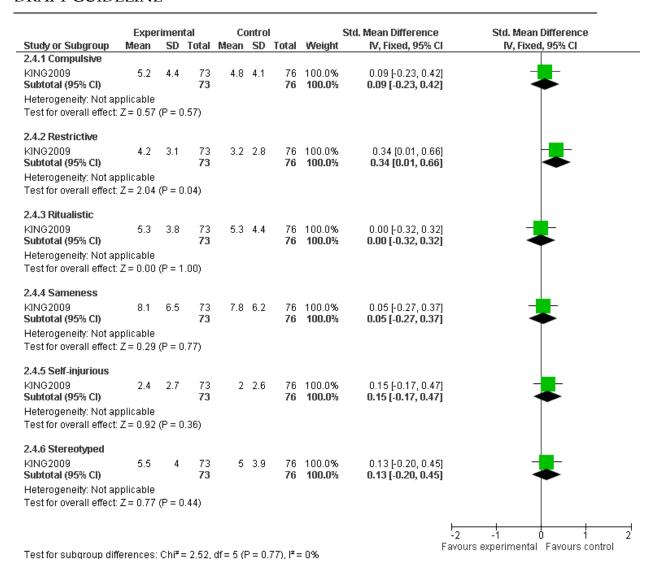
## Global positive treatment response (>25% improvement on CYBOCS-PDD & 'much improved/very improved' on CGI-improvement)

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                          |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|-------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                  |
| KING2009                 | 15          | 73       | 10     | 76    | 100.0% | 1.56 [0.75, 3.25]  |                                     |
| Total (95% CI)           |             | 73       |        | 76    | 100.0% | 1.56 [0.75, 3.25]  |                                     |
| Total events             | 15          |          | 10     |       |        |                    |                                     |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 01 02 05 1 2 5 10                   |
| Test for overall effect: | Z = 1.19 (F | P = 0.23 | )      |       |        |                    | Favours control Favours experimenta |

### Compulsions (CYBOCS-PDD)

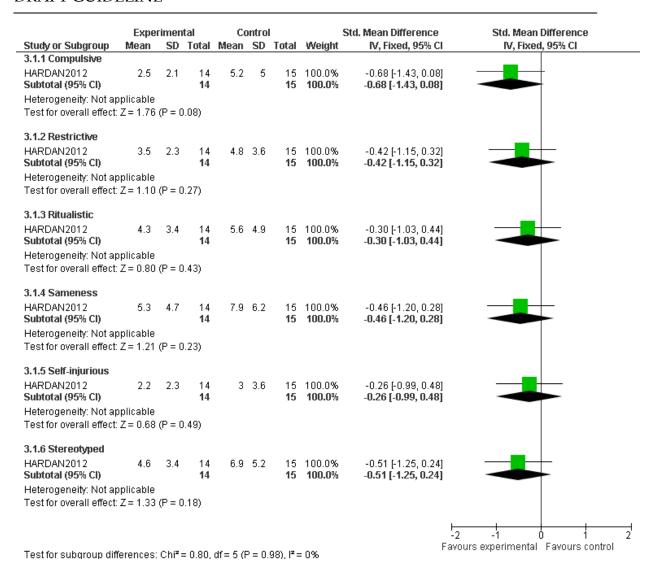


### Repetitive behaviour (RBS)



# 1.6.2 Antioxidants for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

N-acetylcysteine versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

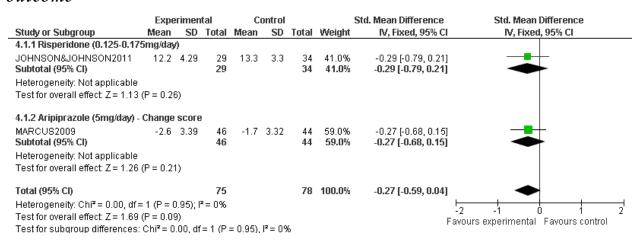


# 1.6.3 Antipsychotics for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Antipsychotics versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

|   | Expe         | rimental    |                   | C     | ontrol |                 |                         | Std. Mean Difference                             | Std. Mean I  | Difference |
|---|--------------|-------------|-------------------|-------|--------|-----------------|-------------------------|--|--------------|------------|
| Study or Subgroup   | Mean         | SD          | Total             | Mean  | SD     | Total           | Weight                  | IV, Fixed, 95% C                                 | I IV, Fixed, | 95% CI     |
| 3.1.1 Risperidone   |              |             |                   |       |        |                 |                         |  |              |            |
| RUPPRISPERIDONE2001   | 11.65        | 4.02        | 49                | 14.21 | 4.81   | 52              | 30.7%                   | -0.57 [-0.97, -0.17                              | "] ——        |            |
| JOHNSON&JOHNSON2011<br>Subtotal (95% CI)                                | 11.6         | 4.57857     | 58<br><b>107</b>  | 13.3  | 3.3    | 34<br><b>86</b> | 26.7%<br><b>57.4</b> %  |  |              |            |
| Heterogeneity: Chi² = 0.31, df =<br>Test for overall effect: Z = 3.32 ( |              | l² = 0%     |                   |       |        |                 |                         |  |              |            |
| 3.1.2 Aripiprazole  |              |             |                   |       |        |                 |                         |  |              |            |
| MARCUS2009<br>Subtotal (95% CI)   | -2.721622    | 3.256739    | 148<br><b>148</b> | -1.7  | 3.32   | 44<br>44        | 42.6%<br>4 <b>2.6</b> % | -0.31 [-0.65, 0.03<br>- <b>0.31 [-0.65, 0.03</b> |              |            |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.80 (    | P = 0.07)    |             |                   |       |        |                 |                         |  |              |            |
| Total (95% CI)  |              |             | 255               |       |        | 130             | 100.0%                  | -0.42 [-0.64, -0.20                              | ı 🔸          |            |
| Heterogeneity: Chi² = 0.96, df =  | 2 (P = 0.62) | $I^2 = 0\%$ |                   |       |        |                 |                         |  | 1 1 1        | 1          |
| Test for overall effect: Z = 3.70 (                                     | n - 0 0000°  |             |                   |       |        |                 |                         |  | -2 -1 0      | 1          |

# Low-dose antipsychotics versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



# 1.7 BIOMEDICAL INTERVENTIONS AIMED AT CORE FEATURES OF AUTISM (OVERALL AUTISTIC BEHAVIOURS)

# 1.7.1 Complementary therapies for overall autistic behaviours as a direct or indirect outcome

Acupressure versus waitlist for overall autistic behaviours as a direct outcome

|   | Ехре      | erimen  | tal             | С         | ontrol  |                   |                          | Std. Mean Difference                            | Std. Mean Difference           |
|---|-----------|---------|-----------------|-----------|---------|-------------------|--------------------------|---|--------------------------------|
| Study or Subgroup                               | Mean      | SD      | Total           | Mean      | SD      | Total             | Weight                   | IV, Fixed, 95% CI                               | IV, Fixed, 95% CI              |
| 1.1.1 Total score                               |           |         |                 |           |         |                   |                          |   |                                |
| CHAN2009<br>Subtotal (95% CI)                   | 0.97      | 0.73    | 16<br><b>16</b> | 0.41      | 0.41    | 16<br><b>16</b>   | 100.0%<br><b>100.0</b> % | 0.92 [0.19, 1.66]<br><b>0.92 [0.19, 1.66]</b>   | -                              |
| Heterogeneity: Not a<br>Test for overall effect |           |         | 1.01)           |           |         |                   |                          |   |                                |
| 1.1.2 Language                                  |           |         |                 |           |         |                   |                          |   |                                |
| CHAN2009<br>Subtotal (95% CI)                   | 1.21      | 0.73    | 16<br><b>16</b> | 0.43      | 0.35    | 16<br><b>16</b>   | 100.0%<br><b>100.0</b> % | 1.33 [0.55, 2.10]<br><b>1.33 [0.55, 2.10]</b>   |                                |
| Heterogeneity: Not a<br>Test for overall effect |           |         | ).0008)         |           |         |                   |                          |   |                                |
| 1.1.3 Social interact                           | ion       |         |                 |           |         |                   |                          |   |                                |
| CHAN2009<br>Subtotal (95% CI)                   | 1.07      | 0.77    | 16<br><b>16</b> | 0.42      | 0.49    | 16<br><b>16</b>   |                          | 0.98 [0.24, 1.72]<br><b>0.98 [0.24, 1.72]</b>   | -                              |
| Heterogeneity: Not a<br>Test for overall effect |           |         | 1.009)          |           |         |                   |                          |   |                                |
| 1.1.4 Stereotyped be                            | ehaviour  |         |                 |           |         |                   |                          |   |                                |
| CHAN2009<br>Subtotal (95% CI)                   | 0.55      | 1.08    | 16<br><b>16</b> | 0.34      | 0.67    | 16<br><b>16</b>   | 100.0%<br><b>100.0</b> % | 0.23 [-0.47, 0.92]<br><b>0.23 [-0.47, 0.92]</b> | -                              |
| Heterogeneity: Not a<br>Test for overall effect |           |         | 1.52)           |           |         |                   |                          |   |                                |
| 1.1.5 Motor function                            | ing       |         |                 |           |         |                   |                          |   |                                |
| CHAN2009<br>Subtotal (95% CI)                   | 1.03      | 1.15    | 16<br><b>16</b> | 0.59      | 0.71    | 16<br><b>16</b>   | 100.0%<br><b>100.0</b> % | 0.45 [-0.25, 1.15]<br><b>0.45 [-0.25, 1.15]</b> |                                |
| Heterogeneity: Not a<br>Test for overall effect |           |         | ).21)           |           |         |                   |                          |   |                                |
|   |           |         |                 |           |         |                   |                          | -   | -2 -1 11 12                    |
| Test for subgroup dit                           | fferences | : Chi²: | = 5.60,         | df = 4 (F | o = 0.2 | 3), <b>I²</b> = 1 | 28.5%                    |   | Favours control Favours experi |

Acupuncture/electro-acupuncture and conventional educational programme versus conventional educational programme only for overall autistic behaviours as a direct outcome

Overall autistic behaviours (ATEC)

### DRAFT GUIDELINE

|  | Exp        | erimenta     | al              | (     | Control |                 |                          | Std. Mean Difference                               | Std. Mean Difference |
|--|------------|--------------|-----------------|-------|---------|-----------------|--------------------------|--|----------------------|
| Study or Subgroup  | Mean       | SD           | Total           | Mean  | SD      | Total           | Weight                   | IV, Fixed, 95% CI                                  | IV, Fixed, 95% CI    |
| <b>2.1.1 Total score</b><br>WONG2008/ CHEUK2011<br><b>Subtotal (95% CI)</b><br>Heterogeneity: Not applicabl<br>Test for overall effect: Z = 0.7            | е          | 17.504       | 18<br><b>18</b> | 1.44  | 19.8    | 18<br><b>18</b> | 100.0%<br><b>100.0</b> % | 0.25 [-0.41, 0.90]<br><b>0.25 [-0.41, 0.90]</b>    | -                    |
| restion overall ellect. Z = 0.7  | 4 (F = 0.  | 40)          |                 |       |         |                 |                          |  |                      |
| 2.1.2 Communication and s<br>WONG2008/ CHEUK2011<br>Subtotal (95% CI)<br>Heterogeneity: Not applicabl<br>Fest for overall effect: Z = 0.1                  | 0.444<br>e | 2.617<br>86) | 18<br><b>18</b> | 0.67  | 4.537   | 18<br><b>18</b> | 100.0%<br><b>100.0</b> % | -0.06 [-0.71, 0.59]<br>- <b>0.06 [-0.71, 0.59]</b> | +                    |
| <b>2.1.3 Sociability</b><br>WONG2008/ CHEUK2011<br><b>Subtotal (95% CI)</b><br>Heterogeneity: Not applicabl<br>Fest for overall effect: Z= 0.4             |            | 7.28<br>67)  | 18<br><b>18</b> | 0.89  | 7.045   |                 | 100.0%<br><b>100.0</b> % | 0.14 [-0.51, 0.80]<br><b>0.14 [-0.51, 0.80]</b>    | -                    |
| 2.1.4 Sensory and cognitive<br>WONG2008/ CHEUK2011<br>Subtotal (95% CI)<br>Heterogeneity: Not applicabl<br>Test for overall effect: Z = 1.2                | 1.611<br>e | 6.572        | 18<br><b>18</b> | -0.89 | 4.922   | 18<br><b>18</b> | 100.0%<br><b>100.0</b> % | 0.42 [-0.24, 1.08]<br>0.42 [-0.24, 1.08]           |                      |
| <b>2.1.5 Physical health and be</b><br>WONG2008/ CHEUK2011<br><b>Subtotal (95% CI)</b><br>Heterogeneity: Not applicabl<br>Test for overall effect: Z = 0.5 | 2.167<br>e | 5.833<br>59) | 18<br><b>18</b> | 0.78  | 8.782   | 18<br><b>18</b> | 100.0%<br><b>100.0</b> % | 0.18 [-0.47, 0.84]<br><b>0.18 [-0.47, 0.84]</b>    | +                    |

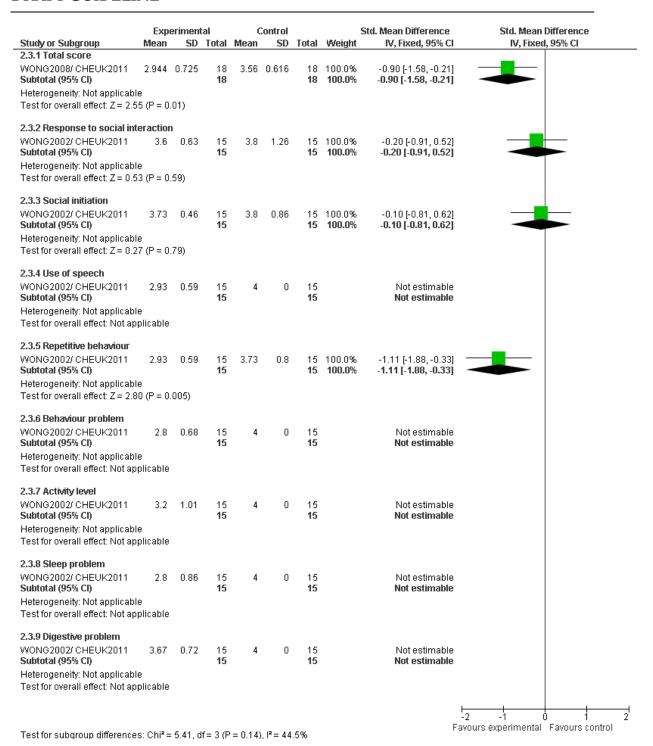
Test for subgroup differences:  $Chi^2 = 1.08$ , df = 4 (P = 0.90),  $I^2 = 0\%$ 

### Overall autistic behaviours (RLRS)

|  |            | rimental    |                 |       | Control | _               |                         | Std. Mean Difference                               | Std. Mean Difference |
|--|------------|-------------|-----------------|-------|---------|-----------------|-------------------------|--|----------------------|
| udy or Subgroup  | Mean       | SD          | Total           | Mean  | SD      | Total           | Weight                  | IV, Fixed, 95% CI                                  | IV, Fixed, 95% CI    |
| 2.1 Total score  |            |             |                 |       |         |                 |                         |  | _                    |
| ONG2002/ CHEUK2011   | 0.1527     |             | 15              |       | 0.2624  | 14              | 42.8%                   | 0.73 [-0.02, 1.49]                                 |                      |
| ONG2008/ CHEUK2011<br>ibtotal (95% Cl)                             | 0.143      | 0.311       | 18<br><b>33</b> | 0.16  | 0.252   | 18<br>32        | 57.2%<br>100.0%         | -0.06 [-0.71, 0.59]<br><b>0.28 [-0.21, 0.77]</b>   |                      |
| eterogeneity: Chi² = 2.42, df:                                     | = 1 (P = 0 | 12):  3=    |                 |       |         | 52              | 100.070                 | 0.20 [-0.21, 0.11]                                 |                      |
| est for overall effect: Z = 1.11                                   |            |             | 3370            |       |         |                 |                         |  |                      |
| 2.2 Motor  |            |             |                 |       |         |                 |                         |  |                      |
| ONG2002/ CHEUK2011   | 0.2487     | 0.5079      | 15              | 0.1   | 0.2941  | 15              | 45.0%                   | 0.35 [-0.37, 1.07]                                 | <del>-   •</del>     |
| ONG2008/ CHEUK2011   | 0.182      | 0.499       | 18              | 0.18  | 0.68    | 18              | 55.0%                   | 0.00 [-0.65, 0.66]                                 | <del>- +</del>       |
| ıbtotal (95% CI)   |            |             | 33              |       |         | 33              | 100.0%                  | 0.16 [-0.33, 0.64]                                 | -                    |
| eterogeneity: Chi² = 0.48, df:<br>est for overall effect: Z = 0.64 | •          |             | 0%              |       |         |                 |                         |  |                      |
|  | (1 - 0.52  | ,           |                 |       |         |                 |                         |  |                      |
| 2.3 Social   |            |             |                 |       |         |                 |                         |  | _                    |
|  | 0.02867    |             | 15              |       | 0.3971  | 15              | 45.0%                   | -0.37 [-1.09, 0.35]                                |                      |
| ONG2008/ CHEUK2011<br>ibtotal (95% Cl)                             | 0.061      | 0.496       | 18<br><b>33</b> | 0.09  | 0.341   | 18<br><b>33</b> | 55.0%<br><b>100.0</b> % | -0.07 [-0.72, 0.59]<br>- <b>0.20 [-0.69, 0.28]</b> |                      |
| eterogeneity: Chi² = 0.37, df:                                     | = 1 (P = 0 | .54); l²=   | 0%              |       |         |                 |                         |  |                      |
| est for overall effect: Z = 0.82                                   |            |             |                 |       |         |                 |                         |  |                      |
| 2.4 Affective  |            |             |                 |       |         |                 |                         |  |                      |
| ONG2002/ CHEUK2011   | 0.3727     | 0.151       | 15              | 0.12  | 0.72    | 15              | 44.7%                   | 0.47 [-0.25, 1.20]                                 | <del>-  </del>       |
| ONG2008/ CHEUK2011   | 0.222      | 0.489       | 18              | 0.26  | 0.515   | 18              | 55.3%                   | -0.07 [-0.73, 0.58]                                |                      |
| ıbtotal (95% CI)   |            |             | 33              |       |         | 33              | 100.0%                  | 0.17 [-0.32, 0.66]                                 | -                    |
| eterogeneity: Chi² = 1.20, df                                      |            |             | 17%             |       |         |                 |                         |  |                      |
| est for overall effect: Z = 0.69                                   | (P = 0.49  | )           |                 |       |         |                 |                         |  |                      |
| 2.5 Sensory  |            |             |                 |       |         |                 |                         |  |                      |
| ONG2002/ CHEUK2011   | 0.157      | 0.281       | 15              | -0.03 | 0.358   | 15              | 44.5%                   | 0.57 [-0.17, 1.30]                                 | _+-                  |
| ONG2008/ CHEUK2011   | 0.15       | 0.325       | 18              | 0.25  | 0.505   | 18              | 55.5%                   | -0.23 [-0.89, 0.43]                                |                      |
| ibtotal (95% CI)   |            |             | 33              |       |         | 33              | 100.0%                  | 0.12 [-0.36, 0.61]                                 |                      |
| eterogeneity: Chi² = 2.52, df:                                     |            |             | 60%             |       |         |                 |                         |  |                      |
| est for overall effect: Z = 0.50                                   | (P = 0.62  | )           |                 |       |         |                 |                         |  |                      |
| 2.6 Language   |            |             |                 |       |         |                 |                         |  |                      |
|  | 0.08667    |             | 15              |       | 0.3754  | 15              | 45.0%                   | 0.45 [-0.28, 1.17]                                 | <del>  _</del>       |
| ONG2008/ CHEUK2011   | 0.1        | 0.341       | 18              | 0     | 0.361   | 18              | 55.0%                   | 0.28 [-0.38, 0.94]                                 |                      |
| ibtotal (95% CI)   |            | <b>-</b> 4: | 33              |       |         | 33              | 100.0%                  | 0.35 [-0.13, 0.84]                                 |                      |
| eterogeneity: Chi² = 0.11, df:                                     | •          |             | U%              |       |         |                 |                         |  |                      |
| est for overall effect: Z = 1.43                                   | (P = 0.15) | )           |                 |       |         |                 |                         |  |                      |
|  |            |             |                 |       |         |                 |                         |  |                      |
|  |            |             |                 |       |         |                 |                         |  | -2 -1 0 1            |

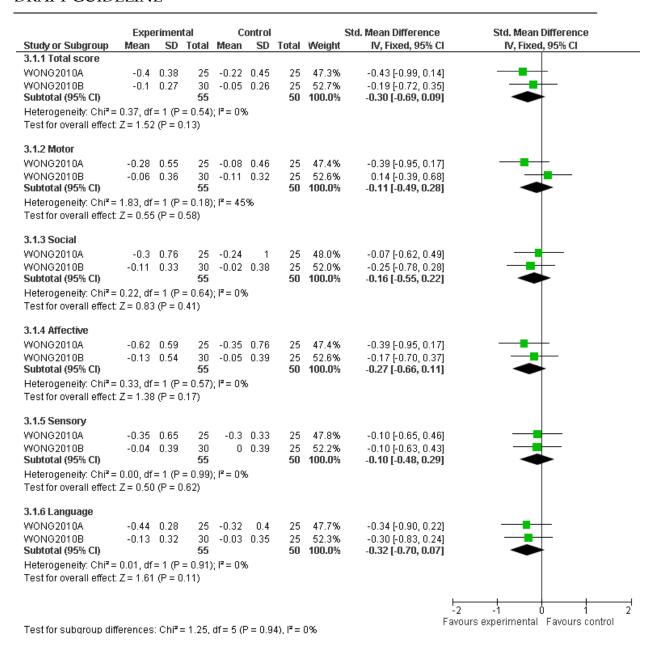
Test for subgroup differences:  $Chi^2 = 3.00$ , df = 5 (P = 0.70),  $I^2 = 0\%$ 

### Overall autistic behaviours (CGI)



Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture for overall autistic behaviours as an indirect outcome

### Overall autistic behaviours (RLRS; change scores)



Positive treatment response (improvement in autistic behaviours; CGI-I)

|                         | Ехрегіт       | ental        | Contr      | ol      |                | Risk Ratio         | Risk Ratio                       |
|-------------------------|---------------|--------------|------------|---------|----------------|--------------------|----------------------------------|
| Study or Subgroup       | Events        | Total        | Events     | Total   | Weight         | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI               |
| 3.2.1 Much improver     | ment          |              |            |         |                |                    |                                  |
| WONG2010B               | 7             | 30           | 1          | 25      | 100.0%         | 5.83 [0.77, 44.28] | +                                |
| Subtotal (95% CI)       |               | 30           |            | 25      | 100.0%         | 5.83 [0.77, 44.28] |                                  |
| Total events            | 7             |              | 1          |         |                |                    |                                  |
| Heterogeneity: Not a    | pplicable     |              |            |         |                |                    |                                  |
| Test for overall effect | : Z = 1.71 (F | P = 0.09     | )          |         |                |                    |                                  |
|                         |               |              |            |         |                |                    |                                  |
| 3.2.2 Minimal improv    | vement        |              |            |         |                |                    | <u>L</u>                         |
| WONG2010B               | 20            | 30           | 14         | 25      | 100.0%         | 1.19 [0.77, 1.83]  | -                                |
| Subtotal (95% CI)       |               | 30           |            | 25      | 100.0%         | 1.19 [0.77, 1.83]  | •                                |
| Total events            | 20            |              | 14         |         |                |                    |                                  |
| Heterogeneity: Not a    | pplicable     |              |            |         |                |                    |                                  |
| Test for overall effect | : Z = 0.80 (F | P = 0.43     | )          |         |                |                    |                                  |
|                         |               |              |            |         |                |                    |                                  |
|                         |               |              |            |         |                |                    | 0.02 0.1 1 10 5                  |
|                         |               |              |            |         |                |                    | Favours control Favours experime |
| Test for subgroup dif   | fferences: 0  | $chi^2 = 2.$ | 26. df = 1 | (P = 0. | 13), $I^2 = 5$ | 5.7%               | ravours control ravours experime |

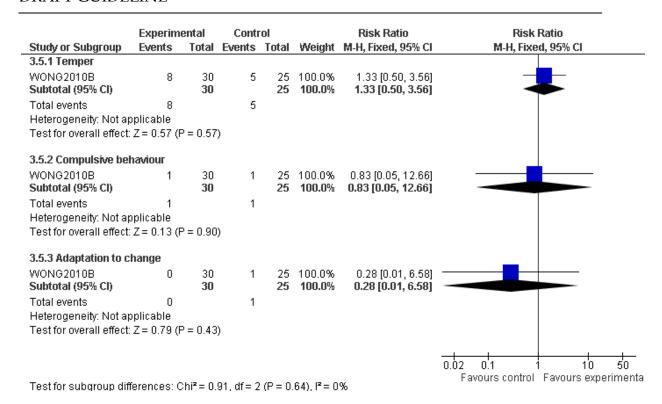
Positive treatment response for social relatedness (study-specific parent-reported 'better than before')

|   | Experime       |                 | Contr    |                 |                          | Risk Ratio                                    | Risk Ratio                      |
|---|----------------|-----------------|----------|-----------------|--------------------------|---|---------------------------------|
| Study or Subgroup                                 | Events         | Total           | Events   | Total           | Weight                   | M-H, Fixed, 95% Cl                            | M-H, Fixed, 95% CI              |
| 3.3.1 Social respons                              |                |                 | _        |                 |                          |   | _                               |
| WONG2010B<br>Subtotal (95% CI)                    | 4              | 30<br><b>30</b> | 5        | 25<br><b>25</b> | 100.0%<br><b>100.0</b> % | 0.67 [0.20, 2.22]<br><b>0.67 [0.20, 2.22]</b> |                                 |
| Total events                                      | 4              | 30              | 5        | 20              | 100.078                  | 0.01 [0.20, 2.22]                             |                                 |
| Heterogeneity: Not ap                             |                |                 | ŭ        |                 |                          |   |                                 |
| Test for overall effect:                          | •              | 9 = 0.51        | )        |                 |                          |   |                                 |
|   |                |                 |          |                 |                          |   |                                 |
| 3.3.2 Social initiation                           |                |                 |          |                 |                          |   | _                               |
| WONG2010B   | 7              | 30              | 0        |                 | 100.0%                   | 12.58 [0.75, 209.98]                          |                                 |
| Subtotal (95% CI)                                 | -              | 30              |          | 25              | 100.0%                   | 12.58 [0.75, 209.98]                          |                                 |
| Total events                                      | 7<br>Splicable |                 | 0        |                 |                          |   |                                 |
| Heterogeneity: Not ap<br>Test for overall effect: | •              | ) = n ng        | ١        |                 |                          |   |                                 |
| restion overall ellect.                           | 2-1.70()       | - 0.00          | ′        |                 |                          |   |                                 |
| 3.3.3 Eye contact                                 |                |                 |          |                 |                          |   |                                 |
| WONG2010B   | 7              | 30              | 4        | 25              | 100.0%                   | 1.46 [0.48, 4.42]                             |                                 |
| Subtotal (95% CI)                                 |                | 30              |          | 25              | 100.0%                   | 1.46 [0.48, 4.42]                             | -                               |
| Total events                                      | 7              |                 | 4        |                 |                          |   |                                 |
| Heterogeneity: Not ap                             |                |                 |          |                 |                          |   |                                 |
| Test for overall effect:                          | Z = 0.67 (F    | ′= 0.50         | )        |                 |                          |   |                                 |
| 3.3.4 Share                                       |                |                 |          |                 |                          |   |                                 |
| WONG2010B   | 0              | 30              | 1        | 25              | 100.0%                   | 0.28 [0.01, 6.58]                             |                                 |
| Subtotal (95% CI)                                 |                | 30              |          | 25              | 100.0%                   | 0.28 [0.01, 6.58]                             |                                 |
| Total events                                      | 0              |                 | 1        |                 |                          |   |                                 |
| Heterogeneity: Not ap                             | •              |                 |          |                 |                          |   |                                 |
| Test for overall effect:                          | Z = 0.79 (F    | ° = 0.43        | )        |                 |                          |   |                                 |
| 3.3.5 Curiosity                                   |                |                 |          |                 |                          |   |                                 |
| WONG2010B   | 0              | 30              | 1        | 25              | 100.0%                   | 0.28 [0.01, 6.58]                             |                                 |
| Subtotal (95% CI)                                 |                | 30              |          | 25              | 100.0%                   | 0.28 [0.01, 6.58]                             |                                 |
| Total events                                      | 0              |                 | 1        |                 |                          |   |                                 |
| Heterogeneity: Not ap                             |                |                 |          |                 |                          |   |                                 |
| Test for overall effect:                          | Z = 0.79 (F    | P = 0.43        | )        |                 |                          |   |                                 |
| 3.3.6 Patience                                    |                |                 |          |                 |                          |   |                                 |
| WONG2010B   | 1              | 30              | 0        | 25              | 100.0%                   | 2.52 [0.11, 59.18]                            |                                 |
| Subtotal (95% CI)                                 |                | 30              | ŭ        | 25              | 100.0%                   | 2.52 [0.11, 59.18]                            |                                 |
| Total events                                      | 1              |                 | 0        |                 |                          | - · · •                                       |                                 |
| Heterogeneity: Not ap                             | plicable       |                 |          |                 |                          |   |                                 |
| Test for overall effect:                          | Z = 0.57 (F    | e 0.57          | )        |                 |                          |   |                                 |
|   |                |                 |          |                 |                          |   |                                 |
|   |                |                 |          |                 |                          |   | 0.005 0.1 1 10 2                |
| Test for subgroup diff                            | farancae: C    | hi² = 5         | 50 df= 5 | /P = 0          | 36) F = Q                | 1%  | Favours control Favours experin |

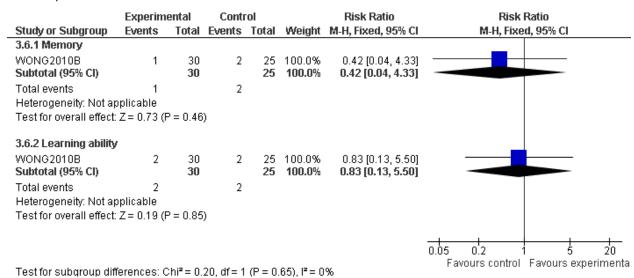
Positive treatment response for non-verbal and verbal communication (study-specific parent-reported 'better than before')

|                          | Experim     | ental    | Contr      | ol    |            | Risk Ratio         | Risk Ratio                      |
|--------------------------|-------------|----------|------------|-------|------------|--------------------|---------------------------------|
| Study or Subgroup        | Events      |          | Events     | Total | Weight     | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI              |
| 3.4.1 Expressive lan     | guage       |          |            |       |            |                    | L                               |
| WONG2010B                | 11          | 30       | 7          |       | 100.0%     | 1.26 [0.58, 2.75]  | -                               |
| Subtotal (95% CI)        |             | 30       |            | 24    | 100.0%     | 1.26 [0.58, 2.75]  | -                               |
| Total events             | 11          |          | 7          |       |            |                    |                                 |
| Heterogeneity: Not a     |             |          |            |       |            |                    |                                 |
| Test for overall effect  | Z = 0.57 (F | ° = 0.57 | )          |       |            |                    |                                 |
| 3.4.2 Receptive lang     | uage        |          |            |       |            |                    |                                 |
| WONG2010B                | 17          | 30       | 5          | 25    | 100.0%     | 2.83 [1.22, 6.59]  | <b></b>                         |
| Subtotal (95% CI)        |             | 30       |            | 25    | 100.0%     | 2.83 [1.22, 6.59]  | •                               |
| Total events             | 17          |          | 5          |       |            |                    |                                 |
| Heterogeneity: Not ap    |             |          |            |       |            |                    |                                 |
| Test for overall effect  | Z = 2.42 (F | P = 0.02 | )          |       |            |                    |                                 |
| 3.4.3 Pointing           |             |          |            |       |            |                    |                                 |
| WONG2010B                | 1           | 30       | 0          | 25    | 100.0%     | 2.52 [0.11, 59.18] |                                 |
| Subtotal (95% CI)        |             | 30       |            | 25    | 100.0%     | 2.52 [0.11, 59.18] |                                 |
| Total events             | 1           |          | 0          |       |            |                    |                                 |
| Heterogeneity: Not ap    |             |          |            |       |            |                    |                                 |
| Test for overall effect  | Z = 0.57 (F | P = 0.57 | )          |       |            |                    |                                 |
| 3.4.4 Imitation          |             |          |            |       |            |                    |                                 |
| WONG2010B                | 1           | 30       | 0          | 25    | 100.0%     | 2.52 [0.11, 59.18] |                                 |
| Subtotal (95% CI)        |             | 30       |            | 25    | 100.0%     | 2.52 [0.11, 59.18] |                                 |
| Total events             | 1           |          | 0          |       |            |                    |                                 |
| Heterogeneity: Not ap    | pplicable   |          |            |       |            |                    |                                 |
| Test for overall effect  | Z = 0.57 (F | P = 0.57 | )          |       |            |                    |                                 |
|                          |             |          |            |       |            |                    |                                 |
|                          |             |          |            |       |            |                    | 0.02 0.1 1 10                   |
| To al 2- a colo anno 192 | ×           | de tra   | 00 46 0    |       |            | ~                  | Favours control Favours experir |
| Test for subgroup dif    | terences: C | :ni*=1.  | 99, at = 3 | (P=0) | 57), I*= 0 | %                  |                                 |

Positive treatment response for stereotypy interest and behaviour (study-specific parent-reported 'better than before')



### Positive treatment response for cognition (study-specific parent-reported 'better than before')



Positive treatment response for motor abnormalities (study-specific parent-reported 'better than before')

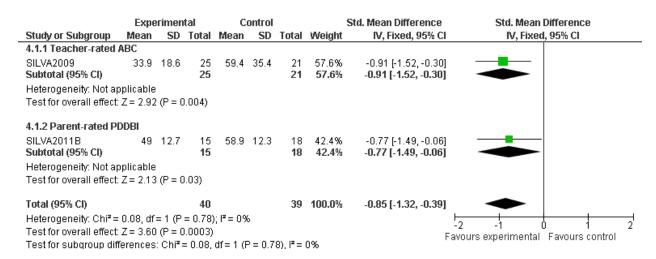
|                                | Experime    | ontal           | Contr      | ol              |                          | Risk Ratio   | Risk Ratio                        |
|--------------------------------|-------------|-----------------|------------|-----------------|--------------------------|--|-----------------------------------|
| Study or Subgroup              | Events      |                 | Events     |                 | Weight                   |  | M-H, Fixed, 95% CI                |
| 3.7.1 Motor skill              |             |                 |            |                 |                          | ,,   |                                   |
| WONG2010B<br>Subtotal (95% CI) | 5           | 30<br><b>30</b> | 0          | 25<br><b>25</b> | 100.0%<br><b>100.0</b> % | 9.23 [0.53, 159.14]<br><b>9.23 [0.53, 159.14</b> ] |                                   |
| Total events                   | 5           |                 | 0          |                 |                          |  |                                   |
| Heterogeneity: Not ap          | plicable    |                 |            |                 |                          |  |                                   |
| Test for overall effect:       | Z = 1.53 (F | 9 = 0.13        | )          |                 |                          |  |                                   |
| 3.7.2 Coordination             |             |                 |            |                 |                          |  |                                   |
| WONG2010B                      | 8           | 30              | 2          | 25              | 100.0%                   | 3.33 [0.78, 14.29]                                 | +-                                |
| Subtotal (95% CI)              |             | 30              |            | 25              | 100.0%                   | 3.33 [0.78, 14.29]                                 |                                   |
| Total events                   | 8           |                 | 2          |                 |                          |  |                                   |
| Heterogeneity: Not ap          | plicable    |                 |            |                 |                          |  |                                   |
| Test for overall effect:       | Z = 1.62 (F | 9 = 0.11        | )          |                 |                          |  |                                   |
| 3.7.3 Drooling                 |             |                 |            |                 |                          |  |                                   |
| WONG2010B                      | 2           | 30              | 1          | 25              | 100.0%                   | 1.67 [0.16, 17.32]                                 |                                   |
| Subtotal (95% CI)              |             | 30              |            | 25              | 100.0%                   | 1.67 [0.16, 17.32]                                 |                                   |
| Total events                   | 2           |                 | 1          |                 |                          |  |                                   |
| Heterogeneity: Not ap          | plicable    |                 |            |                 |                          |  |                                   |
| Test for overall effect:       | Z = 0.43 (F | P = 0.67        | )          |                 |                          |  |                                   |
|                                |             |                 |            |                 |                          |  |                                   |
|                                |             |                 |            |                 |                          |  | 0.01 0.1 1 10 100                 |
|                                |             |                 |            |                 |                          |  | Favours control Favours experimer |
| Test for subgroup diff         | erences: C  | $hi^2 = 0.$     | 83. df = 2 | (P = 0.         | .66), $I^2 = 0$          | %  |                                   |

Positive treatment response for other parent-reported changes (study-specific parent-reported 'better than before')

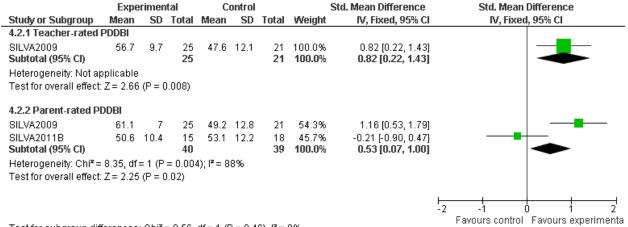
|                          | Experime    |          | Contr  |       |        | Risk Ratio           | Risk Ratio         |
|--------------------------|-------------|----------|--------|-------|--------|----------------------|--------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% Cl   | M-H, Fixed, 95% Cl |
| 3.8.1 Appetite           |             |          |        |       |        |                      | _                  |
| WONG2010B                | 3           | 30       | 1      | 25    | 100.0% | 2.50 [0.28, 22.56]   |                    |
| Subtotal (95% CI)        |             | 30       |        | 25    | 100.0% | 2.50 [0.28, 22.56]   |                    |
| Total events             | 3           |          | 1      |       |        |                      |                    |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                      |                    |
| Test for overall effect: | Z = 0.82 (F | P = 0.41 | )      |       |        |                      |                    |
| 3.8.2 Attention span     |             |          |        |       |        |                      |                    |
| WONG2010B                | 9           | 30       | 0      | 25    | 100.0% | 15.94 [0.97, 260.91] |                    |
| Subtotal (95% CI)        |             | 30       |        | 25    |        | 15.94 [0.97, 260.91] |                    |
| Total events             | 9           |          | 0      |       |        |                      |                    |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                      |                    |
| Test for overall effect: |             | P = 0.05 | )      |       |        |                      |                    |
| 3.8.3 Sleeping patteri   | n           |          |        |       |        |                      |                    |
| WONG2010B                | 7           | 30       | 3      | 25    | 100.0% | 1.94 [0.56, 6.75]    | <b>——</b>          |
| Subtotal (95% CI)        |             | 30       | _      | 25    | 100.0% | 1.94 [0.56, 6.75]    | <b>◆</b>           |
| Total events             | 7           |          | 3      |       |        |                      |                    |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                      |                    |
| Test for overall effect: | •           | P = 0.29 | )      |       |        |                      |                    |
| 3.8.4 "Crafty"           |             |          |        |       |        |                      |                    |
| WONG2010B                | 2           | 30       | 1      | 25    | 100.0% | 1.67 [0.16, 17.32]   |                    |
| Subtotal (95% CI)        |             | 30       |        | 25    | 100.0% | 1.67 [0.16, 17.32]   |                    |
| Total events             | 2           |          | 1      |       |        |                      |                    |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                      |                    |
| Test for overall effect: | •           | e 0.67   | )      |       |        |                      |                    |
| reation overall ellect.  | `           |          |        |       |        |                      |                    |
| restror overall ellect.  |             |          |        |       |        |                      |                    |
| restror overall ellect.  |             |          |        |       |        |                      | 0.005 0.1 1 10 200 |

### Qigong massage training versus waitlist for overall autistic behaviours as an indirect outcome

#### Overall autistic behaviours

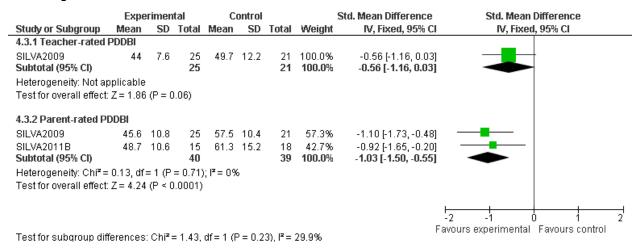


### Social, language, and communication abilities



Test for subgroup differences:  $Chi^2 = 0.56$ , df = 1 (P = 0.46),  $I^2 = 0\%$ 

### Maladaptive behaviour



# 1.7.2 Hormones for overall autistic behaviours as a direct or indirect outcome

Secretin versus placebo for overall autistic behaviours as a direct or indirect outcome

Positive treatment response (decrease of >4.07 points CARS or parent-rated CGI 'much/very much improved')

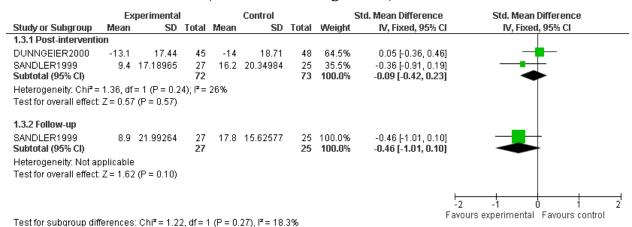
|                                   | Experim      | ental           | Contr               | ol              |                          | Risk Ratio                                    | Risk Ratio                          |
|-----------------------------------|--------------|-----------------|---------------------|-----------------|--------------------------|---|-------------------------------------|
| Study or Subgroup                 | Events       | Total           | Events              | Total           | Weight                   | M-H, Fixed, 95% CI                            | M-H, Fixed, 95% CI                  |
| 1.1.1 Post-treatment              |              |                 |                     |                 |                          |   |                                     |
| CONIGLIO2001<br>Subtotal (95% CI) | 11           | 28<br><b>28</b> | 7                   | 29<br><b>29</b> | 100.0%<br><b>100.0</b> % | 1.63 [0.74, 3.60]<br><b>1.63 [0.74, 3.60]</b> |                                     |
| Total events                      | 11           |                 | 7                   |                 |                          |   |                                     |
| Heterogeneity: Not ap             | plicable     |                 |                     |                 |                          |   |                                     |
| Test for overall effect:          | Z = 1.20 (F  | P = 0.23        | )                   |                 |                          |   |                                     |
| 1.1.2 Follow-up                   |              |                 |                     |                 |                          |   |                                     |
| CONIGLIO2001                      | 10           | 28              | 8                   | 29              | 52.0%                    | 1.29 [0.60, 2.80]                             | <del>-  </del>                      |
| SANDLER1999                       | 9            | 27              | 7                   | 25              | 48.0%                    | 1.19 [0.52, 2.71]                             | <del>-  </del>                      |
| Subtotal (95% CI)                 |              | 55              |                     | 54              | 100.0%                   | 1.24 [0.71, 2.19]                             | -                                   |
| Total events                      | 19           |                 | 15                  |                 |                          |   |                                     |
| Heterogeneity: Chi <sup>2</sup> = | 0.02, df = 1 | 1 (P = 0        | .88); <b> ²</b> = 1 | 0%              |                          |   |                                     |
| Test for overall effect:          | Z = 0.76 (F  | P = 0.45        | )                   |                 |                          |   |                                     |
|                                   |              |                 |                     |                 |                          |   |                                     |
|                                   |              |                 |                     |                 |                          |   | 0.1 0.2 0.5 1 2 5 10                |
| T 1                               |              |                 |                     |                 | 50) 13 0                 |   | Favours control Favours experimenta |

Test for subgroup differences:  $Chi^2 = 0.29$ , df = 1 (P = 0.59),  $I^2 = 0\%$ 

### Overall autistic behaviours (CARS; endpoint or change scores)

|                          | Expe     | erimen   | tal   | C         | ontrol |       |        | Std. Mean Difference | Std. Mo         | ean Differen                                     | ce        |   |
|--------------------------|----------|----------|-------|-----------|--------|-------|--------|----------------------|-----------------|--|-----------|---|
| Study or Subgroup        | Mean     | SD       | Total | Mean      | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, F           | xed, 95% CI                                      |           |   |
| DUNNGEIER2000            | -1.2     | 2.06     | 47    | -1.5      | 2.77   | 48    | 69.6%  | 0.12 [-0.28, 0.52]   |                 |  |           |   |
| MOLLOY2002               | 39.2     | 4.3      | 19    | 38.3      | 5.2    | 23    | 30.4%  | 0.18 [-0.43, 0.79]   | -               | <del> </del>                                     |           |   |
| Total (95% CI)           |          |          | 66    |           |        | 71    | 100.0% | 0.14 [-0.20, 0.48]   |                 | •  |           |   |
| Heterogeneity: Chi²=     |          | ,        |       | ; I² = 09 | 6      |       |        |                      | -2 -1           | <del>                                     </del> | 1         | 7 |
| Test for overall effect: | Z = 0.82 | !(P = 0) | 1.41) |           |        |       |        | F                    | avours experime | ntal Favour:                                     | s control | - |

### Overall autistic behaviours (ABC Total; change score)

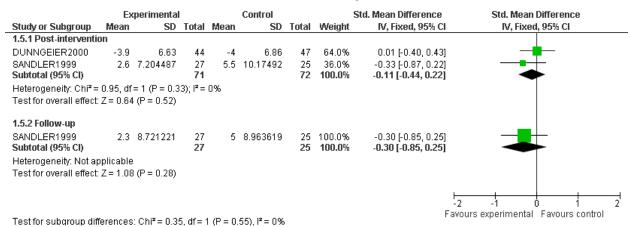


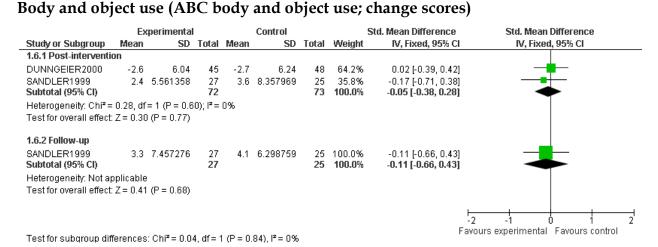
### Sensory function (ABC sensory; change scores)

|                                   | Ex       | perimental   |                 |      | Control  |                 | 9                        | Std. Mean Difference                               | Std. Mean Difference               |
|-----------------------------------|----------|--------------|-----------------|------|----------|-----------------|--------------------------|--|------------------------------------|
| Study or Subgroup                 | Mean     | SD           | Total           | Mean | SD       | Total           | Weight                   | IV, Fixed, 95% CI                                  | IV, Fixed, 95% CI                  |
| 1.4.1 Post-intervention           | n        |              |                 |      |          |                 |                          |  |                                    |
| DUNNGEIER2000                     | -2.4     | 5.25         | 43              | -2.7 | 6.04     | 45              | 63.2%                    | 0.05 [-0.37, 0.47]                                 | <del></del>                        |
| SANDLER1999<br>Subtotal (95% CI)  | 1.5      | 2.780679     | 27<br><b>70</b> | 2.8  | 4.845199 | 25<br><b>70</b> | 36.8%<br><b>100.0</b> %  | -0.33 [-0.88, 0.22]<br>- <b>0.09 [-0.42, 0.25]</b> |                                    |
| Heterogeneity: Chi <sup>2</sup> = | 1.17. df | = 1 (P = 0.2 | 8); l²=         | 14%  |          |                 |                          |  |                                    |
| Test for overall effect:          |          | •            |                 |      |          |                 |                          |  |                                    |
| 1.4.2 Follow-up                   |          |              |                 |      |          |                 |                          |  |                                    |
| SANDLER1999<br>Subtotal (95% CI)  | 1.7      | 3.665441     | 27<br><b>27</b> | 4.3  | 5.935369 | 25<br><b>25</b> | 100.0%<br><b>100.0</b> % | -0.52 [-1.08, 0.03]<br>- <b>0.52 [-1.08, 0.03]</b> |                                    |
| Heterogeneity: Not ap             | plicable | 1            |                 |      |          |                 |                          |  |                                    |
| Test for overall effect:          | Z = 1.85 | (P = 0.06)   |                 |      |          |                 |                          |  |                                    |
|                                   |          |              |                 |      |          |                 |                          |  |                                    |
|                                   |          |              |                 |      |          |                 |                          |  | -2 -1 1                            |
|                                   |          |              |                 |      |          |                 |                          |  | avours experimental Favours contro |

Test for subgroup differences:  $Chi^2 = 1.75$ , df = 1 (P = 0.19),  $I^2 = 43.0\%$ 

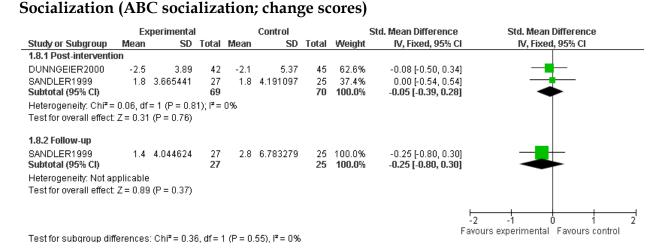
### Social relatedness (ABC social relatedness; change scores)



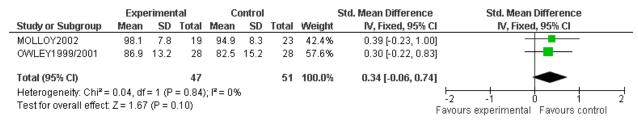


### Language (ABC language; change scores)

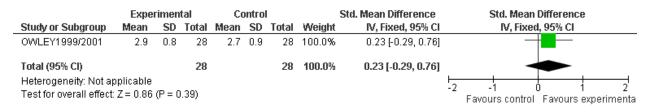
|                                     | Ex       | perimental   | ı               |      | Control  |                 | S                       | td. Mean Difference                                | Std. Mean Difference |
|-------------------------------------|----------|--------------|-----------------|------|----------|-----------------|-------------------------|--|----------------------|
| Study or Subgroup                   | Mean     | SD           | Total           | Mean | SD       | Total           | Weight                  | IV, Fixed, 95% CI                                  | IV, Fixed, 95% CI    |
| 1.7.1 Post-intervention             | 1        |              |                 |      |          |                 |                         |  |                      |
| DUNNGEIER2000                       | -0.9     | 3.89         | 42              | -1.8 | 6.48     | 42              | 62.0%                   | 0.17 [-0.26, 0.60]                                 | <del></del>          |
| SANDLER1999<br>Subtotal (95% CI)    | 1.1      | 4.802991     | 27<br><b>69</b> | 2.6  | 5.208589 | 25<br><b>67</b> | 38.0%<br><b>100.0</b> % | -0.30 [-0.84, 0.25]<br>- <b>0.01 [-0.35, 0.33]</b> | <b>—</b>             |
| Heterogeneity: Chi <sup>2</sup> = 1 | .70. df  | = 1 (P = 0.1 | 9):  ²=         | 41%  |          |                 |                         |  |                      |
| Test for overall effect: Z          |          | •            | -,,,            |      |          |                 |                         |  |                      |
| 1.7.2 Follow-up                     |          |              |                 |      |          |                 |                         |  | _                    |
| SANDLER1999                         | 0.1      | 4.802991     | 27              | 1.6  | 4.481809 | 25              | 100.0%                  | -0.32 [-0.87, 0.23]                                | <del></del>          |
| Subtotal (95% CI)                   |          |              | 27              |      |          | 25              | 100.0%                  | -0.32 [-0.87, 0.23]                                |                      |
| Heterogeneity: Not app              | licable  | !            |                 |      |          |                 |                         |  |                      |
| Test for overall effect: Z          | z = 1.14 | (P = 0.26)   |                 |      |          |                 |                         |  |                      |
|                                     |          |              |                 |      |          |                 |                         |  |                      |
|                                     |          |              |                 |      |          |                 |                         | ⊢  |                      |
|                                     |          |              |                 |      |          |                 |                         |  |                      |



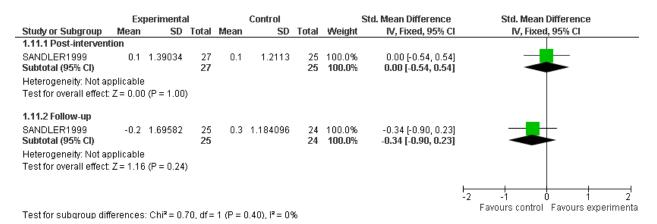
### Overall autistic behaviours (GARS)



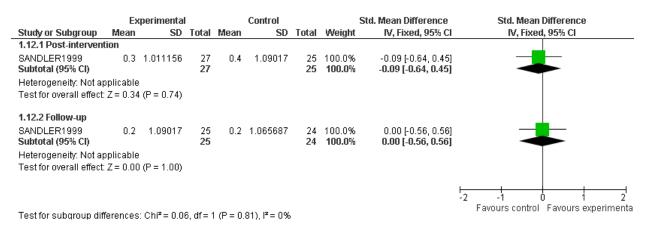
### Overall autistic behaviours (CGI)



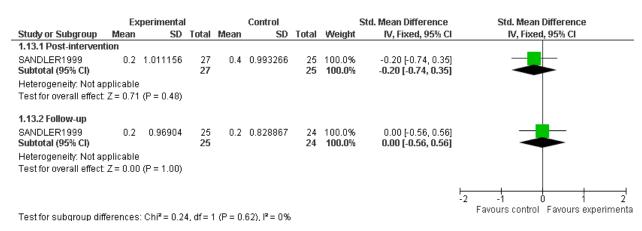
### Response to social interaction (CGI; change scores)



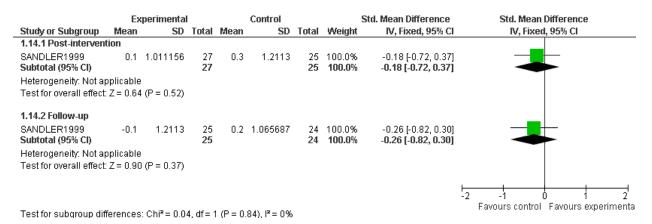
### Social initiation (CGI; change scores)



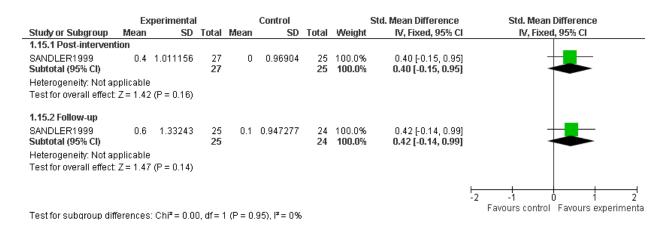
### Use of speech (CGI; change scores)



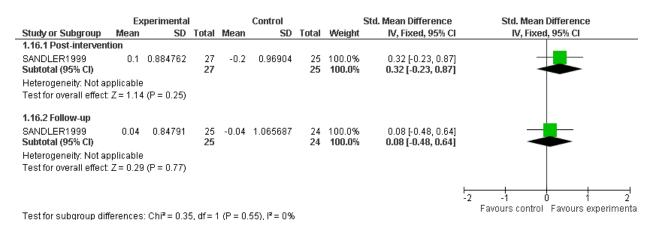
### Types of repetitive behaviour (CGI; change scores)



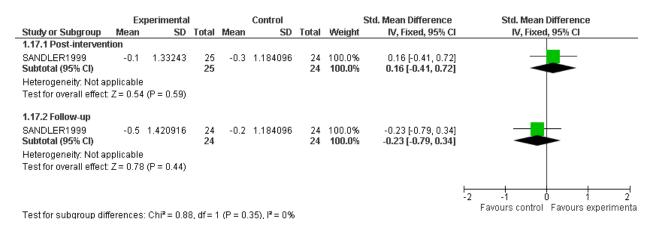
### Behaviour problems (CGI; change scores)



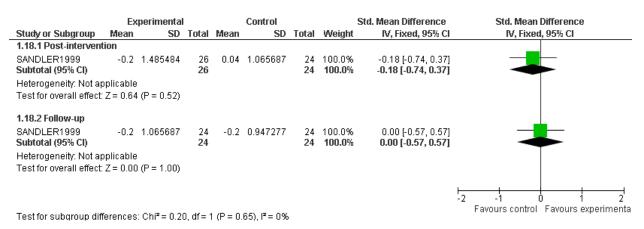
### Activity level (CGI; change scores)



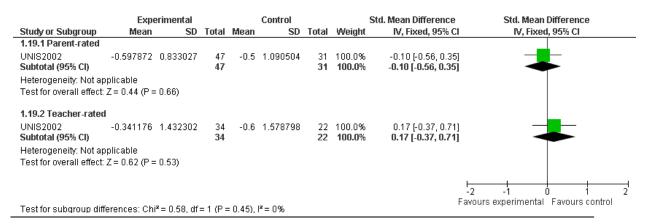
### Sleep problems (CGI; change scores)



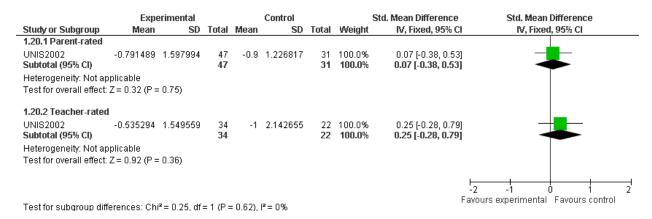
### Digestive problems (CGI; change scores)



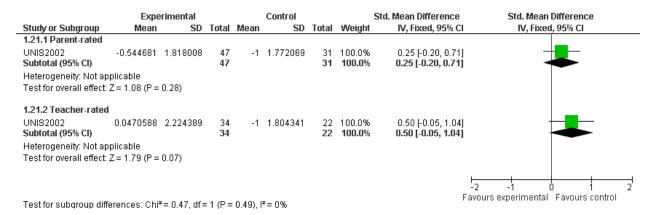
## Overall autistic behaviours (SOS total change score; porcine+synthetic groups combined)



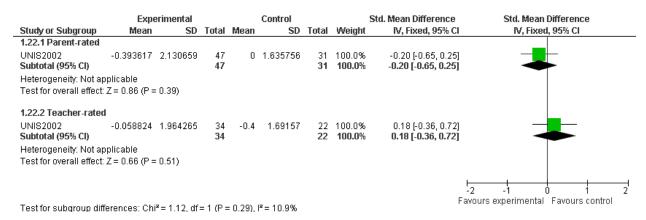
### Social (SOS change score; porcine+synthetic groups combined)



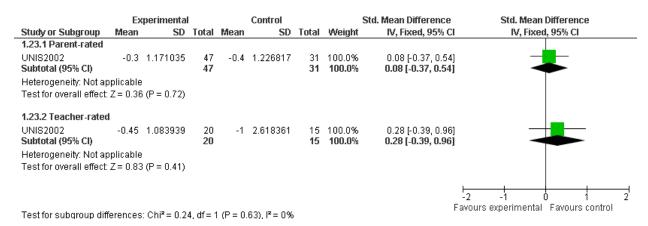
### Communication (SOS change score; porcine+synthetic groups combined)



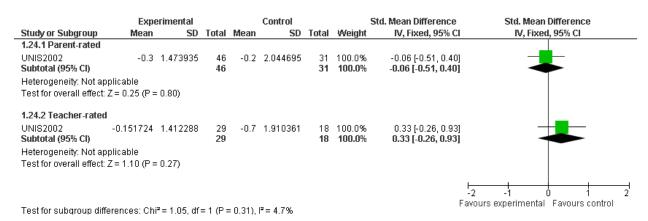
### Repetitive behaviour (SOS change score; porcine+synthetic groups combined)



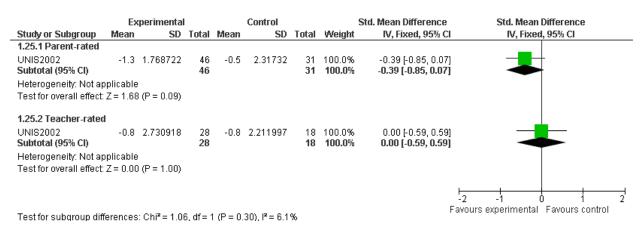
### Digestive (SOS change score; porcine+synthetic groups combined)



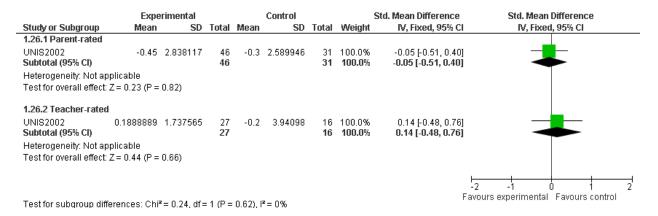
### Mood (SOS change score; porcine+synthetic groups combined)



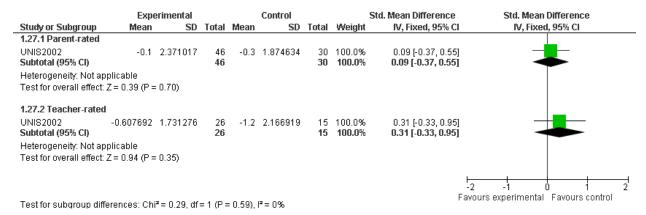
### Sensory (SOS change score; porcine+synthetic groups combined)



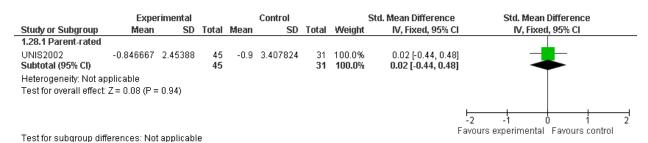
#### Hyperactivity (SOS change score; porcine+synthetic groups combined)



#### Lethargy (SOS change score; porcine+synthetic groups combined)



#### Sleep (SOS change score; porcine+synthetic groups combined)

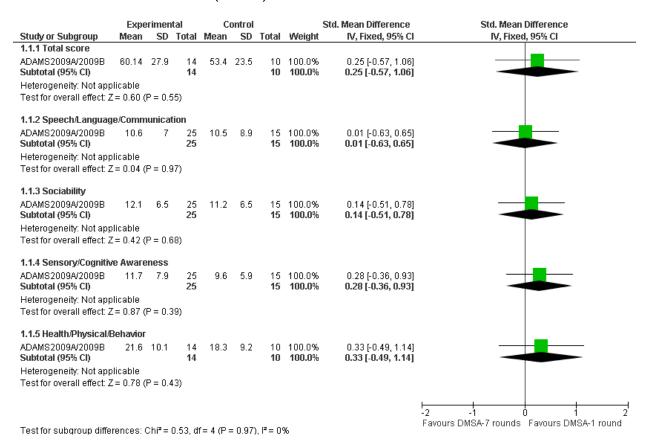


Autism: the management and support of children and young people on the autism spectrum (March 2013)

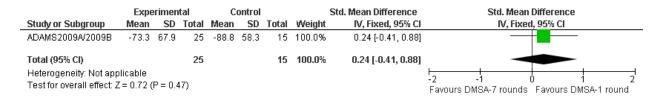
# 1.7.3 Medical procedures for overall autistic behaviours as a direct or indirect outcome

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for overall autistic behaviours as a direct outcome

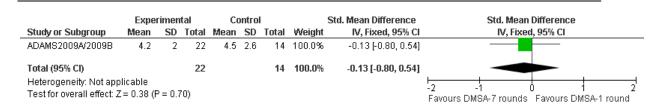
#### Overall autistic behaviours (ATEC)



#### Overall autistic behaviours (PDDBI)

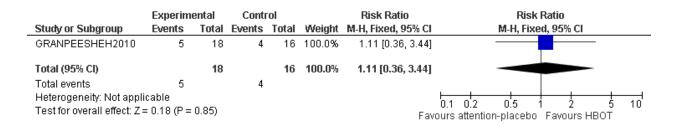


#### Overall autistic behaviours (SAS)

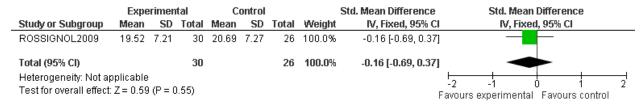


### HBOT versus placebo for overall autistic behaviours as a direct or indirect outcome

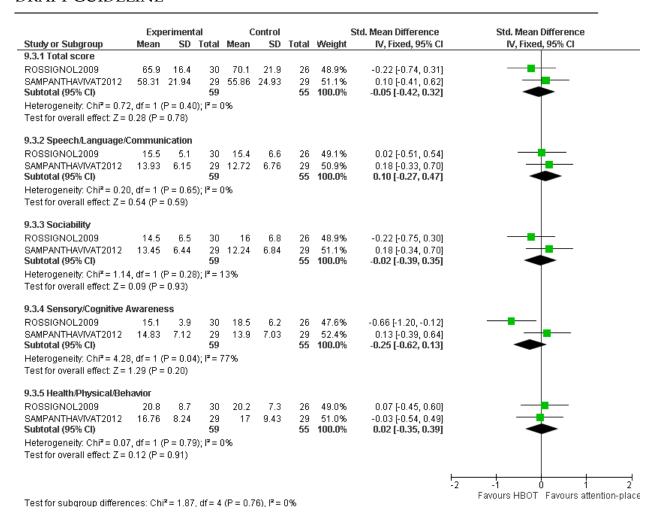
# Positive treatment response (improvement in ADOS diagnostic classification based on total score)



#### Overall autistic behaviours (ADOS total)



#### Overall autistic behaviours (parent-rated ATEC)

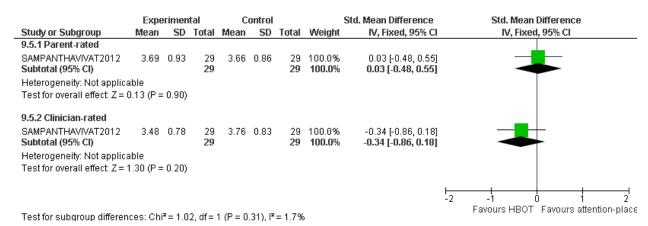


#### Overall autistic behaviours (clinician-rated ATEC)

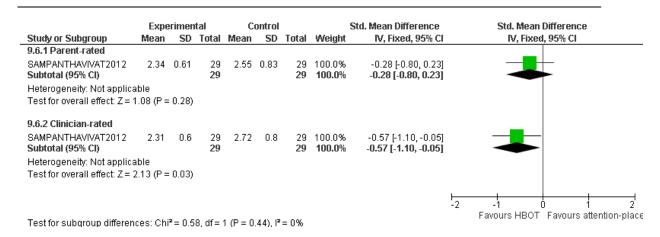
| Study or Subgroup  |            | Experimental |                 |       | ontrol |                 |                          |  |                      |  |
|--|------------|--------------|-----------------|-------|--------|-----------------|--------------------------|--|----------------------|--|
|  | Mean       | SD           | Total           | Mean  | SD     | Total           | Weight                   | IV, Fixed, 95% CI                                  | IV, Fixed, 95% CI    |  |
| 9.4.1 Total score  |            |              |                 |       |        |                 |                          |  |                      |  |
| SAMPANTHAVIVAT2012<br>Subtotal (95% CI)                      | 52.38      | 19.11        | 29<br><b>29</b> | 52.93 | 18.93  | 29<br><b>29</b> | 100.0%<br><b>100.0</b> % | -0.03 [-0.54, 0.49]<br>- <b>0.03 [-0.54, 0.49]</b> | -                    |  |
| Heterogeneity: Not applica                                   | able       |              |                 |       |        |                 |                          |  |                      |  |
| Test for overall effect: Z = 1                               | 0.11 (P =  | 0.91)        |                 |       |        |                 |                          |  |                      |  |
| 9.4.2 Speech/Language/C                                      | Commun     | ication      |                 |       |        |                 |                          |  |                      |  |
| SAMPANTHAVIVAT2012   | 13.66      | 7.25         | 29              | 13.93 | 6.97   | 29              | 100.0%                   | -0.04 [-0.55, 0.48]                                |                      |  |
| Subtotal (95% CI)  |            |              | 29              |       |        | 29              | 100.0%                   | -0.04 [-0.55, 0.48]                                | -                    |  |
| Heterogeneity: Not applica                                   |            |              |                 |       |        |                 |                          |  |                      |  |
| Test for overall effect: Z = 1                               | 0.14 (P =  | 0.89)        |                 |       |        |                 |                          |  |                      |  |
| 9.4.3 Sociability  |            |              |                 |       |        |                 |                          |  |                      |  |
| SAMPANTHAVIVAT2012   | 14.86      | 6.52         | 29              | 13.31 | 4.58   | 29              | 100.0%                   | 0.27 [-0.25, 0.79]                                 | +                    |  |
| Subtotal (95% CI)  |            |              | 29              |       |        | 29              | 100.0%                   | 0.27 [-0.25, 0.79]                                 |                      |  |
| Heterogeneity: Not applica                                   |            |              |                 |       |        |                 |                          |  |                      |  |
| Test for overall effect: Z=                                  | 1.03 (P =  | 0.30)        |                 |       |        |                 |                          |  |                      |  |
| 9.4.4 Sensory/Cognitive A                                    | \warene    | SS           |                 |       |        |                 |                          |  |                      |  |
| SAMPANTHAVIVAT2012   | 13.93      | 5.55         |                 | 14.31 | 4.86   |                 | 100.0%                   | -0.07 [-0.59, 0.44]                                |                      |  |
| Subtotal (95% CI)  |            |              | 29              |       |        | 29              | 100.0%                   | -0.07 [-0.59, 0.44]                                |                      |  |
| Heterogeneity: Not applica<br>Test for overall effect: Z = 1 |            | 0.70\        |                 |       |        |                 |                          |  |                      |  |
| restion overall effect. Z =                                  | 0.27 (F =  | 0.70)        |                 |       |        |                 |                          |  |                      |  |
| 9.4.5 Health/Physical/Beh                                    | naviour    |              |                 |       |        |                 |                          |  |                      |  |
| SAMPANTHAVIVAT2012   | 10.79      | 5.35         | 29              | 12.07 | 6.93   |                 | 100.0%                   | -0.20 [-0.72, 0.31]                                |                      |  |
| Subtotal (95% CI)  | -1-1-      |              | 29              |       |        | 29              | 100.0%                   | -0.20 [-0.72, 0.31]                                |                      |  |
| Heterogeneity: Not applica<br>Test for overall effect: Z = 1 |            | .0.445       |                 |       |        |                 |                          |  |                      |  |
| restroi overali ellect. Z = 1                                | o.rr (i. – | 0.44)        |                 |       |        |                 |                          |  |                      |  |
|  |            |              |                 |       |        |                 |                          | <u> </u>   | 2 -1 11              |  |
| Test for subaroun differen                                   |            |              |                 |       |        |                 |                          |  | Favours HBOT Favours |  |

Test for subgroup differences:  $Chi^2 = 1.75$ , df = 4 (P = 0.78),  $I^2 = 0\%$ 

#### Global severity (CGI-S)



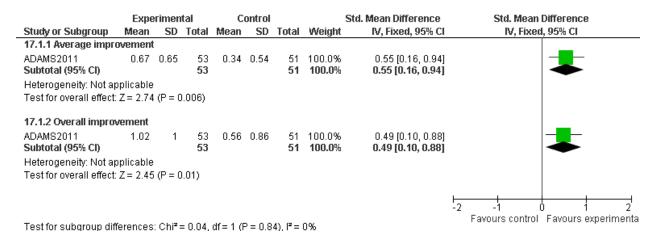
#### Global improvement (CGI-I)



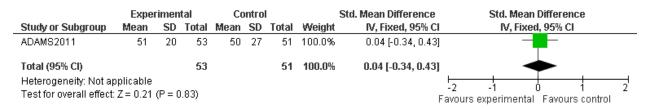
# 1.7.4 Nutritional interventions for overall autistic behaviours as a direct or indirect outcome

Multivitamin/mineral supplement versus placebo for overall autistic behaviours as a direct outcome

#### Overall autistic behaviours (PGI-R)



#### Overall autistic behaviours (ATEC)



#### Overall autistic behaviours (SAS)

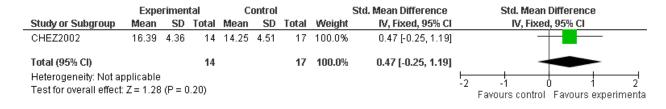
|   | Expe | rimen | ıtal  | Co   | ontro | l     | !      | Std. Mean Difference | Std. Mean Difference                           |
|---|------|-------|-------|------|-------|-------|--------|----------------------|--|
| Study or Subgroup                               | Mean | SD    | Total | Mean | SD    | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                              |
| ADAMS2011                                       | 5.1  | 2.2   | 53    | 5.2  | 2.6   | 51    | 100.0% | -0.04 [-0.43, 0.34]  |  |
| Total (95% CI)                                  |      |       | 53    |      |       | 51    | 100.0% | -0.04 [-0.43, 0.34]  | •  |
| Heterogeneity: Not a<br>Test for overall effect |      |       | 0.83) |      |       |       |        | l<br>-<br>Fa         | -2 -1 0 1 2 vours experimental Favours control |

#### Overall autistic behaviours (PDDBI)

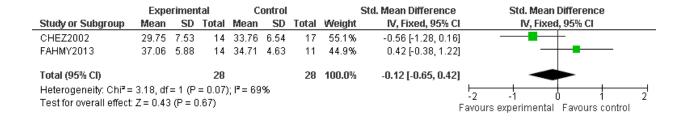
|   | Experimental Control |        |       |      | I  |       | Std. Mean Difference | Std. Mean I        | Difference                      |              |           |
|---|----------------------|--------|-------|------|----|-------|----------------------|--------------------|---------------------------------|--------------|-----------|
| Study or Subgroup                                 | Mean                 | SD     | Total | Mean | SD | Total | Weight               | IV, Fixed, 95% CI  | IV, Fixed                       | 95% CI       |           |
| ADAMS2011   | -78                  | 52     | 53    | -79  | 68 | 51    | 100.0%               | 0.02 [-0.37, 0.40] | _                               | _            |           |
| Total (95% CI)                                    |                      |        | 53    |      |    | 51    | 100.0%               | 0.02 [-0.37, 0.40] | •                               | <b>&gt;</b>  |           |
| Heterogeneity: Not ap<br>Test for overall effect: |                      | (P = 0 | ).93) |      |    |       |                      | F                  | -2 -1 0<br>Favours experimental | Favours cont | 2<br>trol |

## L-carnosine or L-carnitine supplement versus placebo for overall autistic behaviours as a direct outcome

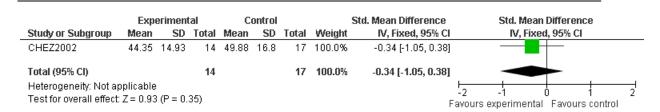
#### Global improvement (PGI-I)



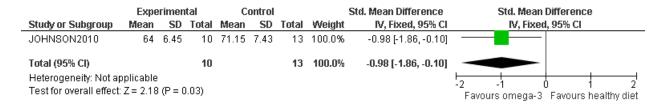
#### Overall autistic behaviours (CARS)



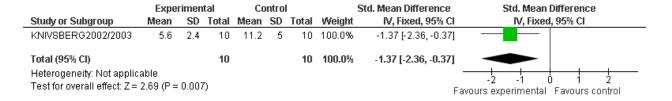
#### Overall autistic behaviours (GARS)



### Omega-3 fatty acids versus placebo for overall autistic behaviours as an indirect outcome

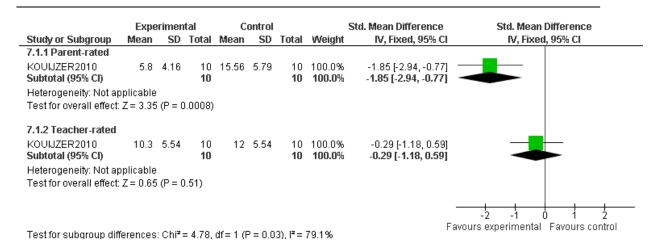


### Gluten-free and casein-free diet versus treatment-as-usual for overall autistic behaviours as a direct outcome

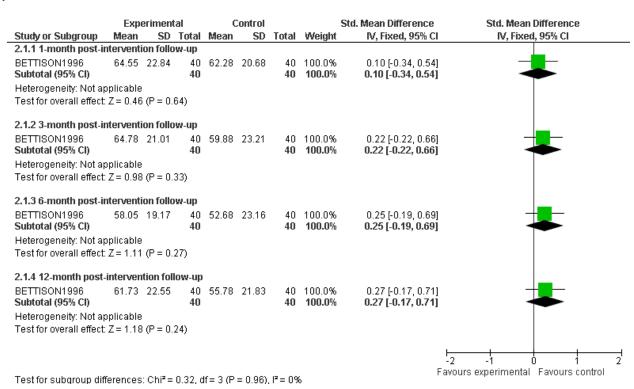


# 1.7.5 Sensory interventions for overall autistic behaviours as a direct or indirect outcome

Neurofeedback versus treatment-as-usual for overall autistic behaviours as a direct outcome



# Auditory integration training versus attention-placebo (structured listening) for overall autistic behaviours as an indirect outcome

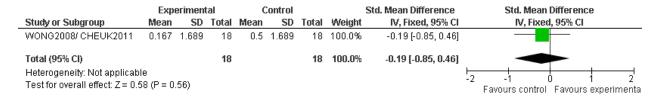


#### 1.8 BIOMEDICAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF IMPAIRED RECIPROCAL SOCIAL COMMUNICATION AND INTERACTION

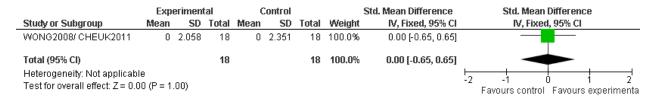
# 1.8.1 Complementary therapies for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Electro-acupuncture and conventional educational programme versus conventional educational programme only for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

#### **Communication (ADOS change score)**



#### Social interaction (ADOS change score)



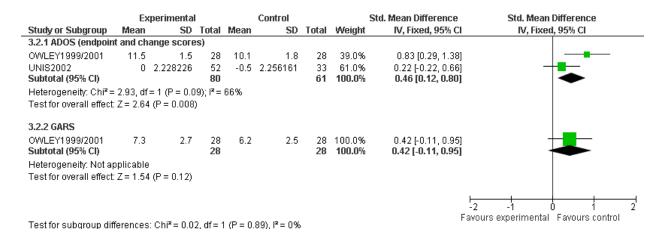
# 1.8.2 Hormones for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Secretin versus placebo for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

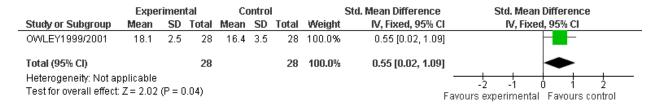
#### Communication

|   |            | <b>es)</b> 28   | Mean<br>6.3 | SD<br>2.2 | Total           | Weight                   | IV, Fixed, 95% CI                                  | IV, Fixed, 95% CI |
|---|------------|-----------------|-------------|-----------|-----------------|--------------------------|--|-------------------|
| OWLEY1999/2001 6<br>UNIS2002 -0<br><b>Subtotal (95% CI)</b>   | 5 1.7      | 28              | 6.3         | 2.2       |                 |                          |  |                   |
| UNIS2002 -0<br><b>Subtotal (95% CI)</b>                       |            |                 | 6.3         | 2.2       |                 |                          |  |                   |
| Subtotal (95% CI)   | 2 1.548616 | 52              |             | 2.2       | 28              | 41.1%                    | 0.10 [-0.42, 0.62]                                 | <del>-  </del>    |
| Hotorogopoite: Chiz = 0.04                                    |            | 80              | 0.2         | 1.833131  | 33<br><b>61</b> | 58.9%<br><b>100.0</b> %  | -0.24 [-0.68, 0.20]<br>- <b>0.10 [-0.44, 0.24]</b> | -                 |
| Test for overall effect: Z = 0                                | •          |                 | U%o         |           |                 |                          |  |                   |
|   | 2 3        | 28<br><b>28</b> | 8           | 3.3       | 28<br><b>28</b> | 100.0%<br><b>100.0</b> % | 0.38 [-0.15, 0.90]<br><b>0.38 [-0.15, 0.90]</b>    |                   |
| Heterogeneity: Not applical<br>Test for overall effect: Z = 1 |            |                 |             |           |                 |                          |  |                   |

#### Social interaction



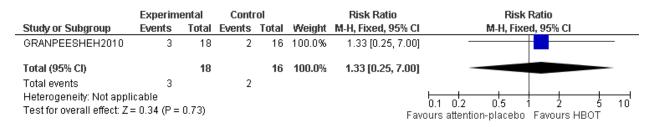
#### Communication and Social Interaction (ADOS; change score)



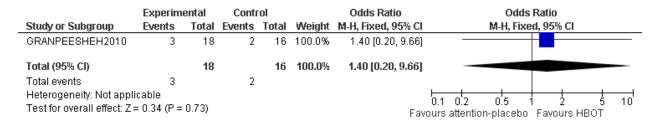
# 1.8.3 Medical procedures for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

Hyperbaric oxygen treatment (HBOT) versus attention-placebo for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

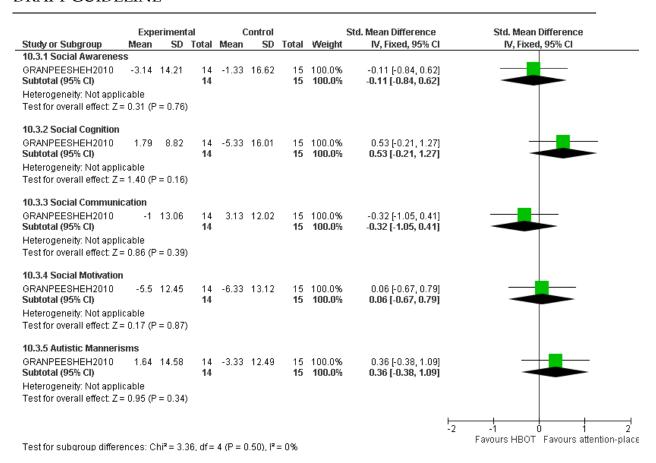
## Positive treatment response (improvement in ADOS diagnostic classification based on Communication domain)



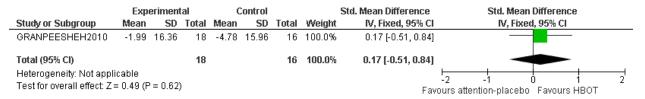
# Positive treatment response (improvement in ADOS diagnostic classification based on Socialization domain)



Social impairment (SRS change score)

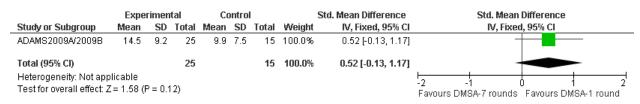


#### Appropriate vocalization (behavioural observation change score)



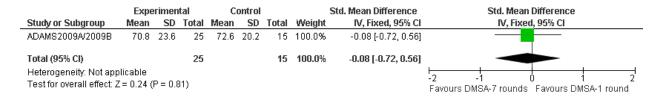
Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

#### Social Pragmatic Problems (PDDBI)



Autism: the management and support of children and young people on the autism spectrum (March 2013)

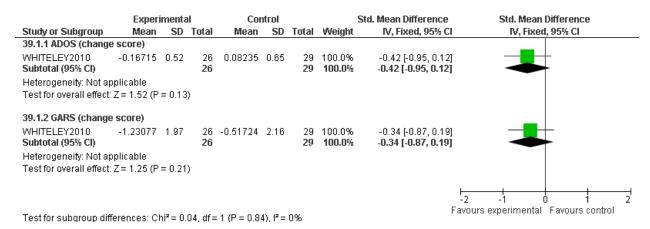
#### Social Approach Behaviours (PDDBI)



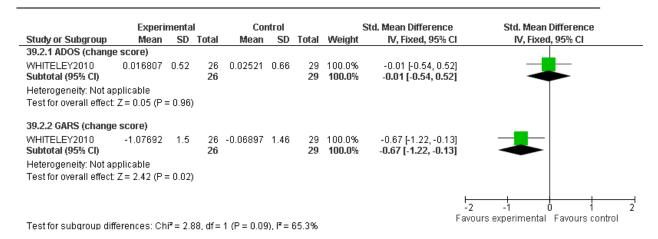
# 1.8.4 Nutritional interventions for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

Gluten-free and casein-free diet versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

#### Communication (direct outcome)



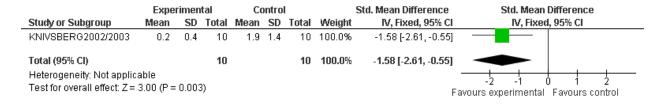
Social Interaction (direct outcome)



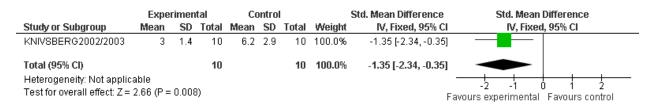
#### Communication and interaction (DIPAB; indirect outcome)

|   | Experimental |       |       | Control |     |       |        | Std. Mean Difference | Std. Mean Difference                               |
|---|--------------|-------|-------|---------|-----|-------|--------|----------------------|--|
| Study or Subgroup                           | Mean         | SD    | Total | Mean    | SD  | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |
| KNIVSBERG2002/2003                          | 6.2          | 1.1   | 10    | 4.5     | 1.6 | 10    | 100.0% | 1.19 [0.22, 2.15]    |  |
| Total (95% CI)<br>Heterogeneity: Not applic | ablo         |       | 10    |         |     | 10    | 100.0% | 1.19 [0.22, 2.15]    |  |
| Test for overall effect: Z=                 |              | 0.02) |       |         |     |       |        |                      | -2 -1 0 1 2<br>Favours control Favours experimenta |

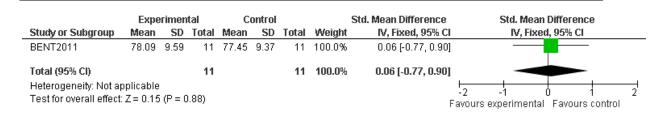
#### Resistance to communication and interaction (DIPAB; indirect outcome)



#### Social isolation (DIPAB; indirect outcome)



## Omega-3 fatty acids versus placebo for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

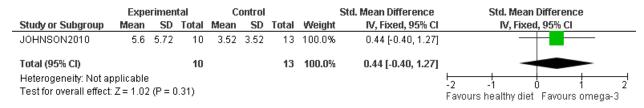


Omega-3 fatty acids versus healthy diet control for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

#### Frequency of positive vocalizations (behavioural observation)

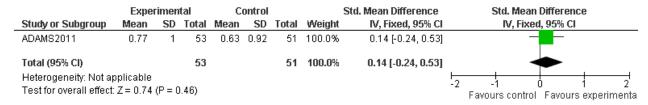
|   | Exp  | Experimental Control |       |       |       |       |        | Std. Mean Difference | Std. Mean Difference                                |
|---|------|----------------------|-------|-------|-------|-------|--------|----------------------|---|
| Study or Subgroup                                 | Mean | SD                   | Total | Mean  | SD    | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                   |
| JOHNSON2010                                       | 16   | 11.02                | 10    | 13.75 | 10.14 | 13    | 100.0% | 0.21 [-0.62, 1.03]   |   |
| Total (95% CI)                                    |      |                      | 10    |       |       | 13    | 100.0% | 0.21 [-0.62, 1.03]   |   |
| Heterogeneity: Not ap<br>Test for overall effect: |      |                      | 63)   |       |       |       |        |                      | -2 -1 0 1 2<br>Favours healthy diet Favours omega-3 |

#### Frequency of social initiations (behavioural observation)

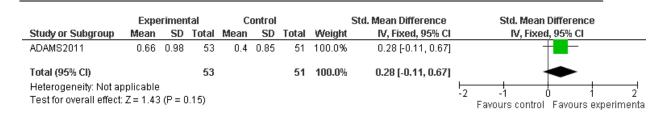


Multivitamin/mineral supplement versus placebo for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

#### Sociability improvement (PGI-R)



#### Eve contact improvement (PGI-R)

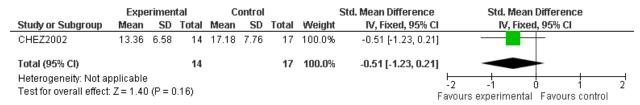


L-carnosine supplement versus placebo for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

#### **Communication (GARS)**

|   | Experimental Control |      |       |       |      |       |        | Std. Mean Difference | Std. Mean Difference                               |
|---|----------------------|------|-------|-------|------|-------|--------|----------------------|--|
| Study or Subgroup                               | Mean                 | SD   | Total | Mean  | SD   | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |
| CHEZ2002  | 18.14                | 6.27 | 14    | 16.88 | 6.48 | 17    | 100.0% | 0.19 [-0.52, 0.90]   |  |
| Total (95% CI)                                  |                      |      | 14    |       |      | 17    | 100.0% | 0.19 [-0.52, 0.90]   |  |
| Heterogeneity: Not a<br>Test for overall effect |                      |      | ).60) |       |      |       |        | F                    | -2 -1 0 1 2<br>avours experimental Favours control |

#### Social interaction (GARS)



# 1.8.5 Sensory interventions for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

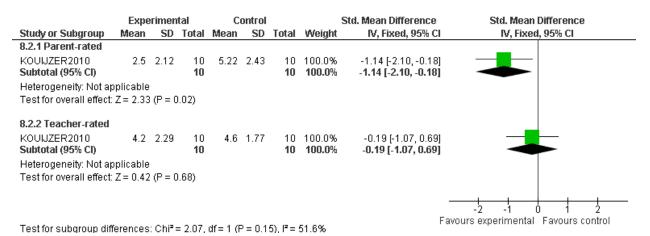
Neurofeedback versus treatment-as-usual for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

Reciprocal social interaction (SCQ)

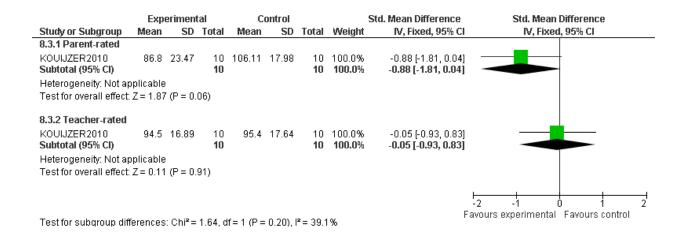
|                          | Expe     | rimen  | tal    | C    | ontrol |       | S      | td. Mean Difference  | Std. Mean Difference             |
|--------------------------|----------|--------|--------|------|--------|-------|--------|----------------------|----------------------------------|
| Study or Subgroup        | Mean     | SD     | Total  | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                |
| 8.1.1 Parent-rated       |          |        |        |      |        |       |        |                      |                                  |
| KOUIJZER2010             | 1.9      | 1.44   | 10     | 5.33 | 2.64   | 10    | 100.0% | -1.54 [-2.57, -0.52] |                                  |
| Subtotal (95% CI)        |          |        | 10     |      |        | 10    | 100.0% | -1.54 [-2.57, -0.52] |                                  |
| Heterogeneity: Not ap    | plicable |        |        |      |        |       |        |                      |                                  |
| Test for overall effect: |          |        | 1.003) |      |        |       |        |                      |                                  |
|                          |          |        |        |      |        |       |        |                      |                                  |
| 8.1.2 Teacher-rated      |          |        |        |      |        |       |        |                      |                                  |
| KOUIJZER2010             | 3.2      | 2.09   | 10     | 4.3  | 3.16   | 10    | 100.0% | -0.39 [-1.28, 0.49]  | <del></del>                      |
| Subtotal (95% CI)        |          |        | 10     |      |        | 10    | 100.0% | -0.39 [-1.28, 0.49]  |                                  |
| Heterogeneity: Not ap    | plicable |        |        |      |        |       |        |                      |                                  |
| Test for overall effect: | Z = 0.87 | (P = 0 | 1.38)  |      |        |       |        |                      |                                  |
|                          |          |        |        |      |        |       |        |                      |                                  |
|                          |          |        |        |      |        |       |        | _                    | -2 -1 0 1 2                      |
| Test for subgroup diffe  |          |        |        |      |        |       |        | Favoi                | urs experimental Favours control |

Test for subgroup differences: Chi² = 2.77, df = 1 (P = 0.10), l² = 63.9%

#### Communication (SCQ)

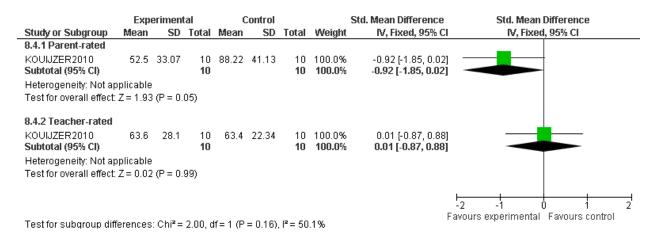


### Communication (CCC-2)

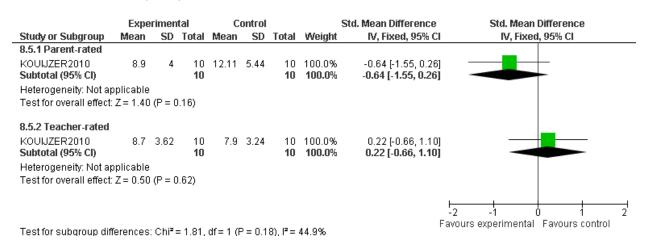


Autism: the management and support of children and young people on the autism spectrum (March 2013)

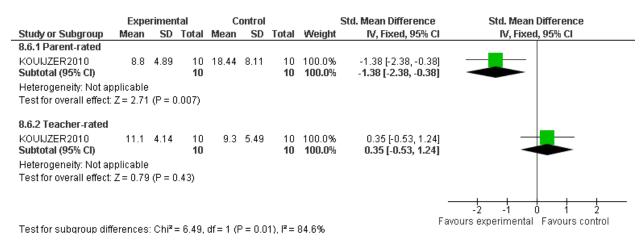
#### Social impairment (SRS)



#### Social Awareness (SRS)

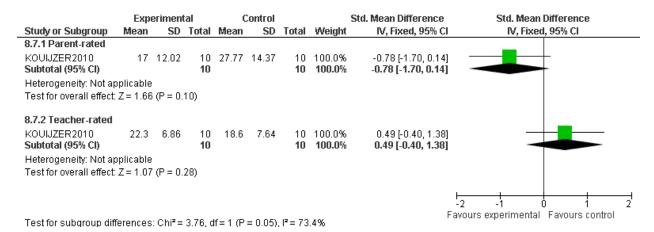


#### Social Cognition (SRS)

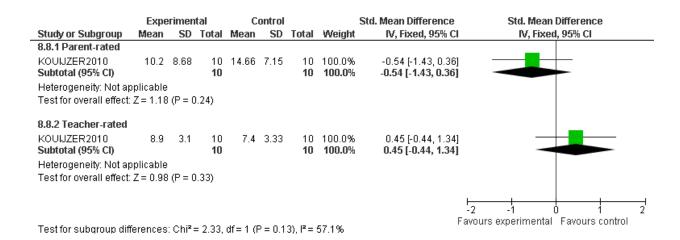


Autism: the management and support of children and young people on the autism spectrum (March 2013)

#### Social Communication (SRS)



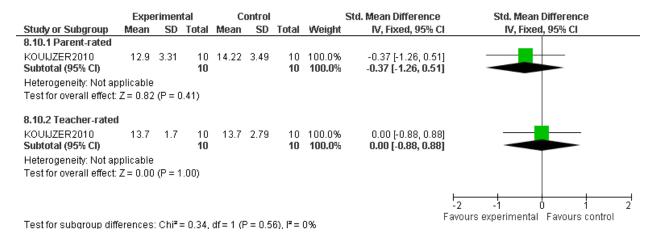
### Social Motivation (SRS)



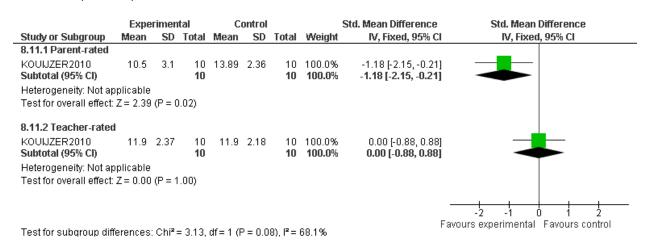
#### **Autistic Mannerisms (SRS)**

|                            | Expe     | rimen   | tal   | (     | Control |       |        | Std. Mean Difference | Std. Mean Difference               |   |
|----------------------------|----------|---------|-------|-------|---------|-------|--------|----------------------|------------------------------------|---|
| Study or Subgroup          | Mean     | SD      | Total | Mean  | SD      | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                  |   |
| 8.9.1 Parent-rated         |          |         |       |       |         |       |        |                      |                                    |   |
| KOUIJZER2010               | 7.6      | 6.36    | 10    | 16.33 | 10.25   | 10    | 100.0% | -0.98 [-1.92, -0.04] |                                    |   |
| Subtotal (95% CI)          |          |         | 10    |       |         | 10    | 100.0% | -0.98 [-1.92, -0.04] |                                    |   |
| Heterogeneity: Not app     | olicable |         |       |       |         |       |        |                      |                                    |   |
| Test for overall effect: 2 | Z = 2.04 | (P = 0  | .04)  |       |         |       |        |                      |                                    |   |
| 8.9.2 Teacher-rated        |          |         |       |       |         |       |        |                      |                                    |   |
|                            |          |         |       |       |         |       |        |                      |                                    |   |
| KOUIJZER2010               | 6.8      | 3.25    | 10    | 8.5   | 4.62    | 10    | 100.0% | -0.41 [-1.30, 0.48]  |                                    |   |
| Subtotal (95% CI)          |          |         | 10    |       |         | 10    | 100.0% | -0.41 [-1.30, 0.48]  |                                    |   |
| Heterogeneity: Not app     | olicable |         |       |       |         |       |        |                      |                                    |   |
| Test for overall effect: 2 | Z = 0.90 | (P = 0) | .37)  |       |         |       |        |                      |                                    |   |
|                            |          |         | ,     |       |         |       |        |                      |                                    |   |
|                            |          |         |       |       |         |       |        |                      |                                    |   |
|                            |          |         |       |       |         |       |        |                      | -2 -1 0 1                          | 2 |
|                            |          |         |       |       |         |       |        | F                    | avours experimental Favours contro | 1 |

#### Social relations (CCC-2)

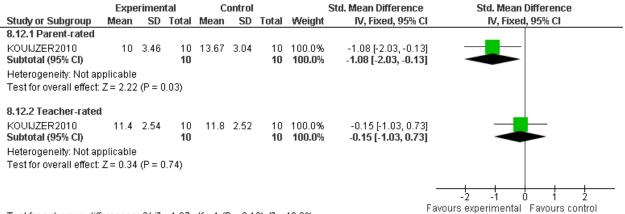


#### Interests (CCC-2)



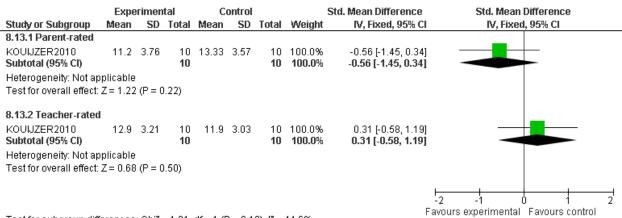
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#### Inappropriate initialization (CCC-2)



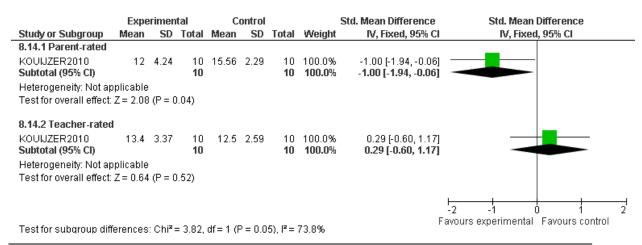
Test for subgroup differences:  $Chi^2 = 1.97$ , df = 1 (P = 0.16),  $I^2 = 49.2\%$ 

#### Stereotyped conversation (CCC-2)



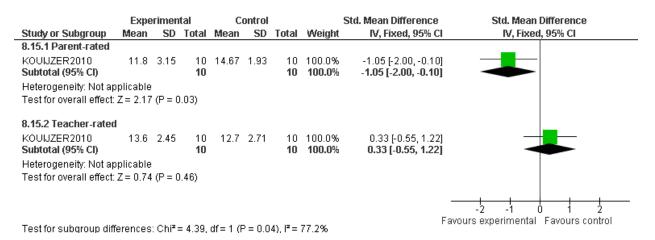
Test for subgroup differences:  $Chi^2 = 1.81$ , df = 1 (P = 0.18),  $I^2 = 44.6\%$ 

#### Context use (CCC-2)

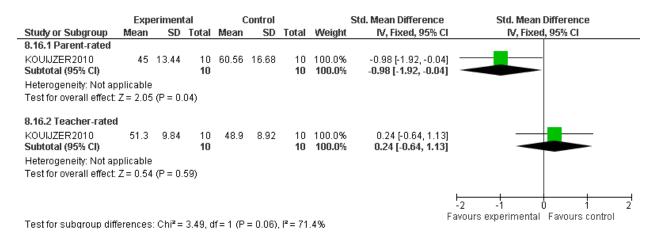


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#### Non-verbal communication (CCC-2)



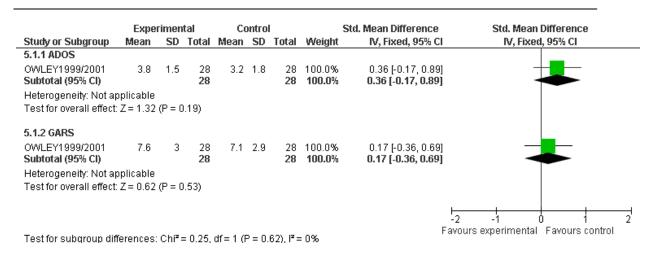
#### **Pragmatics (CCC-2)**



#### 1.9 BIOMEDICAL INTERVENTIONS AIMED AT THE CORE AUTISM FEATURE OF RESTRICTED INTERESTS AND RIGID AND REPETITIVE BEHAVIOURS

# 1.9.1 Hormones for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

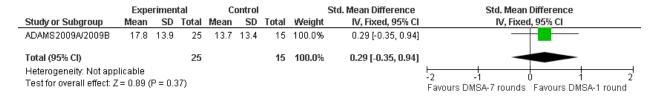
Secretin versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



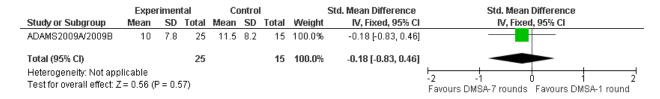
# 1.9.2 Medical procedures for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

#### Sensory/Perceptual Approach Behaviours (PDDBI)



#### Ritualisms/Resistance to Change (PDDBI)

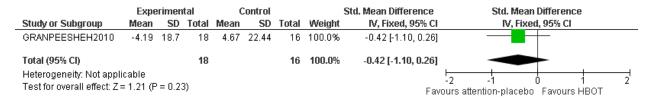


HBOT versus attention-placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

#### Vocal stereotypy (behavioural observation; change score)

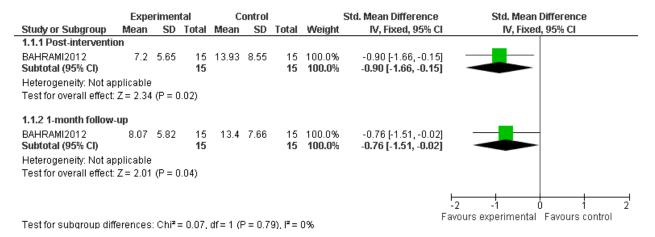
|   | Exp  | eriment   | tal   | (     | ontrol |       | !      | Std. Mean Difference | Std. Me  | an Differ    | ence          |         |
|---|------|-----------|-------|-------|--------|-------|--------|----------------------|--|--------------|---------------|---------|
| Study or Subgroup                                     | Mean | SD        | Total | Mean  | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fit  | ked, 95%     | CI            |         |
| GRANPEESHEH2010                                       | 6.22 | 21.76     | 18    | 12.14 | 17.75  | 16    | 100.0% | -0.29 [-0.97, 0.39]  |  |              |               |         |
| Total (95% CI)  |      |           | 18    |       |        | 16    | 100.0% | -0.29 [-0.97, 0.39]  |  |              |               |         |
| Heterogeneity: Not appl<br>Test for overall effect: Z |      | P = 0.40) | )     |       |        |       |        | H<br>-<br>Fayor      | <del>     </del><br>-2 -1<br>urs attention-place | 0<br>bo Favo | 1<br>ours HBC | 2<br>)T |

#### Physical stereotypy (behavioural observation; change score)



# 1.9.3 Motor intervention for the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome

Kata exercise training versus treatment-as-usual for the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome



# 1.9.4 Nutritional interventions for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Gluten-free and casein-free diet versus treatment-as-usual for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

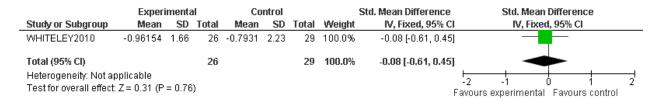
#### Unusual or bizarre behaviour (DIPAB)

|  | Expe | rimen | tal   | Co   | ontro | I     |        | Std. Mean Difference | Std. Mean                    | Difference        |            |
|--|------|-------|-------|------|-------|-------|--------|----------------------|------------------------------|-------------------|------------|
| Study or Subgroup  | Mean | SD    | Total | Mean | SD    | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed                    | i, 95% CI         |            |
| KNIVSBERG2002/2003                                       | 2.6  | 1.7   | 10    | 4.8  | 2.6   | 10    | 100.0% | -0.96 [-1.90, -0.02] |                              | -                 |            |
| Total (95% CI)   |      |       | 10    |      |       | 10    | 100.0% | -0.96 [-1.90, -0.02] |                              |                   |            |
| Heterogeneity: Not applic<br>Test for overall effect: Z= |      | 0.04) |       |      |       |       |        | F                    | -2 -1<br>avours experimental | 0 1<br>Favours co | 2<br>ntrol |

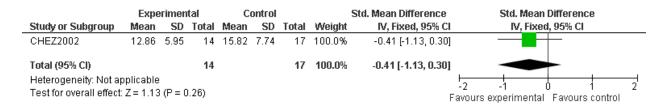
#### Repetitive Behaviours (change score; ADOS)

|   | Experimental Control |        |       |         |      |       | Std. Mean Difference | Std. Mean Difference |  |
|---|----------------------|--------|-------|---------|------|-------|----------------------|----------------------|--|
| Study or Subgroup                                 | Mean                 | SD     | Total | Mean    | SD   | Total | Weight               | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |
| WHITELEY2010                                      | -0.14706             | 0.46   | 26    | 0.03431 | 0.61 | 29    | 100.0%               | -0.33 [-0.86, 0.20]  |  |
| Total (95% CI)                                    |                      |        | 26    |         |      | 29    | 100.0%               | -0.33 [-0.86, 0.20]  |  |
| Heterogeneity: Not ap<br>Test for overall effect: | •                    | = 0.23 | )     |         |      |       |                      | F                    | -2 -1 0 1 2<br>avours experimental Favours control |

#### Stereotyped behaviour (change score; GARS)

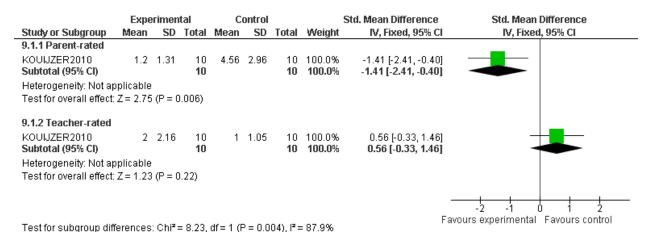


# L-carnosine supplement versus placebo for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome



# 1.9.5 Sensory intervention for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Neurofeedback versus treatment-as-usual for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

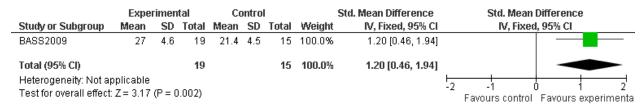


# 1.10PSYCHOSOCIAL INTERVENTIONS AIMED AT BEHAVIOUR THAT CHALLENGES

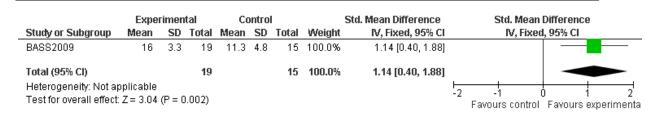
# 1.10.1 Animal-based intervention for behaviour that challenges as an indirect outcome

Horseback riding versus waitlist control for behaviour that challenges as an indirect outcome

#### Inattention/distractability (Sensory Profile)

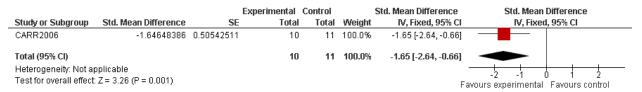


#### **Sedentary (Sensory Profile)**

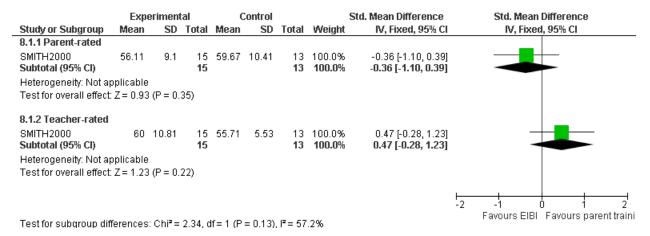


# 1.10.2Behavioural interventions for behaviour that challenges as a direct or indirect outcome

Behavioural and medical intervention versus medical intervention only for behaviour that challenges as a direct outcome



### EIBI versus parent training for behaviour that challenges as an indirect outcome



# 1.10.3 Cognitive-behavioural interventions for behaviour that challenges as a direct or indirect outcome

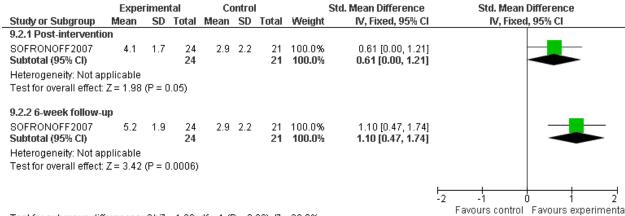
CBT versus waitlist control for behaviour that challenges as a direct outcome

Parent-reported instances of child anger

|                                    | Exper    | rimen   | tal             | Control |     |                 | !                        | Std. Mean Difference                                  | Std. Mean Difference                |  |  |
|------------------------------------|----------|---------|-----------------|---------|-----|-----------------|--------------------------|---|-------------------------------------|--|--|
| Study or Subgroup                  | Mean     | SD      | Total           | Mean    | SD  | Total           | Weight                   | IV, Fixed, 95% CI                                     | IV, Fixed, 95% CI                   |  |  |
| 9.1.1 Post-intervention            | on       |         |                 |         |     |                 |                          |   |                                     |  |  |
| SOFRONOFF2007<br>Subtotal (95% CI) | 3.7      | 3.9     | 24<br><b>24</b> | 7.9     | 5.1 | 21<br><b>21</b> | 100.0%<br><b>100.0</b> % | -0.92 [-1.54, -0.30]<br>- <b>0.92 [-1.54, -0.30]</b>  |                                     |  |  |
| Heterogeneity: Not ap              | plicable |         |                 |         |     |                 |                          |   |                                     |  |  |
| Test for overall effect:           | Z = 2.91 | (P = 0) | 1.004)          |         |     |                 |                          |   |                                     |  |  |
| 9.1.2 6-week follow-u              | up       |         |                 |         |     |                 |                          |   | _                                   |  |  |
| SOFRONOFF2007<br>Subtotal (95% CI) | 3.2      | 3.9     | 24<br>24        | 7.9     | 5.1 | 21<br><b>21</b> | 100.0%<br><b>100.0</b> % | -1.03 [-1.65, -0.40]<br>- <b>1.03 [-1.65, -0.40</b> ] |                                     |  |  |
| Heterogeneity: Not ap              | plicable |         |                 |         |     |                 |                          |   |                                     |  |  |
| Test for overall effect:           | Z = 3.21 | (P = 0) | 1.001)          |         |     |                 |                          |   |                                     |  |  |
|                                    |          |         |                 |         |     |                 |                          |   |                                     |  |  |
|                                    |          |         |                 |         |     |                 |                          |   | -2 -1 1 1                           |  |  |
| Test for subaroun diff             | _        |         |                 |         |     |                 |                          | Fa  | avours experimental Favours control |  |  |

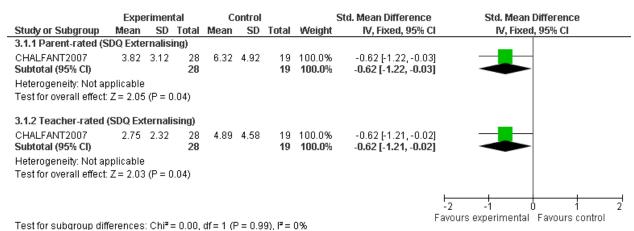
Test for subgroup differences:  $Chi^2 = 0.06$ , df = 1 (P = 0.81),  $I^2 = 0\%$ 

#### Parent confidence in child managing own anger



Test for subgroup differences:  $Chi^2 = 1.26$ , df = 1 (P = 0.26),  $I^2 = 20.8\%$ 

## CBT versus waitlist control for behaviour that challenges as an indirect outcome

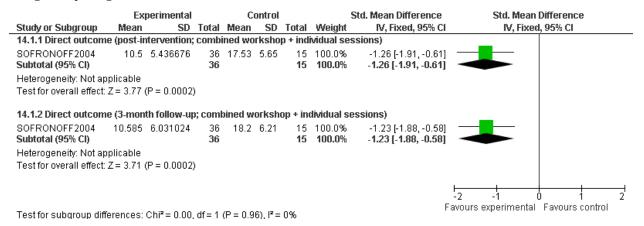


Autism: the management and support of children and young people on the autism spectrum (March 2013)

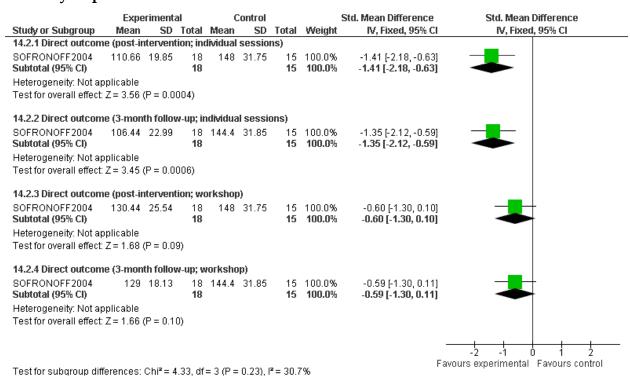
# 1.10.4 Parent training for behaviour that challenges as a direct or indirect outcome

Parent training versus treatment-as-usual for behaviour that challenges as a direct or indirect outcome

#### Frequency of problem behaviours



#### Intensity of problem behaviours

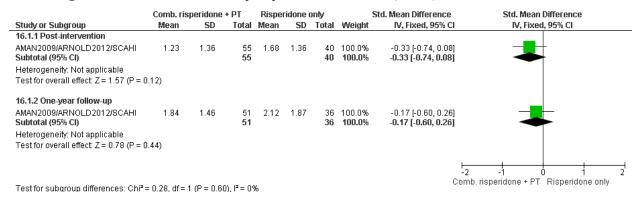


# Problem behaviour (indirect outcome; DBC-TBPS; 6-month follow-up; PEC+PEBM combined)

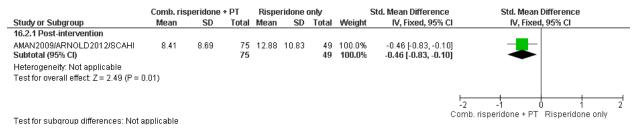
|   | Expe      | Experimental |       |       |       |       | !      | Std. Mean Difference | Std. Mean Difference                            |
|---|-----------|--------------|-------|-------|-------|-------|--------|----------------------|---|
| Study or Subgroup   | Mean      | SD           | Total | Mean  | SD    | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                               |
| TONGE2006/2012  | 55.386471 | 22.23158     | 68    | 63.83 | 27.59 | 35    | 100.0% | -0.35 [-0.76, 0.06]  |   |
| Total (95% CI)  |           |              | 68    |       |       | 35    | 100.0% | -0.35 [-0.76, 0.06]  | -   |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.66 (P = 0.10) |           |              |       |       |       |       |        | F                    | -2 -1 0 1 2 avours experimental Favours control |

# Combined parent training and antipsychotic versus antipsychotic-only for behaviour that challenges as a direct outcome

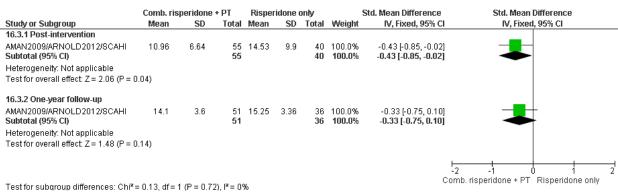
#### Noncompliant behaviour in everyday circumstances (HSQ)



# Noncompliant behaviour in everyday circumstances (Noncompliance index - Daily Living Skills [VABS])



#### Irritability (ABC)



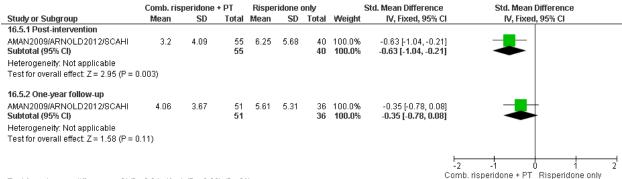
Autism: the management and support of children and young people on the autism spectrum (March 2013)

#### Lethargy/Social withdrawal (ABC)

|   | Comb. ris | peridone | + PT            | Risper | ridone ( | only            | !                        | Std. Mean Difference                                 | Std. Mean Difference                              |
|---|-----------|----------|-----------------|--------|----------|-----------------|--------------------------|--|---|
| Study or Subgroup   | Mean      | SD       | Total           | Mean   | SD       | Total           | Weight                   | IV, Fixed, 95% CI                                    | IV, Fixed, 95% CI                                 |
| 16.4.1 Post-intervention  |           |          |                 |        |          |                 |                          |  |   |
| AMAN2009/ARNOLD2012/SCAHI<br>Subtotal (95% CI)                              | 4.26      | 5.17     | 55<br><b>55</b> | 6.44   | 7.16     | 40<br><b>40</b> | 100.0%<br><b>100.0</b> % | -0.36 [-0.77, 0.06]<br>- <b>0.36 [-0.77, 0.06]</b>   |   |
| Heterogeneity: Not applicable<br>Test for overall effect: $Z = 1.70$ (P = 0 | ).09)     |          |                 |        |          |                 |                          |  |   |
| 16.4.2 One-year follow-up   |           |          |                 |        |          |                 |                          |  |   |
| AMAN2009/ARNOLD2012/SCAHI<br>Subtotal (95% CI)                              | 4.65      | 5.21     | 51<br><b>51</b> | 7.39   | 6.83     | 36<br><b>36</b> | 100.0%<br><b>100.0</b> % | -0.46 [-0.89, -0.03]<br>- <b>0.46 [-0.89, -0.03]</b> | -   |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 2.08 (P = 0   | 0.04)     |          |                 |        |          |                 |                          |  |   |
|   |           |          |                 |        |          |                 |                          | ŀ  |   |
|   |           |          |                 |        |          |                 |                          |  | 2 -1 Ö 1<br>mb. risperidone + PT Risperidone only |

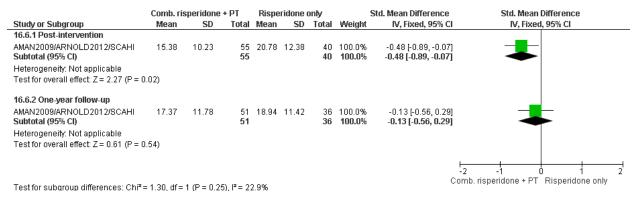
Test for subgroup differences: Chi<sup>2</sup> = 0.11, df = 1 (P = 0.74),  $I^2$  = 0%

#### Stereotypic behaviour (ABC)

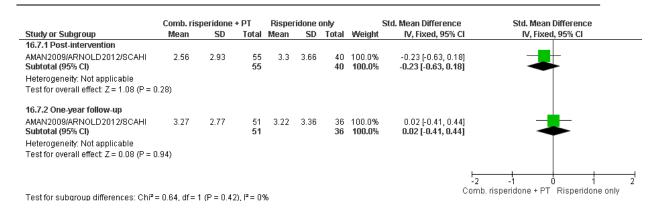


Test for subgroup differences:  $Chi^2 = 0.84$ , df = 1 (P = 0.36),  $I^2 = 0\%$ 

#### Hyperactivity/Noncompliance (ABC)

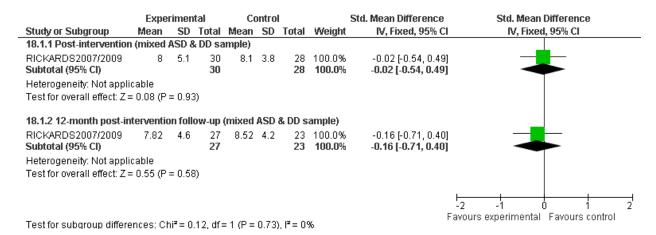


#### Inappropriate speech (ABC)

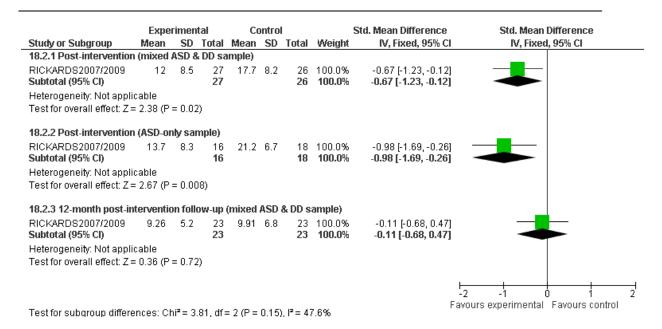


Combined parent training and early intervention centre programme versus early intervention centre programme only for behaviour that challenges as an indirect outcome

#### Parent-reported behaviour that challenges (BSQ)



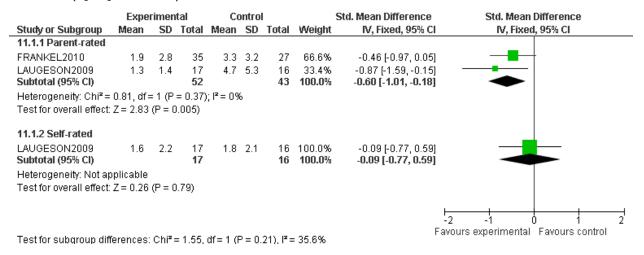
#### Teacher-rated behaviour that challenges (PBCL)



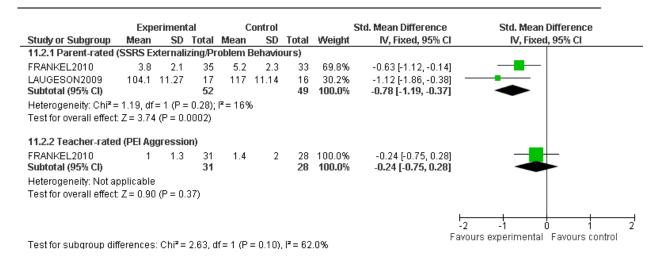
# 1.10.5 Social-communication interventions for behaviour that challenges as an indirect outcome

Social skills group versus treatment-as-usual for behaviour that challenges as an indirect outcome

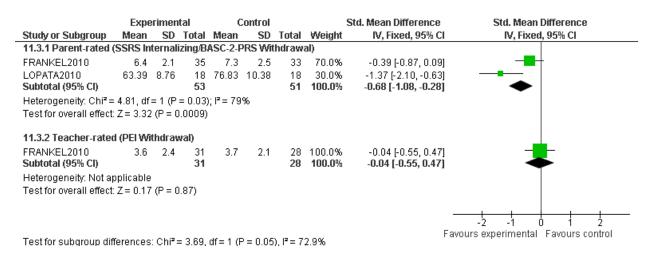
#### **Conflict (QPQ Conflict)**



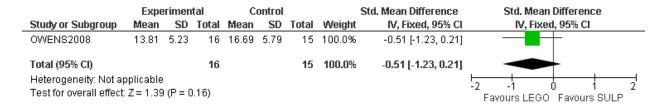
#### Intrusive/aggressive behaviour



#### Social withdrawal



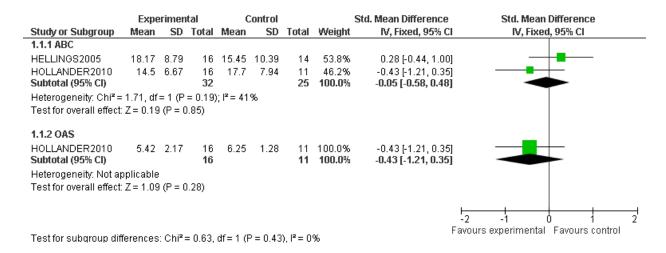
### LEGO therapy versus SULP for behaviour that challenges as an indirect outcome



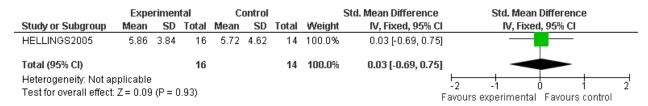
# 1.11PHARMACOLOGICAL INTERVENTIONS AIMED AT BEHAVIOUR THAT CHALLENGES

#### 1.11.1 Anticonvulsants for behaviour that challenges as a direct outcome

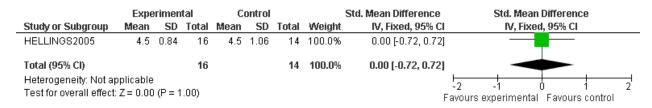
Divalproex versus placebo for behaviour that challenges as a direct outcome Irritability



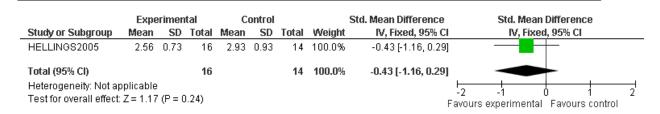
#### Aggression (OAS)



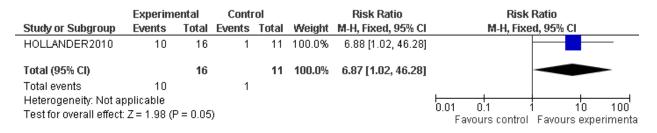
#### Global severity (CGI-S)



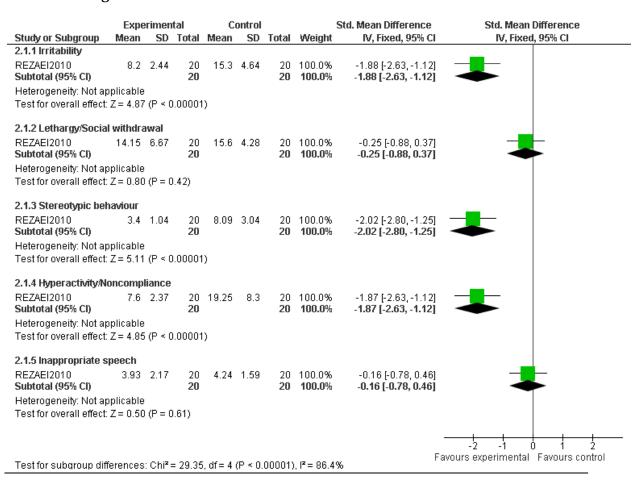
#### Global improvement (CGI-I)



#### Global improvement ('much improved/very improved' on CGI-improvement)



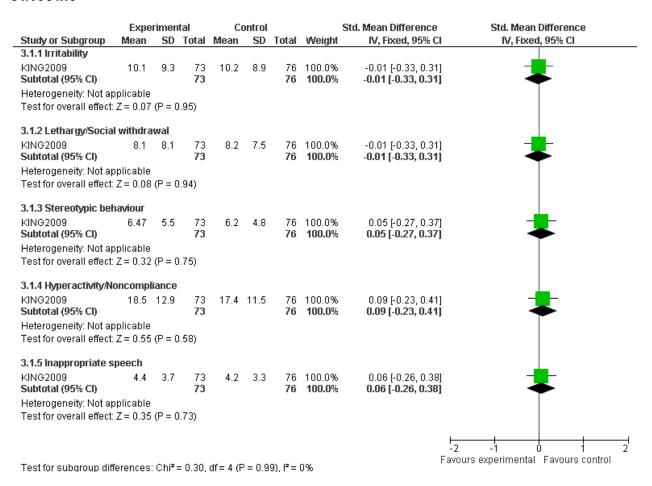
### Topiramate and risperidone versus placebo and risperidone for behaviour that challenges as a direct outcome



Autism: the management and support of children and young people on the autism spectrum (March 2013)

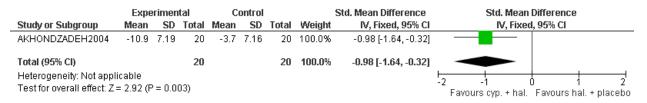
## 1.11.2 Antidepressants for behaviour that challenges as an indirect outcome

Citalopram versus placebo for behaviour that challenges as an indirect outcome



### 1.11.3 Antihistamines for behaviour that challenges as a direct outcome

Cyproheptadine and haloperidol versus placebo and haloperidol for behaviour that challenges as a direct outcome

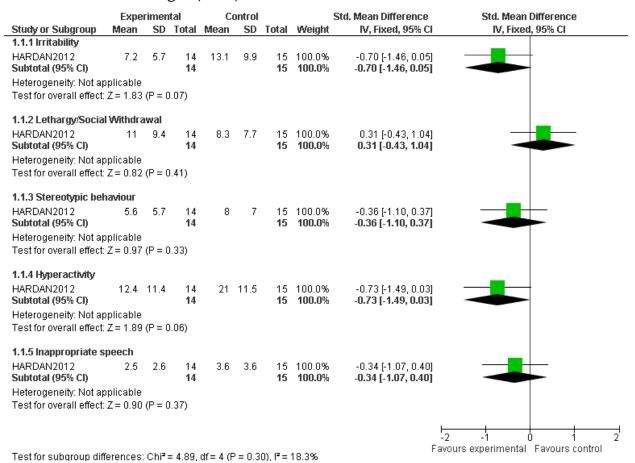


Autism: the management and support of children and young people on the autism spectrum (March 2013)

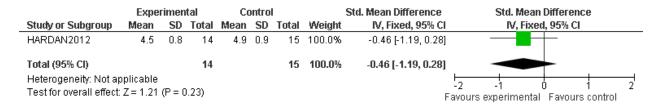
#### 1.11.4 Antioxidants for behaviour that challenges as a direct outcome

N-acetylcysteine versus placebo for behaviour that challenges as a direct outcome

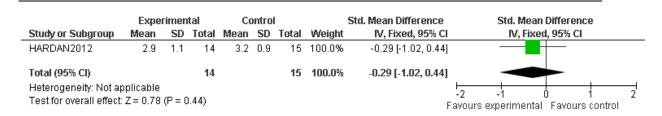
#### Behaviour that challenges (ABC)



#### Global severity (CGI-S)



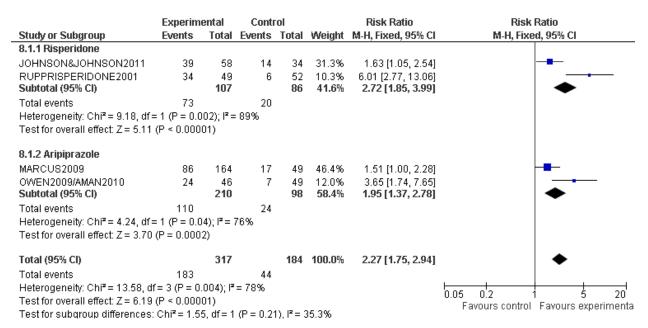
#### Global improvement (CGI-I)



## 1.11.5 Antipsychotics for behaviour that challenges as a direct or indirect outcome

Antipsychotic (risperidone or aripiprazole) versus placebo for behaviour that challenges as a direct outcome

Positive treatment response (clinician-rated: >25% improvement on ABC-Irritability with or without 'much improved/very improved' on CGI-improvement)



#### Positive treatment response (parent-defined target symptoms)

|                                   | Ехрегіт     | ental | Contr  | ol    |        | Risk Ratio         | Risk Ratio                          |
|-----------------------------------|-------------|-------|--------|-------|--------|--------------------|-------------------------------------|
| Study or Subgroup                 | Events      | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                  |
| RUPPRISPERIDONE2001               | 31          | 44    | 9      | 43    | 100.0% | 3.37 [1.83, 6.21]  |                                     |
| Total (95% CI)                    |             | 44    |        | 43    | 100.0% | 3.37 [1.83, 6.21]  | -                                   |
| Total events                      | 31          |       | 9      |       |        |                    |                                     |
| Heterogeneity: Not applicable     |             |       |        |       |        |                    | 0.1 0.2 0.5 1 2 5 10                |
| Test for overall effect: Z = 3.89 | 9 (P = 0.00 | 01)   |        |       |        |                    | Favours control Favours experimenta |

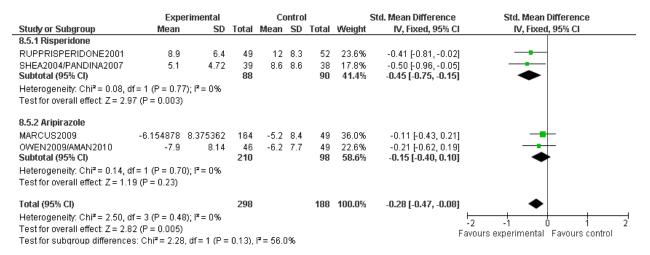
#### Maladaptive behaviour (VABS)

|  | Expe  | rimen | tal   | C     | ontrol |       |        | Std. Mean Difference | Std. Mean                  | Difference           |          |
|--|-------|-------|-------|-------|--------|-------|--------|----------------------|----------------------------|----------------------|----------|
| Study or Subgroup  | Mean  | SD    | Total | Mean  | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed                  | l, 95% CI            |          |
| RUPPRISPERIDONE2001  | 20.34 | 7.93  | 49    | 30.27 | 8.87   | 52    | 100.0% | -1.17 [-1.59, -0.75] | -                          |                      |          |
| Total (95% CI)   |       |       | 49    |       |        | 52    | 100.0% | -1.17 [-1.59, -0.75] | •                          |                      |          |
| Heterogeneity: Not applicabl<br>Test for overall effect: Z = 5.4 |       | 00001 | )     |       |        |       |        | F                    | -2 -1 Favours experimental | ) 1<br>Favours contr | 2<br>rol |

#### Irritability (ABC)

|  | Ex         | perimental            |                  | (             | Control |                  |                        | Std. Mean Difference | Std. Mean Difference                    |  |  |  |
|--|------------|-----------------------|------------------|---------------|---------|------------------|------------------------|----------------------|---|--|--|--|
| Study or Subgroup                            | Mean       | SD                    | Total            | Mean          | SD      | Total            | Weight                 | IV, Fixed, 95% C     | I IV, Fixed, 95% CI                     |  |  |  |
| 8.4.1 Risperidone                            |            |                       |                  |               |         |                  |                        |                      |   |  |  |  |
| JOHNSON&JOHNSON2011                          | 17.65      | 8.815739              | 58               | 25.4          | 12.05   | 34               | 25.0%                  | -0.76 [-1.20, -0.32  | ] <del></del>                           |  |  |  |
| RUPPRISPERIDONE2001                          | 11.3       | 7.4                   | 49               | 21.9          | 9.5     | 52               | 26.4%                  | -1.23 [-1.66, -0.80  | j <del></del>                           |  |  |  |
| SHEA2004/PANDINA2007<br>Subtotal (95% CI)    | 6.7        | 5.6                   | 37<br><b>144</b> | 14.7          | 11.46   | 38<br><b>124</b> | 21.3%<br><b>72.7</b> % |                      |   |  |  |  |
| Heterogeneity: Chi <sup>2</sup> = 2.48, df = | 2 (P = 0)  | $0.29$ ); $I^2 = 19$  | 1%               |               |         |                  |                        |                      |   |  |  |  |
| Test for overall effect: $Z = 7.35$          | (P < 0.00  | 0001)                 |                  |               |         |                  |                        |                      |   |  |  |  |
| 8.4.2 Aripiprazole                           |            |                       |                  |               |         |                  |                        |                      |   |  |  |  |
| OWEN2009/AMAN2010<br>Subtotal (95% CI)       | -12.9      | 9.5                   | 46<br><b>46</b>  | -5            | 9.8     | 49<br><b>49</b>  | 27.3%<br><b>27.3</b> % |                      |   |  |  |  |
| Heterogeneity: Not applicable                |            |                       |                  |               |         |                  |                        |                      |   |  |  |  |
| Test for overall effect: $Z = 3.79$          | (P = 0.00) | 001)                  |                  |               |         |                  |                        |                      |   |  |  |  |
| Total (95% CI)                               |            |                       | 190              |               |         | 173              | 100.0%                 | -0.92 [-1.14, -0.70] | 1 ◆                                     |  |  |  |
| Heterogeneity: Chi <sup>2</sup> = 2.85, df = | 3 (P = 0   | $0.42$ ); $I^2 = 0.9$ | 6                |               |         |                  |                        |                      | 1 d                                     | <del>!                                    </del> |  |  |
| Test for overall effect: $Z = 8.25$          | (P < 0.00  | 0001)                 |                  |               |         |                  |                        |                      | -2 -1 0<br>Favours experimental Favours | 1<br>control                                     |  |  |
| Test for subgroup differences:               | Chi² = 0   | .37. df = 1 (l        | P = 0.5          | 4), $ ^2 = 0$ | 1%      |                  |                        |                      | ravours experimental ravours            | COLLLOI  |  |  |

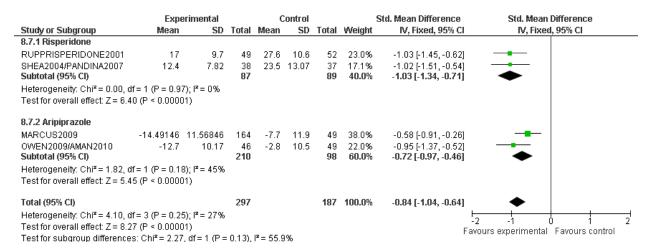
#### Lethargy/Social withdrawal (ABC)



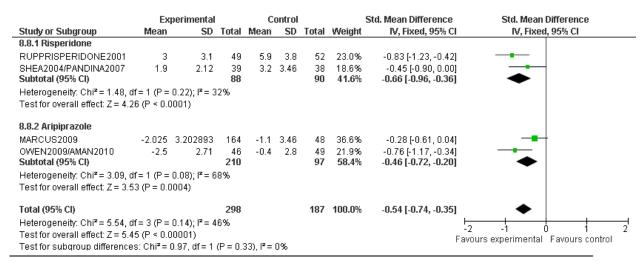
#### Stereotypic behaviour (ABC)

|                                    | Expe              | erimental          |         | Ci       | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                 |
|------------------------------------|-------------------|--------------------|---------|----------|--------|-------|--------|----------------------|--------------------------------------|
| Study or Subgroup                  | Mean              | SD                 | Total   | Mean     | SD     | Total | Weight | IV, Fixed, 95% CI    | I IV, Fixed, 95% CI                  |
| 8.6.1 Risperidone                  |                   |                    |         |          |        |       |        |                      |                                      |
| RUPPRISPERIDONE2001                | 5.8               | 4.6                | 49      | 7.3      | 4.8    | 52    | 24.2%  | -0.32 [-0.71, 0.08]  | ı <del></del>                        |
| SHEA2004/PANDINA2007               | 3.7               | 3.66               | 38      | 5.7      | 6.4    | 38    | 18.1%  | -0.38 [-0.83, 0.07]  |                                      |
| Subtotal (95% CI)                  |                   |                    | 87      |          |        | 90    | 42.4%  | -0.34 [-0.64, -0.05] | •                                    |
| Heterogeneity: Chi² = 0.04, i      | df = 1 (P = 0.84) | 4); I² = 0%        |         |          |        |       |        |                      |                                      |
| Test for overall effect: $Z = 2$ . | 27 (P = 0.02)     |                    |         |          |        |       |        |                      |                                      |
| 8.6.2 Aripiprazole                 |                   |                    |         |          |        |       |        |                      |                                      |
| MARCUS2009                         | -4.392073         | 4.846254           | 164     | -1.8     | 4.83   | 49    | 35.8%  | -0.53 [-0.86, -0.21] | ı <del></del>                        |
| OWEN2009/AMAN2010                  | -4.8              | 4.07               | 46      | -2       | 4.2    | 49    | 21.8%  | -0.67 [-1.09, -0.26] | i <del></del>                        |
| Subtotal (95% CI)                  |                   |                    | 210     |          |        | 98    | 57.6%  | -0.59 [-0.84, -0.33] | •                                    |
| Heterogeneity: Chi² = 0.26,        | df = 1 (P = 0.61) | l); l² = 0%        |         |          |        |       |        |                      |                                      |
| Test for overall effect: $Z = 4$ . | 51 (P < 0.0000    | 11)                |         |          |        |       |        |                      |                                      |
| Total (95% CI)                     |                   |                    | 297     |          |        | 188   | 100.0% | -0.48 [-0.68, -0.29] | · •                                  |
| Heterogeneity: Chi² = 1.78,        | df = 3 (P = 0.62) | 2): <b> ²</b> = 0% |         |          |        |       |        |                      | <u> </u>                             |
| Test for overall effect: $Z = 4$ . | ,                 |                    |         |          |        |       |        |                      | 2                                    |
| Test for subgroup difference       | ,                 |                    | . 0 221 | E - 22 C | 106    |       |        |                      | Favours experimental Favours control |

#### Hyperactivity (ABC)



#### Inappropriate speech (ABC)

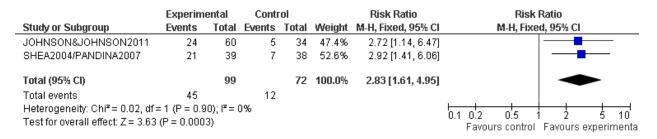


Autism: the management and support of children and young people on the autism spectrum (March 2013)

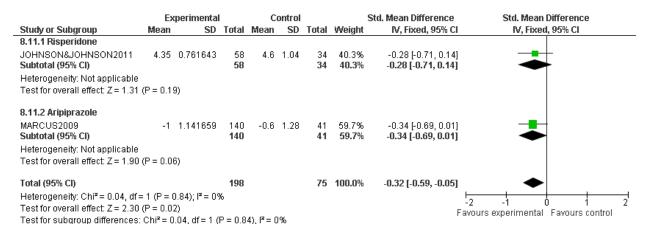
#### Parent-defined target symptoms

|                                  | Expe      | erimen | tal              | (    | ontrol |       |        | Std. Mean Difference | Std. Mean            | Difference       |      |
|----------------------------------|-----------|--------|------------------|------|--------|-------|--------|----------------------|----------------------|------------------|------|
| Study or Subgroup                | Mean      | SD     | Total            | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed            | I, 95% CI        |      |
| RUPPRISPERIDONE2001              | 2.8       | 1.16   | 44               | 4.5  | 1.28   | 43    | 48.8%  | -1.38 [-1.85, -0.91] | _                    |                  |      |
| SHEA2004/PANDINA2007             | 42.6      | 26     | 39               | 58.6 | 30.33  | 37    | 51.2%  | -0.56 [-1.02, -0.10] | _                    |                  |      |
| Total (95% CI)                   |           |        | 83               |      |        | 80    | 100.0% | -0.96 [-1.29, -0.63] | •                    |                  |      |
| Heterogeneity: Chi² = 5.96, d    | f=1 (P=   | 0.01)  | ; <b>I²</b> = 83 | 3%   |        |       |        |                      | -2 -1                | <del>     </del> |      |
| Test for overall effect: Z = 5.7 | 4 (P < 0. | 00001  | )                |      |        |       |        | 1                    | Favours experimental | Favours con      | trol |

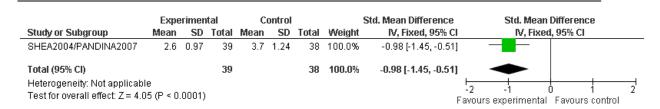
#### Global state: Positive treatment response (CGI)



#### Global severity (CGI-S)

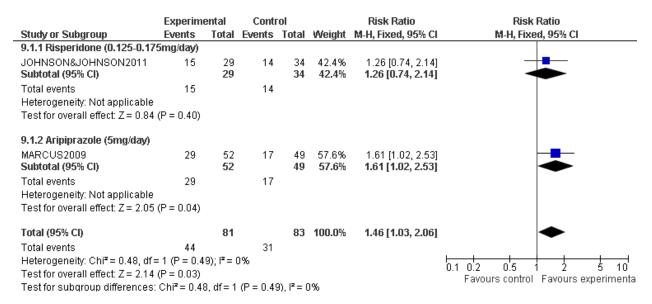


#### Global improvement (CGI-I)



Low dose antipsychotic (risperidone or aripiprazole) versus placebo for behaviour that challenges as a direct outcome

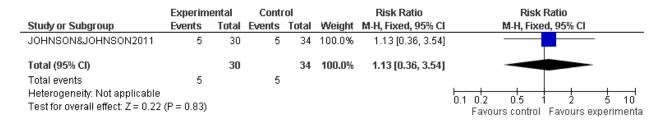
Positive treatment response (clinician-rated: >25% improvement on ABC-Irritability with or without 'much improved/very improved' on CGI-improvement)



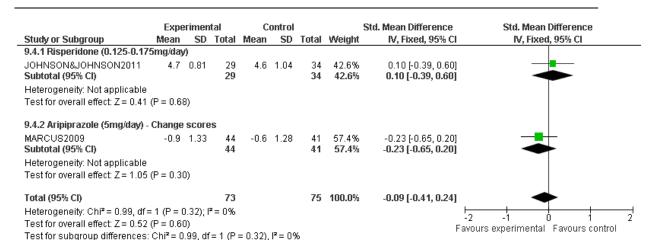
Behaviour that challenges (ABC)

|  | Expe        | eriment  | al              | (        | Control             |                 |                          | Std. Mean Difference                                 | Std. Mean Difference                         |
|--|-------------|----------|-----------------|----------|---------------------|-----------------|--------------------------|--|--|
| Study or Subgroup  | Mean        |          |                 | Mean     | SD                  | Total           | Weight                   | IV, Fixed, 95% CI                                    | IV, Fixed, 95% CI                            |
| 9.2.1 Irritability   |             |          |                 |          |                     |                 |                          |  |  |
| JOHNSON&JOHNSON2011<br>Subtotal (95% CI)                           | 19.7        | 9.24     | 29<br><b>29</b> | 25.4     | 12.05               | 34<br><b>34</b> | 100.0%<br><b>100.0</b> % | -0.52 [-1.02, -0.01]<br>- <b>0.52 [-1.02, -0.01]</b> | •  |
| Heterogeneity: Not applicable Test for overall effect: $Z = 2.02$  | (P = 0.04   | 1)       |                 |          |                     |                 |                          |  |  |
| 9.2.2 Lethargy/Social withdra                                      | wal (cha    | nge sc   | оге)            |          |                     |                 |                          |  |  |
| MARCUS2009<br>Subtotal (95% CI)                                    | -5.8        | 8.65     | 52<br><b>52</b> | -5.2     | 8.4                 | 49<br><b>49</b> | 100.0%<br><b>100.0</b> % | -0.07 [-0.46, 0.32]<br>- <b>0.07 [-0.46, 0.32]</b>   | -  |
| Heterogeneity: Not applicable Test for overall effect: $Z = 0.35$  | (P = 0.73   | 3)       |                 |          |                     |                 |                          |  |  |
| 9.2.3 Stereotypic behaviour (d                                     | :hange s    | соге)    |                 |          |                     |                 |                          |  | _  |
| MARCUS2009<br>Subtotal (95% CI)                                    | -4.5        | 4.9      | 52<br><b>52</b> | -1.8     | 4.83                | 49<br><b>49</b> | 100.0%<br><b>100.0</b> % | -0.55 [-0.95, -0.15]<br>- <b>0.55 [-0.95, -0.15]</b> | -  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 2.71 | (P = 0.00   | 07)      |                 |          |                     |                 |                          |  |  |
| 9.2.4 Hyperactivity (change so                                     | соге)       |          |                 |          |                     |                 |                          |  |  |
| MARCUS2009   |             | 11.54    | 52              | -7.7     | 11.9                |                 | 100.0%                   | -0.53 [-0.93, -0.14]                                 | -  |
| Subtotal (95% CI)  |             |          | 52              |          |                     | 49              | 100.0%                   | -0.53 [-0.93, -0.14]                                 | •  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 2.63 | (P = 0.00   | 18)      |                 |          |                     |                 |                          |  |  |
| 9.2.5 Inappropriate speech (c                                      | hange s     | соге)    |                 |          |                     |                 |                          |  |  |
| MARCUS2009   | -2          | 3.61     | 52              | -1.1     | 3.46                |                 | 100.0%                   | -0.25 [-0.65, 0.14]                                  |  |
| Subtotal (95% CI)  |             |          | 52              |          |                     | 48              | 100.0%                   | -0.25 [-0.65, 0.14]                                  |  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.26 | (P = 0.21   | )        |                 |          |                     |                 |                          |  |  |
|  |             |          |                 |          |                     |                 |                          | ŀ  |  |
|  |             |          |                 |          |                     |                 |                          |  | 2 -1 Ó 1<br>vours experimental Favours contr |
| Test for subgroup differences:                                     | $Chi^2 = 4$ | .39, df= | 4 (P =          | 0.36), I | <sup>2</sup> = 8.9% | 5               |                          | ran  | vouis experimental - ravours contr           |

#### Global state: Positive treatment response (CGI)

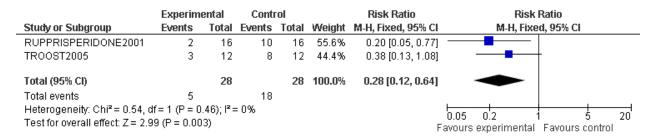


#### Global severity (CGI-S)

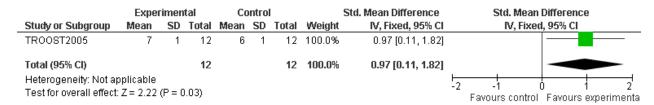


### Continued risperidone versus switch to placebo for behaviour that challenges as a direct outcome

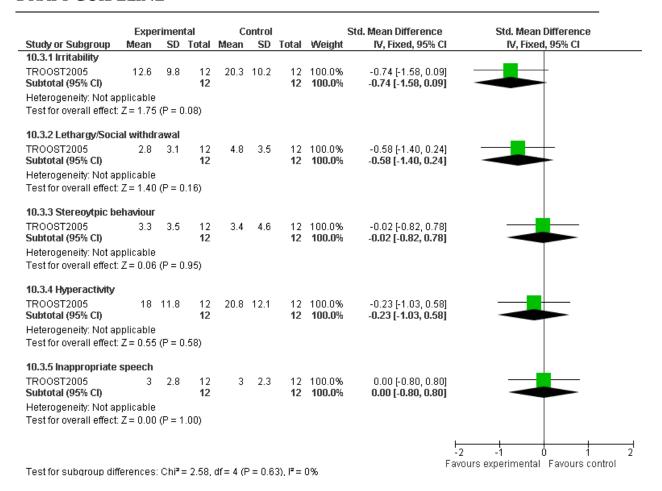
#### Relapse rate after discontinuation



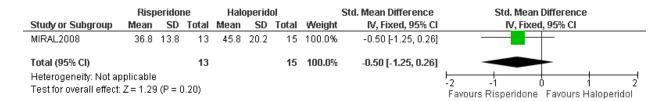
#### Time to relapse after discontinuation (in weeks)



#### Behaviour that challenges (ABC)



### Risperidone versus haloperidol for behaviour that challenges as an indirect outcome



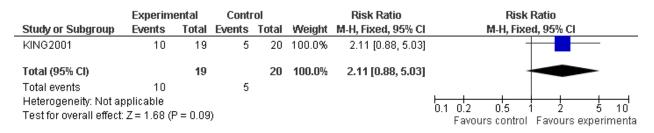
#### 1.11.6 Antivirals for behaviour that challenges as a direct outcome

Amantadine hydrochloride versus placebo for behaviour that challenges as a direct outcome

Positive parent-rated treatment response (>25% improvement on ABC-Irritability and/or hyperactivity)

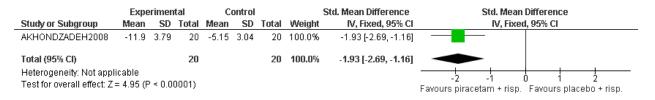
|                         | Experim     | ental    | Contr  | rol   |        | Risk Ratio         | Risk Ratio                          |
|-------------------------|-------------|----------|--------|-------|--------|--------------------|-------------------------------------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                  |
| KING2001                | 9           | 19       | 7      | 19    | 100.0% | 1.29 [0.60, 2.74]  | <del></del>                         |
| Total (95% CI)          |             | 19       |        | 19    | 100.0% | 1.29 [0.60, 2.74]  |                                     |
| Total events            | 9           |          | 7      |       |        |                    |                                     |
| Heterogeneity: Not ap   | pplicable   |          |        |       |        |                    | 01 02 05 1 2 5 10                   |
| Test for overall effect | Z = 0.65 (F | P = 0.51 | )      |       |        |                    | Favours control Favours experimenta |

### Positive investigator-rated treatment response ('much improved/very improved' on CGI-improvement)



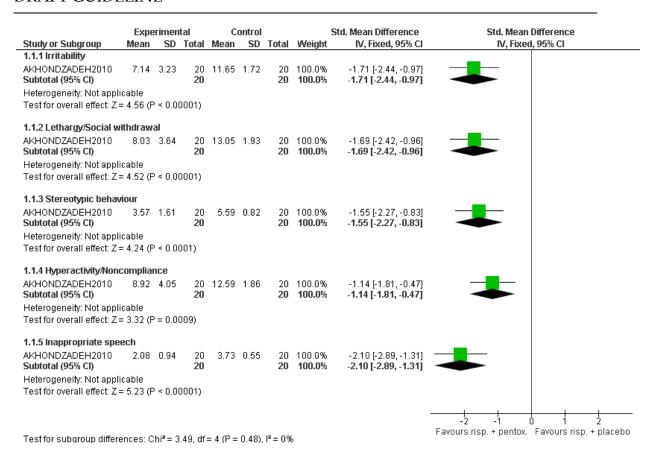
### 1.11.7Cognitive enhancers for behaviour that challenges as a direct outcome

Piracetam and risperidone versus placebo and risperidone for behaviour that challenges as a direct outcome



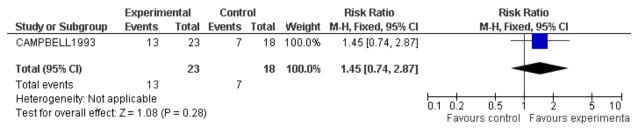
#### 1.11.8 Methylxanthines for behaviour that challenges as a direct outcome

Pentoxifylline and risperidone versus placebo and risperidone for behaviour that challenges as a direct outcome



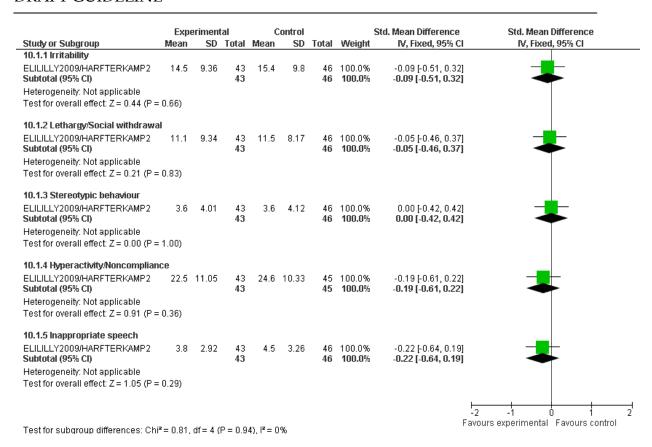
### 1.11.9Opioid antagonists for behaviour that challenges as a direct outcome

Naltrexone versus placebo for behaviour that challenges as a direct outcome



# 1.11.10 Selective noradrenaline reuptake inhibitors (SNRIs) for behaviour that challenges as an indirect outcome

Atomoxetine versus placebo for behaviour that challenges as an indirect outcome



# 1.12BIOMEDICAL INTERVENTIONS AIMED AT BEHAVIOUR THAT CHALLENGES

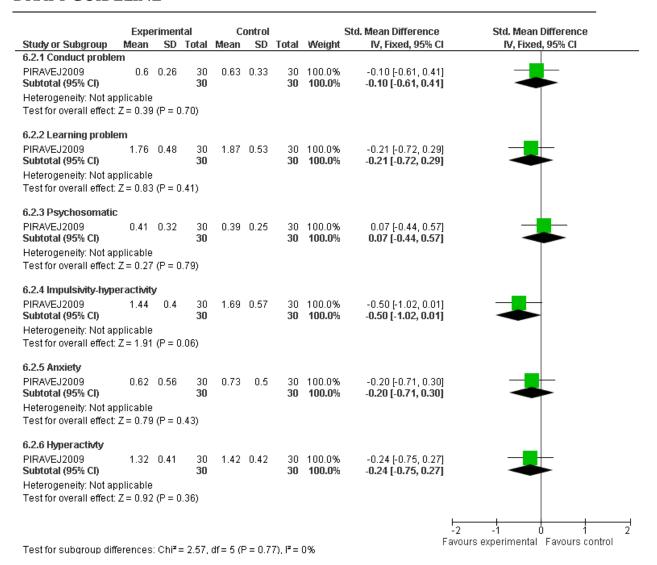
# 1.12.1 Complementary therapies for behaviour that challenges as a direct or indirect outcome

Thai massage and sensory integration therapy versus sensory integration therapy only for behaviour that challenges as a direct outcome

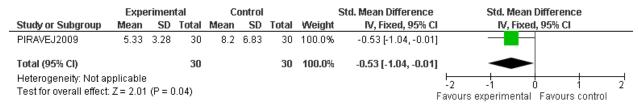
Teacher-rated behaviour that challenges (CTRS)

|                          | _        |         |         | _         |         |          |        |                      |   |
|--------------------------|----------|---------|---------|-----------|---------|----------|--------|----------------------|---|
|                          |          | rimen   |         |           | ontrol  |          |        | Std. Mean Difference | Std. Mean Difference                    |
| Study or Subgroup        | Mean     | SD      | Total   | Mean      | SD      | Total    | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                       |
| 6.1.1 Conduct proble     | m        |         |         |           |         |          |        |                      |   |
| PIRAVEJ2009              | 0.64     | 0.35    | 30      | 0.71      | 0.26    | 30       | 100.0% | -0.22 [-0.73, 0.28]  | <del></del>                             |
| Subtotal (95% CI)        |          |         | 30      |           |         | 30       | 100.0% | -0.22 [-0.73, 0.28]  |   |
| Heterogeneity: Not ap    | plicable |         |         |           |         |          |        |                      |   |
| Test for overall effect: | Z = 0.87 | (P = 0) | 1.39)   |           |         |          |        |                      |   |
| 6.1.2 Hyperactivity      |          |         |         |           |         |          |        |                      |   |
| PIRAVEJ2009              | 1.24     | 0.5     | 30      | 1.49      | 0.37    | 30       | 100.0% | -0.56 [-1.08, -0.04] |   |
| Subtotal (95% CI)        |          |         | 30      |           |         | 30       | 100.0% | -0.56 [-1.08, -0.04] |   |
| Heterogeneity: Not ap    | plicable |         |         |           |         |          |        |                      |   |
| Test for overall effect: | Z= 2.13  | (P = 0  | 1.03)   |           |         |          |        |                      |   |
| 6.1.3 Inattention-pass   | eivitv   |         |         |           |         |          |        |                      |   |
| PIRAVEJ2009              | 1.18     | 0.51    | 30      | 1 24      | 0.36    | 20       | 100.0% | -0.36 [-0.87, 0.15]  |   |
| Subtotal (95% CI)        | 1.10     | 0.51    | 30      | 1.34      | 0.30    | 30<br>30 | 100.0% | -0.36 [-0.87, 0.15]  | •                                       |
| Heterogeneity: Not ap    | plicable |         |         |           |         |          |        |                      |   |
| Test for overall effect: | Z=1.37   | (P = 0  | 1.17)   |           |         |          |        |                      |   |
| 6.1.4 Hyperactivity in   | dex      |         |         |           |         |          |        |                      |   |
| PIRAVEJ2009              | 1.1      | 0.49    | 30      | 1.28      | 0.4     | 30       | 100.0% | -0.40 [-0.91, 0.11]  |   |
| Subtotal (95% CI)        | • • • •  | 0.10    | 30      |           | 0       | 30       | 100.0% | -0.40 [-0.91, 0.11]  | •                                       |
| Heterogeneity: Not ap    | plicable |         |         |           |         |          |        |                      |   |
| Test for overall effect: |          |         | ).13)   |           |         |          |        |                      |   |
|                          |          |         | ,       |           |         |          |        |                      |   |
|                          |          |         |         |           |         |          |        | <u>⊢</u> -2          | <u> </u>                                |
|                          |          |         |         |           |         |          |        | _                    | : -1 U 1<br>ours experimental Favours c |
| Test for subaroup diff   | erences  | : Chi²: | = 0.84, | df = 3 (F | o = 0.8 | 4), I² = | 0%     | ravu                 | ours experimental Lavouis C             |

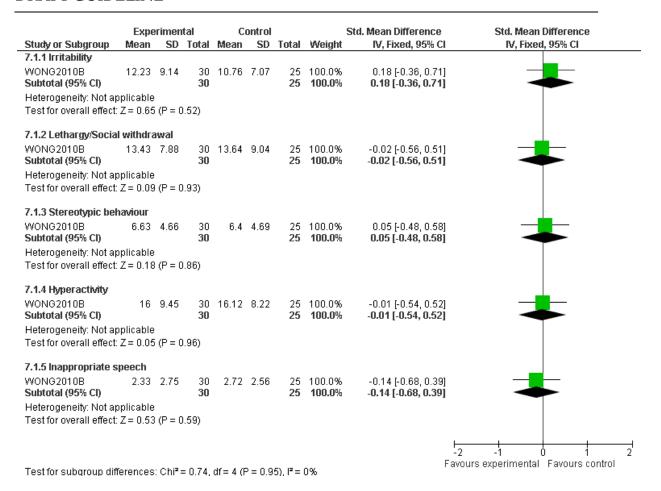
#### Parent-rated behaviour that challenges (CPRS)



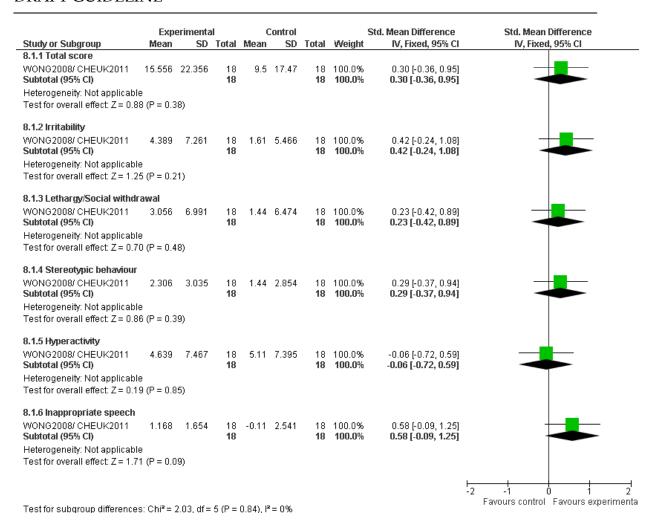
#### Parent-rated sleep-related problems (sleep diary)



Electro-acupuncture versus sham electro-acupuncture for behaviour that challenges as an indirect outcome



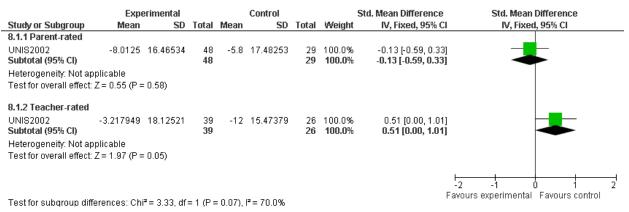
Electro-acupuncture and conventional educational programme versus conventional educational programme only for behaviour that challenges as an indirect outcome



#### 1.12.2 Hormones for behaviour that challenges as an indirect outcome

Secretin versus placebo for behaviour that challenges as an indirect outcome

### Behaviour that challenges (ABC total change score; porcine+synthetic groups combined)

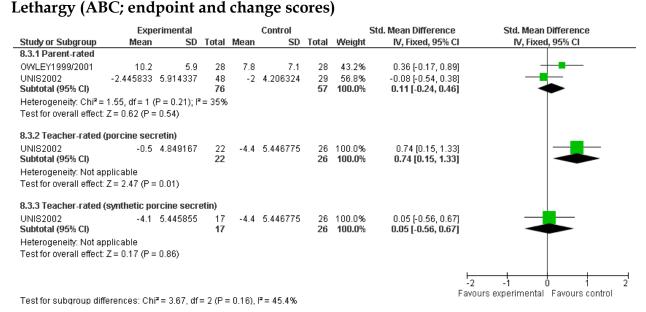


Autism: the management and support of children and young people on the autism spectrum (March 2013)

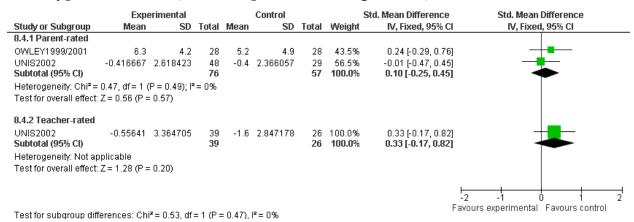
#### Irritability (ABC; endpoint and change scores)

|   | Experimental  |              |                 |          |          |                 |                          | Std. Mean Difference                                | Std. Mean Difference              |
|---|---------------|--------------|-----------------|----------|----------|-----------------|--------------------------|---|-----------------------------------|
| Study or Subgroup                                 | Mean          | SD           | Total           | Mean     | SD       | Total           | Weight                   | IV, Fixed, 95% CI                                   | IV, Fixed, 95% CI                 |
| 8.2.1 Parent-rated                                |               |              |                 |          |          |                 |                          |   |                                   |
| OWLEY1999/2001                                    | 10.1          | 10.2         | 28              | 10.9     | 8.1      | 28              | 43.7%                    | -0.09 [-0.61, 0.44]                                 | <del></del>                       |
| UNIS2002<br>Subtotal (95% CI)                     | -2.133333     | 5.002897     | 48<br><b>76</b> | -1.5     | 5.126457 | 29<br><b>57</b> | 56.3%<br><b>100.0</b> %  | -0.12 [-0.59, 0.34]<br>- <b>0.11 [-0.45, 0.24</b> ] | -                                 |
| Heterogeneity: Chi² =<br>Test for overall effect: |               |              | = 0%            |          |          |                 |                          |   |                                   |
| 8.2.2 Teacher-rated                               |               |              |                 |          |          |                 |                          |   |                                   |
| UNIS2002<br>Subtotal (95% CI)                     | -0.215385     | 6.192379     | 39<br><b>39</b> | -1.5     | 6.808469 | 26<br><b>26</b> | 100.0%<br><b>100.0</b> % | 0.20 [-0.30, 0.69]<br><b>0.20 [-0.30, 0.69]</b>     | -                                 |
| Heterogeneity: Not as                             | pplicable     |              |                 |          |          |                 |                          |   |                                   |
| Test for overall effect:                          | Z = 0.78 (P = | 0.44)        |                 |          |          |                 |                          |   |                                   |
|   |               |              |                 |          |          |                 |                          | ⊢<br>-2   | 2 -1 0 1                          |
| Test for subgroup diff                            | ferences: Chi | ²= 0.97, df: | = 1 (P =        | = 0.33), | l² = 0%  |                 |                          | Fav   | ours experimental Favours control |

#### Lathanna (ADC) and maint and alconsonance

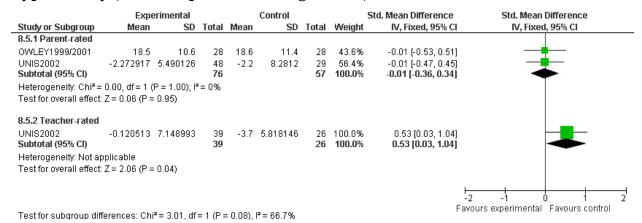


#### Stereotyped behaviour (ABC; endpoint and change scores)

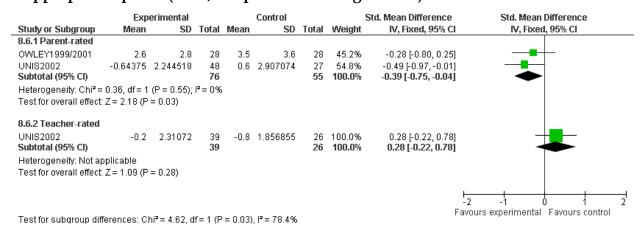


Autism: the management and support of children and young people on the autism spectrum (March 2013)

#### Hyperactivity (ABC; endpoint and change scores)



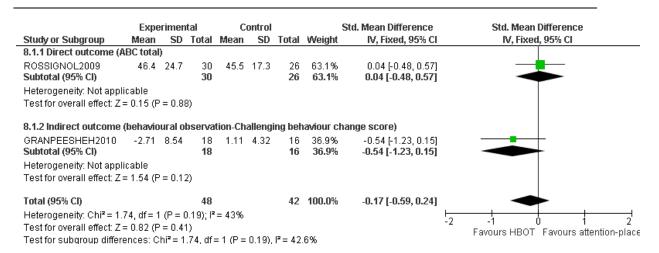
#### Inappropriate speech (ABC; endpoint and change scores)



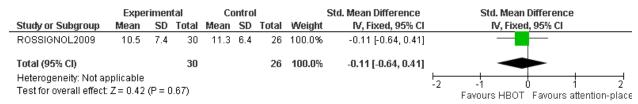
## 1.12.3 Medical procedures for behaviour that challenges as a direct or indirect outcome

HBOT versus attention-placebo for behaviour that challenges as a direct or indirect outcome

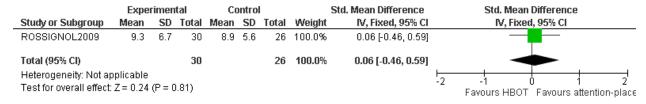
#### Behaviour that challenges



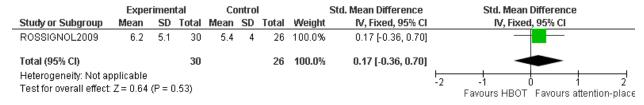
#### Irritability (ABC; direct outcome)



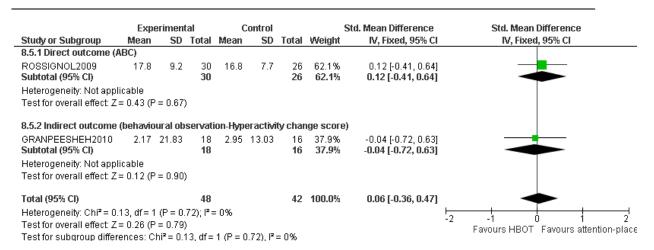
#### Lethargy/Social withdrawal (ABC; direct outcome)



#### Stereotypy (ABC; direct outcome)



#### Hyperactivity

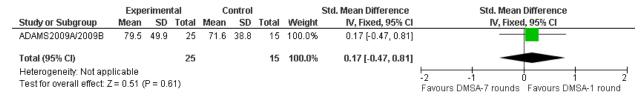


#### Inappropriate speech (ABC; direct outcome)

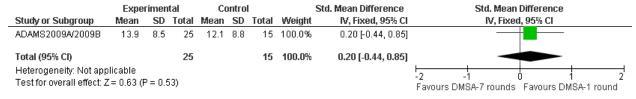
|  | Expe   | xperimental Control |       |      |     |       |        | Std. Mean Difference | Std. Mean Difference                 |
|--|--------|---------------------|-------|------|-----|-------|--------|----------------------|--------------------------------------|
| Study or Subgroup  | Mean   | SD                  | Total | Mean | SD  | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                    |
| ROSSIGNOL2009  | 2.6    | 2.5                 | 30    | 3.3  | 3.2 | 26    | 100.0% | -0.24 [-0.77, 0.28]  | _                                    |
| <b>Total (95% CI)</b><br>Heterogeneity: Not ap<br>Test for overall effect: |        |                     | 30    |      |     | 26    | 100.0% | -0.24 [-0.77, 0.28]  | -2 -1 0 1 2                          |
| restroi overali ellect.  | 2-0.90 | 0 - 0               | 1.57) |      |     |       |        |                      | Favours HBOT Favours attention-place |

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for behaviour that challenges as an indirect outcome

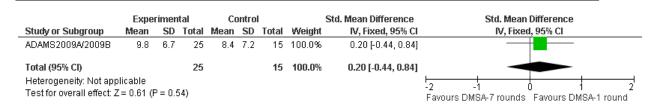
#### Maladaptive Behaviours Composite (PDDBI)



#### Arousal Regulation Problems (PDDBI)



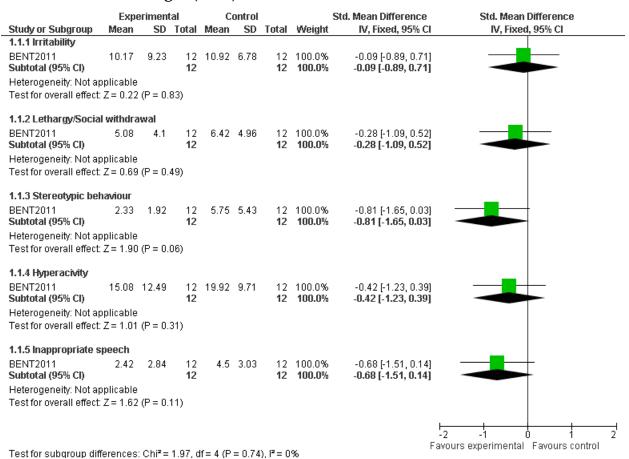
#### Aggressiveness (PDDBI)



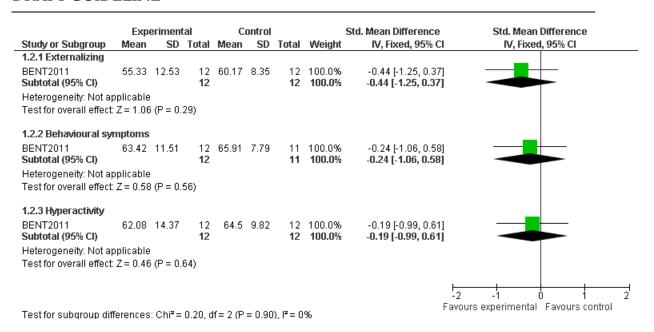
### 1.12.4 Nutritional interventions for behaviour that challenges as a direct or indirect outcome

Omega-3 fatty acids versus placebo for behaviour that challenges as a direct outcome

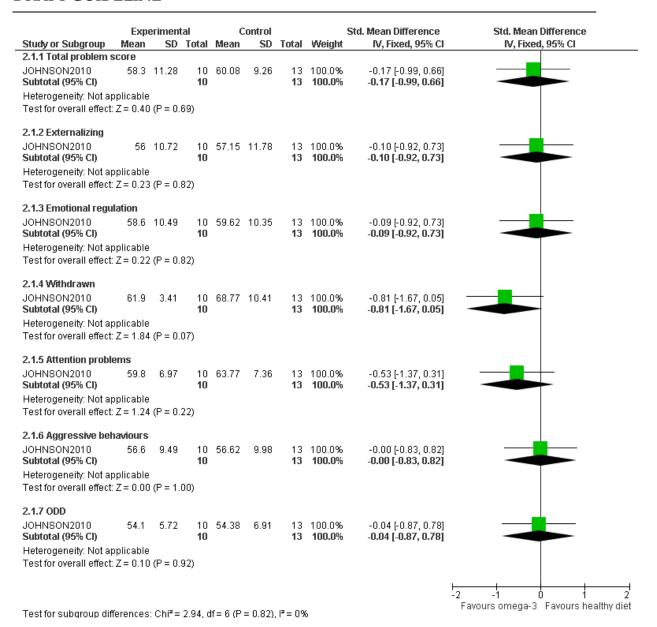
#### Behaviour that challenges (ABC)



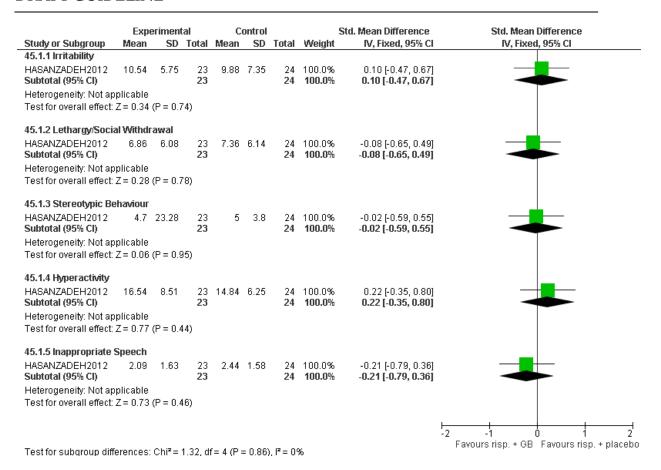
#### Behaviour that challenges (BASC)



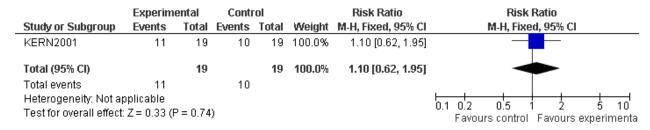
Omega-3 fatty acids versus healthy diet control for behaviour that challenges as a direct outcome



Ginkgo biloba and risperidone versus placebo and risperidone for behaviour that challenges as a direct outcome

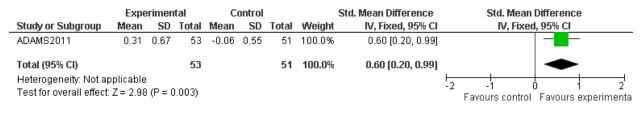


### Dimethylglycine supplement versus placebo for behaviour that challenges as a direct outcome



### Multivitamin/mineral supplement versus placebo for behaviour that challenges as an indirect outcome

#### Hyperactivity improvement (PGI-R)

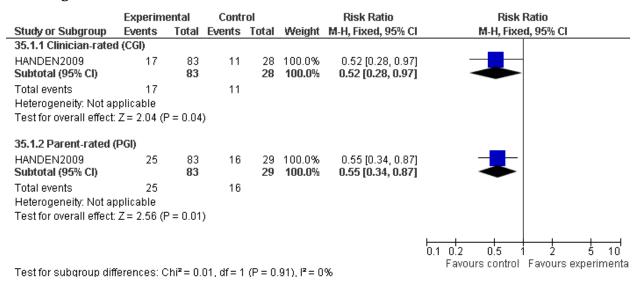


Autism: the management and support of children and young people on the autism spectrum (March 2013)

#### **Tantrumming improvement (PGI-R)**

|   | Expe | erimen | tal    | Co   | ontro | I     |        | Std. Mean Difference |           | Std. Mear            | n Difference     | 9                |
|---|------|--------|--------|------|-------|-------|--------|----------------------|-----------|----------------------|------------------|------------------|
| Study or Subgroup                                 | Mean | SD     | Total  | Mean | SD    | Total | Weight | IV, Fixed, 95% CI    |           | IV, Fixe             | d, 95% CI        |                  |
| ADAMS2011   | 0.4  | 1.08   | 53     | -0.1 | 0.8   | 51    | 100.0% | 0.52 [0.13, 0.91]    |           |                      |                  |                  |
| Total (95% CI)                                    |      |        | 53     |      |       | 51    | 100.0% | 0.52 [0.13, 0.91]    |           |                      | -                |                  |
| Heterogeneity: Not ap<br>Test for overall effect: | •    |        | 0.009) |      |       |       |        |                      | <u>-2</u> | -1<br>Favours contro | 0 1<br>I Favours | 2<br>experimenta |

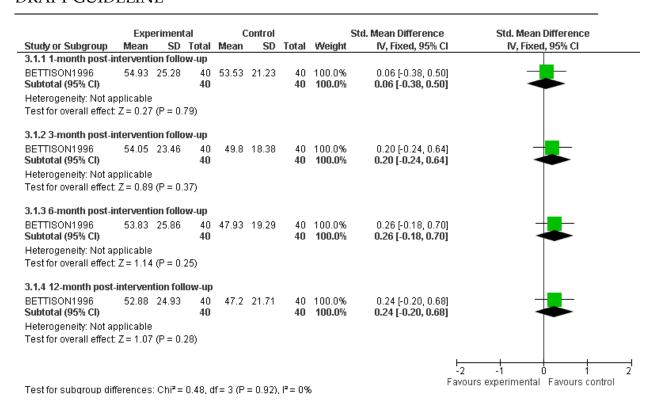
### Immunoglobulin (dosages combined) versus placebo for behaviour that challenges as an indirect outcome



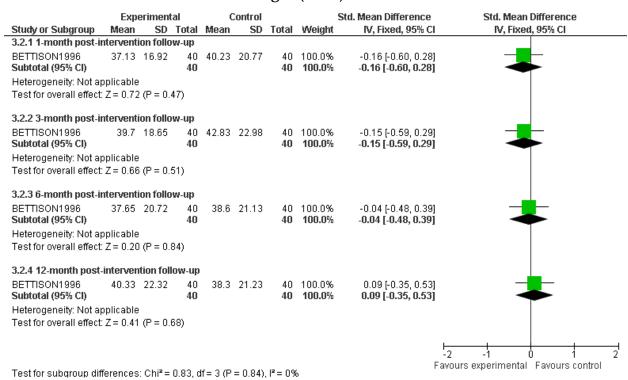
# 1.12.5 Sensory interventions for behaviour that challenges as an indirect outcome

Auditory integration training versus attention-placebo (structured listening) for behaviour that challenges as an indirect outcome

Parent-rated behaviour that challenges (DBC)



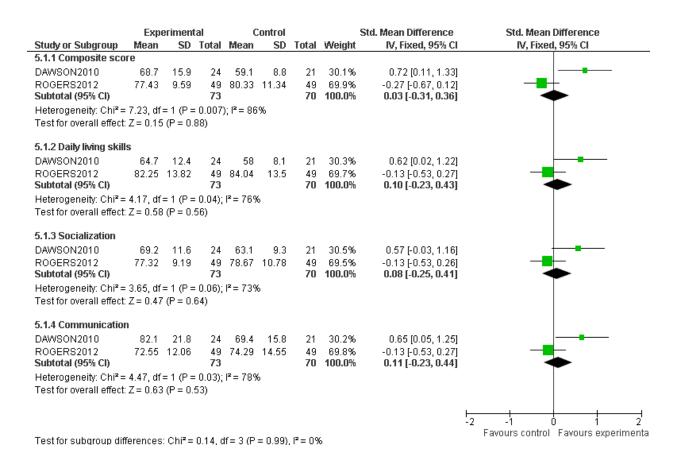
#### Teacher-rated behaviour that challenges (DBC)



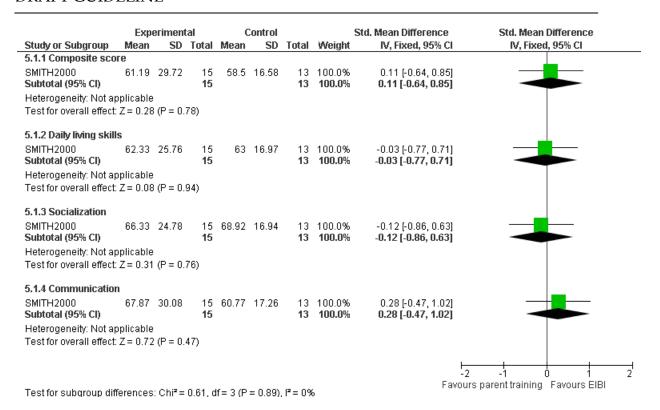
# 1.13PSYCHOSOCIAL INTERVENTIONS AIMED AT ADAPTIVE BEHAVIOUR

### 1.13.1 Behavioural interventions for adaptive behaviour as a direct or indirect outcome

EIBI or EBI (ESDM or P-ESDM) versus treatment-as-usual for adaptive behaviour as a direct or indirect outcome

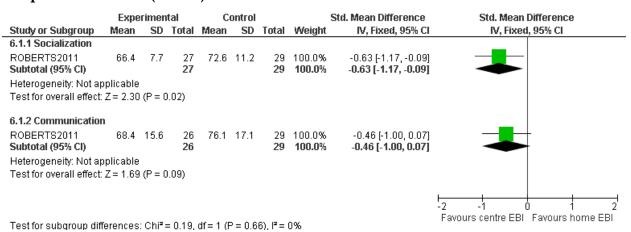


EIBI versus parent training for adaptive behaviour as a direct outcome



### Home-based EBI versus centre-based EBI for adaptive behaviour as a direct outcome

#### Adaptive behaviour (VABS)

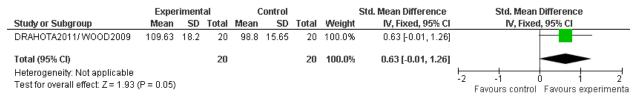


#### Adaptive functioning and psychopathology (DBC total)

|   | Expe | erimen | tal   | C    | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                               |
|---|------|--------|-------|------|--------|-------|--------|----------------------|--|
| Study or Subgroup                               | Mean | SD     | Total | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |
| ROBERTS2011                                     | 52.9 | 29.3   | 22    | 55.7 | 19.5   | 22    | 100.0% | -0.11 [-0.70, 0.48]  | <b>_</b> _   |
| Total (95% CI)                                  |      |        | 22    |      |        | 22    | 100.0% | -0.11 [-0.70, 0.48]  |  |
| Heterogeneity: Not a<br>Test for overall effect |      |        | 0.71) |      |        |       |        |                      | -2 -1 0 1 3<br>Favours home EBI Favours centre EBI |

### 1.13.2Cognitive-behavioural interventions for adaptive behaviour as an indirect outcome

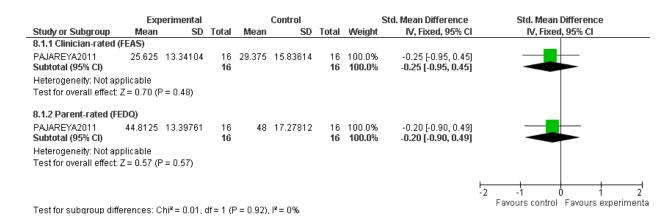
#### CBT versus waitlist for adaptive behaviour as an indirect outcome



### 1.13.3 Parent training for adaptive behaviour as a direct or indirect outcome

Parent training versus treatment-as-usual for adaptive behaviour as a direct or indirect outcome

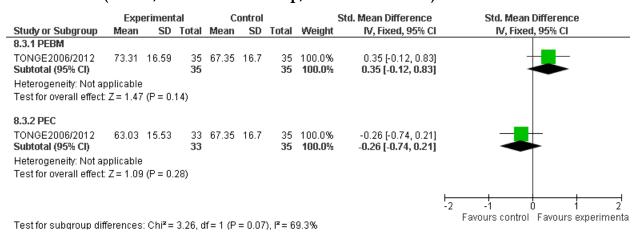
#### Functional emotional development (direct outcome)



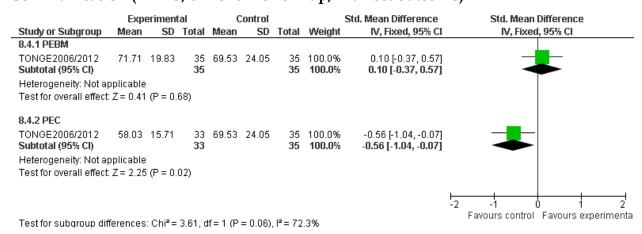
#### Daily living skills (VABS; 6-month follow-up; indirect outcome)

|                                     | Expe     | eriment    | al              | 0     | ontrol |                 | 9                        | Std. Mean Difference                                | Std. Mean Difference |
|-------------------------------------|----------|------------|-----------------|-------|--------|-----------------|--------------------------|---|----------------------|
| Study or Subgroup                   | Mean     | SD         | Total           | Mean  | SD     | Total           | Weight                   | IV, Fixed, 95% CI                                   | IV, Fixed, 95% CI    |
| 8.2.1 PEBM                          |          |            |                 |       |        |                 |                          |   |                      |
| TONGE2006/2012<br>Subtotal (95% CI) | 68.26    | 16.46      | 35<br><b>35</b> | 60.09 | 18.59  | 35<br><b>35</b> | 100.0%<br><b>100.0</b> % | 0.46 [-0.01, 0.94]<br><b>0.46 [-0.01, 0.94]</b>     |                      |
| Heterogeneity: Not ap               | plicable |            |                 |       |        |                 |                          |   |                      |
| Test for overall effect:            | Z = 1.90 | P = 0.0    | 06)             |       |        |                 |                          |   |                      |
| 8.2.2 PEC                           | 57.04    | 42.00      | 22              | 60.00 | 10.50  | 25              | 400.00                   | 0441064.0341  |                      |
| TONGE2006/2012<br>Subtotal (95% CI) | 57.81    | 13.98      | 33<br><b>33</b> | 60.09 | 18.59  | 35<br><b>35</b> | 100.0%<br><b>100.0</b> % | -0.14 [-0.61, 0.34]<br>- <b>0.14 [-0.61, 0.34</b> ] | -                    |
| Heterogeneity: Not ap               | plicable |            |                 |       |        |                 |                          |   |                      |
| Toot for averall offeet             | Z = 0.56 | i(P = 0.5) | 57)             |       |        |                 |                          |   |                      |
| Test for overall effect:            |          |            |                 |       |        |                 |                          |   |                      |
| restior overall ellect.             |          |            |                 |       |        |                 |                          |   | I                    |
| Test for overall effect.            |          |            |                 |       |        |                 |                          |   | -2 -1 0 1 2          |

#### Socialization (VABS; 6-month follow-up; indirect outcome)



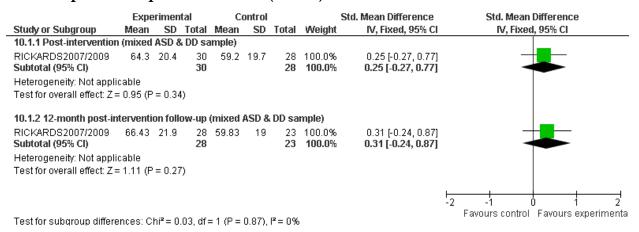
#### Communication (VABS; 6-month follow-up; indirect outcome)

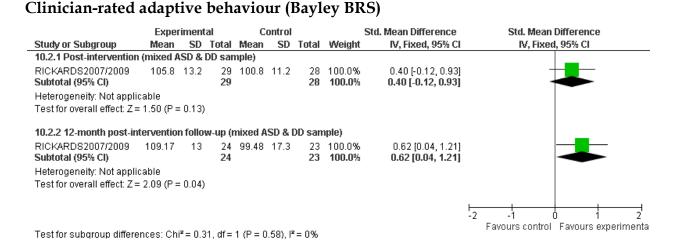


Combined parent training and early intervention centre programme versus early intervention centre programme only for adaptive behaviour as a direct outcome

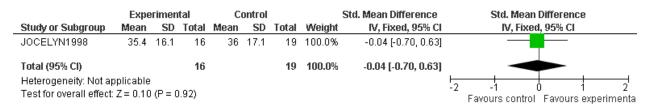
Autism: the management and support of children and young people on the autism spectrum (March 2013)

#### Parent-reported adaptive behaviour (VABS)





### Parent and day-care staff training versus standard day-care for adaptive behaviour as an indirect outcome

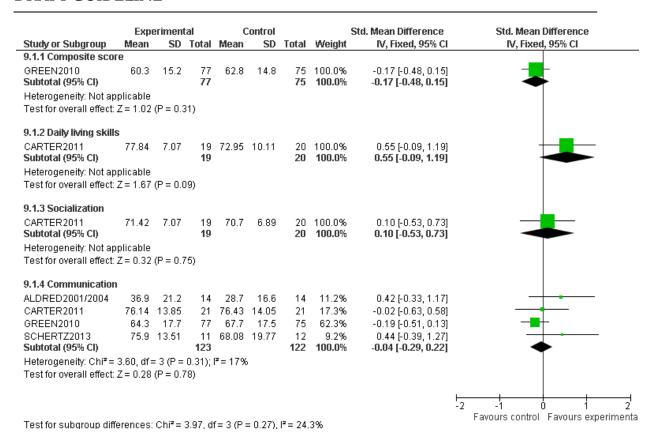


Combined parent training and antipsychotic versus antipsychotic-only for adaptive behaviour as an indirect outcome

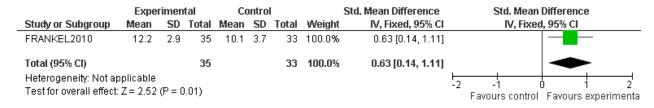
|   | Comb. ris    | speridone | + PT            | Rispe | ridone d | only             |                          | Std. Mean Difference                           | Std. Mean Difference  |
|---|--------------|-----------|-----------------|-------|----------|------------------|--------------------------|--|---|
| Study or Subgroup                         | Mean         | SD        | Total           | Mean  | SD       | Total            | Weight                   | IV, Fixed, 95% CI                              | IV, Fixed, 95% CI   |
| 12.1.1 Composite score                    |              |           |                 |       |          |                  |                          |  |   |
| AMAN2009/SCAHILL2012<br>Subtotal (95% CI) | 57.87        | 19.03     | 75<br><b>75</b> | 47.84 | 15.81    | 49<br>4 <b>9</b> | 100.0%<br><b>100.0</b> % | 0.56 [0.19, 0.93]<br><b>0.56 [0.19, 0.93</b> ] |   |
| Heterogeneity: Not applicable             | Э            |           |                 |       |          |                  |                          |  |   |
| Test for overall effect: Z = 2.9          | 9 (P = 0.00) | 3)        |                 |       |          |                  |                          |  |   |
| 12.1.2 Daily living skills                |              |           |                 |       |          |                  |                          |  |   |
| AMAN2009/SCAHILL2012<br>Subtotal (95% CI) | 55.65        | 21.86     | 75<br><b>75</b> | 45.34 | 20.48    | 49<br><b>49</b>  | 100.0%<br><b>100.0</b> % | 0.48 [0.12, 0.85]<br><b>0.48 [0.12, 0.85]</b>  | -   |
| Heterogeneity: Not applicable             | Э            |           |                 |       |          |                  |                          |  |   |
| Test for overall effect: $Z = 2.5$        | 8 (P = 0.01) | 0)        |                 |       |          |                  |                          |  |   |
| 12.1.3 Socialization                      |              |           |                 |       |          |                  |                          |  |   |
| AMAN2009/SCAHILL2012<br>Subtotal (95% CI) | 67.42        | 18.48     | 75<br><b>75</b> | 56.59 | 17.38    | 49<br><b>49</b>  | 100.0%<br><b>100.0</b> % | 0.60 [0.23, 0.96]<br><b>0.60 [0.23, 0.96]</b>  | 🖶   |
| Heterogeneity: Not applicable             | Э            |           |                 |       |          |                  |                          |  |   |
| Test for overall effect: Z = 3.1          | B (P = 0.00° | 1)        |                 |       |          |                  |                          |  |   |
| 12.1.4 Communication                      |              |           |                 |       |          |                  |                          |  |   |
| AMAN2009/SCAHILL2012<br>Subtotal (95% CI) | 63.9         | 22.65     | 75<br><b>75</b> | 53.57 | 20.23    | 49<br>49         | 100.0%<br><b>100.0</b> % | 0.47 [0.11, 0.84]<br><b>0.47 [0.11, 0.84</b> ] |   |
| Heterogeneity: Not applicable             | 9            |           |                 |       |          |                  |                          |  |   |
| Test for overall effect: Z = 2.5          | 4 (P = 0.01) | ı         |                 |       |          |                  |                          |  |   |
|   |              |           |                 |       |          |                  |                          |  |   |
|   |              |           |                 |       |          |                  |                          |  | -2 -1 0 1<br>Favours risperidone only Favours risperidone + P |

# 1.13.4 Social-communication interventions for adaptive behaviour as an indirect outcome

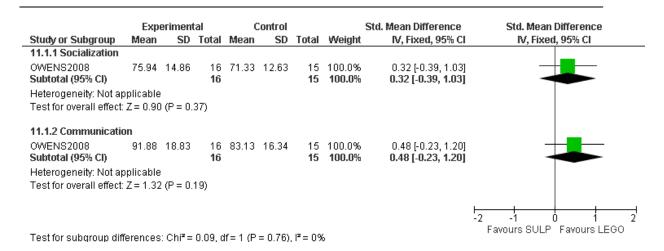
Caregiver-mediated social communication intervention versus treatment-asusual for adaptive behaviour as an indirect outcome



### Social skills group versus treatment-as-usual for adaptive behaviour as an indirect outcome



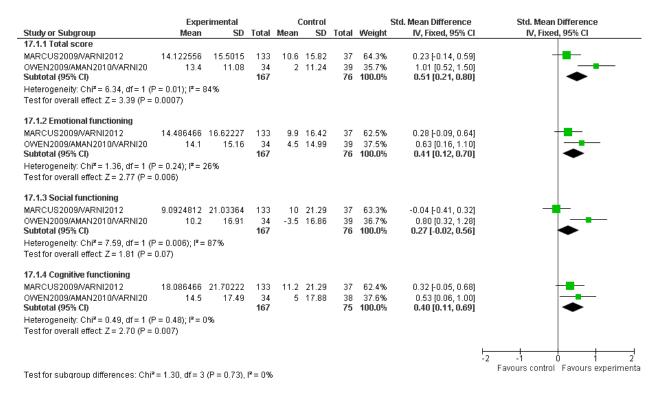
#### LEGO® therapy versus SULP for adaptive behaviour as an indirect outcome



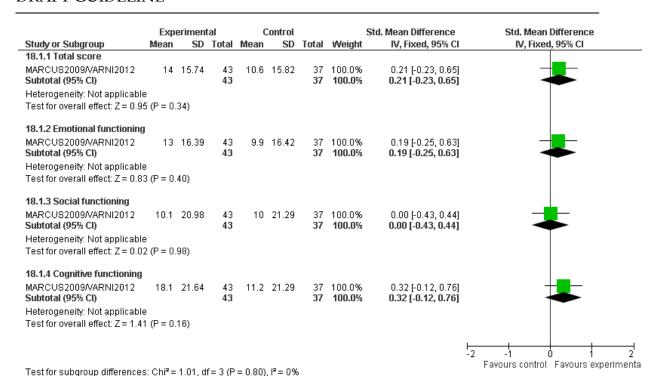
# 1.14PHARMACOLOGICAL INTERVENTIONS AIMED AT ADAPTIVE BEHAVIOUR

#### 1.14.1 Antipsychotics for adaptive behaviour as an indirect outcome

Aripiprazole versus placebo for adaptive behaviour as an indirect outcome



Low dose aripiprazole versus placebo for adaptive behaviour as an indirect outcome

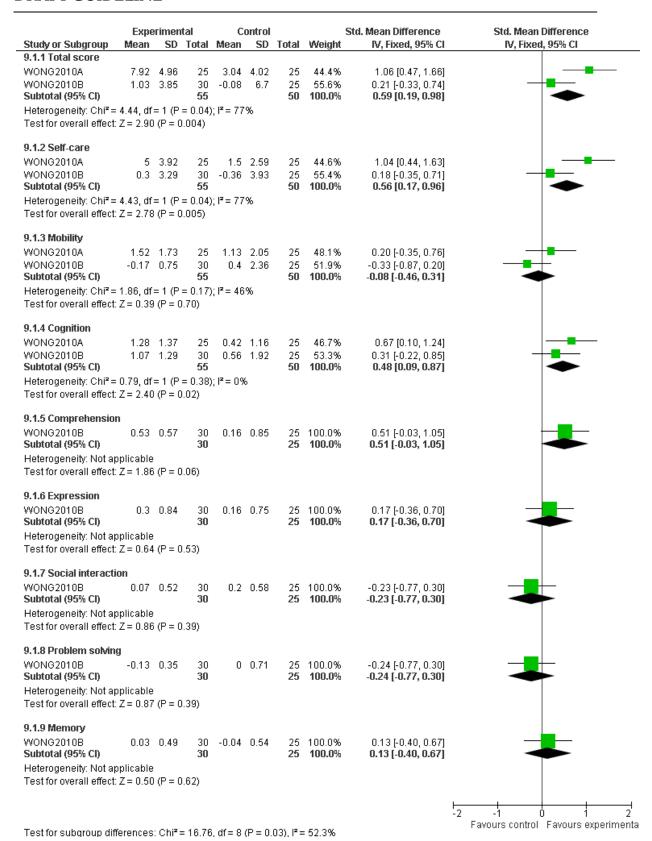


# 1.15BIOMEDICAL INTERVENTIONS AIMED AT ADAPTIVE BEHAVIOUR

# 1.15.1 Complementary therapies for adaptive behaviour as an indirect outcome

Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture for adaptive behaviour as an indirect outcome

Adaptive behaviour (WeeFIM; change scores)

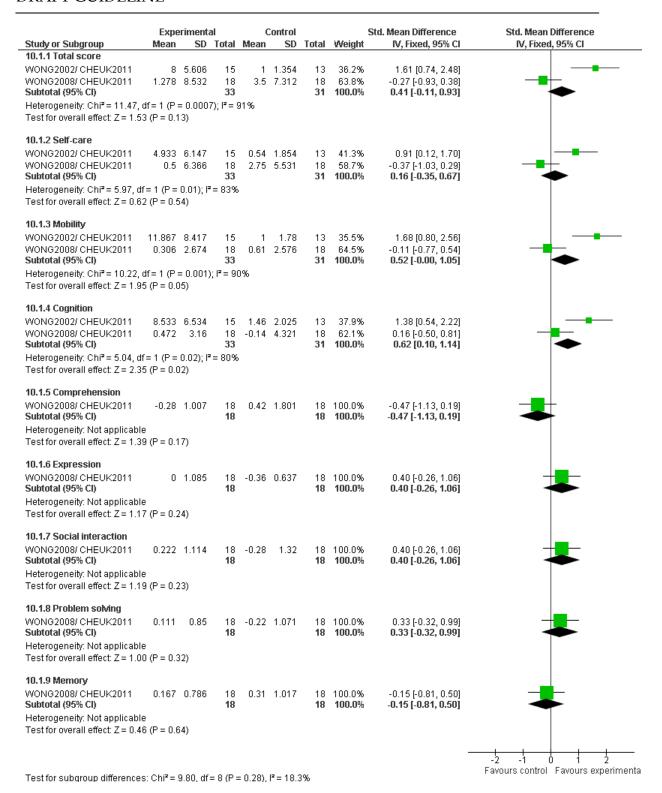


### Adaptive behaviour (PEDI)

Autism: the management and support of children and young people on the autism spectrum (March 2013)

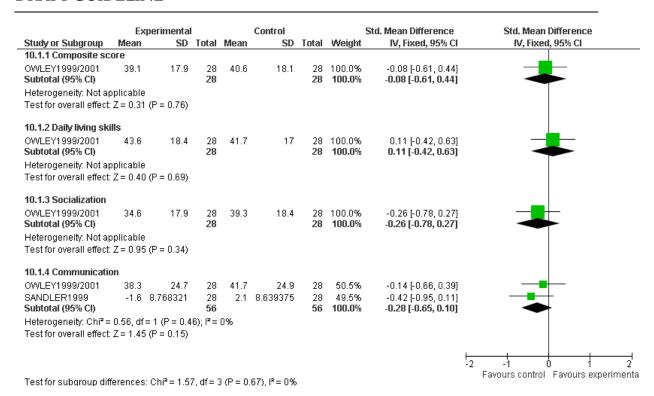
|   | Expe        | eriment   |                 |           | Control  |                 |                          | Std. Mean Difference                               | Std. Mean Difference    |
|---|-------------|-----------|-----------------|-----------|----------|-----------------|--------------------------|--|-------------------------|
| Study or Subgroup                               | Mean        |           | Total           | Mean      | SD       | Total           | Weight                   | IV, Fixed, 95% CI                                  | IV, Fixed, 95% CI       |
| 9.2.1 Self-care (fund                           |             |           |                 |           |          |                 |                          |  | _                       |
| WONG2010B<br>Subtotal (95% Cl)                  | 60.33       | 10.17     | 30<br><b>30</b> | 62.56     | 9.75     | 25<br><b>25</b> | 100.0%<br><b>100.0</b> % | -0.22 [-0.75, 0.31]<br>- <b>0.22 [-0.75, 0.31]</b> | -                       |
| Heterogeneity: Not a                            | pplicable   |           |                 |           |          |                 |                          |  |                         |
| Test for overall effect                         | t: Z = 0.81 | (P = 0.4) | 12)             |           |          |                 |                          |  |                         |
| 9.2.2 Self-care (inde                           | ependenc    | e)        |                 |           |          |                 |                          |  |                         |
| WONG2010B                                       | 29.7        | 8.23      | 30              | 33.12     | 7.11     | 25              | 100.0%                   | -0.44 [-0.97, 0.10]                                | <del></del>             |
| Subtotal (95% CI)                               |             |           | 30              |           |          | 25              | 100.0%                   | -0.44 [-0.97, 0.10]                                |                         |
| Heterogeneity: Not a                            | pplicable   |           |                 |           |          |                 |                          |  |                         |
| Test for overall effect                         | t: Z = 1.59 | (P = 0.1) | 11)             |           |          |                 |                          |  |                         |
| 9.2.3 Mobility (functi                          | ional skill | )         |                 |           |          |                 |                          |  |                         |
| WONG2010B                                       | 57.5        | 1.43      |                 | 57.68     | 1.77     |                 | 100.0%                   | -0.11 [-0.64, 0.42]                                |                         |
| Subtotal (95% CI)                               |             |           | 30              |           |          | 25              | 100.0%                   | -0.11 [-0.64, 0.42]                                |                         |
| Heterogeneity: Not a                            |             |           |                 |           |          |                 |                          |  |                         |
| Test for overall effect                         | t: Z = 0.41 | (P = 0.6  | 08)             |           |          |                 |                          |  |                         |
| 9.2.4 Mobility (indep                           | endence)    | )         |                 |           |          |                 |                          |  |                         |
| WONG2010B                                       | 33.3        | 2.12      |                 | 33.68     | 1.87     |                 | 100.0%                   | -0.19 [-0.72, 0.35]                                |                         |
| Subtotal (95% CI)                               |             |           | 30              |           |          | 25              | 100.0%                   | -0.19 [-0.72, 0.35]                                |                         |
| Heterogeneity: Not a<br>Test for overall effect |             |           | 10)             |           |          |                 |                          |  |                         |
| restior overall ellec                           | ı. ∠= ∪.69  | (P = 0.4  | +9)             |           |          |                 |                          |  |                         |
| 9.2.5 Social function                           | n (function | nal skill | )               |           |          |                 |                          |  |                         |
| WONG2010B                                       | 29.43       | 16.26     |                 | 28.76     | 14.14    |                 | 100.0%                   | 0.04 [-0.49, 0.57]                                 |                         |
| Subtotal (95% CI)                               |             |           | 30              |           |          | 25              | 100.0%                   | 0.04 [-0.49, 0.57]                                 | _                       |
| Heterogeneity: Not a                            |             |           | 771             |           |          |                 |                          |  |                         |
| Test for overall effect                         | 1. ∠= 0.16  | (P = 0.8  | 37)             |           |          |                 |                          |  |                         |
| 9.2.6 Social function                           | ı (indeper  | ndence)   | 1               |           |          |                 |                          |  |                         |
| WONG2010B                                       | 12.3        | 6.56      | 30              | 13.2      | 5.92     |                 | 100.0%                   | -0.14 [-0.67, 0.39]                                |                         |
| Subtotal (95% CI)                               |             |           | 30              |           |          | 25              | 100.0%                   | -0.14 [-0.67, 0.39]                                |                         |
| Heterogeneity: Not a                            |             |           | 203             |           |          |                 |                          |  |                         |
| Test for overall effect                         | ι. ∠ = 0.52 | (P = 0.8  | 00)             |           |          |                 |                          |  |                         |
|   |             |           |                 |           |          |                 |                          |  | -2 -1 0                 |
|   |             |           |                 |           |          |                 |                          |  | Favours control Favours |
| Test for subgroup di                            | fferences   | : Chi²=   | 1.65, d         | lf = 5 (P | = 0.90), | $J^2 = 0.9$     | 6                        |  | care commer i aroure c  |

Acupuncture/electro-acupuncture and conventional educational programme versus conventional educational programme only for adaptive behaviour as an indirect outcome



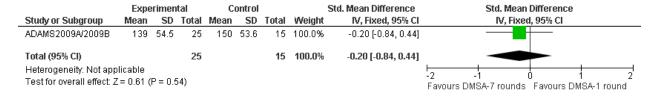
### 1.15.2 Hormones for adaptive behaviour as an indirect outcome

Secretin versus placebo for adaptive behaviour as an indirect outcome



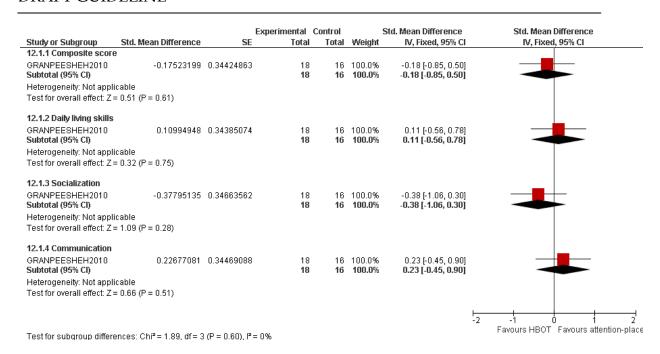
## 1.15.3 Medical procedures for adaptive behaviour as an indirect outcome

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for adaptive behaviour as an indirect outcome

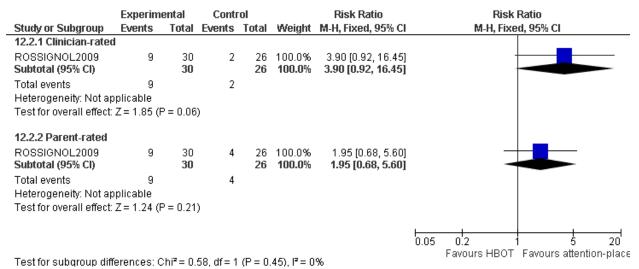


HBOT versus attention-placebo for adaptive behaviour as an indirect outcome

Adaptive behaviours (VABS; change scores)



### Positive treatment response ('much improved/very improved' on CGI/PGIimprovement for overall functioning)



# 1.15.4 Nutritional interventions for adaptive behaviour as an indirect outcome

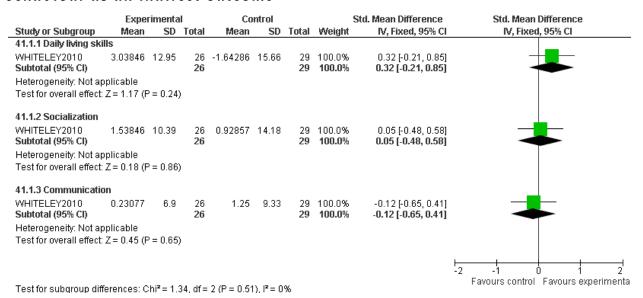
Omega-3 fatty acids versus placebo for adaptive behaviour as an indirect outcome

|  | Expe  | erimen | tal   | C    | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                        |
|--|-------|--------|-------|------|--------|-------|--------|----------------------|---|
| Study or Subgroup                                | Mean  | SD     | Total | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                           |
| BENT2011   | 29.25 | 8.47   | 12    | 31   | 8.64   | 12    | 100.0% | -0.20 [-1.00, 0.60]  | <del></del>                                 |
| Total (95% CI)                                   |       |        | 12    |      |        | 12    | 100.0% | -0.20 [-1.00, 0.60]  |   |
| Heterogeneity: Not ap<br>Test for overall effect |       |        | ).63) |      |        |       |        | ⊢<br>-∑<br>Fav       | 2 -1 0 1 vours experimental Favours control |

## Omega-3 fatty acids versus healthy diet control for adaptive behaviour as an indirect outcome

|  | Expe | Experimental C |       |       | Control |       |        | Std. Mean Difference | Std. Mean Difference                             |
|--|------|----------------|-------|-------|---------|-------|--------|----------------------|--|
| Study or Subgroup                                | Mean | SD             | Total | Mean  | SD      | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                |
| JOHNSON2010                                      | 28.5 | 4.95           | 10    | 23.84 | 8.06    | 13    | 100.0% | 0.65 [-0.20, 1.50]   |  |
| Total (95% CI)                                   |      |                | 10    |       |         | 13    | 100.0% | 0.65 [-0.20, 1.50]   |  |
| Heterogeneity: Not ap<br>Test for overall effect |      |                | ).13) |       |         |       |        |                      | -2 -1 0 1 2 Favours healthy diet Favours omega-3 |

## Gluten-free and casein-free diet versus treatment-as-usual for adaptive behaviour as an indirect outcome

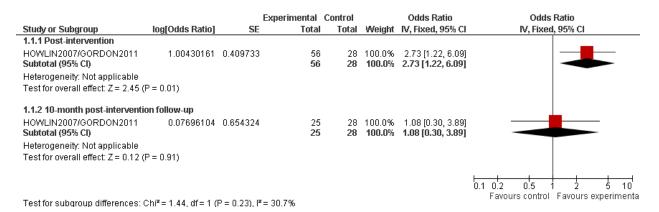


# 1.16PSYCHOSOCIAL INTERVENTIONS AIMED AT SPEECH AND LANGUAGE

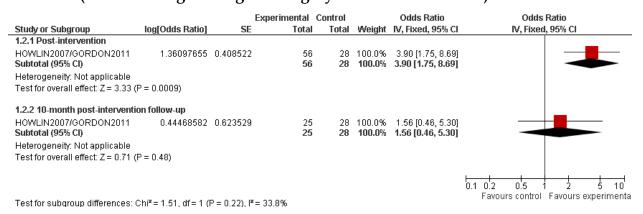
## 1.16.1 AAC interventions for speech and language as a direct outcome

PECS training for teachers versus treatment-as-usual for speech and language as a direct outcome

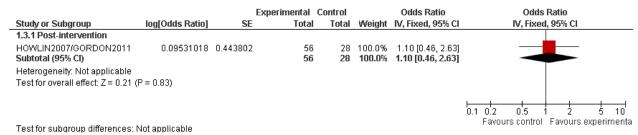
# Spontaneous child communicative initiations (odds of being in a higher initiation category)



### PECS use (odds of being in a higher category for rate of PECS use)



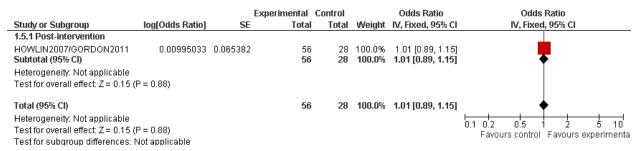
# Speech/vocalisation use (odds of being in a higher category for rate of speech/vocalisation use)



### Receptive language (odds of being in a higher category on BPVS)

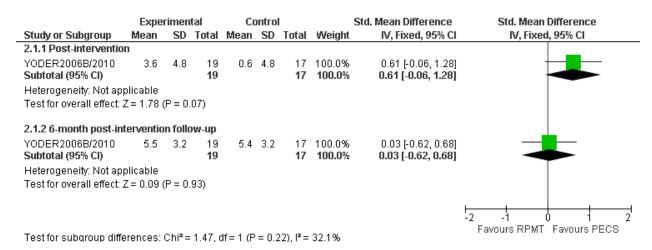
|                                       |                 |          | Experimental | Control |        | Odds Ratio        | Odds Ratio  |
|---------------------------------------|-----------------|----------|--------------|---------|--------|-------------------|---|
| Study or Subgroup                     | log[Odds Ratio] | SE       | Total        | Total   | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI   |
| 1.4.1 Post-intervention               |                 |          |              |         |        |                   |   |
| HOWLIN2007/GORDON2011                 | 0.43178242      | 0.552769 | 56           | 28      | 100.0% | 1.54 [0.52, 4.55] | <del>-   •</del>  |
| Subtotal (95% CI)                     |                 |          | 56           | 28      | 100.0% | 1.54 [0.52, 4.55] |   |
| Heterogeneity: Not applicable         |                 |          |              |         |        |                   |   |
| Test for overall effect: $Z = 0.78$ ( | (P = 0.43)      |          |              |         |        |                   |   |
| Total (95% CI)                        |                 |          | 56           | 28      | 100.0% | 1.54 [0.52, 4.55] |   |
| Heterogeneity: Not applicable         |                 |          |              |         |        |                   | 01 02 05 1 2 5 10   |
| Test for overall effect: $Z = 0.78$ ( | (P = 0.43)      |          |              |         |        |                   | 0.1 0.2 0.5 1 2 5 10<br>Favours control Favours experiments |
| Test for subgroup differences:        | Not applicable  |          |              |         |        |                   | ravours control ravours experiment                          |

### Expressive language (odds of being in a higher category on EOWPVT)

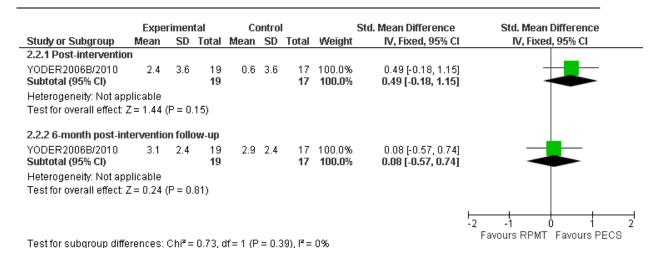


#### PECS versus RPMT for speech and language as a direct outcome

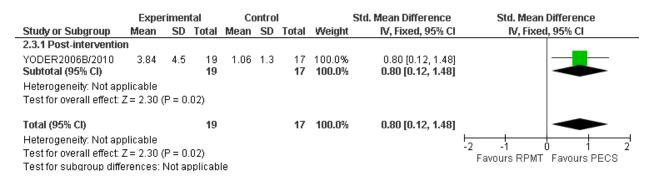
#### Frequency of nonimitative spoken acts



#### Number of different nonimitative words



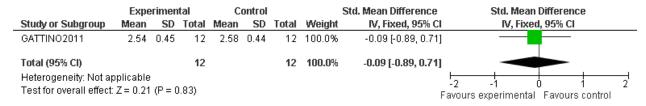
### Number of picture exchanges (EScs-Abridged)



# 1.16.2 Arts-based interventions for speech and language as a direct outcome

Music therapy versus treatment-as-usual for speech and language as a direct outcome

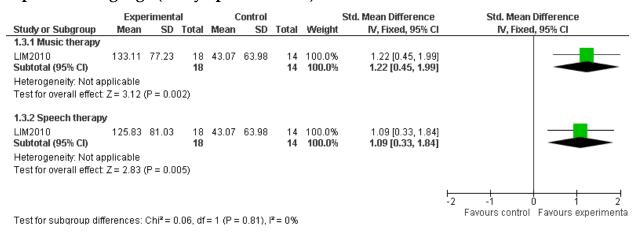
#### Verbal communication (CARS-BR)



### Non-verbal communication (CARS-BR)

|  | Ехре | erimen | tal   | C    | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                          |
|--|------|--------|-------|------|--------|-------|--------|----------------------|---|
| Study or Subgroup                                | Mean | SD     | Total | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                             |
| GATTINO2011                                      | 2.5  | 0.37   | 12    | 2.33 | 0.54   | 12    | 100.0% | 0.35 [-0.45, 1.16]   |   |
| Total (95% CI)                                   |      |        | 12    |      |        | 12    | 100.0% | 0.35 [-0.45, 1.16]   |   |
| Heterogeneity: Not ap<br>Test for overall effect |      |        | ).39) |      |        |       |        | -2<br>Favo           | -1 0 1 2<br>ours experimental Favours control |

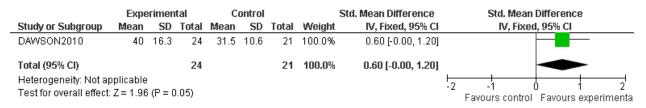
#### Expressive language (study-specific VPES)



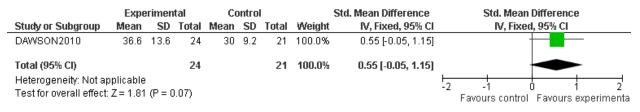
# 1.16.3 Behavioural interventions for speech and language as an indirect outcome

EIBI (ESDM) versus treatment-as-usual for speech and language as an indirect outcome

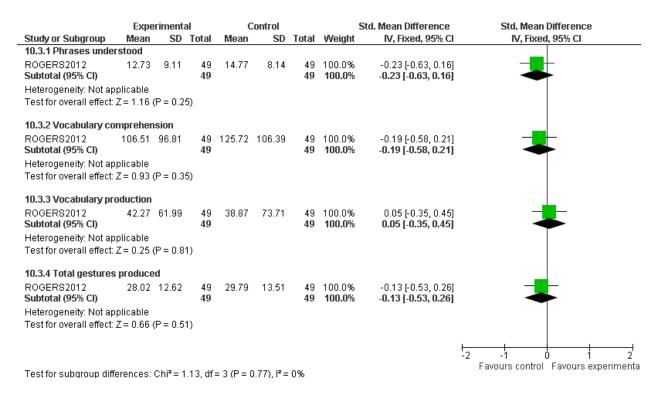
### Receptive language (MSEL)



#### **Expressive language (MSEL)**

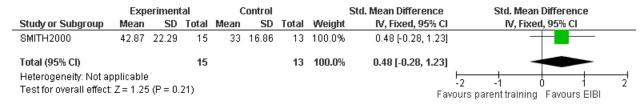


EBI (P-ESDM) versus treatment-as-usual for speech and language as an indirect outcome

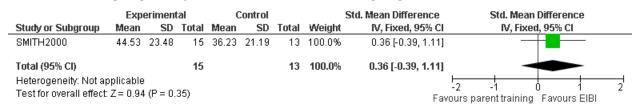


EIBI versus parent training for speech and language as an indirect outcome

### Receptive language (Reynell Developmental Language Scale-Comprehension)



### Expressive language (Reynell Developmental Language Scale-Expressive)

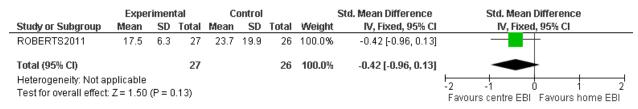


# Receptive + Expressive language (Reynell Developmental Language Scale-Comprehension+Expression)

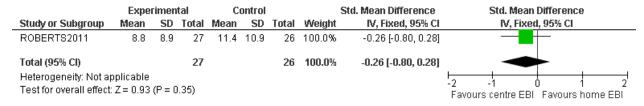
|   | Exp  | eriment | tal   | 0     | Control |       |        | Std. Mean Difference | Std. Mean | Difference |   |
|---|------|---------|-------|-------|---------|-------|--------|----------------------|-----------|------------|---|
| Study or Subgroup                           | Mean | SD      | Total | Mean  | SD      | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed | , 95% CI   |   |
| SMITH2000                                   | 87.4 | 46.21   | 15    | 61.33 | 31.88   | 13    | 100.0% | 0.63 [-0.13, 1.39]   | _         |            | - |
| Total (95% CI)                              |      |         | 15    |       |         | 13    | 100.0% | 0.63 [-0.13, 1.39]   | -         |            | - |
| Heterogeneity: Not<br>Test for overall effe |      |         | 44)   |       |         |       |        | H <sub>-</sub>       | 2 -1 (    | 5 1        |   |

## Home-based EBI versus centre-based EBI for speech and language as an indirect outcome

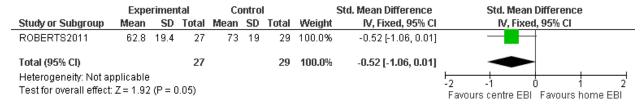
### Receptive language (Reynell Developmental Language Scale-Comprehension)



### Expressive language (Reynell Developmental Language Scale-Expressive)



### **Everyday language functioning (Pragmatics Profile)**



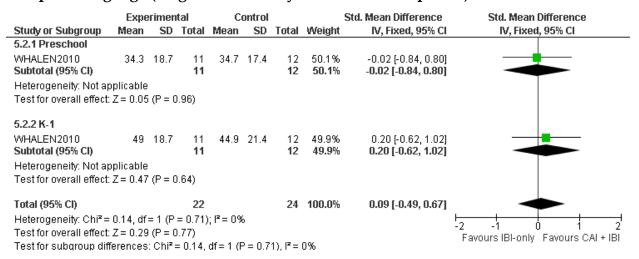
# 1.16.4Educational interventions for speech and language as a direct or indirect outcome

Combined TeachTown and IBI versus IBI-only for speech and language as a direct outcome

Receptive language (PPVT-III)

|                                   | Expe      | erimen | tal                               | C                       | ontrol |       |        | Std. Mean Difference | Std. Mean Difference |
|-----------------------------------|-----------|--------|-----------------------------------|-------------------------|--------|-------|--------|----------------------|----------------------|
| Study or Subgroup                 | Mean      | SD     | Total                             | Mean                    | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI    |
| 5.1.1 Preschool                   |           |        |                                   |                         |        |       |        |                      |                      |
| WHALEN2010                        | 23.4      | 21.7   | 11                                | 14.9                    | 19.6   | 12    | 49.7%  | 0.40 [-0.43, 1.22]   | <del>-   -</del>     |
| Subtotal (95% CI)                 |           |        | 11                                |                         |        | 12    | 49.7%  | 0.40 [-0.43, 1.22]   |                      |
| Heterogeneity: Not ap             | pplicable | !      |                                   |                         |        |       |        |                      |                      |
| Test for overall effect           | Z = 0.94  | (P = 0 | ).35)                             |                         |        |       |        |                      |                      |
| 5.1.2 K-1                         |           |        |                                   |                         |        |       |        |                      |                      |
| WHALEN2010                        | 36.1      | 26.3   | 11                                | 29.8                    | 18.7   | 12    | 50.3%  | 0.27 [-0.55, 1.09]   | <del></del>          |
| Subtotal (95% CI)                 |           |        | 11                                |                         |        | 12    | 50.3%  | 0.27 [-0.55, 1.09]   |                      |
| Heterogeneity: Not a              | pplicable | !      |                                   |                         |        |       |        |                      |                      |
| Test for overall effect           | Z= 0.64   | (P = 0 | ).52)                             |                         |        |       |        |                      |                      |
| Total (95% CI)                    |           |        | 22                                |                         |        | 24    | 100.0% | 0.33 [-0.25, 0.92]   | •                    |
| Heterogeneity: Chi <sup>2</sup> = | 0.05, df  | = 1 (P | = 0.83)                           | $  \mathbf{r}  ^2 = 09$ | 6      |       |        |                      | <u> </u>             |
| Test for overall effect           |           |        | -2 -1 U 1                         |                         |        |       |        |                      |                      |
| Test for subgroup dif             |           |        | Favours IBI-only Favours CAI + II |                         |        |       |        |                      |                      |

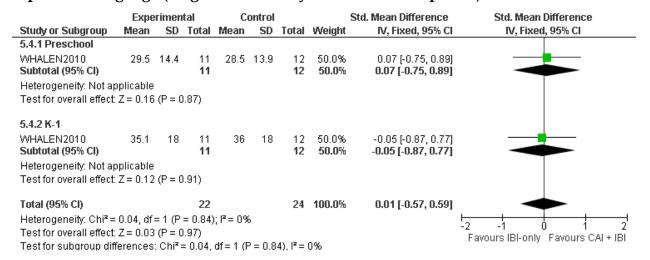
### Receptive language (Brigance Inventory of Child Development)



### **Expressive language (EVT)**

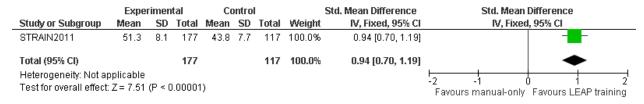
|                                   | Expe       | rimen   | ıtal    | C         | ontrol  |          |        | Std. Mean Difference | Std. Mean Difference                           |
|-----------------------------------|------------|---------|---------|-----------|---------|----------|--------|----------------------|--|
| Study or Subgroup                 | Mean       | SD      | Total   | Mean      | SD      | Total    | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                              |
| 5.3.1 Preschool                   |            |         |         |           |         |          |        |                      |  |
| WHALEN2010                        | 21.9       | 16.7    | 11      | 16.1      | 17.3    | 12       | 49.8%  | 0.33 [-0.50, 1.15]   | <del>-   •</del>                               |
| Subtotal (95% CI)                 |            |         | 11      |           |         | 12       | 49.8%  | 0.33 [-0.50, 1.15]   |  |
| Heterogeneity: Not as             | pplicable  |         |         |           |         |          |        |                      |  |
| Test for overall effect           | Z = 0.78   | (P = 0  | 0.43)   |           |         |          |        |                      |  |
| 5.3.2 K-1                         |            |         |         |           |         |          |        |                      |  |
| WHALEN2010                        | 32         | 15.6    | 11      | 28.4      | 16.3    | 12       | 50.2%  | 0.22 [-0.60, 1.04]   | <del></del>                                    |
| Subtotal (95% CI)                 |            |         | 11      |           |         | 12       | 50.2%  | 0.22 [-0.60, 1.04]   |  |
| Heterogeneity: Not as             | pplicable  |         |         |           |         |          |        |                      |  |
| Test for overall effect           | Z= 0.52    | P = 0   | 0.60)   |           |         |          |        |                      |  |
| Total (95% CI)                    |            |         | 22      |           |         | 24       | 100.0% | 0.27 [-0.31, 0.85]   | -  |
| Heterogeneity: Chi <sup>2</sup> = | 0.04, df   | = 1 (P  | = 0.85  | );        | 6       |          |        |                      | <u> </u>                                       |
| Test for overall effect           | : Z = 0.92 | (P = 0  | 0.36)   |           |         |          |        |                      | -2 -1 0 1<br>Favours IBI-only Favours CAI + II |
| Test for subgroup dif             | ferences   | : Chi²: | = 0.04, | df = 1 (F | o = 0.8 | 5), I² = | 0%     |                      | ravours ibi-only ravours CAL+II                |

#### Expressive language (Brigance Inventory of Child Development)

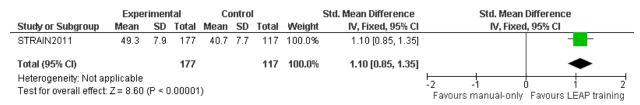


## LEAP training versus manual-only control for speech and language as an indirect outcome

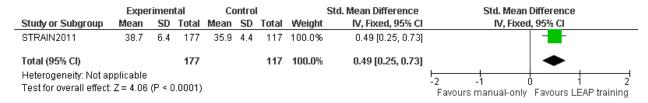
#### Total language score (PLS-4)



#### Receptive language (MSEL; language age in months)



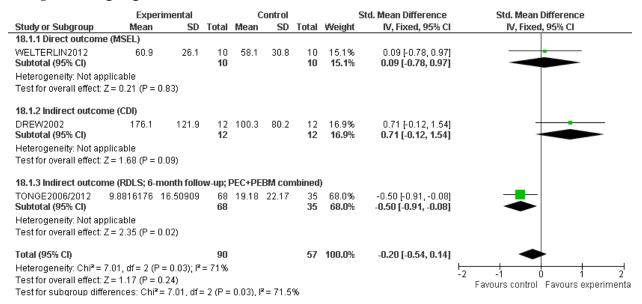
### Expressive language (MSEL; language age in months)



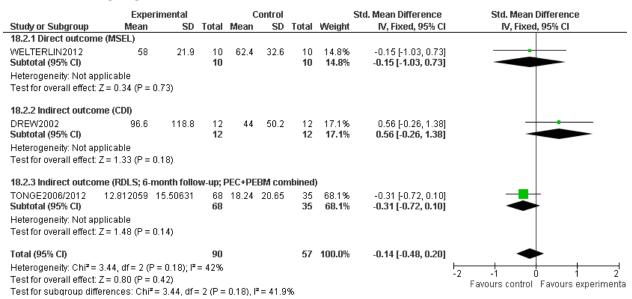
# 1.16.5 Parent training for speech and language as a direct or indirect outcome

Parent training versus treatment-as-usual for speech and language as a direct or indirect outcome

### Receptive language



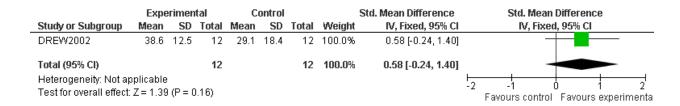
### **Expressive language**



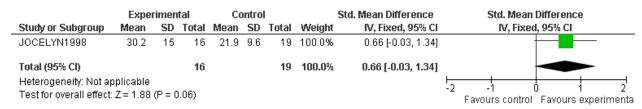
### Overall language rating (ADI-R; indirect outcome)

|                            | Experim     | ental    | Contr  | ol    |        | Risk Ratio          | Risk Ratio                           |
|----------------------------|-------------|----------|--------|-------|--------|---------------------|--------------------------------------|
| Study or Subgroup          | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI  | M-H, Fixed, 95% CI                   |
| 18.3.1 Non-verbal (<5      | words)      |          |        |       |        |                     |                                      |
| DREW2002                   | 4           | 12       | 9      | 12    | 100.0% | 0.44 [0.19, 1.05]   |                                      |
| Subtotal (95% CI)          |             | 12       |        | 12    | 100.0% | 0.44 [0.19, 1.05]   | •                                    |
| Total events               | 4           |          | 9      |       |        |                     |                                      |
| Heterogeneity: Not app     |             |          |        |       |        |                     |                                      |
| Test for overall effect: 2 | Z = 1.84 (F | P = 0.07 | )      |       |        |                     |                                      |
| 18.3.2 Single word sp      | eech        |          |        |       |        |                     |                                      |
| DREW2002                   | 5           | 12       | 3      | 12    | 100.0% | 1.67 [0.51, 5.46]   | <del>-</del>                         |
| Subtotal (95% CI)          |             | 12       |        | 12    | 100.0% | 1.67 [0.51, 5.46]   | <b>*</b>                             |
| Total events               | 5           |          | 3      |       |        |                     |                                      |
| Heterogeneity: Not app     | olicable    |          |        |       |        |                     |                                      |
| Test for overall effect: 2 | Z = 0.84 (F | P = 0.40 | )      |       |        |                     |                                      |
| 18.3.3 Phrase speech       | 1           |          |        |       |        |                     |                                      |
| DREW2002                   | 3           | 12       | 0      | 12    | 100.0% | 7.00 [0.40, 122.44] |                                      |
| Subtotal (95% CI)          |             | 12       |        | 12    | 100.0% | 7.00 [0.40, 122.44] |                                      |
| Total events               | 3           |          | 0      |       |        |                     |                                      |
| Heterogeneity: Not app     | olicable    |          |        |       |        |                     |                                      |
| Test for overall effect: 2 | Z = 1.33 (F | P = 0.18 | )      |       |        |                     |                                      |
|                            |             |          |        |       |        |                     |                                      |
|                            |             |          |        |       |        |                     | 0.01 0.1 1 10 1                      |
|                            |             |          |        |       |        |                     | Favours experimental Favours control |

## Total gestures produced (CDI; indirect outcome)



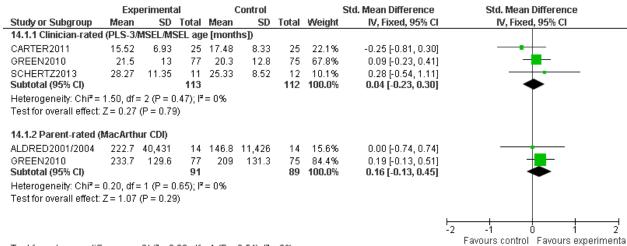
# Parent and day-care staff training versus standard day-care for speech and language as an indirect outcome



# 1.16.6 Social-communication interventions for speech and language as an indirect outcome

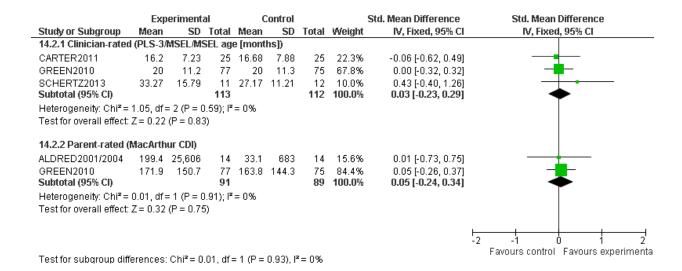
Caregiver-mediated social communication intervention versus treatment-asusual for speech and language as an indirect outcome

### Receptive language

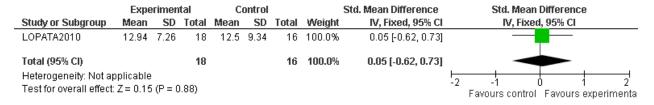


Test for subgroup differences:  $Chi^2 = 0.38$ , df = 1 (P = 0.54),  $I^2 = 0\%$ 

#### **Expressive language**

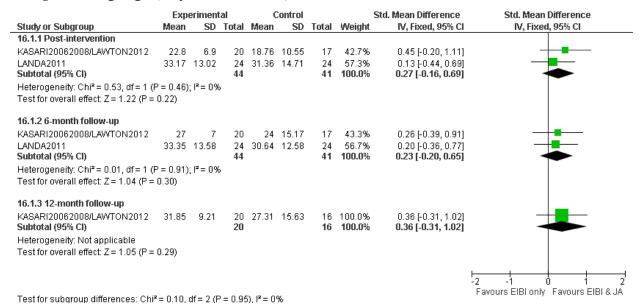


## Social skills group versus treatment-as-usual for speech and language as an indirect outcome



# Joint attention training and EBI/EIBI versus EBI/EIBI only for speech and language as an indirect outcome

### Receptive language (Reynell or MSEL)



### Expressive language (Reynell or MSEL)

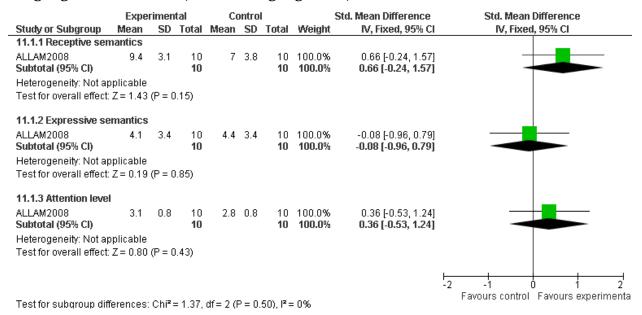
|   | Exp       | erimen       | tal   | (     | Control |       |        | Std. Mean Difference | Std. Mean Difference                             |
|---|-----------|--------------|-------|-------|---------|-------|--------|----------------------|--|
| Study or Subgroup                                 | Mean      | SD           | Total | Mean  | SD      | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                |
| 16.2.1 Post-intervention                          |           |              |       |       |         |       |        |                      |  |
| KASARI20062008/LAWTON2012                         | 23.15     | 6.43         | 20    | 21.18 | 9.11    | 17    | 43.2%  | 0.25 [-0.40, 0.90]   | <del>-   •</del>                                 |
| LANDA2011   | 34.08     | 14.59        | 24    | 31.92 | 13.67   | 24    | 56.8%  | 0.15 [-0.42, 0.72]   | <del>-  </del>                                   |
| Subtotal (95% CI)                                 |           |              | 44    |       |         | 41    | 100.0% | 0.19 [-0.23, 0.62]   | -  |
| Heterogeneity: Chi <sup>2</sup> = 0.05, df = 1 (l | P = 0.82  | $ I^2 = 09 $ | 6     |       |         |       |        |                      |  |
| Test for overall effect: Z = 0.88 (P =            | 0.38)     |              |       |       |         |       |        |                      |  |
| 16.2.2 6-month follow-up                          |           |              |       |       |         |       |        |                      |  |
| KASARI20062008/LAWTON2012                         | 27.35     | 7.36         | 20    | 24.18 | 11.32   | 17    | 43.2%  | 0.33 [-0.32, 0.98]   | <del></del>                                      |
| LANDA2011   | 34.52     | 12.33        | 24    | 31.36 | 12.12   | 24    | 56.8%  | 0.25 [-0.31, 0.82]   | <del>-   •</del>                                 |
| Subtotal (95% CI)                                 |           |              | 44    |       |         | 41    | 100.0% | 0.29 [-0.14, 0.72]   | -  |
| Heterogeneity: Chi <sup>2</sup> = 0.03, df = 1 (l | P = 0.86) | $ I^2 = 09 $ | 6     |       |         |       |        |                      |  |
| Test for overall effect: $Z = 1.31$ (P =          | 0.19)     |              |       |       |         |       |        |                      |  |
| 16.2.3 12-month follow-up                         |           |              |       |       |         |       |        |                      |  |
| KASARI20062008/LAWTON2012                         | 35.7      | 12.57        | 20    | 28.06 | 13.52   | 16    | 100.0% | 0.57 [-0.10, 1.25]   | <del>                                     </del> |
| Subtotal (95% CI)                                 |           |              | 20    |       |         | 16    | 100.0% | 0.57 [-0.10, 1.25]   |  |
| Heterogeneity: Not applicable                     |           |              |       |       |         |       |        |                      |  |
| Test for overall effect: Z = 1.68 (P =            | 0.09)     |              |       |       |         |       |        |                      |  |
|   |           |              |       |       |         |       |        |                      |  |
|   |           |              |       |       |         |       |        |                      | -2 -1 0 1  |
| Toot for outbaroup difforonces: Obii              |           | -16 O (F     |       |       | ۰,      |       |        |                      | Favours EBI/EIBI only Favours EBI/EIBI 8         |

# 1.17BIOMEDICAL INTERVENTIONS AIMED AT SPEECH AND LANGUAGE

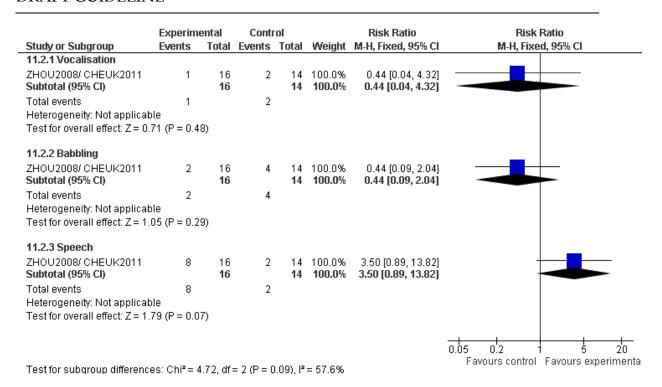
# 1.17.1 Complementary therapies for speech and language as a direct or indirect outcome

Acupuncture/acupressure and language therapy versus language therapy only for speech and language as a direct outcome

### Language and attention (Arabic Language Test)



Positive treatment response (improvement in basic developmental assessment)



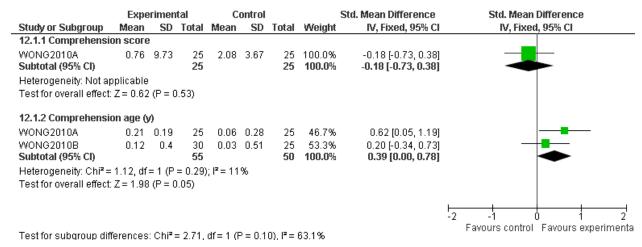
Positive treatment response (number of participants improved on CRRC signsignificance relations scale)

| Study or Subgroup   | Experime<br>Events |                 | Conti      |           | Weight                   | Risk Ratio<br>M-H, Fixed, 95% CI                  | Risk Ratio<br>M-H, Fixed, 95% Cl |
|---|--------------------|-----------------|------------|-----------|--------------------------|---|----------------------------------|
| 11.3.1 Speech comprehens  |                    | Total           | LVCIICS    | rotai     | ricigit                  | III-11, 1 IACU, 33 / CI                           | m-ri, rincu, oo a ci             |
| ZHOU2008/ CHEUK2011<br>Subtotal (95% Cl)  | 5                  | 16<br><b>16</b> | 5          | 14<br>14  | 100.0%<br><b>100.0</b> % | 0.88 [0.32, 2.40]<br><b>0.87 [0.32, 2.40]</b>     | #                                |
| Total events  | 5                  |                 | 5          |           |                          |   |                                  |
| Heterogeneity: Not applicab<br>Test for overall effect: Z = 0.3                 |                    | 0)              |            |           |                          |   |                                  |
| 11.3.2 Speech expression  |                    |                 |            |           |                          |   |                                  |
| ZHOU2008/ CHEUK2011<br>Subtotal (95% Cl)  | 4                  | 16<br><b>16</b> | 3          | 14<br>14  | 100.0%<br><b>100.0</b> % | 1.17 [0.31, 4.34]<br><b>1.17 [0.31, 4.34</b> ]    |                                  |
| Total events<br>Heterogeneity: Not applicab<br>Test for overall effect: Z = 0.3 |                    | 2)              | 3          |           |                          |   |                                  |
| 11.3.3 Speech imitation   |                    |                 |            |           |                          |   | _                                |
| ZHOU2008/ CHEUK2011<br>Subtotal (95% CI)  | 1                  | 16<br><b>16</b> | 2          | 14<br>14  | 100.0%<br><b>100.0</b> % | 0.44 [0.04, 4.32]<br><b>0.44 [0.04, 4.32]</b>     |                                  |
| Total events  | 1                  |                 | 2          |           |                          |   |                                  |
| Heterogeneity: Not applicab<br>Test for overall effect: Z = 0.3                 |                    | 3)              |            |           |                          |   |                                  |
| 11.3.4 Vocabulary compreh   |                    |                 | -          |           | 400.55                   | 0.74 (0.70 )                                      | _                                |
| ZHOU2008/ CHEUK2011<br>Subtotal (95% CI)  | 5                  | 16<br><b>16</b> | 0          | 14<br>14  |                          | 9.71 [0.58, 161.31]<br><b>9.71 [0.58, 161.31]</b> |                                  |
| Total events  | . 5                |                 | 0          |           |                          |   |                                  |
| Heterogeneity: Not applicab<br>Test for overall effect: Z = 1.9                 |                    | 1)              |            |           |                          |   |                                  |
| 11.3.5 Vocabulary express   |                    |                 |            |           |                          |   | _                                |
| ZHOU2008/ CHEUK2011<br>Subtotal (95% CI)  | 5                  | 16<br><b>16</b> | 0          |           |                          | 9.71 [0.58, 161.31]<br>9.71 [0.58, 161.31]        |                                  |
| Total events  | 5                  |                 | 0          |           |                          |   |                                  |
| Heterogeneity: Not applicab<br>Test for overall effect: Z = 1.5                 |                    | 1)              |            |           |                          |   |                                  |
| 11.3.6 Phrase comprehens  | sion               |                 |            |           |                          |   |                                  |
| ZHOU2008/ CHEUK2011<br>Subtotal (95% CI)  | 1                  | 16<br><b>16</b> | 0          | 14<br>14  | 100.0%<br><b>100.0</b> % | 2.65 [0.12, 60.21]<br><b>2.65 [0.12, 60.21]</b>   |                                  |
| Total events  | . 1                |                 | 0          |           |                          |   |                                  |
| Heterogeneity: Not applicab<br>Test for overall effect: Z = 0.6                 |                    | 4)              |            |           |                          |   |                                  |
| 11.3.7 Phrase expression  |                    |                 |            |           |                          |   |                                  |
| ZHOU2008/ CHEUK2011<br>Subtotal (95% CI)  | 1                  | 16<br><b>16</b> | 0          |           | 100.0%<br><b>100.0</b> % | 2.65 [0.12, 60.21]<br><b>2.65 [0.12, 60.21]</b>   |                                  |
| Total events  | 1                  |                 | 0          |           |                          |   |                                  |
| Heterogeneity: Not applicab<br>Test for overall effect: Z = 0.6                 |                    | 4)              |            |           |                          |   |                                  |
| 11.3.8 Communication attit  |                    |                 |            |           |                          |   |                                  |
| ZHOU2008/ CHEUK2011<br>Subtotal (95% CI)  | 15                 | 16<br><b>16</b> | 8          | 14<br>14  | 100.0%<br><b>100.0</b> % | 1.64 [1.02, 2.63]<br><b>1.64 [1.02, 2.63]</b>     |                                  |
| Total events Heterogeneity: Not applicab  |                    | 0               | 8          |           |                          |   |                                  |
| Test for overall effect: $Z = 2.0$  | 0.0 (F = 0.0)      | +)              |            |           |                          |   |                                  |
|   |                    |                 |            |           |                          |   | 0.01 0.1 1 10 10                 |
| Test for subgroup difference  | es: Chi² = 6       | .12, df         | = 7 (P = 0 | ).53), I² | = 0%                     |   | Favours control Favours experime |

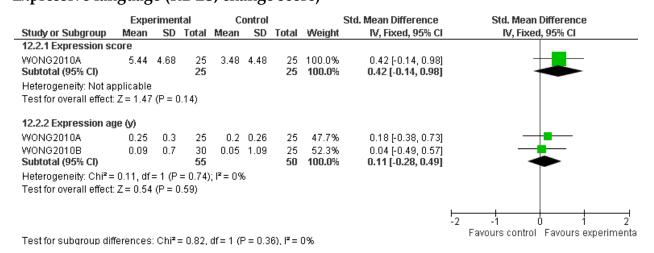
Autism: the management and support of children and young people on the autism spectrum (March 2013)

# Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture for speech and language as an indirect outcome

### Receptive language (RDLS; change score)



## Expressive language (RDLS; change score)



### 1.17.2 Hormones for speech and language as an indirect outcome

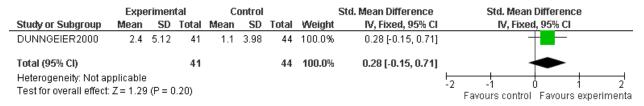
Secretin versus placebo for speech and language as an indirect outcome Receptive Language (PLS-3/MSEL/PPVT-III or MSEL)

|   | Favou | rs con | trol  | C                    | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                               |
|---|-------|--------|-------|----------------------|--------|-------|--------|----------------------|--|
| Study or Subgroup   | Mean  | SD     | Total | Mean                 | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |
| DUNNGEIER2000   | 1.5   | 3.98   | 44    | 0.6                  | 2.68   | 45    | 47.8%  | 0.26 [-0.15, 0.68]   | +=-  |
| MOLLOY2002  | 19    | 10.1   | 19    | 20.3                 | 10.9   | 23    | 22.5%  | -0.12 [-0.73, 0.49]  | <del></del>  |
| OWLEY1999/2001  | 29.1  | 21.8   | 28    | 40.1                 | 31.6   | 28    | 29.7%  | -0.40 [-0.93, 0.13]  | <del></del>  |
| Total (95% CI)  |       |        | 91    |                      |        | 96    | 100.0% | -0.02 [-0.31, 0.27]  | •  |
| Heterogeneity: Chi <sup>z</sup> =<br>Test for overall effect: | •     | ,      |       | I <sup>2</sup> = 489 | %      |       |        |                      | -2 -1 0 1 2<br>Favours control Favours experimenta |

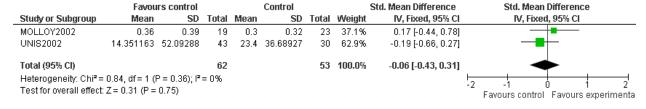
# Expressive language (PLS-3 change score/MLU behavioural observation/EOWPVT-R change score)

|   | Expe      | rimental |       |      | Control  |       |        | Std. Mean Difference | Std. Mean Difference                |
|---|-----------|----------|-------|------|----------|-------|--------|----------------------|-------------------------------------|
| Study or Subgroup   | Mean      | SD       | Total | Mean | SD       | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                   |
| DUNNGEIER2000   | 0.6       | 2.59     | 42    | 0.6  | 2.65     | 44    | 41.7%  | 0.00 [-0.42, 0.42]   | <del>-</del>                        |
| MOLLOY2002  | 1.2       | 1.28     | 19    | 1.24 | 1.24     | 23    | 20.2%  | -0.03 [-0.64, 0.58]  | <del></del>                         |
| UNIS2002  | 0.2313725 | 3.794916 | 51    | 2.1  | 5.499393 | 33    | 38.1%  | -0.41 [-0.85, 0.03]  | <del></del>                         |
| Total (95% CI)  |           |          | 112   |      |          | 100   | 100.0% | -0.16 [-0.43, 0.11]  | •                                   |
| Heterogeneity: Chi <sup>2</sup> =<br>Test for overall effect: |           |          | = 0%  |      |          |       |        |                      | -2 -1 0 1 2                         |
|   |           | ,        |       |      |          |       |        |                      | Favours control Favours experiment: |

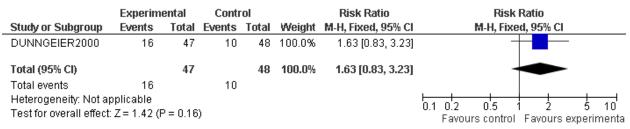
### Receptive and expressive language (PLS-3 total; change score)



### Vocabulary (type-token ratio behavioural observation or CDI vocabulary)

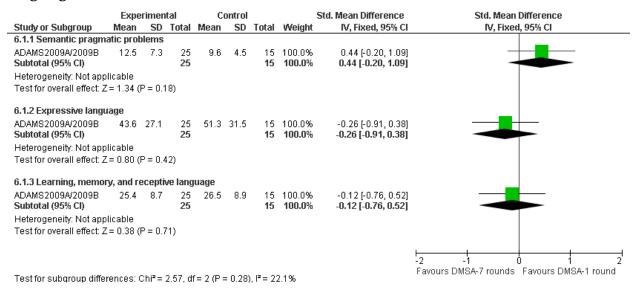


### Positive treatment response (>=4 points improvement on PLS-3)

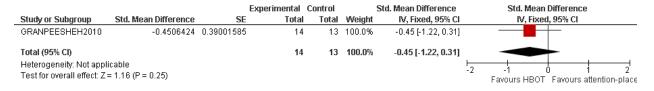


### 1.17.3 Medical procedures for speech and language as an indirect outcome

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for speech and language as an indirect outcome



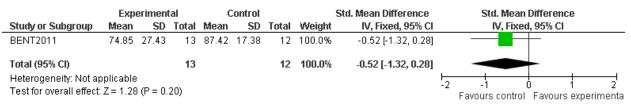
## HBOT versus attention-placebo for speech and language as an indirect outcome



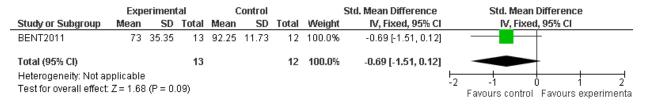
# 1.17.4 Nutritional interventions for speech and language as an indirect outcome

Omega-3 fatty acids versus placebo for speech and language as an indirect outcome

### Receptive language (PPVT)



#### Expressive language (EVT)

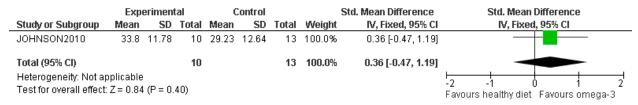


## Omega-3 fatty acids versus healthy diet control for speech and language as an indirect outcome

#### Receptive language (MSEL)

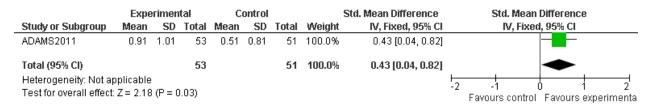
|   | Exp  | eriment | al    | (    | Control |       |        | Std. Mean Difference | Std. Mean Difference                                |
|---|------|---------|-------|------|---------|-------|--------|----------------------|---|
| Study or Subgroup                                 | Mean | SD      | Total | Mean | SD      | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                   |
| JOHNSON2010                                       | 34.5 | 12.87   | 10    | 31   | 17.64   | 13    | 100.0% | 0.21 [-0.61, 1.04]   |   |
| Total (95% CI)                                    |      |         | 10    |      |         | 13    | 100.0% | 0.21 [-0.61, 1.04]   |   |
| Heterogeneity: Not ap<br>Test for overall effect: |      |         | 61)   |      |         |       |        |                      | -2 -1 0 1 2<br>Favours healthy diet Favours omega-3 |

### **Expressive language (MSEL)**



## Multivitamin/ mineral supplement versus placebo for speech and language as an indirect outcome

#### Receptive language improvement (PGI-R)

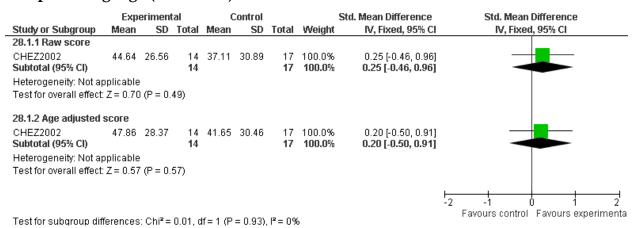


### Expressive language improvement (PGI-R)

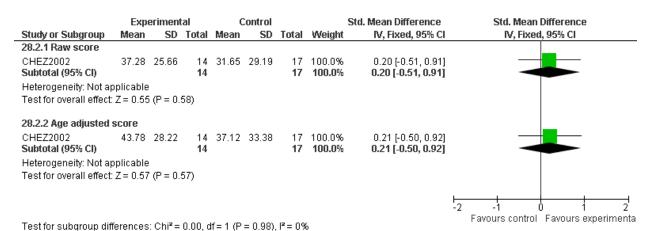
|   | Experimental Control |      |       |      |      | !     | Std. Mean Difference | Std. Mean Difference |   |  |  |  |
|---|----------------------|------|-------|------|------|-------|----------------------|----------------------|---|--|--|--|
| Study or Subgroup                                 | Mean                 | SD   | Total | Mean | SD   | Total | Weight               | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                 |  |  |  |
| ADAMS2011   | 1.09                 | 1.11 | 53    | 0.71 | 0.92 | 51    | 100.0%               | 0.37 [-0.02, 0.76]   | _   |  |  |  |
| Total (95% CI)                                    |                      |      | 53    |      |      | 51    | 100.0%               | 0.37 [-0.02, 0.76]   | •   |  |  |  |
| Heterogeneity: Not ap<br>Test for overall effect: |                      |      | ).06) |      |      |       |                      |                      | -2 -1 0 1 2<br>Favours control Favours experiment |  |  |  |

## L-carnosine supplement versus placebo for speech and language as an indirect outcome

### Receptive language (ROWPVT)



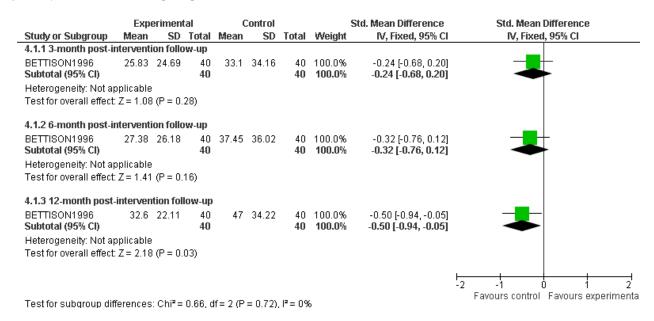
### **Expressive language (EOWPVT)**



Autism: the management and support of children and young people on the autism spectrum (March 2013)

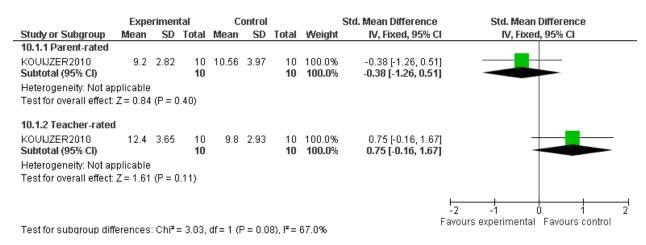
# 1.17.5 Sensory interventions for speech and language as an indirect outcome

Auditory integration training versus attention-placebo (structured listening) for speech and language as an indirect outcome



## Neurofeedback versus treatment-as-usual for speech and language as an indirect outcome

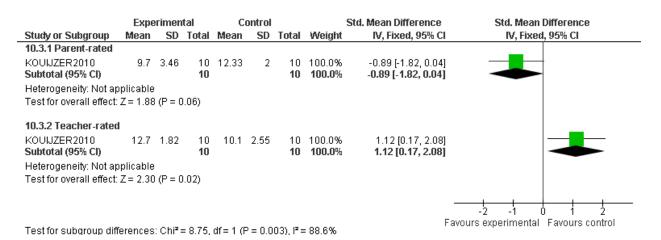
### **Speech production (CCC-2)**



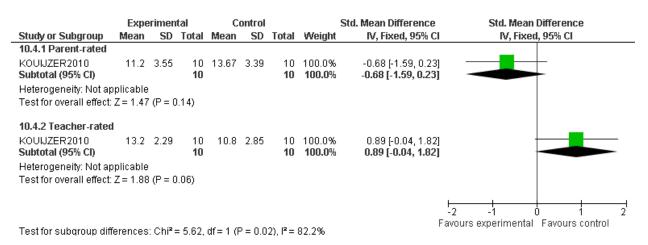
### Syntax (CCC-2)

|                            | Expe     | rimen   | tal   | C     | ontrol |       | 9      | Std. Mean Difference | Std. Mean Difference              |
|----------------------------|----------|---------|-------|-------|--------|-------|--------|----------------------|-----------------------------------|
| Study or Subgroup          | Mean     | SD      | Total | Mean  | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                 |
| 10.2.1 Parent-rated        |          |         |       |       |        |       |        |                      |                                   |
| KOUIJZER2010               | 10.7     | 3.74    | 10    | 12.56 | 2.74   | 10    | 100.0% | -0.54 [-1.44, 0.35]  | <del></del>                       |
| Subtotal (95% CI)          |          |         | 10    |       |        | 10    | 100.0% | -0.54 [-1.44, 0.35]  |                                   |
| Heterogeneity: Not ap      | plicable |         |       |       |        |       |        |                      |                                   |
| Test for overall effect:   | Z = 1.19 | (P = 0  | 1.23) |       |        |       |        |                      |                                   |
| 10.2.2 Teacher-rated       |          |         |       |       |        |       |        |                      |                                   |
| KOUIJZER2010               | 12.5     | 4.06    | 10    | 11.8  | 2.25   | 10    | 100.0% | 0.20 [-0.68, 1.08]   | <del></del>                       |
| Subtotal (95% CI)          |          |         | 10    |       |        | 10    | 100.0% | 0.20 [-0.68, 1.08]   |                                   |
| Heterogeneity: Not ap      | plicable |         |       |       |        |       |        |                      |                                   |
| Test for overall effect: : | Z = 0.46 | (P = 0) | 1.65) |       |        |       |        |                      |                                   |
|                            |          |         |       |       |        |       |        |                      |                                   |
|                            |          |         |       |       |        |       |        | H                    | 2 -1 1 1                          |
|                            |          |         |       |       |        |       |        | F                    | ours experimental Favours control |

## Semantics (CCC-2)



### Coherence (CCC-2)



Autism: the management and support of children and young people on the autism spectrum (March 2013)

# 1.18PSYCHOSOCIAL INTERVENTIONS AIMED AT IQ AND ACADEMIC SKILLS

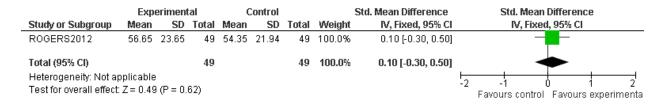
# 1.18.1 Behavioural interventions for IQ and/or academic skills as a direct or indirect outcome

EIBI or EBI (ESDM or P-ESDM) versus treatment-as-usual for IQ as a direct or indirect outcome

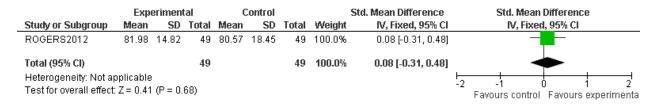
### IQ (MSEL - Early-learning composite score; Developmental quotient)

|                                   | Expe     | rimen   | tal  | (             | Control  |                       |                        | Std. Mean Difference                             | Std. Mean Difference                |
|-----------------------------------|----------|---------|--|---------------|----------|-----------------------|------------------------|--|-------------------------------------|
| Study or Subgroup                 | Mean     | SD      | Total  | Mean          | SD       | Total                 | Weight                 | IV, Fixed, 95% CI                                | IV, Fixed, 95% CI                   |
| 13.1.1 ESDM                       |          |         |  |               |          |                       |                        |  |                                     |
| DAWSON2010<br>Subtotal (95% CI)   | 78.6     | 24.2    | 24<br>24   | 66.3          | 15.3     | 21<br><b>21</b>       | 30.4%<br><b>30.4</b> % | 0.59 [-0.01, 1.19]<br><b>0.59 [-0.01, 1.19</b> ] |                                     |
| Heterogeneity: Not ap             | plicable |         |  |               |          |                       |                        |  |                                     |
| Test for overall effect:          | Z=1.92   | (P = 0  | 1.05)  |               |          |                       |                        |  |                                     |
| 13.1.2 P-ESDM                     |          |         |  |               |          |                       |                        |  |                                     |
| ROGERS2012                        | 69.82    | 17.9    | 49   | 67.92         | 17.93    | 49                    | 69.6%                  | 0.11 [-0.29, 0.50]                               | <b>——</b>                           |
| Subtotal (95% CI)                 |          |         | 49   |               |          | 49                    | 69.6%                  | 0.11 [-0.29, 0.50]                               | -                                   |
| Heterogeneity: Not ap             | plicable |         |  |               |          |                       |                        |  |                                     |
| Test for overall effect:          | Z = 0.52 | P = 0   | 1.60)  |               |          |                       |                        |  |                                     |
| Total (95% CI)                    |          |         | 73   |               |          | 70                    | 100.0%                 | 0.25 [-0.08, 0.58]                               | •                                   |
| Heterogeneity: Chi <sup>2</sup> = | 1.74, df | = 1 (P  | = 0.19)  | $  1 ^2 = 42$ | %        |                       |                        |  |                                     |
| Test for overall effect:          | Z = 1.50 |         | -2 -1 0 1 2<br>Favours control Favours experimenta |               |          |                       |                        |  |                                     |
| Test for subgroup diff            | erences  | : Chi²: | = 1.74,  | df = 1 (F     | P = 0.19 | ), l <sup>2</sup> = 4 | 2.4%                   |  | ravouis control ravours experimenta |

### Verbal developmental quotient (MSEL)



### Non-verbal developmental quotient (MSEL)



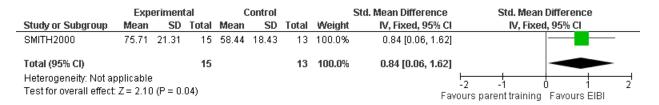
Autism: the management and support of children and young people on the autism spectrum (March 2013)

## EIBI versus parent training for IQ and academic skills as an indirect outcome

### IQ (Bayley Scales of Infant Development - Mental Development Index)

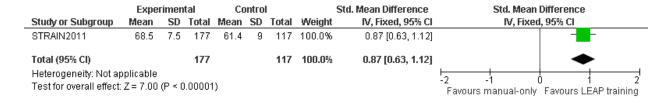
|   | Exp   | eriment | tal   | (     | Control |       |        | Std. Mean Difference | Std. Mean Differ                  | ence            |
|---|-------|---------|-------|-------|---------|-------|--------|----------------------|-----------------------------------|-----------------|
| Study or Subgroup                               | Mean  | SD      | Total | Mean  | SD      | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95%                    | CI              |
| SMITH2000                                       | 66.49 | 24.08   | 15    | 49.67 | 19.74   | 13    | 100.0% | 0.74 [-0.04, 1.51]   |                                   |                 |
| Total (95% CI)                                  |       |         | 15    |       |         | 13    | 100.0% | 0.74 [-0.04, 1.51]   |                                   |                 |
| Heterogeneity: Not a<br>Test for overall effect |       |         | 06)   |       |         |       |        | Favi                 | -2 -1 0 ours parent training Favo | 1 2<br>urs EIBI |

### Academic skills (WIAT total score)



### 1.18.2 Educational interventions for IQ as an indirect outcome

#### LEAP training versus manual-only control for IQ as an indirect outcome

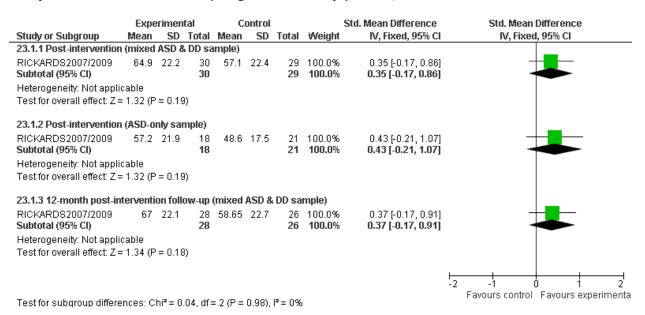


## 1.18.3 Parent training for IQ as an indirect outcome

Parent training versus treatment-as-usual for IQ as an indirect outcome

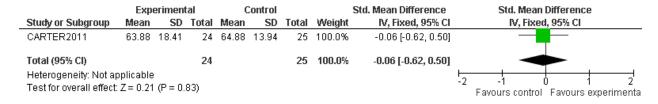
|   | Expe      | erimental |       | C     | Control |       |        | Std. Mean Difference | Std. Mean Difference                               |
|---|-----------|-----------|-------|-------|---------|-------|--------|----------------------|--|
| Study or Subgroup   | Mean      | SD        | Total | Mean  | SD      | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |
| DREW2002  | 77.9      | 14.8      | 12    | 66.1  | 17.1    | 12    | 16.6%  | 0.71 [-0.12, 1.54]   | <del></del>  |
| TONGE2006/2012  | 63.328235 | 24.30453  | 68    | 67.72 | 28.14   | 35    | 68.6%  | -0.17 [-0.58, 0.24]  | <del></del>  |
| WELTERLIN2012   | 63.7      | 17.4      | 10    | 58.1  | 25      | 10    | 14.8%  | 0.25 [-0.63, 1.13]   | -  |
| Total (95% CI)  |           |           | 90    |       |         | 57    | 100.0% | 0.04 [-0.30, 0.38]   | •  |
| Heterogeneity: Chi <sup>z</sup> =<br>Test for overall effect: |           |           | = 47% |       |         |       |        |                      | -2 -1 0 1 2<br>Favours control Favours experiments |

# Combined parent training and early intervention centre programme versus early intervention centre programme only for IQ as an indirect outcome



### 1.18.4 Social-communication interventions for IQ as an indirect outcome

Caregiver-mediated social communication intervention versus treatment-asusual for IQ as an indirect outcome



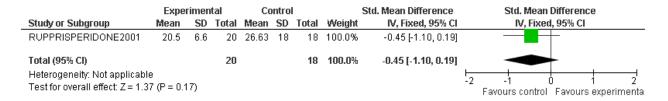
# Joint attention training and EIBI versus EIBI only for IQ as an indirect outcome

|   | Exp   | eriment | tal   | (     | Control |       |        | Std. Mean Difference | 5               | itd. Mean        | Differen    | ce          |           |
|---|-------|---------|-------|-------|---------|-------|--------|----------------------|-----------------|------------------|-------------|-------------|-----------|
| Study or Subgroup   | Mean  | SD      | Total | Mean  | SD      | Total | Weight | IV, Fixed, 95% CI    |                 | IV, Fixed        | I, 95% C    |             |           |
| KASARI20062008/LAWTON2012   | 71.54 | 20.68   | 20    | 58.68 | 26.31   | 16    | 100.0% | 0.54 [-0.13, 1.21]   |                 | -                |             | _           |           |
| Total (95% CI)  |       |         | 20    |       |         | 16    | 100.0% | 0.54 [-0.13, 1.21]   |                 | -                | •           | _           |           |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.58 (P = | 0.12) |         |       |       |         |       |        |                      | -2 -<br>Favours | 1<br>1 EIBI only | )<br>Favour | 1<br>s EIBI | 2<br>& JA |

# 1.19PHARMACOLOGICAL INTERVENTIONS AIMED AT ACADEMIC SKILLS

### 1.19.1 Antipsychotics for academic skills as an indirect outcome

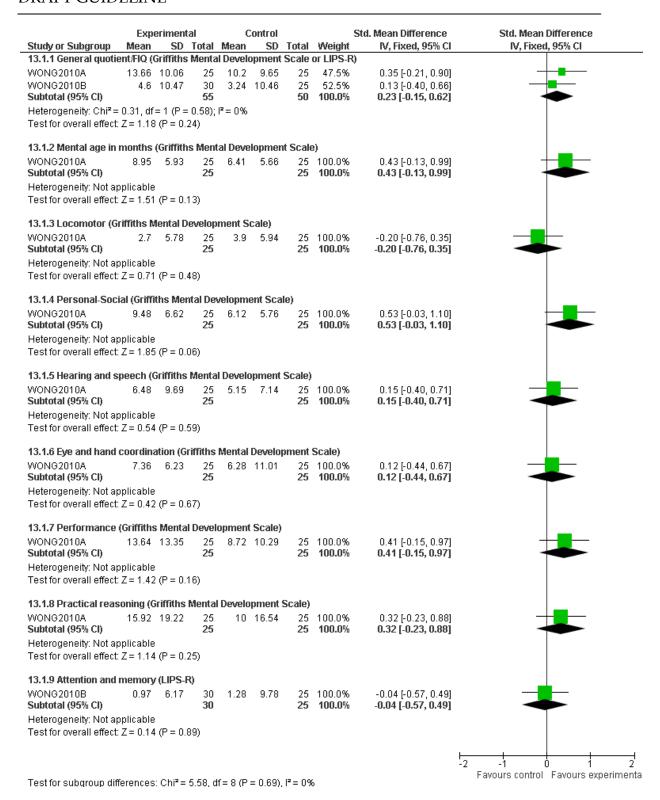
Risperidone versus placebo for academic skills as an indirect outcome



## 1.20BIOMEDICAL INTERVENTIONS AIMED AT IQ

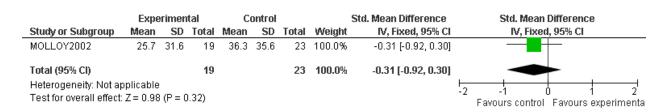
## 1.20.1 Complementary therapies for IQ as a direct outcome

Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture for IQ as a direct outcome



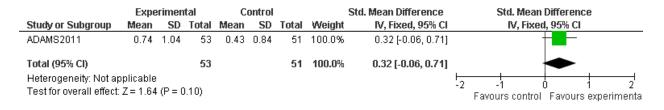
## 1.20.2 Hormones for IQ as an indirect outcome

Secretin versus placebo for IQ as an indirect outcome



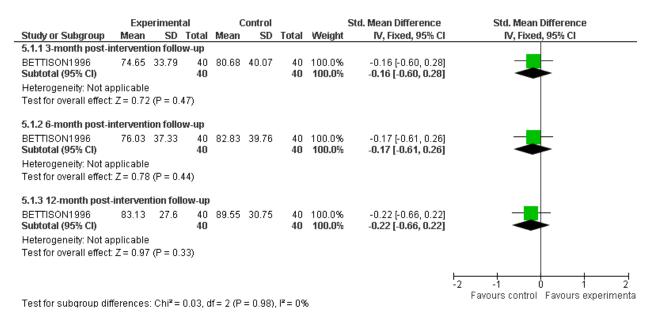
### 1.20.3 Nutritional intervention for IQ as an indirect outcome

## Multivitamin/ mineral supplement versus placebo for IQ as an indirect outcome



### 1.20.4 Sensory intervention for IQ as an indirect outcome

Auditory integration training versus attention-placebo (structured listening) for IQ as an indirect outcome



# 1.21PSYCHOSOCIAL INTERVENTIONS AIMED AT SENSORY SENSITIVITIES

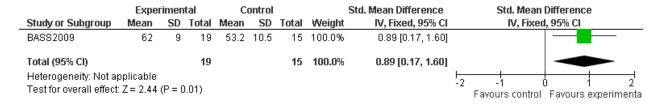
# 1.21.1 Animal-based interventions for sensory sensitivities as an indirect outcome

Horseback riding versus waitlist control for sensory sensitivities as an indirect outcome

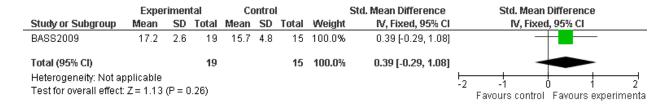
### Sensory problems (Sensory Profile Total)

|   | Experimental Control |      |       |       | Std. Mean Difference | Std. Mean Difference |        |                    |   |
|---|----------------------|------|-------|-------|----------------------|----------------------|--------|--------------------|---|
| Study or Subgroup                               | Mean                 | SD   | Total | Mean  | SD                   | Total                | Weight | IV, Fixed, 95% CI  | IV, Fixed, 95% CI                               |
| BASS2009  | 269.4                | 51.6 | 19    | 245.7 | 50.3                 | 15                   | 100.0% | 0.45 [-0.23, 1.14] | _   |
| Total (95% CI)                                  |                      |      | 19    |       |                      | 15                   | 100.0% | 0.45 [-0.23, 1.14] |   |
| Heterogeneity: Not a<br>Test for overall effect | • •                  |      | 1.20) |       |                      |                      |        |                    | -2 -1 0 1 2 Favours control Favours experimenta |

#### Sensory seeking (Sensory Profile)

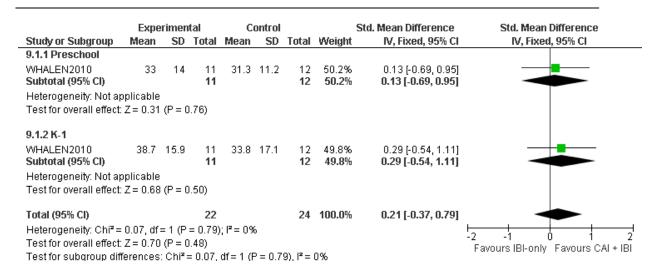


#### Sensory sensitivity (Sensory Profile)



# 1.21.2Educational interventions for sensory sensitivities as an indirect outcome

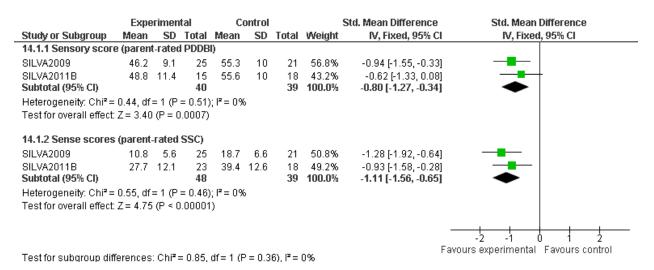
Combined TeachTown and IBI versus IBI-only for sensory sensitivities as an indirect outcome



# 1.22BIOMEDICAL INTERVENTIONS AIMED AT SENSORY SENSITIVITIES

## 1.22.1 Complementary therapies for sensory sensitivities as a direct outcome

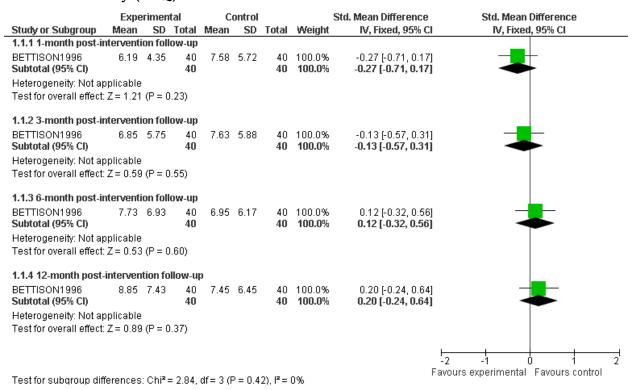
Qigong massage training versus waitlist for sensory sensitivities as a direct outcome



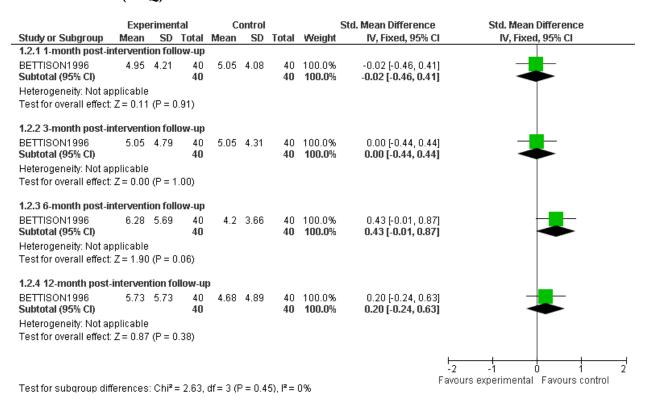
#### 1.22.2 Sensory interventions for sensory sensitivities as a direct outcome

Auditory integration training versus attention-placebo (structured listening) for sensory sensitivities as a direct outcome

#### Sound sensitivity (SSQ)

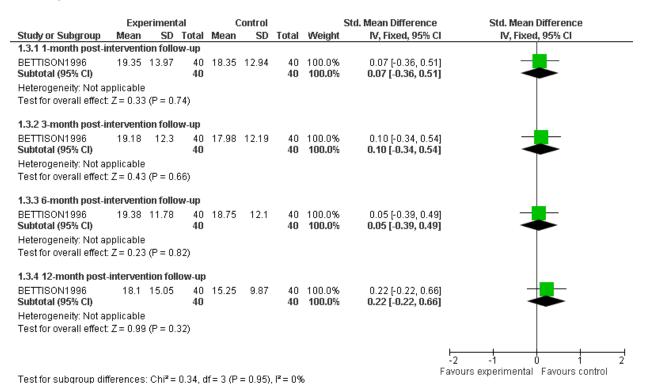


#### Sound distress (SSQ)

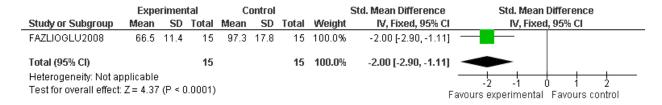


Autism: the management and support of children and young people on the autism spectrum (March 2013)

#### Sensory self-stimulation (SP)



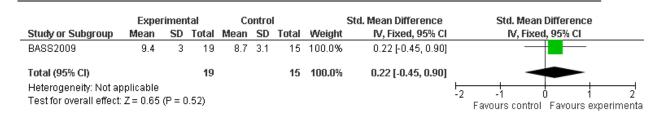
### Sensory integration therapy versus treatment-as-usual for sensory sensitivities as a direct outcome



# 1.23PSYCHOSOCIAL INTERVENTIONS AIMED AT MOTOR SKILLS

#### 1.23.1 Animal-based interventions for motor skills as an indirect outcome

Horseback riding versus waitlist control for motor skills as an indirect outcome



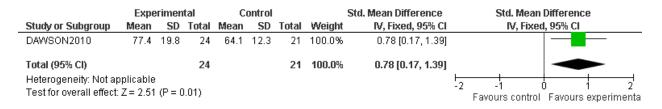
#### 1.23.2Behavioural interventions for motor skills as an indirect outcome

### EIBI (ESDM) versus treatment-as-usual for motor skills as an indirect outcome

#### Fine motor skills (MSEL)

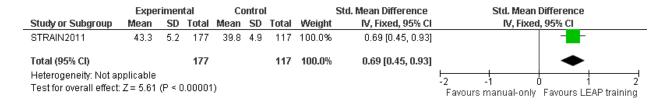
|   | Expe | rimen | tal   | Co   | ontro | I     |        | Std. Mean Difference | Std. Mean Difference                            |
|---|------|-------|-------|------|-------|-------|--------|----------------------|---|
| Study or Subgroup                                 | Mean | SD    | Total | Mean | SD    | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                               |
| DAWSON2010  | 33.5 | 12.2  | 24    | 28.5 | 9.5   | 21    | 100.0% | 0.45 [-0.15, 1.04]   | +   |
| Total (95% CI)                                    |      |       | 24    |      |       | 21    | 100.0% | 0.45 [-0.15, 1.04]   | -   |
| Heterogeneity: Not ap<br>Test for overall effect: | •    |       | 0.14) |      |       |       |        |                      | -2 -1 0 1 2 Favours control Favours experimenta |

#### Motor skills (VABS)



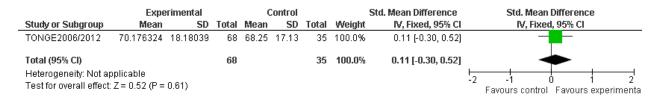
#### 1.23.3 Educational interventions for motor skills as an indirect outcome

### LEAP training versus manual-only control for motor skills as an indirect outcome



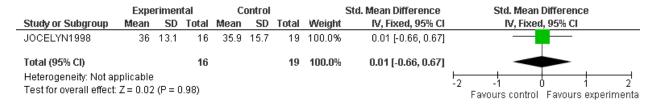
#### 1.23.4 Parent training for motor skills as an indirect outcome

Parent training versus treatment-as-usual for motor skills as an indirect outcome

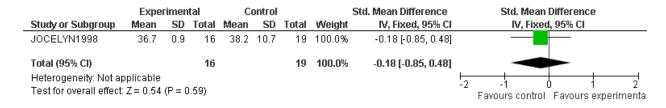


Parent and day-care staff training versus standard day-care for motor skills as an indirect outcome

#### Perceptual/Fine Motor Skills (EIDP/PSDP developmental age)



#### Gross Motor Skills (EIDP/PSDP developmental age)



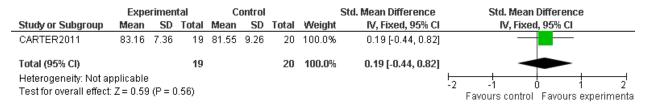
### 1.23.5 Social-communication interventions for motor skills as an indirect outcome

Caregiver-mediated social-communication intervention versus treatment-asusual for motor skills as an indirect outcome

Fine motor skills (MSEL age [months])

|   | Expe | rimen | tal   | C     | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                               |
|---|------|-------|-------|-------|--------|-------|--------|----------------------|--|
| Study or Subgroup                               | Mean | SD    | Total | Mean  | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |
| CARTER2011                                      | 22   | 3.5   | 25    | 21.92 | 4.09   | 25    | 100.0% | 0.02 [-0.53, 0.58]   | -  |
| Total (95% CI)                                  |      |       | 25    |       |        | 25    | 100.0% | 0.02 [-0.53, 0.58]   | -  |
| Heterogeneity: Not a<br>Test for overall effect |      |       | ).94) |       |        |       |        |                      | -2 -1 0 1 2<br>Favours control Favours experimenta |

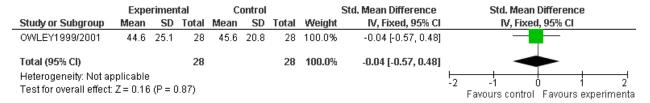
#### Motor skills (VABS)



# 1.24BIOMEDICAL INTERVENTIONS AIMED AT MOTOR SKILLS

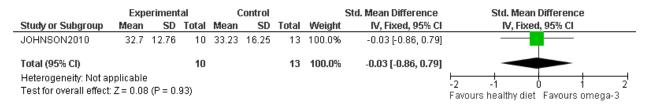
#### 1.24.1 Hormones for motor skills as an indirect outcome

Secretin versus placebo for motor skills as an indirect outcome

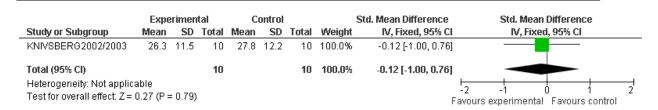


#### 1.24.2 Nutritional interventions for motor skills as an indirect outcome

### Omega-3 fatty acids versus healthy diet control for motor skills as an indirect outcome



### Gluten-free and casein-free diet versus treatment-as-usual for motor skills as an indirect outcome



# 1.25PSYCHOSOCIAL INTERVENTIONS AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

#### 1.25.1 Cognitive-behavioural interventions for anxiety as a direct outcome

CBT versus treatment-as-usual for anxiety as a direct outcome

#### No longer meet anxiety disorder diagnosis

|  | Ехрегіт     | ental | Conti  | rol   |        | Risk Ratio           | Risk Ratio                          |
|--|-------------|-------|--------|-------|--------|----------------------|-------------------------------------|
| Study or Subgroup                            | Events      | Total | Events | Total | Weight | M-H, Fixed, 95% CI   | M-H, Fixed, 95% CI                  |
| CHALFANT2007                                 | 20          | 28    | 0      | 19    | 25.8%  | 28.28 [1.81, 440.96] |                                     |
| DRAHOTA2011/WOOD2009                         | 9           | 17    | 2      | 23    | 74.2%  | 6.09 [1.50, 24.64]   | <del></del>                         |
| Total (95% CI)                               |             | 45    |        | 42    | 100.0% | 11.82 [3.14, 44.50]  | •                                   |
| Total events                                 | 29          |       | 2      |       |        |                      |                                     |
| Heterogeneity: Chi <sup>2</sup> = 1.25, df = | •           |       | :0%    |       |        |                      | 0.002 0.1 1 10 500                  |
| Test for overall effect: $Z = 3.65$          | (m = 0.000. | 5)    |        |       |        |                      | Favours control Favours experimenta |

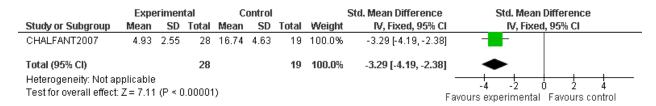
#### Improvement in anxiety symptoms (CGI- Improvement)

|                                     | Ехрегіт     | ental         | Contr  | ol    |        | Risk Ratio         | Risk Ratio                          |
|-------------------------------------|-------------|---------------|--------|-------|--------|--------------------|-------------------------------------|
| Study or Subgroup                   | Events      | Total         | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% CI                  |
| DRAHOTA2011/WOOD2009                | 13          | 17            | 2      | 23    | 47.7%  | 8.79 [2.28, 33.93] |                                     |
| REAVEN2012                          | 10          | 20            | 2      | 23    | 52.3%  | 5.75 [1.43, 23.20] | <del></del>                         |
| Total (95% CI)                      |             | 37            |        | 46    | 100.0% | 7.20 [2.74, 18.91] | •                                   |
| Total events                        | 23          |               | 4      |       |        |                    |                                     |
| Heterogeneity: Chi² = 0.18, df =    | 1 (P = 0.6) | 7); $I^2 = 0$ | 1%     |       |        |                    | 0.02 0.1 1 10 50                    |
| Test for overall effect: Z = 4.01 ( | (P < 0.0001 | )             |        |       |        |                    | Favours control Favours experimenta |

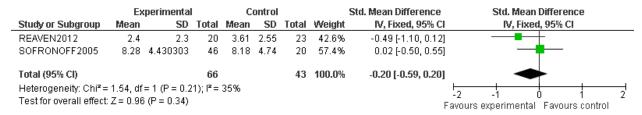
#### Anxiety

| Subtotal (95% CI)       42       41         Heterogeneity: Chi² = 24.92, df = 1 (P < 0.00001); P = 96%         Test for overall effect: Z = 4.04 (P < 0.0001)         1.3.2 Parent-reported (SCAS-P; MASC)         CHALFANT2007       13.96       5.11       28       44.16       9.04       19         DRAHOTA2011/WOOD2009       58.48       14.72       14       76.57       14.65       22         SOFRONOFF2005       34.124783       15.36961       46       35.61       13.34       20         Subtotal (95% CI)       88       61         Heterogeneity: Chi² = 47.24, df = 2 (P < 0.00001); I² = 96%         Test for overall effect: Z = 4.91 (P < 0.00001)         1.3.3 Clinician-rated anxiety (ADIS-P/C)         DRAHOTA2011/WOOD2009       2.36       1.15       14       4.77       0.81       22         REAVEN2012       2.25       0.91       20       2.83       0.98       23 | Peight   N, Fixed, 95% Cl   N, Fixed, 95% Cl                    |
|--|---|
| CHALFANT2007 13.79 10.96 28 41.37 9.09 19 DRAHOTA2011/WOOD2009 46.93 14.76 14 46.5 15.83 22 Subtotal (95% CI) 42 41  Heterogeneity. Chi² = 24.92, df = 1 (P < 0.00001); I² = 96% Test for overall effect: Z = 4.04 (P < 0.0001)  1.3.2 Parent-reported (SCAS-P; MASC)  CHALFANT2007 13.96 5.11 28 44.16 9.04 19 DRAHOTA2011/WOOD2009 58.48 14.72 14 76.57 14.65 22 SOFRONOF52005 34.124783 15.36961 46 35.61 13.34 20 Subtotal (95% CI) 88 61  Heterogeneity. Chi² = 47.24, df = 2 (P < 0.00001); I² = 96% Test for overall effect: Z = 4.91 (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C) DRAHOTA2011/WOOD2009 2.36 1.15 14 4.77 0.81 22 REAVEN2012 2.25 0.91 20 2.83 0.98 23 Subtotal (95% CI) 34  Heterogeneity: Chi² = 11.26, df = 1 (P = 0.00008); I² = 91%   | 9.2% 0.03 [-0.64, 0.70]   |
| DRAHOTA2011/WOOD2009   | 9.2% 0.03 [-0.64, 0.70]   |
| Subtotal (95% CI) 42 41  Heterogeneity: Chi² = 24.92, df = 1 (P < 0.00001); i² = 96% Test for overall effect: Z = 4.04 (P < 0.00001)  1.3.2 Parent-reported (SCAS-P; MASC)  CHALFANT2007 13.96 5.11 28 44.16 9.04 19  DRAHOTA2011/ WOOD2009 58.48 14.72 14 76.57 14.65 22  SOFRONOFF2005 34.124783 15.36961 46 35.61 13.34 20  Subtotal (95% CI) 88 61  Heterogeneity: Chi² = 47.24, df = 2 (P < 0.00001); i² = 96% Test for overall effect: Z = 4.91 (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C)  DRAHOTA2011/ WOOD2009 2.36 1.15 14 4.77 0.81 22  REAVEN2012 2.25 0.91 20 2.83 0.98 23  Subtotal (95% CI) 34 45  Heterogeneity: Chi² = 11.26, df = 1 (P = 0.00008); i² = 91%   |   |
| Heterogeneity: Chi² = 24.92, df = 1 (P < 0.00001); i² = 96% Test for overall effect: $Z = 4.04$ (P < 0.0001)  1.3.2 Parent-reported (SCAS-P; MASC)  CHALFANT2007 13.96 5.11 28 44.16 9.04 19 DRAHOTA2011/WOOD2009 58.48 14.72 14 76.57 14.65 22 SOFRONOFF2005 34.124783 15.36961 46 35.61 13.34 20 Subtotal (95% Cl) 88 61  Heterogeneity: Chi² = 47.24, df = 2 (P < 0.00001); i² = 96% Test for overall effect: $Z = 4.91$ (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C)  DRAHOTA2011/WOOD2009 2.36 1.15 14 4.77 0.81 22 REAVEN2012 2.25 0.91 20 2.83 0.98 23 Subtotal (95% Cl) 34 45  Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); i² = 91%   | 0.0% -1.06 [-1.58, -0.55]                                       |
| Test for overall effect: Z = 4.04 (P < 0.0001)  1.3.2 Parent-reported (SCAS-P; MASC)  CHALFANT2007 13.96 5.11 28 44.16 9.04 19  DRAHOTA2011/WOOD2009 58.48 14.72 14 76.57 14.65 22  SOFRONOFF2005 34.124783 15.36961 46 35.61 13.34 20  Subtotal (95% Cl) 88 61  Heterogeneity: Chi² = 47.24, df = 2 (P < 0.00001); I² = 96%  Test for overall effect: Z = 4.91 (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C)  DRAHOTA2011/WOOD2009 2.36 1.15 14 4.77 0.81 22  REAVEN2012 2.25 0.91 20 2.83 0.98 23  Subtotal (95% Cl) 34 45  Heterogeneity: Chi² = 11.26, df = 1 (P = 0.00008); I² = 91%  |   |
| 1.3.2 Parent-reported (SCAS-P; MASC)  CHALFANT2007 13.96 5.11 28 44.16 9.04 19  DRAHOTA2011/WOOD2009 58.48 14.72 14 76.57 14.65 22  SOFRONOFF2005 34.124783 15.36961 46 35.61 13.34 20  Subtotal (95% Cl) 88 61  Heterogeneity: Chi² = 47.24, df = 2 (P < 0.00001); i² = 96%  Test for overall effect: Z = 4.91 (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C)  DRAHOTA2011/ WOOD2009 2.36 1.15 14 4.77 0.81 22  REAVEN2012 2.25 0.91 20 2.83 0.98 23  Subtotal (95% Cl) 34 45  Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); i² = 91%  |   |
| CHALFANT2007 13.96 5.11 28 44.16 9.04 19 DRAHOTA2011/WOOD2009 58.48 14.72 14 76.57 14.65 22 SOFRONOFF2005 34.124783 15.36961 46 35.61 13.34 20 Subtotal (95% CI) 88 61  Heterogeneity: Chi² = 47.24, df = 2 (P < 0.00001); i² = 96%  Test for overall effect: Z = 4.91 (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C) DRAHOTA2011/WOOD2009 2.36 1.15 14 4.77 0.81 22 REAVEN2012 2.25 0.91 20 2.83 0.98 23 Subtotal (95% CI) 34 45  Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); i² = 91%   |   |
| DRAHOTA2011/WOOD2009 58.48 14.72 14 76.57 14.65 22 BOFRONOFF2005 34.124783 15.36961 46 35.61 13.34 20 Subtotal (95% CI) 88 61 Heterogeneity: Chi² = 47.24, df = 2 (P < 0.00001); I² = 96% Test for overall effect: Z = 4.91 (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C) DRAHOTA2011/WOOD2009 2.36 1.15 14 4.77 0.81 22 REAVEN2012 2.25 0.91 20 2.83 0.98 23 Subtotal (95% CI) 34 45 Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); I² = 91%   |   |
| 80FRONOFF2005 34.124783 15.36961 46 35.61 13.34 20 Subtotal (95% CI) 88 61 Heterogeneity: Chi² = 47.24, df = 2 (P < 0.00001); I³ = 96% Test for overall effect: Z = 4.91 (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C)  DRAHOTA2011/ WOOD2009 2.36 1.15 14 4.77 0.81 22 REAVEN2012 2.25 0.91 20 2.83 0.98 23 Subtotal (95% CI) 34 45 Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); I³ = 91%  | 3.6% -4.27 [-5.34, -3.20]                                       |
| Subtotal (95% CI) 88 61  Heterogeneity: Chi² = 47.24, df = 2 (P < 0.00001); i² = 96%  Test for overall effect: Z = 4.91 (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C)  DRAHOTA2011/WOOD2009 2.36 1.15 14 4.77 0.81 22  REAVEN2012 2.25 0.91 20 2.83 0.98 23  Subtotal (95% CI) 34 45  Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); i² = 91%   | 9.3% -1.21 [-1.94, -0.47]                                       |
| Heterogeneity: Chi² = 47.24, df = 2 (P < 0.00001); i² = 96%  Test for overall effect: Z = 4.91 (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C)  DRAHOTA2011/ WOOD2009 2.36 1.15 14 4.77 0.81 22  REAVEN2012 2.25 0.91 20 2.83 0.98 23  Subtotal (95% Cl) 34 45  Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); i² = 91%   | i7.0% -0.10 [-0.62, 0.43] <del></del>                           |
| Test for overall effect: Z = 4.91 (P < 0.00001)  1.3.3 Clinician-rated anxiety (ADIS-P/C)  DRAHOTA2011/WOOD2009 2.36 1.15 14 4.77 0.81 22  REAVEN2012 2.25 0.91 20 2.83 0.98 23  Subtotal (95% Cl) 34 45  Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); i² = 91%   | 00.0% -0.99 [-1.39, -0.60]                                      |
| 1.3.3 Clinician-rated anxiety (ADIS-P/C)  DRAHOTA2011/WOOD2009 2.36 1.15 14 4.77 0.81 22  REAVEN2012 2.25 0.91 20 2.83 0.98 23  Subtotal (95% Cl) 34 45  Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); l² = 91%  |   |
| DRAHOTA2011/WOOD2009     2.36     1.15     14     4.77     0.81     22       REAVEN2012     2.25     0.91     20     2.83     0.98     23       Subtotal (95% CI)     34     45       Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008);  ² = 91%   |   |
| REAVEN2012 2.25 0.91 20 2.83 0.98 23<br><b>Subtotal (95% CI)</b> 34 45<br>Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); l² = 91%   |   |
| Subtotal (95% CI) 34 45 Heterogeneity: Chi²= 11.26, df= 1 (P = 0.0008); l²= 91%  | 11.6% -2.47 [-3.37, -1.57] ———————————————————————————————————— |
| Heterogeneity: Chi² = 11.26, df = 1 (P = 0.0008); l² = 91%   | 8.4% -0.60 [-1.21, 0.01] ———                                    |
|  | 00.0% -1.19 [-1.70, -0.68]                                      |
| Toot for our off off 7 = 4 60 /D = 0 00004)  |   |
| restror overall effect. $Z = 4.00  (F \le 0.00001)$  |   |
|  | I I   |
|  |   |
|  | -4 -2 0 2   |

#### Chronic anxiety (RCMAS)



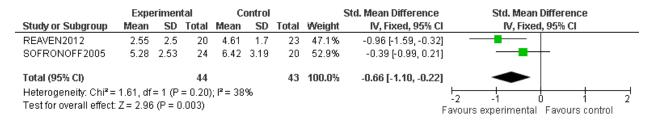
#### Social anxiety (ADIS-P or SCAS-P; post-treatment)



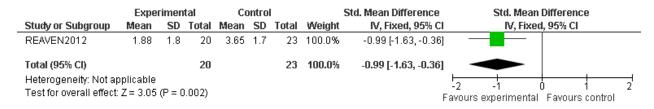
#### Separation anxiety (ADIS-P or SCAS-P; post-treatment)



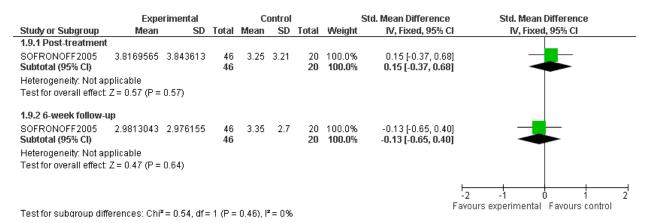
#### Generalized Anxiety Disorder (ADIS-P or SCAS-P; post-treatment)



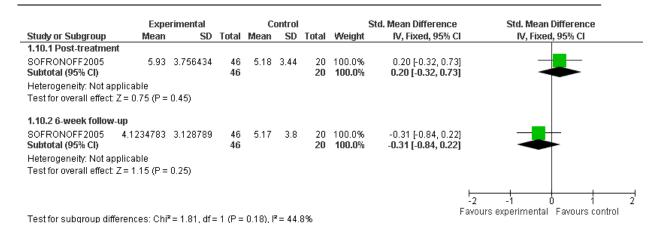
#### Anxiety relating to a specific phobia (ADIS-P)



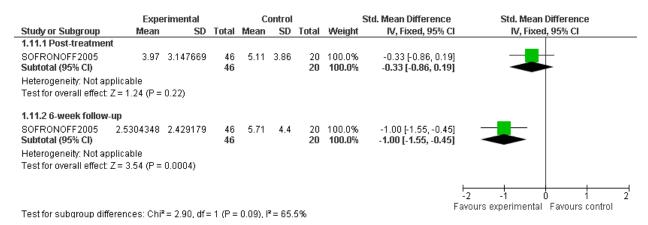
#### Panic (SCAS-P; child-only and child and parent combined)



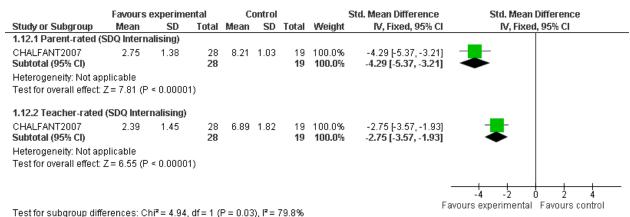
Fear of personal injury (SCAS-P; child-only and child and parent combined)



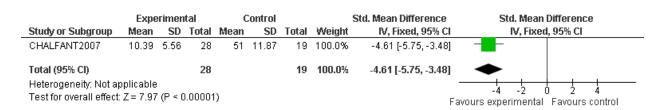
#### OCD (SCAS-P; child-only and child and parent combined)



#### **Emotional symptoms**



#### Self-directed negative thoughts (CATS: internalising)



#### Outward-directed negative thoughts (CATS: Hostile Intent)

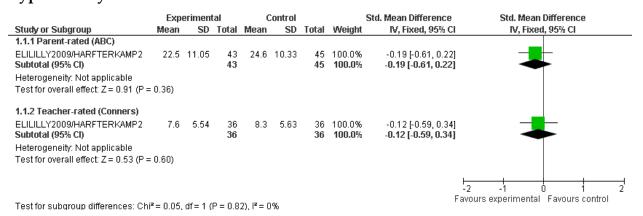
|  | Ехре | erimen | tal   | C     | ontrol |       |        | Std. Mean Difference | St                   | d. Mean Differe         | ence        |   |
|--|------|--------|-------|-------|--------|-------|--------|----------------------|----------------------|-------------------------|-------------|---|
| Study or Subgroup                                | Mean | SD     | Total | Mean  | SD     | Total | Weight | IV, Fixed, 95% CI    |                      | IV, Fixed, 95%          | CI          |   |
| CHALFANT2007                                     | 9.54 | 5.64   | 28    | 11.37 | 5.25   | 19    | 100.0% | -0.33 [-0.91, 0.26]  | -                    |                         |             |   |
| Total (95% CI)                                   |      |        | 28    |       |        | 19    | 100.0% | -0.33 [-0.91, 0.26]  |                      |                         |             |   |
| Heterogeneity: Not ap<br>Test for overall effect |      |        | ).27) |       |        |       |        | F                    | -2 -1<br>avours expe | U<br>O<br>rimental Favo | urs control | 2 |

# 1.26PHARMACOLOGICAL INTERVENTIONS AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

#### 1.26.1 SNRIs for ADHD as a direct outcome

Atomoxetine versus placebo for ADHD as a direct outcome

#### Hyperactivity



#### **ADHD symptoms**

|  | Exp    | eriment | al    | C    | ontrol |       |        | Std. Mean Difference | Std. Mean Difference              |
|--|--------|---------|-------|------|--------|-------|--------|----------------------|-----------------------------------|
| Study or Subgroup                      | Mean   | SD      | Total | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                 |
| 1.2.1 Parent-rated (DSM-IV rating      | scale) |         |       |      |        |       |        |                      |                                   |
| ELILILLY2009/HARFTERKAMP2              | 32.3   | 10.97   | 43    | 37.3 | 9.57   | 47    | 100.0% | -0.48 [-0.90, -0.06] | <b>—</b>                          |
| Subtotal (95% CI)                      |        |         | 43    |      |        | 47    | 100.0% | -0.48 [-0.90, -0.06] | •                                 |
| Heterogeneity: Not applicable          |        |         |       |      |        |       |        |                      |                                   |
| Test for overall effect: Z = 2.26 (P = | 0.02)  |         |       |      |        |       |        |                      |                                   |
| 1.2.2 Teacher-rated (Conners)          |        |         |       |      |        |       |        |                      |                                   |
| ELILILLY2009/HARFTERKAMP2              | 15.8   | 9.85    | 36    | 17.2 | 8.69   | 36    | 100.0% | -0.15 [-0.61, 0.31]  | <b>—</b>                          |
| Subtotal (95% CI)                      |        |         | 36    |      |        | 36    | 100.0% | -0.15 [-0.61, 0.31]  | -                                 |
| Heterogeneity: Not applicable          |        |         |       |      |        |       |        |                      |                                   |
| Test for overall effect: Z = 0.63 (P = | 0.53)  |         |       |      |        |       |        |                      |                                   |
|  |        |         |       |      |        |       |        |                      |                                   |
|  |        |         |       |      |        |       |        | ⊢<br>-2              | -1 1                              |
|  |        |         |       |      |        |       |        | -                    | ours experimental Favours control |

Test for subgroup differences:  $Chi^2 = 1.10$ , df = 1 (P = 0.29),  $I^2 = 8.9\%$ 

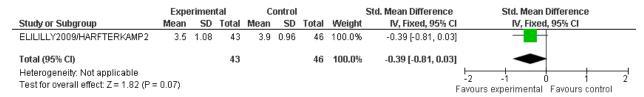
#### **Inattention (Conners)**

|   | Expe  | erimen | tal   | C    | ontrol |       |        | Std. Mean Difference |                  | Std. Me            | an Differ      | ence     |       |
|---|-------|--------|-------|------|--------|-------|--------|----------------------|------------------|--------------------|----------------|----------|-------|
| Study or Subgroup   | Mean  | SD     | Total | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    |                  | IV, Fi             | xed, 95%       | CI       |       |
| ELILILLY2009/HARFTERKAMP2   | 6.1   | 4.56   | 34    | 4.6  | 3.53   | 36    | 100.0% | 0.37 [-0.11, 0.84]   |                  |                    | +              | _        |       |
| Total (95% CI)  |       |        | 34    |      |        | 36    | 100.0% | 0.37 [-0.11, 0.84]   |                  |                    |                | <b>-</b> |       |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.51 (P = | 0.13) |        |       |      |        |       |        | F                    | -2<br>avours ext | +<br>-1<br>perimer | 0<br>ntal Favo | urs cor  | ntrol |

#### **Oppositional (Conners)**

|   | Expe  | rimen | tal   | C    | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                            |
|---|-------|-------|-------|------|--------|-------|--------|----------------------|---|
| Study or Subgroup   | Mean  | SD    | Total | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                               |
| ELILILLY2009/HARFTERKAMP2   | 3.8   | 4.43  | 36    | 3.4  | 3.35   | 36    | 100.0% | 0.10 [-0.36, 0.56]   | -   |
| Total (95% CI)  |       |       | 36    |      |        | 36    | 100.0% | 0.10 [-0.36, 0.56]   | <b>*</b>  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.43 (P = | 0.67) |       |       |      |        |       |        | F                    | -2 -1 0 1 2 avours experimental Favours control |

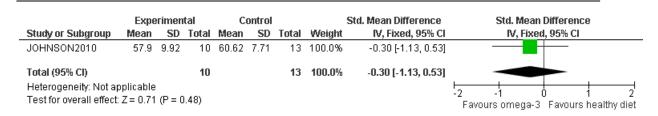
#### Improvement in ADHD symptoms (CGI-ADHD-I)



# 1.27BIOMEDICAL INTERVENTIONS AIMED AT COEXISTING MENTAL HEALTH PROBLEMS

#### 1.27.1 Nutritional interventions for ADHD as an indirect outcome

Omega-3 fatty acids versus healthy diet control for ADHD as an indirect outcome

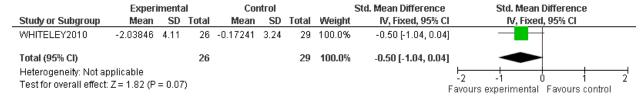


### Gluten-free and casein-free diet versus treatment-as-usual for ADHD as an indirect outcome

#### Inattention (change score; ADHD-IV)

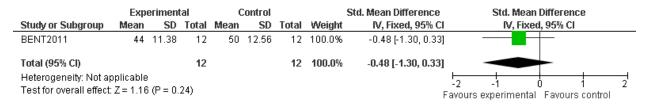
|   | Ехрегі   | imenta | il    | Cor     | ntrol |       |        | Std. Mean Difference | 5                   | Std. Mean             | Difference        |        |
|---|----------|--------|-------|---------|-------|-------|--------|----------------------|---------------------|-----------------------|-------------------|--------|
| Study or Subgroup                                 | Mean     | SD     | Total | Mean    | SD    | Total | Weight | IV, Fixed, 95% CI    |                     | IV, Fixed             | I, 95% CI         |        |
| WHITELEY2010                                      | -2.15385 | 4.67   | 26    | 0.31034 | 3.52  | 29    | 100.0% | -0.59 [-1.13, -0.05] | _                   |                       |                   |        |
| Total (95% CI)                                    |          |        | 26    |         |       | 29    | 100.0% | -0.59 [-1.13, -0.05] | -                   | <b>~</b>              |                   |        |
| Heterogeneity: Not ap<br>Test for overall effect: | •        | = 0.03 | )     |         |       |       |        | F                    | -2 -<br>Favours exp | l<br>1 (<br>erimental | ) 1<br>Favours co | ontrol |

#### Hyperactivity (change score; ADHD-IV)

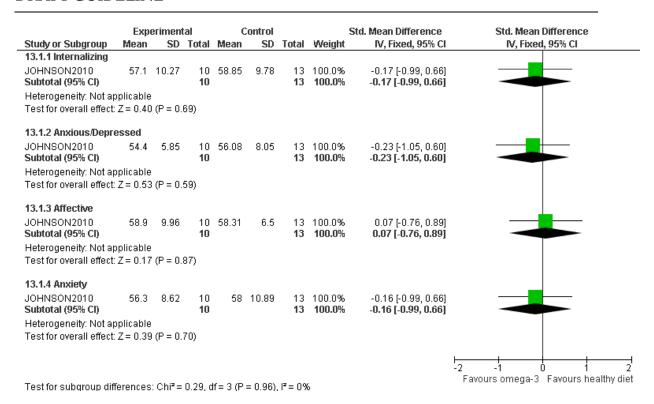


#### 1.27.2 Nutritional interventions for anxiety as an indirect outcome

#### Omega-3 fatty acids versus placebo for anxiety as an indirect outcome

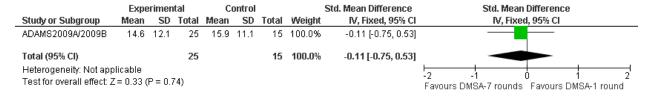


### Omega-3 fatty acids versus healthy diet control for anxiety as an indirect outcome



#### 1.27.3 Medical procedures for anxiety as an indirect outcome

Long-term chelation (7-rounds of DMSA therapy) versus short-term chelation (1-round of DMSA therapy and 6-rounds of placebo) for anxiety as an indirect outcome



# 1.28PSYCHOSOCIAL AND PHARMACOLOGICAL INTERVENTIONS AIMED AT COEXISTING MEDICAL OR FUNCTIONAL PROBLEMS

## 1.28.1 Cognitive-behavioural interventions for sleep problems as a direct outcome

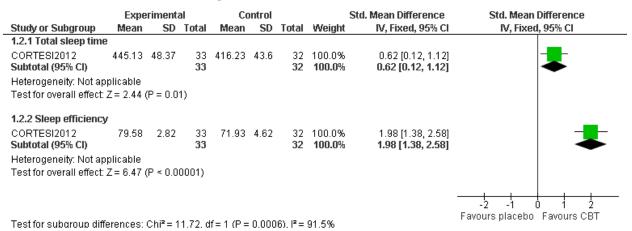
CBT versus placebo for sleep problems as a direct outcome

Sleep problems (actigraph)

|                         | F.m.        |          | ial.   | ,        | antral  |         |        | Ctd Maan Difference  | Ctd Maan Difference          |
|-------------------------|-------------|----------|--------|----------|---------|---------|--------|----------------------|------------------------------|
| Ot 1 O 1                | -           | eriment  |        |          | control | T-4-1   |        | Std. Mean Difference | Std. Mean Difference         |
| Study or Subgroup       | Mean        | SD       | Total  | Mean     | SD      | Total   | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI            |
| 1.1.1 Sleep onset la    | -           |          |        |          |         |         |        |                      | _                            |
| CORTESI2012             | 59.13       | 27.6     | 33     | 79.6     | 31.85   | 32      |        |                      |                              |
| Subtotal (95% CI)       |             |          | 33     |          |         | 32      | 100.0% | -0.68 [-1.18, -0.18] | -                            |
| Heterogeneity: Not a    | pplicable   |          |        |          |         |         |        |                      |                              |
| Test for overall effect | t: Z = 2.66 | (P = 0.  | 008)   |          |         |         |        |                      |                              |
| 1.1.2 Wake after sle    | ep onset    | :        |        |          |         |         |        |                      |                              |
| CORTESI2012             | 61.17       |          | 33     | 70.15    | 42.76   | 32      | 100.0% | -0.24 [-0.73, 0.24]  | <b>——</b>                    |
| Subtotal (95% CI)       |             |          | 33     |          |         | 32      |        |                      | <b>-</b>                     |
| Heterogeneity: Not a    | pplicable   |          |        |          |         |         |        |                      |                              |
| Test for overall effect |             |          | 33)    |          |         |         |        |                      |                              |
|                         |             |          |        |          |         |         |        |                      |                              |
| 1.1.3 Nap time          |             |          |        |          |         |         |        |                      |                              |
| CORTESI2012             | 12.29       | 24.24    | 33     | 36.1     | 33.2    | 32      | 100.0% | -0.81 [-1.32, -0.30] | <b></b> _                    |
| Subtotal (95% CI)       |             |          | 33     |          |         | 32      | 100.0% | -0.81 [-1.32, -0.30] | <b>◆</b>                     |
| Heterogeneity: Not a    | pplicable   |          |        |          |         |         |        |                      |                              |
| Test for overall effect | t: Z = 3.14 | (P = 0.  | 002)   |          |         |         |        |                      |                              |
|                         |             |          |        |          |         |         |        |                      |                              |
| 1.1.4 Bedtime           |             |          |        |          |         |         |        |                      |                              |
| CORTESI2012             | 22.55       | 1.01     | 33     | 23.51    | 1.12    | 32      |        |                      |                              |
| Subtotal (95% CI)       |             |          | 33     |          |         | 32      | 100.0% | -0.89 [-1.40, -0.38] | <b>◆</b>                     |
| Heterogeneity: Not a    | pplicable   |          |        |          |         |         |        |                      |                              |
| Test for overall effect | t: Z = 3.41 | (P = 0.  | 0006)  |          |         |         |        |                      |                              |
|                         |             |          |        |          |         |         |        |                      |                              |
|                         |             |          |        |          |         |         |        | H                    | 2 -1 1 1                     |
|                         |             |          |        |          |         |         |        | -                    | Favours CBT Favours placeb   |
| Test for subaroup di    | fferences   | : Chi² = | 3 91 6 | f= 3 (P) | = 0.27) | 12 = 23 | 3%     |                      | 1 around OD1 1 around places |

Test for subgroup differences:  $Chi^2 = 3.91$ , df = 3 (P = 0.27),  $I^2 = 23.3\%$ 

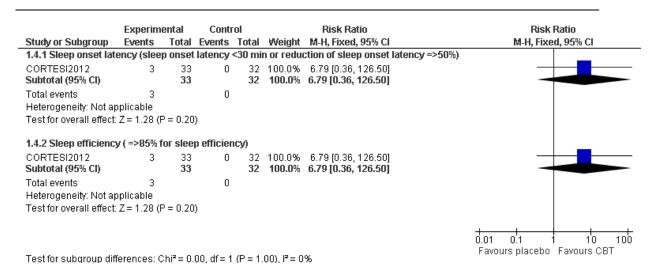
#### Positive sleep behaviour (actigraph)



#### Sleep problems (Childrens Sleep Habits Questionnaire)

| Study or Subgroup   | Expe<br>Mean | rimen<br>SD |                 | Co<br>Mean | ontrol<br>SD | Total           | Weight                   | Std. Mean Difference<br>IV, Fixed, 95% CI                    | Std. Mean Difference<br>IV, Fixed, 95% CI |
|---|--------------|-------------|-----------------|------------|--------------|-----------------|--------------------------|--|---|
| 1.3.1 Total score   | INICALI      | 30          | rotal           | wealt      | 30           | rotal           | rreignt                  | 1v, 11AGG, 33/8 CI   | 19,11AGU, 33/8 GI                         |
| CORTESI2012<br>Subtotal (95% CI)                          | 60.06        | 4.71        | 33<br><b>33</b> | 64.8       | 4.52         | 32<br><b>32</b> | 100.0%<br><b>100.0</b> % | -1.01 [-1.53, -0.50]<br>- <b>1.01 [-1.53, -0.50</b> ]        | <b>-</b>                                  |
| Heterogeneity: Not ap<br>Fest for overall effect:         |              |             | .0001)          |            |              |                 |                          |  |   |
| 1.3.2 Bed resistance                                      |              |             |                 |            |              |                 |                          |  |   |
| CORTESI2012<br>Subtotal (95% CI)                          | 11.62        | 2.22        | 33<br><b>33</b> | 14.1       | 1.93         |                 | 100.0%<br><b>100.0</b> % | -1.18 [-1.71, -0.65]<br>- <b>1.18 [-1.71, -0.65]</b>         | <b>-</b>                                  |
| Heterogeneity: Not ap<br>Fest for overall effect:         | •            |             | .0001)          |            |              |                 |                          |  |   |
| .3.3 Sleep onset del                                      | av           |             |                 |            |              |                 |                          |  |   |
| CORTESI2012<br>Subtotal (95% CI)                          | _            | 0.57        | 33<br><b>33</b> | 2.93       | 0.25         |                 | 100.0%<br><b>100.0</b> % | -0.94 [-1.45, -0.42]<br>- <b>0.94 [-1.45, -0.42</b> ]        | -   |
| Heterogeneity: Not ap<br>Fest for overall effect:         |              |             | .0003)          |            |              |                 |                          |  |   |
| 1.3.4 Sleep anxiety                                       |              |             |                 |            |              |                 |                          |  |   |
| CORTESI2012<br>Subtotal (95% CI)                          | 7.17         | 1.48        | 33<br><b>33</b> | 7.93       | 1.99         |                 | 100.0%<br><b>100.0</b> % | -0.43 [-0.92, 0.06]<br>- <b>0.43 [-0.92, 0.06]</b>           |   |
| Heterogeneity: Not ap<br>Fest for overall effect:         |              |             | .09)            |            |              |                 |                          |  |   |
| I.3.5 Night-wakings                                       |              |             |                 |            |              |                 |                          |  |   |
| CORTESI2012<br>Subtotal (95% CI)                          | 7.06         | 1.06        | 33<br><b>33</b> | 7.86       | 0.81         |                 | 100.0%<br><b>100.0</b> % | -0.84 [-1.34, -0.33]<br>- <b>0.84 [-1.34, -0.33</b> ]        | <b>-</b>                                  |
| Heterogeneity: Not ap<br>Fest for overall effect:         | •            | (P = 0      |                 |            |              |                 |                          |  |   |
| 1.3.6 Sleep duration                                      |              |             |                 |            |              |                 |                          |  |   |
| CORTESI2012<br>Subtotal (95% CI)                          | 6.68         | 1.16        | 33<br><b>33</b> | 6.4        | 1.29         |                 | 100.0%<br><b>100.0</b> % | 0.23 [-0.26, 0.71]<br><b>0.23 [-0.26, 0.71]</b>              |   |
| Heterogeneity: Not ap<br>Fest for overall effect:         |              |             | .36)            |            |              |                 |                          |  |   |
| I.3.7 Parasomnias   |              |             |                 |            |              |                 |                          |  |   |
| CORTESI2012<br>Subtotal (95% CI)                          | 9.82         | 2.25        | 33<br><b>33</b> | 9.16       | 1.53         |                 | 100.0%<br><b>100.0</b> % | 0.34 [-0.15, 0.83]<br><b>0.34 [-0.15, 0.83</b> ]             |   |
| Heterogeneity: Not ap<br>Fest for overall effect:         |              |             | .18)            |            |              |                 |                          |  |   |
| l 2 0 Cloop dioord  | od brood     | hine        | -               |            |              |                 |                          |  |   |
| 1.3.8 Sleep disordere<br>CORTES 2012<br>Subtotal (95% Cl) |              | 0.41        | 33<br><b>33</b> | 3.2        | 0.44         |                 | 100.0%<br><b>100.0</b> % | 0.00 [-0.49, 0.49]<br><b>0.00 [-0.49, 0.49]</b>              | <u> </u>                                  |
| Heterogeneity: Not ap                                     |              |             |                 |            |              | JZ              | 100.070                  | 0.00 [-0.49, 0.49]   |   |
| Test for overall effect:                                  | ∠= 0.00      | (F = 1      | .00)            |            |              |                 |                          |  |   |
| .3.9 Daytime sleepin                                      |              |             |                 |            |              |                 |                          |  | _   |
| CORTESI2012<br>Subtotal (95% CI)                          | 11.96        |             | 33<br><b>33</b> | 12.96      | 1.97         |                 | 100.0%<br><b>100.0</b> % | -0.50 [-1.00, -0.01]<br>- <b>0.50 [-1.00,</b> - <b>0.01]</b> | -   |
| Heterogeneity: Not ap<br>Fest for overall effect:         | -            |             | .05)            |            |              |                 |                          |  |   |
|   |              |             |                 |            |              |                 |                          |  | -2 -1 0 1                                 |
|   |              |             |                 |            |              |                 |                          |  | -2 -1 0 1                                 |

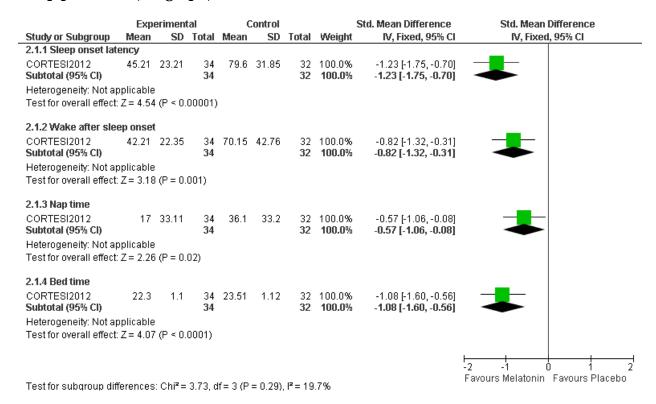
#### Positive treatment response



#### 1.28.2 Melatonin for sleep problems as a direct outcome

Melatonin versus placebo for sleep problems as a direct outcome

#### Sleep problems (actigraph)



#### Positive sleep behaviour (actigraph)

|                                  | Exp        | eriment | tal             | Co     | ntrol |                 |                          | Std. Mean Difference                          | Std. Mean Difference |  |
|----------------------------------|------------|---------|-----------------|--------|-------|-----------------|--------------------------|---|----------------------|--|
| Study or Subgroup                | Mean       | SD      | Total           | Mean   | SD    | Total           | Weight                   | IV, Fixed, 95% CI                             | IV, Fixed, 95% CI    |  |
| 2.2.1 Total sleep tim            | ie         |         |                 |        |       |                 |                          |   |                      |  |
| CORTESI2012<br>Subtotal (95% CI) | 481.1      | 45.07   | 34<br><b>34</b> | 416.23 | 43.6  | 32<br><b>32</b> | 100.0%<br><b>100.0</b> % | 1.45 [0.90, 1.99]<br><b>1.45 [0.90, 1.99]</b> |                      |  |
| Heterogeneity: Not a             | pplicable  |         |                 |        |       |                 |                          |   |                      |  |
| Test for overall effect          | . Z = 5.19 | (P < 0. | 00001)          |        |       |                 |                          |   |                      |  |
| 2.2.2 Sleep efficiend            | у          |         |                 |        |       |                 |                          |   | _                    |  |
| CORTESI2012<br>Subtotal (95% CI) | 82.71      | 4       | 34<br><b>34</b> | 71.93  | 4.62  | 32<br><b>32</b> | 100.0%<br><b>100.0</b> % | 2.47 [1.82, 3.12]<br>2.47 [1.82, 3.12]        | 👢                    |  |
| Heterogeneity: Not a             | pplicable  |         |                 |        |       |                 |                          |   |                      |  |
| Test for overall effect          |            |         | 00001)          |        |       |                 |                          |   |                      |  |
|                                  |            | •       | ,               |        |       |                 |                          |   |                      |  |
|                                  |            |         |                 |        |       |                 |                          | <u> </u>                                      | 4 -2 0 3             |  |
|                                  |            |         |                 |        |       |                 |                          |   |                      |  |

Sleep problems (Children's Sleep Habits Questionnaire)

|   | Expe     | rimen  |                 |       | ontrol |       | ,                        | Std. Mean Difference                                  | Std. Mean Difference |
|---|----------|--------|-----------------|-------|--------|-------|--------------------------|---|----------------------|
| Study or Subgroup                                   | Mean     | SD     | Total           | Mean  | SD     | Total | Weight                   | IV, Fixed, 95% CI                                     | IV, Fixed, 95% CI    |
| 2.3.1 Total score                                   | E4 70    | 0.00   | ٠.              | 040   | 4.50   |       | 400.00                   | 4.04.10.00 4.00                                       |                      |
| CORTESI2012<br>Subtotal (95% CI)                    | 54.78    | 6.22   | 34<br><b>34</b> | 64.8  | 4.52   |       | 100.0%<br><b>100.0</b> % | -1.81 [-2.39, -1.23]<br>- <b>1.81 [-2.39, -1.23]</b>  | •                    |
| Heterogeneity: Not ap<br>Test for overall effect: . |          | (P < 0 | .00001          | )     |        |       |                          |   |                      |
| 2.3.2 Bed resistance                                |          |        |                 |       |        |       |                          |   |                      |
| CORTESI2012<br>Subtotal (95% CI)                    | 10.5     | 2.2    | 34<br><b>34</b> | 14.1  | 1.93   |       | 100.0%<br><b>100.0</b> % | -1.72 [-2.29, -1.15]<br>- <b>1.72 [-2.29, -1.15</b> ] | <b>.</b>             |
| Heterogeneity: Not ap<br>Test for overall effect: . |          | (P < 0 | .00001          | )     |        |       |                          |   |                      |
| .3.3 Sleep onset dela                               | ay       |        |                 |       |        |       |                          |   |                      |
| CORTESI2012<br>Subtotal (95% CI)                    | 2.1      | 0.68   | 34<br><b>34</b> | 2.93  | 0.25   |       | 100.0%<br><b>100.0</b> % | -1.58 [-2.14, -1.03]<br>- <b>1.58 [-2.14, -1.03</b> ] | <b>.</b>             |
| Heterogeneity: Not ap<br>Test for overall effect: . |          | (P < 0 | .00001          | )     |        |       |                          | ,   |                      |
| 2.3.4 Sleep anxiety                                 |          |        |                 |       |        |       |                          |   |                      |
| CORTESI2012<br>Subtotal (95% CI)                    | 7.21     | 1.87   | 34<br><b>34</b> | 7.93  | 1.99   |       | 100.0%<br><b>100.0</b> % | -0.37 [-0.86, 0.12]<br>- <b>0.37 [-0.86, 0.12]</b>    |                      |
| Heterogeneity: Not ap<br>Test for overall effect: . |          | (P = 0 |                 |       |        | -     |                          | 5.5. [ 0.00, 0.12]                                    |                      |
| .3.5 Night-wakings                                  |          |        |                 |       |        |       |                          |   |                      |
| CORTESI2012<br>Subtotal (95% CI)                    | 5.03     | 1.1    | 34<br>34        | 7.86  | 0.81   |       | 100.0%<br><b>100.0</b> % | -2.88 [-3.58, -2.18]<br>- <b>2.88 [-3.58, -2.18]</b>  | <b>±</b>             |
| Heterogeneity: Not ap<br>Test for overall effect: . |          | /P < ∩ |                 | ١     |        | 32    | 100.0%                   | -2.00 [-3.30, -2.10]                                  |                      |
| Cotton overall ellect.                              | 2 - 0.01 | (, . 0 | .00001          | ,     |        |       |                          |   |                      |
| 2.3.6 Sleep duration                                |          |        |                 |       |        |       |                          |   | _                    |
| CORTESI2012<br>Subtotal (95% CI)                    | 4.82     | 0.94   | 34<br><b>34</b> | 6.4   | 1.29   |       | 100.0%<br><b>100.0</b> % | -1.39 [-1.93, -0.85]<br>- <b>1.39 [-1.93, -0.85</b> ] | -                    |
| Heterogeneity: Not ap<br>Test for overall effect: . |          | (P < 0 | .00001          | )     |        |       |                          |   |                      |
| 2.3.7 Parasomnias                                   |          |        |                 |       |        |       |                          |   |                      |
| CORTESI2012<br>Subtotal (95% CI)                    | 9.35     | 1.78   | 34<br><b>34</b> | 9.16  | 1.53   |       | 100.0%<br><b>100.0</b> % | 0.11 [-0.37, 0.60]<br><b>0.11 [-0.37, 0.60</b> ]      | <u> </u>             |
| Heterogeneity: Not ap<br>Test for overall effect: . |          | (P = 0 |                 |       |        | Ű.    | 1001011                  | orr [ olor, oloo]                                     | Ţ                    |
|   |          | `      | ,               |       |        |       |                          |   |                      |
| 2.3.8 Sleep disordere                               |          |        |                 |       |        |       | 400.00                   | 0.44.0 == 0   | <u> </u>             |
| CORTESI2012<br>Subtotal (95% CI)                    | 3.15     | 0.48   | 34<br><b>34</b> | 3.2   | 0.44   |       | 100.0%<br><b>100.0</b> % | -0.11 [-0.59, 0.38]<br>- <b>0.11 [-0.59, 0.38]</b>    | -                    |
| Heterogeneity: Not ap<br>Test for overall effect: . |          | (P = 0 | .66)            |       |        |       |                          |   |                      |
| 2.3.9 Daytime sleepin                               | ess      |        |                 |       |        |       |                          |   |                      |
| CORTESI2012<br>Subtotal (95% CI)                    | 11.39    | 2.34   | 34<br><b>34</b> | 12.96 | 1.97   |       | 100.0%<br><b>100.0</b> % | -0.72 [-1.21, -0.22]<br>- <b>0.72 [-1.21, -0.22]</b>  | -                    |
| Heterogeneity: Not ap<br>Test for overall effect: . |          | (P = 0 | .005)           |       |        |       |                          |   | -                    |
|   |          |        | ,               |       |        |       |                          |   |                      |
|   |          |        |                 |       |        |       |                          |   | -4 -2 0 2            |

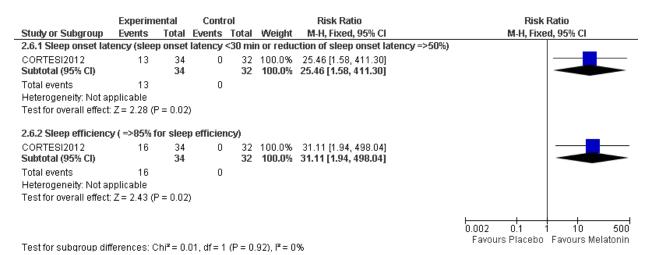
#### Sleep onset latency (sleep diary)

|   | Exp   | erimen | tal   | (    | ontrol |       |        | Std. Mean Difference | Std. Mean                  | Difference         |       |
|---|-------|--------|-------|------|--------|-------|--------|----------------------|----------------------------|--------------------|-------|
| Study or Subgroup                               | Mean  | SD     | Total | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixe                   | d, 95% CI          |       |
| GRINGRAS2012                                    | 47.13 | 44.21  | 25    | 88.6 | 61.45  | 24    | 100.0% | -0.76 [-1.35, -0.18] |                            |                    |       |
| Total (95% CI)                                  |       |        | 25    |      |        | 24    | 100.0% | -0.76 [-1.35, -0.18] | •                          |                    |       |
| Heterogeneity: Not a<br>Test for overall effect |       |        | 010)  |      |        |       |        |                      | -2 -1<br>Favours Melatonin | 0 1<br>Favours Pla | ecebo |

#### Total sleep time (sleep diary)

|   | Experimental |          |       | C      | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                             |
|---|--------------|----------|-------|--------|--------|-------|--------|----------------------|--|
| Study or Subgroup                                 | Mean         | SD       | Total | Mean   | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                |
| GRINGRAS2012                                      | 567.36       | 73.85    | 23    | 556.43 | 73.57  | 24    | 100.0% | 0.15 [-0.43, 0.72]   |  |
| Total (95% CI)                                    |              |          | 23    |        |        | 24    | 100.0% | 0.15 [-0.43, 0.72]   | -  |
| Heterogeneity: Not ap<br>Test for overall effect: |              | (P = 0.6 | 2)    |        |        |       |        |                      | -2 -1 0 1 2<br>Favours Placebo Favours Melatonin |

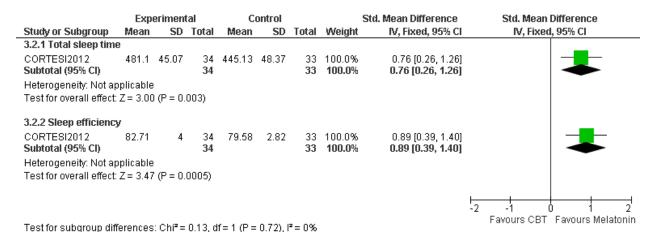
#### Positive treatment response



Melatonin versus CBT for sleep problems as a direct outcome Sleep problems (actigraph)

|                         | Expo     | eriment   |       |       | Control |       |        | Std. Mean Difference | Std. Mean Difference |
|-------------------------|----------|-----------|-------|-------|---------|-------|--------|----------------------|----------------------|
| tudy or Subgroup        | Mean     | SD        | Total | Mean  | SD      | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI    |
| .1.1 Sleep onset late   | ency     |           |       |       |         |       |        |                      |                      |
| ORTESI2012              | 45.21    | 23.21     | 34    | 59.13 | 27.6    | 33    | 100.0% | -0.54 [-1.03, -0.05] | <b>———</b>           |
| ubtotal (95% CI)        |          |           | 34    |       |         | 33    | 100.0% | -0.54 [-1.03, -0.05] | -                    |
| leterogeneity: Not ap   | plicable |           |       |       |         |       |        |                      |                      |
| est for overall effect: | Z = 2.17 | (P = 0.1) | 03)   |       |         |       |        |                      |                      |
| .1.2 Wake after slee    | p onset  |           |       |       |         |       |        |                      |                      |
| ORTESI2012              | 42.21    | 22.35     | 34    | 61.17 | 28.93   | 33    | 100.0% | -0.73 [-1.22, -0.23] | <b>—</b>             |
| ubtotal (95% CI)        |          |           | 34    |       |         | 33    | 100.0% | -0.73 [-1.22, -0.23] | -                    |
| leterogeneity: Not ap   | plicable |           |       |       |         |       |        |                      |                      |
| est for overall effect: | Z = 2.87 | (P = 0.1  | 004)  |       |         |       |        |                      |                      |
| .1.3 Nap time           |          |           |       |       |         |       |        |                      |                      |
| ORTESI2012              | 17       | 33.11     | 34    | 12.29 | 24.24   | 33    | 100.0% | 0.16 [-0.32, 0.64]   | _ <b></b>            |
| ubtotal (95% CI)        |          |           | 34    |       |         | 33    | 100.0% | 0.16 [-0.32, 0.64]   | -                    |
| leterogeneity: Not ap   | plicable |           |       |       |         |       |        |                      |                      |
| est for overall effect: | Z = 0.65 | (P = 0.9) | 51)   |       |         |       |        |                      |                      |
| .1.4 Bed time           |          |           |       |       |         |       |        |                      |                      |
| ORTESI2012              | 22.3     | 1.1       | 34    | 22.55 | 1.01    | 33    | 100.0% | -0.23 [-0.71, 0.25]  | — <b>——</b>          |
| ubtotal (95% CI)        |          |           | 34    |       |         | 33    | 100.0% | -0.23 [-0.71, 0.25]  | -                    |
| leterogeneity: Not ap   | plicable |           |       |       |         |       |        |                      |                      |
| est for overall effect: | Z = 0.95 | (P = 0.3) | 34)   |       |         |       |        |                      |                      |
|                         |          |           |       |       |         |       |        |                      |                      |
|                         |          |           |       |       |         |       |        |                      | -2 -1 1 1            |

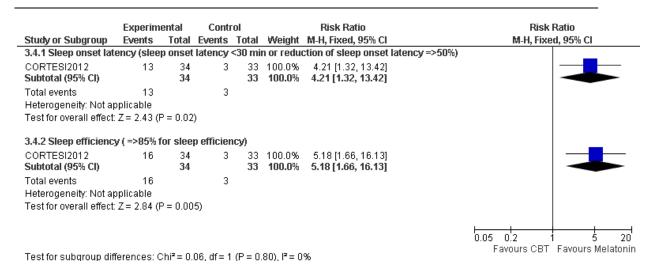
#### Positive sleep behaviour (actigraph)



#### Sleep problems (Children's sleep habits questionnaire)

| Study or Subgroup                                 | Expe<br>Mean | rimen<br>SD |                 | Co<br>Mean | ontrol<br>SD | Total           | Weight                   | Std. Mean Difference<br>IV, Fixed, 95% CI             | Std. Mean Difference<br>IV, Fixed, 95% CI |
|---|--------------|-------------|-----------------|------------|--------------|-----------------|--------------------------|---|---|
| 3.3.1 Total score                                 | weall        | 50          | · o.ui          | modil      | JD           | . o.ui          | Oignt                    | 11,11nou,0070 O                                       | 12,11004,007.01                           |
| ORTESI2012<br>Subtotal (95% CI)                   | 54.78        | 6.22        | 34<br><b>34</b> | 60.06      | 4.71         | 33<br><b>33</b> | 100.0%<br><b>100.0</b> % | -0.94 [-1.45, -0.44]<br>- <b>0.94 [-1.45, -0.44</b> ] | <b>.</b>                                  |
| leterogeneity: Not ap<br>est for overall effect:  |              |             | .0003)          |            |              |                 |                          |   |   |
| 3.3.2 Bed resistance                              | !            |             |                 |            |              |                 |                          |   | _   |
| ORTESI2012<br>Subtotal (95% CI)                   | 10.5         | 2.2         | 34<br><b>34</b> | 11.62      | 2.22         |                 | 100.0%<br><b>100.0</b> % | -0.50 [-0.99, -0.01]<br>- <b>0.50 [-0.99, -0.01]</b>  | -   |
| Heterogeneity: Not ap<br>Test for overall effect: | •            | (P = 0      | .04)            |            |              |                 |                          |   |   |
| 3.3.3 Sleep onset del                             | lay          |             |                 |            |              |                 |                          |   | _   |
| ORTESI2012<br>Subtotal (95% CI)                   | 2.1          | 0.68        | 34<br><b>34</b> | 2.51       | 0.57         |                 | 100.0%<br><b>100.0</b> % | -0.65 [-1.14, -0.15]<br>- <b>0.65 [-1.14, -0.15]</b>  | -   |
| Heterogeneity: Not ap<br>Test for overall effect: | •            | (P = 0      | .01)            |            |              |                 |                          |   |   |
| 3.3.4 Sleep anxiety                               |              |             |                 |            |              |                 |                          |   | $\perp$                                   |
| ORTESI2012<br>Subtotal (95% CI)                   | 7.21         | 1.87        | 34<br><b>34</b> | 7.17       | 1.48         |                 | 100.0%<br><b>100.0</b> % | 0.02 [-0.46, 0.50]<br><b>0.02 [-0.46, 0.50]</b>       | -   |
| Heterogeneity: Not ap<br>Fest for overall effect: |              |             | .92)            |            |              |                 |                          |   |   |
| 3.3.5 Night-wakings                               |              |             |                 |            |              |                 |                          |   |   |
| CORTESI2012<br>Subtotal (95% CI)                  | 5.03         | 1.1         | 34<br><b>34</b> | 7.06       | 1.06         |                 | 100.0%<br><b>100.0</b> % | -1.86 [-2.44, -1.28]<br>- <b>1.86 [-2.44, -1.28</b> ] | <b>+</b>                                  |
| Heterogeneity: Not ap<br>Fest for overall effect: | •            | (P < 0      | .00001          | )          |              |                 |                          | • , •   |   |
| 3.3.6 Sleep duration                              |              |             |                 |            |              |                 |                          |   |   |
| CORTESI2012<br>Subtotal (95% CI)                  | 4.82         | 0.94        | 34<br><b>34</b> | 6.68       | 1.16         |                 | 100.0%<br><b>100.0</b> % | -1.74 [-2.31, -1.18]<br>- <b>1.74 [-2.31, -1.18</b> ] | -   |
| Heterogeneity: Not ap<br>Fest for overall effect: | •            | (P < 0      | .00001          | )          |              |                 |                          |   |   |
| 3.3.7 Parasomnias                                 |              |             |                 |            |              |                 |                          |   |   |
| CORTESI2012<br>Subtotal (95% CI)                  | 9.35         | 1.78        | 34<br><b>34</b> | 9.82       | 2.25         |                 | 100.0%<br><b>100.0</b> % | -0.23 [-0.71, 0.25]<br>- <b>0.23 [-0.71, 0.25]</b>    | <b>±</b>                                  |
| Heterogeneity: Not ap<br>Test for overall effect: | •            |             |                 |            |              |                 |                          | ,   |   |
| 3.3.8 Sleep disorder                              | ed breatl    | hina        |                 |            |              |                 |                          |   |   |
| CORTESI2012<br>Subtotal (95% CI)                  | 3.15         | _           | 34<br><b>34</b> | 3.2        | 0.41         |                 | 100.0%<br><b>100.0</b> % | -0.11 [-0.59, 0.37]<br>- <b>0.11 [-0.59, 0.37</b> ]   | <b>±</b>                                  |
| Heterogeneity: Not ap<br>Fest for overall effect: |              |             |                 |            |              | 00              | .551011                  | 5[ start ata1]  |   |
| 3.3.9 Daytime sleepii                             |              | ,           | •               |            |              |                 |                          |   |   |
| CORTESI2012                                       | 11.39        | 2.34        |                 | 11.96      | 1.97         |                 | 100.0%                   | -0.26 [-0.74, 0.22]                                   | _   |
| Subtotal (95% CI)<br>Heterogeneity: Not ap        |              |             | 34              |            |              | 33              | 100.0%                   | -0.26 [-0.74, 0.22]                                   |   |
| Fest for overall effect:                          | Z=1.06       | (P = 0      | 1.29)           |            |              |                 |                          |   |   |
|   |              |             |                 |            |              |                 |                          |   | -2 -1 0 1                                 |
|   |              |             |                 |            |              |                 | , I² = 84.1              | F   | avours Melatonin Favours (                |

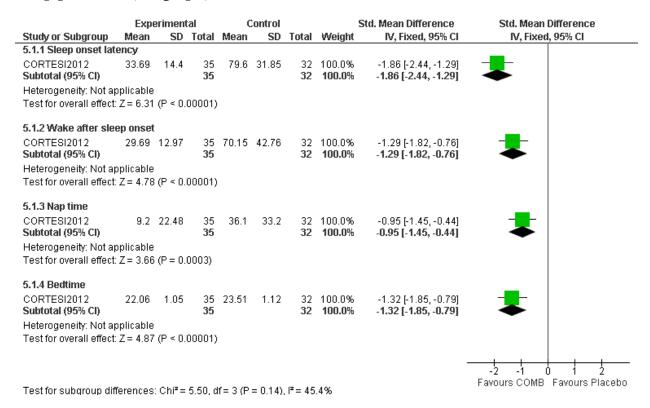
#### Positive treatment response



# 1.28.3 Combined cognitive-behavioural intervention and melatonin for sleep problems as a direct outcome

COMB versus placebo for sleep problems as a direct outcome

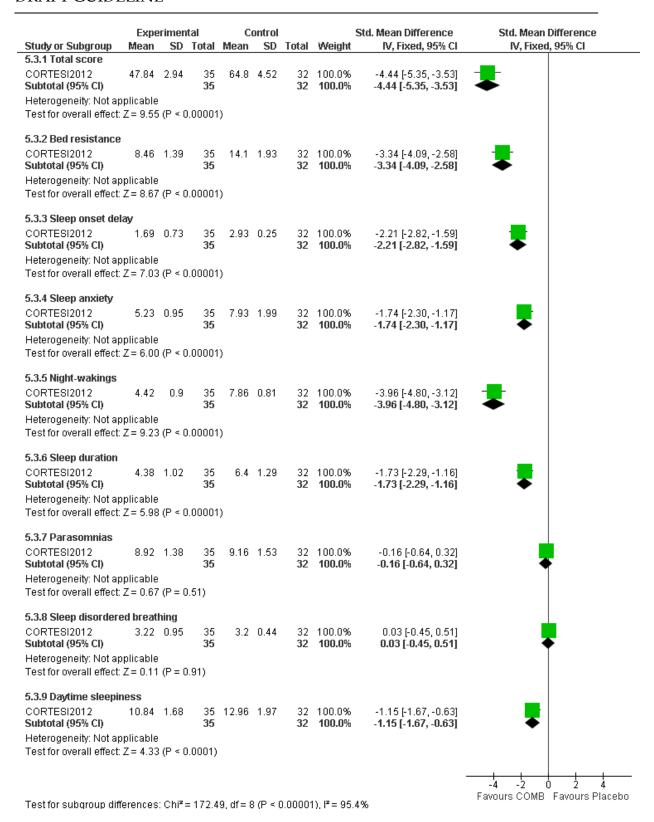
#### Sleep problems (actigraph)



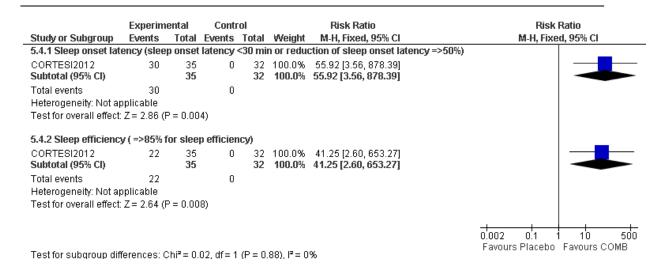
#### Positive sleep behaviour (actigraph)

|                                  | Expe          | riment      | al              | Co          | ntrol    |                 |                          | Std. Mean Difference                          | Std. Mean Difference                             |  |  |
|----------------------------------|---------------|-------------|-----------------|-------------|----------|-----------------|--------------------------|---|--|--|--|
| Study or Subgroup                | Mean          | SD          | Total           | Mean        | SD       | Total           | Weight                   | IV, Fixed, 95% CI                             | IV, Fixe   | d, 95% CI  |  |
| 5.2.1 Total sleep tim            | ie            |             |                 |             |          |                 |                          |   |  |  |  |
| CORTESI2012<br>Subtotal (95% CI) | 505.01        | 31.18       | 35<br><b>35</b> | 416.23      | 43.6     | 32<br><b>32</b> | 100.0%<br><b>100.0</b> % | 2.33 [1.70, 2.96]<br><b>2.33 [1.70, 2.96]</b> |  | -  |  |
| Heterogeneity: Not a             | pplicable     |             |                 |             |          |                 |                          |   |  |  |  |
| Test for overall effect          | t: Z = 7.27 ( | (P < 0.0    | 0001)           |             |          |                 |                          |   |  |  |  |
| 5.2.2 Sleep efficiend            | у             |             |                 |             |          |                 |                          |   |  |  |  |
| CORTESI2012<br>Subtotal (95% CI) | 84.46         | 4.23        | 35<br><b>35</b> | 71.93       | 4.62     | 32<br><b>32</b> | 100.0%<br><b>100.0</b> % | 2.80 [2.12, 3.49]<br><b>2.80 [2.12, 3.49]</b> |  |  |  |
| Heterogeneity: Not a             | pplicable     |             |                 |             |          |                 |                          |   |  |  |  |
| Test for overall effect          |               | (P < 0.0    | 0001)           |             |          |                 |                          |   |  |  |  |
|                                  |               |             | ,               |             |          |                 |                          |   |  |  |  |
|                                  |               |             |                 |             |          |                 |                          |   | <del>                                     </del> | <del>                                     </del> |  |
|                                  |               |             |                 |             |          |                 |                          |   | 7 4  | Favours COMB                                     |  |
| Test for subgroup dit            | fferences:    | $Chi^2 = 0$ | 0.98, df        | = 1 (P = 0) | 0.32), 1 | $r^2 = 0\%$     |                          |   | i avouis i lacebo                                | 1 GYOGIS COMD                                    |  |

#### Sleep problems (Children's sleep habits questionnaire)

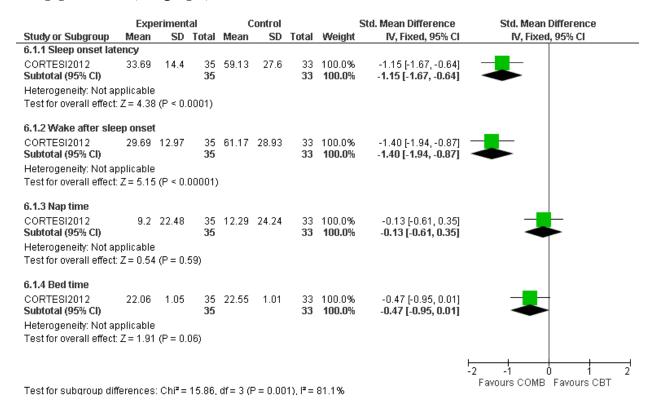


#### Positive treatment response



#### COMB versus CBT-only for sleep problems as a direct outcome

#### Sleep problems (actigraph)



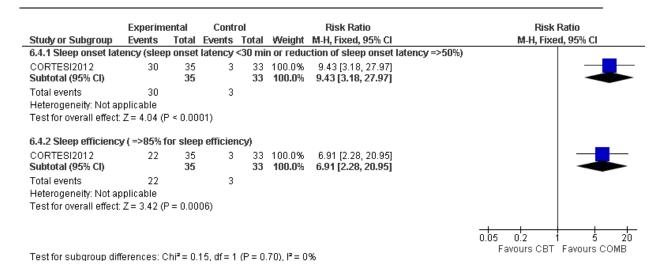
#### Positive sleep behaviour (actigraph)

|  | Expe               | eriment  | al              | C      | ontrol |                 |                          | Std. Mean Difference                          | Std. Mean Difference |
|--|--------------------|----------|-----------------|--------|--------|-----------------|--------------------------|---|----------------------|
| Study or Subgroup  | Mean               | SD       | Total           | Mean   | SD     | Total           | Weight                   | IV, Fixed, 95% CI                             | IV, Fixed, 95% CI    |
| 6.2.1 Total sleep tim                                    | e                  |          |                 |        |        |                 |                          |   |                      |
| CORTESI2012<br>Subtotal (95% CI)                         | 505.01             | 31.18    | 35<br><b>35</b> | 445.13 | 48.37  | 33<br><b>33</b> | 100.0%<br><b>100.0</b> % | 1.46 [0.93, 2.00]<br><b>1.46 [0.93, 2.00]</b> |                      |
| Heterogeneity: Not a                                     | pplicable          |          |                 |        |        |                 |                          |   |                      |
| Test for overall effect                                  | : Z= 5.32 i        | (P < 0.0 | 0001)           |        |        |                 |                          |   |                      |
| 6.2.2 Sleep efficienc                                    | .,                 |          |                 |        |        |                 |                          |   |                      |
|  |                    |          |                 |        |        |                 |                          |   |                      |
|  | -                  |          |                 |        |        |                 |                          |   | _                    |
| CORTESI2012<br>Subtotal (95% CI)                         | 84.46              | 4.23     | 35<br><b>35</b> | 79.58  | 2.82   | 33<br><b>33</b> | 100.0%<br><b>100.0</b> % | 1.33 [0.81, 1.86]<br><b>1.33 [0.81, 1.86]</b> | -                    |
| CORTESI2012<br>Subtotal (95% CI)                         | 84.46              | 4.23     |                 | 79.58  | 2.82   |                 |                          |   | -                    |
| CORTESI2012<br>Subtotal (95% CI)<br>Heterogeneity: Not a | 84.46<br>pplicable |          | 35              | 79.58  | 2.82   |                 |                          |   | <b>‡</b>             |
| CORTESI2012<br>Subtotal (95% CI)                         | 84.46<br>pplicable |          | 35              | 79.58  | 2.82   |                 |                          |   | *                    |
| CORTESI2012<br>Subtotal (95% CI)<br>Heterogeneity: Not a | 84.46<br>pplicable |          | 35              | 79.58  | 2.82   |                 |                          |   | *                    |

Sleep problems (Children's sleep habits questionnaire)

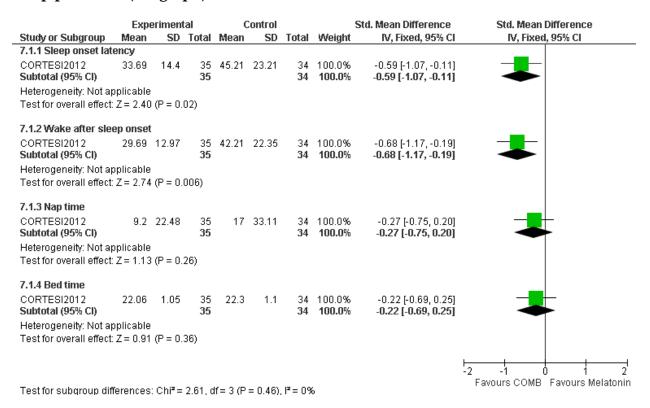
| tude or Cuberous                                  | -          | rimen    |                 |       | ontrol | Total |                          | Std. Mean Difference  | Std. Mean Difference   |
|---|------------|----------|-----------------|-------|--------|-------|--------------------------|---|------------------------|
| Study or Subgroup<br>i.3.1 Total score            | Mean       | 30       | rutai           | Mean  | ЭD     | Total | Weight                   | IV, Fixed, 95% CI   | IV, Fixed, 95% CI      |
| ORTESI2012<br>Subtotal (95% CI)                   | 47.84      | 2.94     | 35<br><b>35</b> | 60.06 | 4.71   |       | 100.0%<br><b>100.0</b> % | -3.10 [-3.81, -2.38]<br>- <b>3.10 [-3.81, -2.38]</b>          | <b>±</b>               |
| Heterogeneity: Not ap<br>Test for overall effect: | •          |          |                 | `     |        | 00    | 1001011                  | 0.10[0.0.1, 2.00]   |                        |
|   |            | ( - > 0  | .00001          | ,     |        |       |                          |   |                        |
| i <b>.3.2 Bed resistance</b><br>CORTESI2012       |            | 1.39     | 35              | 11.62 | 2 22   | 33    | 100.0%                   | -1.70 [-2.26, -1.14]  | _                      |
| Subtotal (95% CI)                                 |            |          | 35              | 11.02 | 2.22   |       | 100.0%                   | -1.70 [-2.26, -1.14]  | •                      |
| leterogeneity: Not ap<br>est for overall effect:  |            |          | .00001          | )     |        |       |                          |   |                        |
| .3.3 Sleep onset de                               | lay        |          |                 |       |        |       |                          |   | _                      |
| ORTESI2012<br>Subtotal (95% CI)                   | 1.69       | 0.73     | 35<br><b>35</b> | 2.51  | 0.57   |       | 100.0%<br><b>100.0</b> % | -1.23 [-1.75, -0.71]<br>- <b>1.23 [-1.75, -0.71</b> ]         |                        |
| leterogeneity: Not ap                             |            |          | 00004           |       |        |       |                          |   |                        |
| est for overall effect:                           | .∠= 4.04   | י(ריינו  | .00001          | ,     |        |       |                          |   |                        |
| :3.4 Sleep anxiety<br>CORTESI2012                 | 5 22       | 0.95     | 35              | 7.17  | 1 // 0 | 22    | 100.0%                   | -1.55 [-2.10, -1.01]  |                        |
| Subtotal (95% CI)                                 |            |          | 35              | 7.17  | 1.40   |       | 100.0%                   | -1.55 [-2.10, -1.01]<br>-1.55 [-2.10, -1.01]                  | ₹                      |
| leterogeneity: Not ap<br>est for overall effect:  | •          |          | .00001          | )     |        |       |                          |   |                        |
| .3.5 Night-wakings                                |            |          |                 |       |        |       |                          |   |                        |
| ORTESI2012<br>Subtotal (95% CI)                   | 4.42       | 0.9      | 35<br><b>35</b> | 7.06  | 1.06   |       | 100.0%<br><b>100.0</b> % | -2.66 [-3.32, -2.00]<br>- <b>2.66 [-3.32, -2.00</b> ]         | <b>1</b>               |
| Heterogeneity: Not ap<br>Test for overall effect: |            |          |                 | ١     |        | 00    | 1001011                  | -2.00 [-0.02, -2.00]  |                        |
|   | . 2 - 1.00 | . (1 - 0 | .00001          | ,     |        |       |                          |   |                        |
| i.3.6 Sleep duration<br>CORTESI2012               | 4 38       | 1.02     | 35              | 6.68  | 1 16   | 33    | 100.0%                   | -2.09 [-2.68, -1.49]  |                        |
| Subtotal (95% CI)                                 |            |          | 35              | 0.00  | 1.10   |       | 100.0%                   | -2.09 [-2.68, -1.49]  | •                      |
| leterogeneity: Not ap<br>est for overall effect:  | •          |          | .00001          | )     |        |       |                          |   |                        |
| .3.7 Parasomnias                                  |            |          |                 |       |        |       |                          |   |                        |
| ORTESI2012<br>Subtotal (95% CI)                   | 8.92       | 1.38     | 35<br><b>35</b> | 9.82  | 2.25   |       | 100.0%<br><b>100.0</b> % | -0.48 [-0.96, 0.00]<br>- <b>0.48 [-0.96, 0.00]</b>            | <b>.</b>               |
| leterogeneity: Not ap                             |            |          |                 |       |        |       |                          |   | -                      |
| est for overall effect:                           | : Z= 1.95  | (P=0     | .05)            |       |        |       |                          |   |                        |
| .3.8 Sleep disorder                               |            | _        | 0.5             |       | 0.44   |       | 400.00                   | 0.001.045.050   | <u> </u>               |
| ORTESI2012<br>Subtotal (95% CI)                   | 3.22       | 0.95     | 35<br><b>35</b> | 3.2   | 0.41   |       | 100.0%<br><b>100.0</b> % | 0.03 [-0.45, 0.50]<br><b>0.03 [-0.45, 0.50]</b>               | -                      |
| Heterogeneity: Not ap<br>Test for overall effect: |            |          | .91)            |       |        |       |                          |   |                        |
| i.3.9 Daytime sleepii                             | ness       |          |                 |       |        |       |                          |   |                        |
| ORTESI2012<br>Subtotal (95% CI)                   | 10.84      | 1.68     | 35<br><b>35</b> | 11.96 | 1.97   |       | 100.0%<br><b>100.0</b> % | -0.61 [-1.09, -0.12]<br>- <b>0.61 [-1.09</b> , - <b>0.12]</b> |                        |
| leterogeneity: Not ap                             |            |          |                 |       |        | 55    | 1001011                  | 5.5.[ 1.00, -0.12]  | •                      |
| est for overall effect:                           | : Z= 2.44  | (P=0     | .01)            |       |        |       |                          |   |                        |
|   |            |          |                 |       |        |       |                          |   | -4 -2 0 2              |
|   |            |          |                 |       |        |       |                          |   | Favours COMB Favours C |

#### Positive treatment response



### COMB versus melatonin-only for sleep problems as a direct outcome

#### Sleep problems (actigraph)



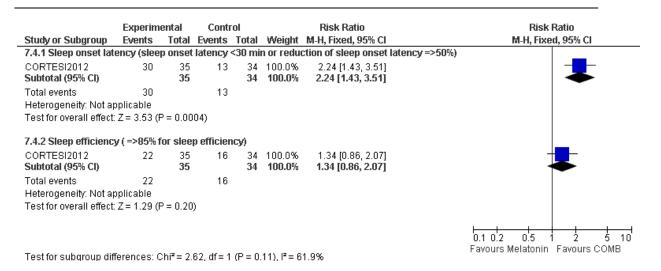
#### Positive sleep behaviour (actigraph)

|                                  |          | rimenta           | 31              |       | Control |                 | ;                        | Std. Mean Difference                            | Std. Mean Difference                  |  |  |
|----------------------------------|----------|-------------------|-----------------|-------|---------|-----------------|--------------------------|---|---------------------------------------|--|--|
| Study or Subgroup                | Mean     | SD                | Total           | Mean  | SD      | Total           | Weight                   | IV, Fixed, 95% CI                               | IV, Fixed, 95% CI                     |  |  |
| 7.2.1 Total sleep time           |          |                   |                 |       |         |                 |                          |   |                                       |  |  |
| CORTESI2012<br>Subtotal (95% CI) | 505.01   | 31.18             | 35<br><b>35</b> | 481.1 | 45.07   | 34<br><b>34</b> | 100.0%<br><b>100.0</b> % | 0.61 [0.13, 1.10]<br><b>0.61 [0.13, 1.10]</b>   | -                                     |  |  |
| Heterogeneity: Not appl          | licable  |                   |                 |       |         |                 |                          |   |                                       |  |  |
| Test for overall effect: Z       | = 2.48 ( | $P = 0.0^{\circ}$ | 1)              |       |         |                 |                          |   |                                       |  |  |
| 7.2.2 Sleep efficiency           |          |                   |                 |       |         |                 |                          |   | _                                     |  |  |
| CORTESI2012<br>Subtotal (95% CI) | 84.46    | 4.23              | 35<br><b>35</b> | 82.71 | 4       | 34<br><b>34</b> | 100.0%<br><b>100.0</b> % | 0.42 [-0.06, 0.90]<br><b>0.42 [-0.06, 0.90]</b> | -                                     |  |  |
| Heterogeneity: Not appl          |          | (D. 0.0)          | 0)              |       |         |                 |                          |   |                                       |  |  |
| Test for overall effect: Z       | = 1.72 ( | ,P = 0.08         | 8)              |       |         |                 |                          |   |                                       |  |  |
|                                  |          |                   |                 |       |         |                 |                          | 1   | · · · · · · · · · · · · · · · · · · · |  |  |
|                                  |          |                   |                 |       |         |                 |                          |   | -2 -1 0 1                             |  |  |

Sleep problems (Children's sleep habits questionnaire)

| tudy or Subgroup                                       | Expe<br>Mean | rimen<br>SD | tal<br>Total    |       | ontrol<br>SD | Total           |                          | Std. Mean Difference<br>IV, Fixed, 95% CI                     | Std. Mean Difference<br>IV. Fixed, 95% CI |
|--|--------------|-------------|-----------------|-------|--------------|-----------------|--------------------------|---|---|
| .3.1 Total score                                       | wean         | 30          | rotal           | Medil | JU           | rotal           | rreignt                  | iv, i incu, 33/8 Cl   | 17, 1760, 53/II CI                        |
| ORTESI2012<br>Subtotal (95% CI)                        | 47.84        | 2.94        | 35<br><b>35</b> | 54.78 | 6.22         | 34<br><b>34</b> | 100.0%<br><b>100.0</b> % | -1.42 [-1.95, -0.89]<br>- <b>1.42 [-1.95, -0.89</b> ]         | <b>+</b>                                  |
| leterogeneity: Not ap<br>est for overall effect:       | •            |             | .00001          | )     |              |                 |                          |   |   |
| .3.2 Bed resistance                                    |              |             |                 |       |              |                 |                          |   |   |
| ORTESI2012<br>Subtotal (95% CI)                        | 8.46         | 1.39        | 35<br><b>35</b> | 10.5  | 2.2          |                 | 100.0%<br><b>100.0</b> % | -1.10 [-1.61, -0.59]<br>- <b>1.10 [-1.61,</b> - <b>0.59</b> ] | -   |
| Heterogeneity: Not ap<br>Test for overall effect:      |              |             | .0001)          |       |              |                 |                          |   |   |
| .3.3 Sleep onset del                                   | av           |             |                 |       |              |                 |                          |   |   |
| ORTESI2012<br>Subtotal (95% CI)                        | _            | 0.73        | 35<br><b>35</b> | 2.1   | 0.68         |                 | 100.0%<br><b>100.0</b> % | -0.57 [-1.06, -0.09]<br>- <b>0.57 [-1.06, -0.09</b> ]         | -   |
| Heterogeneity: Not ap<br>Test for overall effect:      | •            |             | .02)            |       |              |                 |                          |   |   |
| 3.4 Sleep anxiety                                      |              |             |                 |       |              |                 |                          |   |   |
| ORTESI2012<br>Subtotal (95% CI)                        | 5.23         | 0.95        | 35<br><b>35</b> | 7.21  | 1.87         |                 | 100.0%<br><b>100.0</b> % | -1.33 [-1.85, -0.80]<br>- <b>1.33 [-1.85, -0.80</b> ]         | <b>-</b>                                  |
| Heterogeneity: Not ap<br>Test for overall effect:      | •            |             |                 | )     |              |                 |                          | . ,   |   |
|  |              | , -         |                 | -     |              |                 |                          |   |   |
| :3.5 Night-wakings<br>CORTESI2012<br>Subtotal (95% CI) | 4.42         | 0.9         | 35<br><b>35</b> | 5.03  | 1.1          |                 | 100.0%<br><b>100.0</b> % | -0.60 [-1.08, -0.12]<br>- <b>0.60 [-1.08, -0.12]</b>          | <u></u>                                   |
| Heterogeneity: Not ap<br>Test for overall effect:      | •            |             |                 |       |              | 34              | 100.0 /4                 | -0.00 [- 1.00, -0.12]   |   |
| 26 Class duration                                      |              |             |                 |       |              |                 |                          |   |   |
| CORTESI2012  | 4.38         | 1.02        | 35              | 4.82  | 0.94         |                 | 100.0%                   | -0.44 [-0.92, 0.03]   |   |
| i <b>ubtotal (95% Cl)</b><br>Heterogeneity: Not ap     | plicable     |             | 35              |       |              | 34              | 100.0%                   | -0.44 [-0.92, 0.03]   |   |
| est for overall effect:                                | Z=1.82       | (P = 0      | .07)            |       |              |                 |                          |   |   |
| .3.7 Parasomnias                                       |              |             |                 |       |              |                 |                          |   | _   |
| ORTESI2012<br>Subtotal (95% CI)                        | 8.92         | 1.38        | 35<br><b>35</b> | 9.35  | 1.78         | 34<br><b>34</b> | 100.0%<br><b>100.0</b> % | -0.27 [-0.74, 0.21]<br>- <b>0.27 [-0.74, 0.21]</b>            |   |
| leterogeneity: Not ap<br>est for overall effect:       | •            |             | .27)            |       |              |                 |                          |   |   |
| .3.8 Sleep disordere                                   | ed breati    | hina        |                 |       |              |                 |                          |   |   |
| CORTESI2012<br>Subtotal (95% CI)                       |              | 0.95        | 35<br><b>35</b> | 3.15  | 0.48         | 34<br><b>34</b> | 100.0%<br><b>100.0</b> % | 0.09 [-0.38, 0.56]<br><b>0.09 [-0.38, 0.56</b> ]              | <b>*</b>                                  |
| Heterogeneity: Not ap<br>Test for overall effect:      |              |             |                 |       |              | _ 3             |                          | ,   |   |
|  |              |             | •               |       |              |                 |                          |   |   |
| '. <b>3.9 Daytime sleepin</b><br>ORTESI2012            | 10.84        | 1,68        | 35              | 11.39 | 2.34         | 34              | 100.0%                   | -0.27 [-0.74, 0.21]   |   |
| Subtotal (95% CI)<br>Heterogeneity: Not ap             |              |             | 35              |       |              | 34              | 100.0%                   | -0.27 [-0.74, 0.21]   | <b>→</b>                                  |
| est for overall effect:                                |              |             | .27)            |       |              |                 |                          |   |   |
|  |              |             |                 |       |              |                 |                          |   | -2 -1 0 1                                 |
|  |              |             |                 |       |              |                 |                          |   | -2 -1 6 1                                 |

#### Positive treatment response



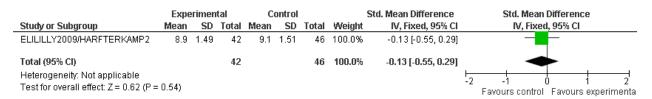
#### 1.28.4 SNRIs for sleep problems as an indirect outcome

Atomoxetine versus placebo for sleep problems as an indirect outcome

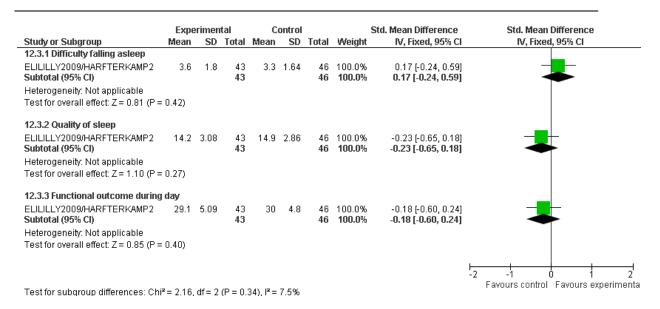
#### Time to fall asleep

|   | Favours | ехрегіт | ental | C    | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                             |
|---|---------|---------|-------|------|--------|-------|--------|----------------------|--|
| Study or Subgroup   | Mean    | SD      | Total | Mean | SD     | Total | Weight | IV, Fixed, 95% C     | I IV, Fixed, 95% CI                              |
| ELILILLY2009/HARFTERKAMP2   | 2.6     | 1.43    | 43    | 3    | 1.34   | 46    | 100.0% | -0.29 [-0.70, 0.13   |  |
| Total (95% CI)  |         |         | 43    |      |        | 46    | 100.0% | -0.29 [-0.70, 0.13   | ı, , 🔷   |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.34 (P = | 0.18)   |         |       |      |        |       |        |                      | -2 -1 0 1 2 Favours experimental Favours control |

#### Total hours of sleep



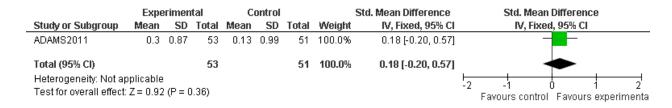
#### Sleep problems



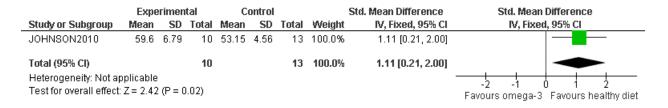
# 1.29BIOMEDICAL INTERVENTIONS AIMED AT COEXISTING MEDICAL OR FUNCTIONAL PROBLEMS

#### 1.29.1 Nutritional interventions for sleep problems as an indirect outcome

Multivitamin/mineral supplement versus placebo for sleep problems as an indirect outcome

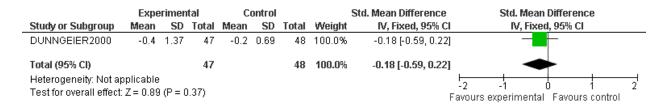


Omega-3 fatty acids versus healthy diet control for sleep problems as an indirect outcome



#### 1.29.2 Hormones for gastrointestinal symptoms as an indirect outcome

### Secretin versus placebo for gastrointestinal symptoms as an indirect outcome

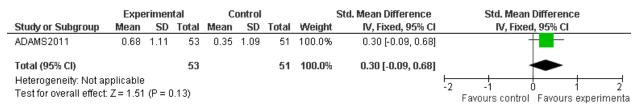


### 1.29.3 Nutritional interventions for gastrointestinal symptoms as a direct or indirect outcome

### Immunoglobulin versus placebo for gastrointestinal symptoms as a direct outcome

|  | Experimental |       | Control |       | Risk Ratio |                    | Risk Ratio                          |
|--|--------------|-------|---------|-------|------------|--------------------|-------------------------------------|
| Study or Subgroup                              | Events       | Total | Events  | Total | Weight     | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                  |
| HANDEN2009                                     | 31           | 94    | 14      | 31    | 100.0%     | 0.73 [0.45, 1.18]  | -                                   |
| Total (95% CI)                                 |              | 94    |         | 31    | 100.0%     | 0.73 [0.45, 1.18]  | -                                   |
| Total events                                   | 31           |       | 14      |       |            |                    |                                     |
| Heterogeneity: Not applicable                  |              |       |         |       |            |                    | 01 02 05 1 2 5 10                   |
| Test for overall effect: $Z = 1.28$ (P = 0.20) |              |       |         |       |            |                    | Favours control Favours experimenta |

### Multivitamin/ mineral supplement versus placebo for gastrointestinal symptoms as an indirect outcome

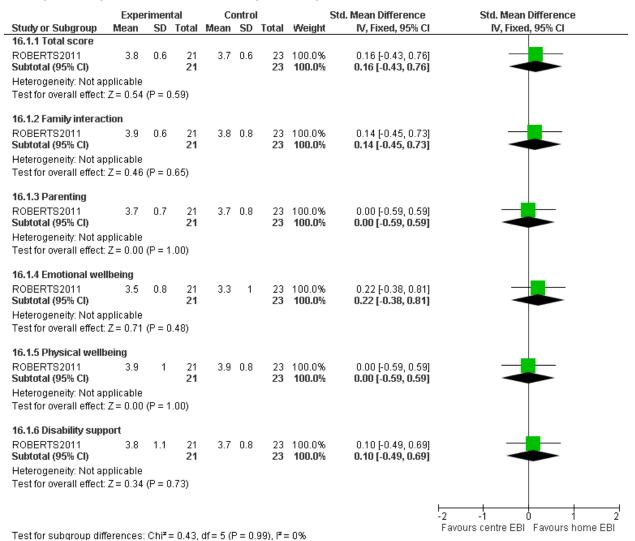


# 1.30PSYCHOSOCIAL INTERVENTIONS AIMED AT IMPROVING THE IMPACT OF AUTISM ON THE FAMILY

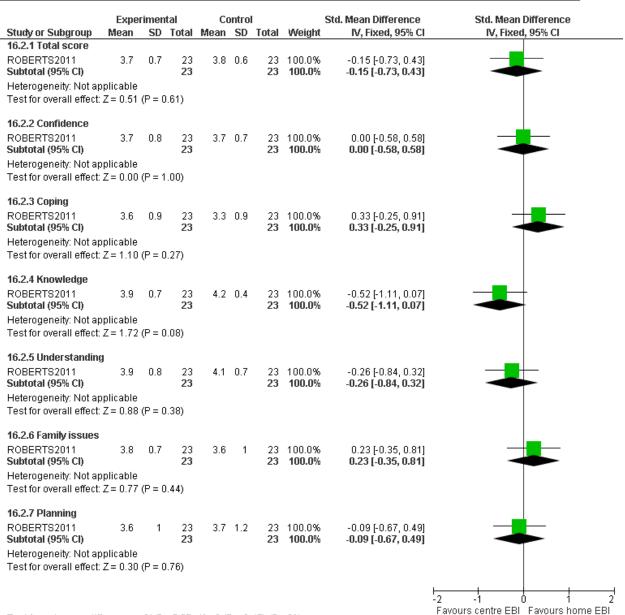
# 1.30.1 Behavioural interventions for improving the impact of autism on the family as an indirect outcome

Home-based EBI versus centre-based EBI for improving the impact of autism on the family as an indirect outcome

#### Family quality of life (Beach Family Quality of Life Questionnaire)

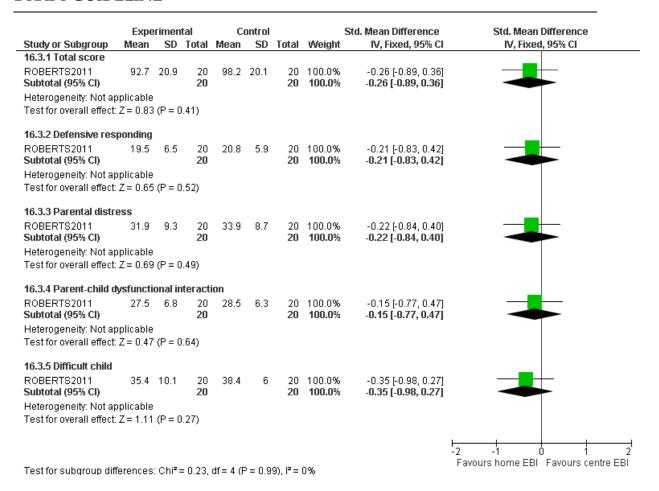


Parental coping skills (study-specific questionnaire)



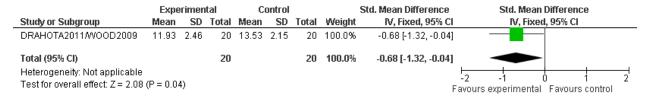
Test for subgroup differences:  $Chi^2 = 5.57$ , df = 6 (P = 0.47),  $I^2 = 0\%$ 

#### Parental stress (PSI)



# 1.30.2 Cognitive-behavioural interventions for improving the impact of autism on the family as an indirect outcome

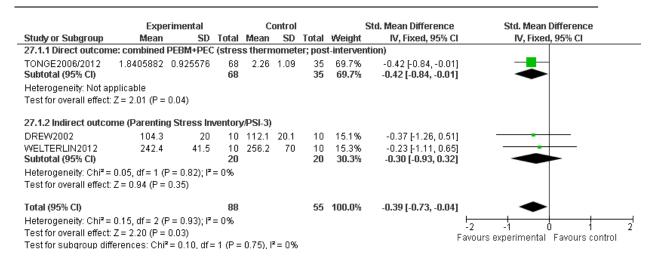
CBT versus waitlist for improving the impact of autism on the family as an indirect outcome



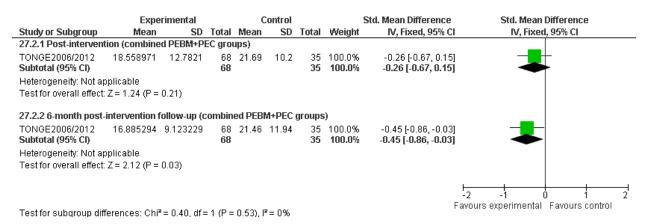
# 1.30.3 Parent training for improving the impact of autism on the family as a direct or indirect outcome

Parent training versus treatment as usual for improving the impact of autism on the family as a direct or indirect outcome

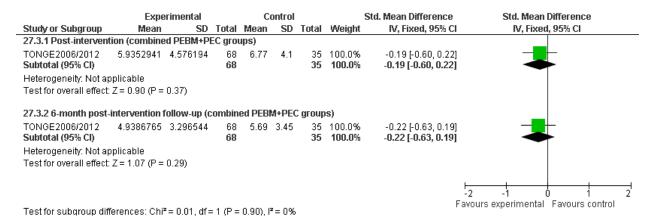
#### Parental stress



#### Parental mental health (GHQ-28)

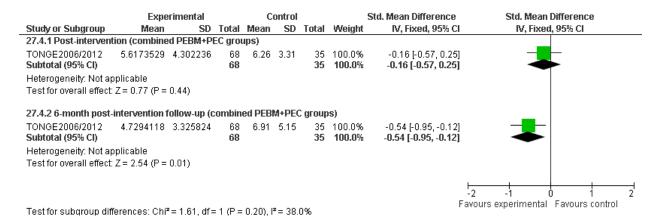


#### Parental somatic symptoms (GHQ-28)

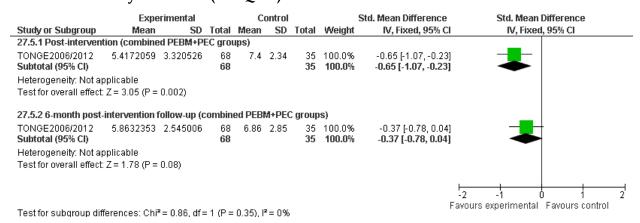


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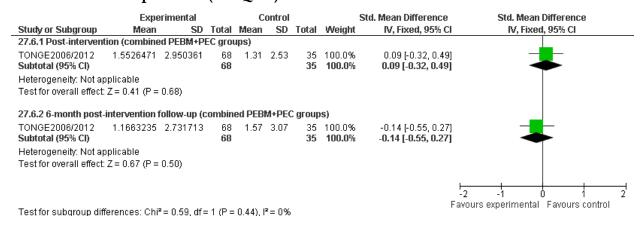
#### Parental anxiety and insomnia (GHQ-28)



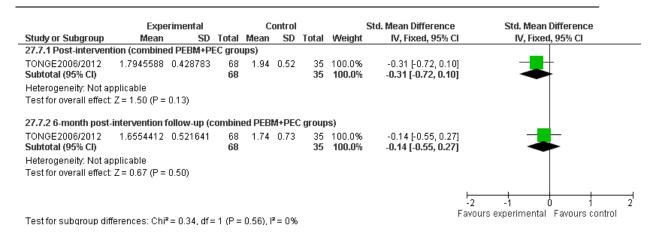
# Parental social dysfunction (GHQ-28)



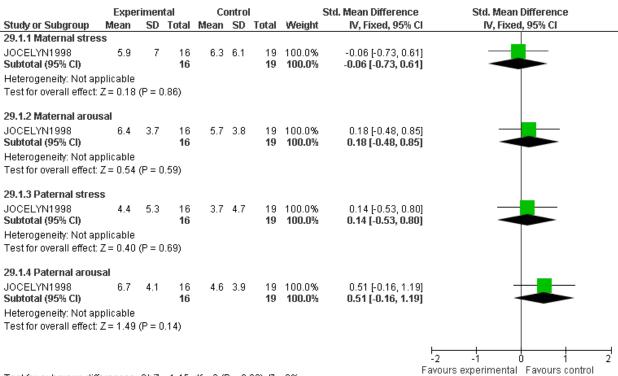
#### Parental severe depression (GHQ-28)



## General family function (FAD)



# Parent and day-care staff training versus standard day-care for improving the impact of autism on the family as an indirect outcome



Test for subgroup differences:  $Chi^2 = 1.45$ , df = 3 (P = 0.69),  $I^2 = 0\%$ 

# 1.31PHARMACOLOGICAL INTERVENTIONS AIMED AT IMPROVING THE IMPACT OF AUTISM ON THE FAMILY

# 1.31.1SNRIs for improving the impact of autism on the family as an indirect outcome

Atomoxetine versus placebo for improving the impact of autism on the family as an indirect outcome

### Parental mental health (GHQ)

|   | Expe  | rimen | tal   | C    | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                               |
|---|-------|-------|-------|------|--------|-------|--------|----------------------|--|
| Study or Subgroup   | Mean  | SD    | Total | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                  |
| ELILILLY2009/HARFTERKAMP2   | 2.3   | 3.35  | 43    | 3.1  | 3.31   | 46    | 100.0% | -0.24 [-0.66, 0.18]  |  |
| Total (95% CI)  |       |       | 43    |      |        | 46    | 100.0% | -0.24 [-0.66, 0.18]  | •  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1,12 (P = | 0.26) |       |       |      |        |       |        | F:                   | -2 -1 0 1 2<br>avours experimental Favours control |

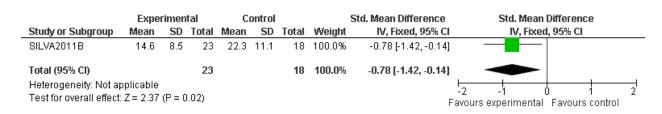
#### Parental stress (NOSI)

|   | Expo  | eriment | al    | (     | Control |       |        | Std. Mean Difference | Std. Mean Difference                             |
|---|-------|---------|-------|-------|---------|-------|--------|----------------------|--|
| Study or Subgroup   | Mean  | SD      | Total | Mean  | SD      | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                |
| ELILILLY2009/HARFTERKAMP2   | 350   | 75.07   | 38    | 368.8 | 81.83   | 39    | 100.0% | -0.24 [-0.69, 0.21]  | -  |
| Total (95% CI)  |       |         | 38    |       |         | 39    | 100.0% | -0.24 [-0.69, 0.21]  | •  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.04 (P = | 0.30) |         |       |       |         |       |        | F                    | -2 -1 0 1 2 Favours experimental Favours control |

# 1.32BIOMEDICAL INTERVENTIONS AIMED AT IMPROVING THE IMPACT OF AUTISM ON THE FAMILY

# 1.32.1 Complementary therapies for improving the impact of autism on the family as an indirect outcome

Qigong massage training versus waitlist for improving the impact of autism on the family as an indirect outcome



# 1.33ADVERSE EVENTS ASSOCIATED WITH PHARMACOLOGICAL INTERVENTIONS

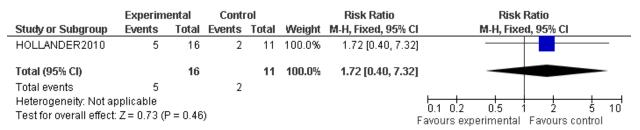
#### 1.33.1 Adverse events associated with anticonvulsants

Adverse events associated with divalproex versus placebo

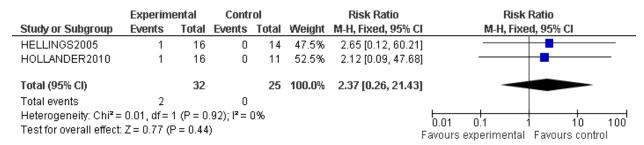
#### Any adverse event

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| HELLINGS2005             | 15          | 16       | 11     | 14    | 100.0% | 1.19 [0.88, 1.61]  | -                                    |
| Total (95% CI)           |             | 16       |        | 14    | 100.0% | 1.19 [0.88, 1.61]  | •                                    |
| Total events             | 15          |          | 11     |       |        |                    |                                      |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 01 02 05 1 2 5 10                    |
| Test for overall effect: | Z = 1.15 (F | P = 0.25 | )      |       |        | 1                  | Favours experimental Favours control |

#### More than one adverse event



#### Discontinuation due to adverse event



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#### Weight gain (in kg or lb)

|   | Expe     | rimen | tal   | C         | ontrol |       |        | Std. Mean Difference | Std. Mean I         | Difference  |       |
|---|----------|-------|-------|-----------|--------|-------|--------|----------------------|---------------------|-------------|-------|
| Study or Subgroup                                 | Mean     | SD    | Total | Mean      | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed           | , 95% CI    |       |
| HELLINGS2005                                      | 1.98     | 1.88  | 16    | 1.1       | 1.1    | 14    | 52.3%  | 0.55 [-0.19, 1.28]   | -                   | _           | -     |
| HOLLANDER2010                                     | 3.02     | 6.41  | 16    | 2.95      | 3.37   | 11    | 47.7%  | 0.01 [-0.76, 0.78]   |                     | <del></del> |       |
| Total (95% CI)                                    |          |       | 32    |           |        | 25    | 100.0% | 0.29 [-0.24, 0.82]   | -                   |             |       |
| Heterogeneity: Chi² =<br>Test for overall effect: |          | ,     |       | ; I² = 0% | ,<br>0 |       |        |                      | -2 -1 0             | 1           | 2     |
| restion overall ellect.                           | Z = 1.00 | (1 0  | .20)  |           |        |       |        | F                    | avours experimental | Favours co  | ntrol |

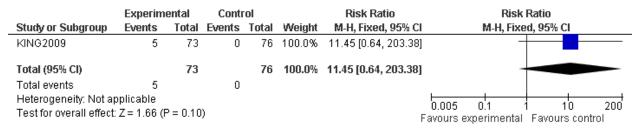
# 1.33.2 Adverse events associated with antidepressants

Adverse events associated with citalopram versus placebo

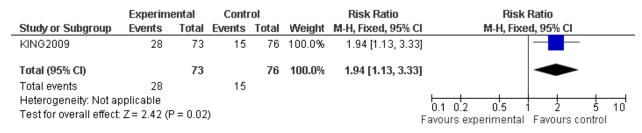
## Any adverse event

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| KING2009                 | 71          | 73       | 66     | 76    | 100.0% | 1.12 [1.02, 1.23]  | •                                    |
| Total (95% CI)           |             | 73       |        | 76    | 100.0% | 1.12 [1.02, 1.23]  | <b>•</b>                             |
| Total events             | 71          |          | 66     |       |        |                    |                                      |
| Heterogeneity: Not ap    | oplicable   |          |        |       |        |                    | 01 02 05 1 2 5 10                    |
| Test for overall effect: | Z = 2.32 (F | P = 0.02 | )      |       |        | F                  | Favours experimental Favours control |

# **Nightmares**



## Increased energy level



## Anger or irritability

|                         | Ехрегіт       | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|-------------------------|---------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup       | Events        | Total    | Events | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixed, 95% Cl                 |
| KING2009                | 18            | 73       | 13     | 76    | 100.0% | 1.44 [0.76, 2.73  |                                      |
| Total (95% CI)          |               | 73       |        | 76    | 100.0% | 1.44 [0.76, 2.73  | 1 📥                                  |
| Total events            | 18            |          | 13     |       |        |                   |                                      |
| Heterogeneity: Not a    | pplicable     |          |        |       |        |                   | 01 02 05 1 2 5 10                    |
| Test for overall effect | : Z = 1.13 (F | P = 0.26 | i)     |       |        |                   | Favours experimental Favours control |

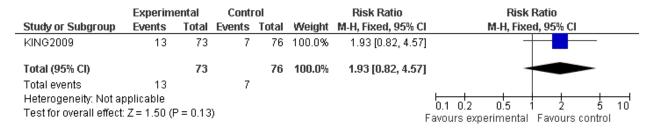
# Aggression or hostility

|                          | Experim     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                              |
|--------------------------|-------------|----------|--------|-------|--------|-------------------|---|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | M-H, Fixed, 95% CI                      |
| KING2009                 | 17          | 73       | 13     | 76    | 100.0% | 1.36 [0.71, 2.60  | ı — — — — — — — — — — — — — — — — — — — |
| Total (95% CI)           |             | 73       |        | 76    | 100.0% | 1.36 [0.71, 2.60  | 1 🔷                                     |
| Total events             | 17          |          | 13     |       |        |                   |   |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                   | 01 02 05 1 2 5 10                       |
| Test for overall effect: | Z = 0.94 (F | P = 0.35 | )      |       |        |                   | Favours experimental Favours control    |

# Headache or migraine

|                         | Experim     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|-------------------------|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | M-H, Fixed, 95% CI                   |
| KING2009                | 15          | 73       | 10     | 76    | 100.0% | 1.56 [0.75, 3.25  | +                                    |
| Total (95% CI)          |             | 73       |        | 76    | 100.0% | 1.56 [0.75, 3.25] |                                      |
| Total events            | 15          |          | 10     |       |        |                   |                                      |
| Heterogeneity: Not ap   | oplicable   |          |        |       |        |                   | 01 02 05 1 2 5 10                    |
| Test for overall effect | Z = 1.19 (F | P = 0.23 | )      |       |        |                   | Favours experimental Favours control |

#### Restlessness or difficulty settling down



# Disinhibited, impulsive, or intrusive behaviour

|                         | Experim     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|-------------------------|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixed, 95% Cl                 |
| KING2009                | 14          | 73       | 5      | 76    | 100.0% | 2.92 [1.11, 7.68  | 1                                    |
| Total (95% CI)          |             | 73       |        | 76    | 100.0% | 2.92 [1.11, 7.68] |                                      |
| Total events            | 14          |          | 5      |       |        |                   |                                      |
| Heterogeneity: Not a    | pplicable   |          |        |       |        |                   | 01 02 05 1 2 5 10                    |
| Test for overall effect | Z = 2.16 (F | P = 0.03 | )      |       |        |                   | Favours experimental Favours control |

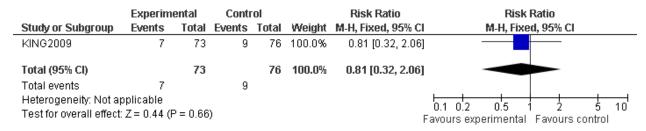
#### **Silliness**

|                          | Experim     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| KING2009                 | 9           | 73       | 10     | 76    | 100.0% | 0.94 [0.40, 2.17]  |                                      |
| Total (95% CI)           |             | 73       |        | 76    | 100.0% | 0.94 [0.40, 2.17]  |                                      |
| Total events             | 9           |          | 10     |       |        |                    |                                      |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 01 02 05 1 2 5 10                    |
| Test for overall effect: | Z = 0.15 (F | P = 0.88 | )      |       |        |                    | Favours experimental Favours control |

# Anxiety

|   | Ехрегіт  | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|---|----------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup                                 | Events   | Total    | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                 |
| KING2009  | 8        | 73       | 9      | 76    | 100.0% | 0.93 [0.38, 2.27  |                                      |
| Total (95% CI)                                    |          | 73       |        | 76    | 100.0% | 0.93 [0.38, 2.27] |                                      |
| Total events                                      | 8        |          | 9      |       |        |                   |                                      |
| Heterogeneity: Not ap<br>Test for overall effect: | •        | P = N 87 | )      |       |        |                   | 0.1 0.2 0.5 1 2 5 10                 |
| 1 COLIOI OVCIAII CIICCE                           | 2-0.11 ( | - 0.01   | /      |       |        |                   | Favours experimental Favours control |

# Mood lability



# **Increased speech**

|                         | Ехрегіт        | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|-------------------------|----------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup       | Events         | Total    | Events | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixed, 95% Cl                 |
| KING2009                | 8              | 73       | 4      | 76    | 100.0% | 2.08 [0.66, 6.62  | 1                                    |
| Total (95% CI)          |                | 73       |        | 76    | 100.0% | 2.08 [0.66, 6.62  |                                      |
| Total events            | 8              |          | 4      |       |        |                   |                                      |
| Heterogeneity: Not ap   | pplicable      |          |        |       |        |                   | 01 02 05 1 2 5 10                    |
| Test for overall effect | :: Z = 1.24 (F | P = 0.21 | )      |       |        |                   | Favours experimental Favours control |

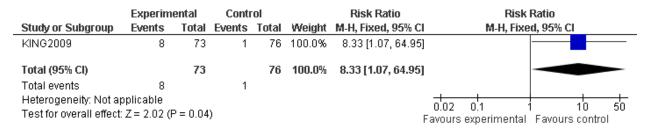
#### Decreased attention and concentration

|                         | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|-------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| KING2009                | 9           | 73       | 2      | 76    | 100.0% | 4.68 [1.05, 20.96] |                                      |
| Total (95% CI)          |             | 73       |        | 76    | 100.0% | 4.68 [1.05, 20.96] |                                      |
| Total events            | 9           |          | 2      |       |        |                    |                                      |
| Heterogeneity: Not ap   | pplicable   |          |        |       |        |                    | 0.05 0.2 1 5 20                      |
| Test for overall effect | Z = 2.02 (F | P = 0.04 | )      |       |        |                    | Favours experimental Favours control |

# Hyperactivity

|                         | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio        | Risk                 | Ratio     |
|-------------------------|-------------|----------|--------|-------|--------|-------------------|----------------------|-----------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixe          | d, 95% CI |
| KING2009                | 9           | 73       | 2      | 76    | 100.0% | 4.68 [1.05, 20.96 | ]                    |           |
| Total (95% CI)          |             | 73       |        | 76    | 100.0% | 4.68 [1.05, 20.96 | l                    |           |
| Total events            | 9           |          | 2      |       |        |                   |                      |           |
| Heterogeneity: Not ap   | pplicable   |          |        |       |        |                   | 0.05 0.2             | 5 20      |
| Test for overall effect | Z = 2.02 (F | P = 0.04 | )      |       |        |                   | Favours experimental |           |

# Stereotypy



#### Diarrhoea or loose stools

|                         | Ехрегіт       | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|-------------------------|---------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup       | Events        | Total    | Events | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixed, 95% Cl                 |
| KING2009                | 19            | 73       | 9      | 76    | 100.0% | 2.20 [1.06, 4.54  | 1                                    |
| Total (95% CI)          |               | 73       |        | 76    | 100.0% | 2.20 [1.06, 4.54] |                                      |
| Total events            | 19            |          | 9      |       |        |                   |                                      |
| Heterogeneity: Not a    |               |          |        |       |        |                   | 0.1 0.2 0.5 1 2 5 10                 |
| Test for overall effect | : Z = 2.13 (F | P = 0.03 | i)     |       |        |                   | Favours experimental Favours control |

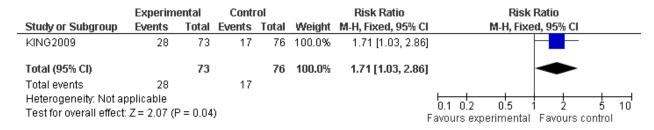
#### Abdominal discomfort

|                          | Experim     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                 |
| KING2009                 | 13          | 73       | 9      | 76    | 100.0% | 1.50 [0.68, 3.30  | 1                                    |
| Total (95% CI)           |             | 73       |        | 76    | 100.0% | 1.50 [0.68, 3.30  |                                      |
| Total events             | 13          |          | 9      |       |        |                   |                                      |
| Heterogeneity: Not ap    | oplicable   |          |        |       |        |                   | 01 02 05 1 2 5 10                    |
| Test for overall effect: | Z = 1.02 (F | P = 0.31 | )      |       |        |                   | Favours experimental Favours control |

# Vomiting or nausea

|                          | Experim     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | CI M-H, Fixed, 95% CI                |
| KING2009                 | 14          | 73       | 6      | 76    | 100.0% | 2.43 [0.99, 5.98  | 8]                                   |
| Total (95% CI)           |             | 73       |        | 76    | 100.0% | 2.43 [0.99, 5.98] | 8]                                   |
| Total events             | 14          |          | 6      |       |        |                   |                                      |
| Heterogeneity: Not as    |             |          |        |       |        |                   | 0.1 0.2 0.5 1 2 5 10                 |
| Test for overall effect: | Z = 1.93 (F | P = 0.05 | )      |       |        |                   | Favours experimental Favours control |

# Any insomnia



# Initial insomnia or difficulty falling asleep

|   | Experim     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|---|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup                               | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixed, 95% Cl                 |
| KING2009  | 17          | 73       | 7      | 76    | 100.0% | 2.53 [1.11, 5.74  | .]                                   |
| Total (95% CI)                                  |             | 73       |        | 76    | 100.0% | 2.53 [1.11, 5.74  |                                      |
| Total events                                    | 17          |          | 7      |       |        |                   |                                      |
| Heterogeneity: Not a<br>Test for overall effect |             | 2 – 0 02 | Λ.     |       |        |                   | 0.1 0.2 0.5 1 2 5 10                 |
| restroi overan enect                            | 2 – 2.22 (1 | - 0.03   | '      |       |        |                   | Favours experimental Favours control |

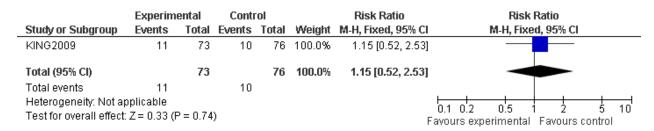
# Midcycle or other insomnia

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| KING2009                 | 13          | 73       | 9      | 76    | 100.0% | 1.50 [0.68, 3.30]  | +                                    |
| Total (95% CI)           |             | 73       |        | 76    | 100.0% | 1.50 [0.68, 3.30]  |                                      |
| Total events             | 13          |          | 9      |       |        |                    |                                      |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 01 02 05 1 2 5 10                    |
| Test for overall effect: | Z = 1.02 (F | P = 0.31 | )      |       |        | F                  | Favours experimental Favours control |

# Cold, flu or other systemic infection

|  | Ехрегіт | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio   |
|--|---------|----------|--------|-------|--------|-------------------|--|
| Study or Subgroup                                | Events  | Total    | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                                       |
| KING2009   | 31      | 73       | 26     | 76    | 100.0% | 1.24 [0.82, 1.87  | 1 -  |
| Total (95% CI)                                   |         | 73       |        | 76    | 100.0% | 1.24 [0.82, 1.87  | ı 🔷  |
| Total events                                     | 31      |          | 26     |       |        |                   |  |
| Heterogeneity: Not ap<br>Test for overall effect | • •     | P = 0.30 | )      |       |        |                   | 0.1 0.2 0.5 1 2 5 10  Favours experimental Favours control |

# Decreased appetite



# **Increased appetite**

|                         | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|-------------------------|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | M-H, Fixed, 95% CI                   |
| KING2009                | 7           | 73       | 8      | 76    | 100.0% | 0.91 [0.35, 2.38  | 1 -                                  |
| Total (95% CI)          |             | 73       |        | 76    | 100.0% | 0.91 [0.35, 2.38] |                                      |
| Total events            | 7           |          | 8      |       |        |                   |                                      |
| Heterogeneity: Not ap   | pplicable   |          |        |       |        |                   | 01 02 05 1 2 5 10                    |
| Test for overall effect | Z = 0.19 (F | P = 0.85 | )      |       |        |                   | Favours experimental Favours control |

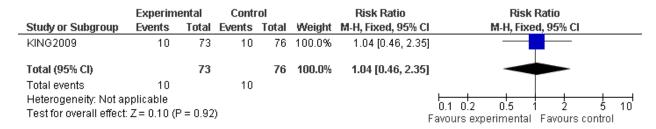
#### Rash

|                          | Experim     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | M-H, Fixed, 95% CI                   |
| KING2009                 | 12          | 73       | 8      | 76    | 100.0% | 1.56 [0.68, 3.60  |                                      |
| Total (95% CI)           |             | 73       |        | 76    | 100.0% | 1.56 [0.68, 3.60] |                                      |
| Total events             | 12          |          | 8      |       |        |                   |                                      |
| Heterogeneity: Not as    | oplicable   |          |        |       |        |                   | 01 02 05 1 2 5 10                    |
| Test for overall effect: | Z = 1.05 (F | P = 0.30 | )      |       |        |                   | Favours experimental Favours control |

#### Other skin or subcutaneous tissue disorder

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk                | Ratio     |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|---------------------|-----------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixe           | d, 95% CI |
| KING2009                 | 9           | 73       | 1      | 76    | 100.0% | 9.37 [1.22, 72.12] |                     |           |
| Total (95% CI)           |             | 73       |        | 76    | 100.0% | 9.37 [1.22, 72.12] |                     |           |
| Total events             | 9           |          | 1      |       |        |                    |                     |           |
| Heterogeneity: Not ap    | oplicable   |          |        |       |        |                    | 0.02 0.1            | 10 50     |
| Test for overall effect: | Z = 2.15 (F | P = 0.03 | )      |       |        | F                  | avours experimental |           |

# **Fatigue**



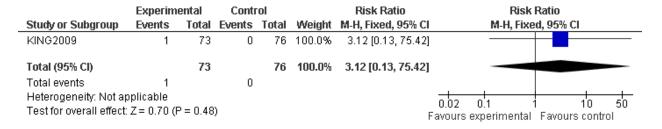
# Allergies

|                         | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|-------------------------|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                 |
| KING2009                | 15          | 73       | 11     | 76    | 100.0% | 1.42 [0.70, 2.88  |                                      |
| Total (95% CI)          |             | 73       |        | 76    | 100.0% | 1.42 [0.70, 2.88  | 1                                    |
| Total events            | 15          |          | 11     |       |        |                   |                                      |
| Heterogeneity: Not a    | pplicable   |          |        |       |        |                   | 01 02 05 1 2 5 10                    |
| Test for overall effect | Z = 0.97 (F | P = 0.33 | )      |       |        |                   | Favours experimental Favours control |

#### Cough

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| KING2009                 | 10          | 73       | 5      | 76    | 100.0% | 2.08 [0.75, 5.80]  | +-                                   |
| Total (95% CI)           |             | 73       |        | 76    | 100.0% | 2.08 [0.75, 5.80]  |                                      |
| Total events             | 10          |          | 5      |       |        |                    |                                      |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 01.02 05 1 2 5 10                    |
| Test for overall effect: | Z = 1.40 (F | P = 0.16 | )      |       |        |                    | Favours experimental Favours control |

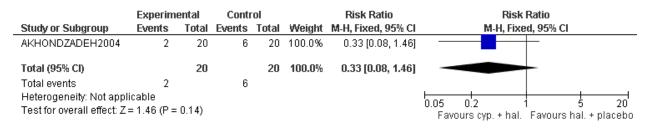
#### Any serious adverse event



#### 1.33.3 Adverse events associated with antihistamines

Adverse events associated with cyproheptadine and haloperidol versus placebo and haloperidol

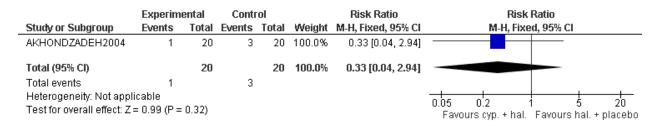
#### **Extrapyramidal symptoms**



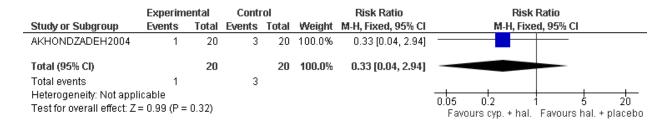
#### Trouble swallowing

|                             | Ехрегіт     | ental | Contr  | ol    |        | Risk Ratio         | Risk                | Ratio  |      |
|-----------------------------|-------------|-------|--------|-------|--------|--------------------|---------------------|--|------|
| Study or Subgroup           | Events      | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixe           | d, 95% CI  |      |
| AKHONDZADEH2004             | 2           | 20    | 4      | 20    | 100.0% | 0.50 [0.10, 2.43]  |                     |  |      |
| Total (95% CI)              |             | 20    |        | 20    | 100.0% | 0.50 [0.10, 2.43]  |                     |  |      |
| Total events                | 2           |       | 4      |       |        |                    |                     |  |      |
| Heterogeneity: Not appli    | cable       |       |        |       |        |                    | 01 02 05            | <del>                                     </del> | 5 10 |
| Test for overall effect: Z: | = 0.86 (P = | 0.39) |        |       |        |                    | Favours cyp. + hal. | Favours hal.                                     | 0 .0 |

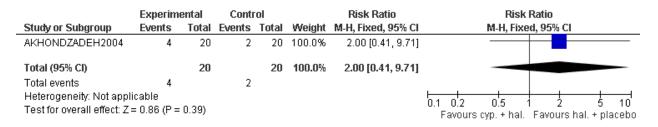
#### Stiffness



#### Slow movement



#### Constipation



#### Diarrhoea

|                            | Ехрегіт     | ental | Contr  | ol    |        | Risk Ratio         | Risk Ratio               |        |
|----------------------------|-------------|-------|--------|-------|--------|--------------------|--------------------------|--------|
| Study or Subgroup          | Events      | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95%          | 6 CI   |
| AKHONDZADEH2004            | 2           | 20    | 3      | 20    | 100.0% | 0.67 [0.12, 3.57]  |                          |        |
| Total (95% CI)             |             | 20    |        | 20    | 100.0% | 0.67 [0.12, 3.57]  |                          |        |
| Total events               | 2           |       | 3      |       |        |                    |                          |        |
| Heterogeneity: Not appli   | cable       |       |        |       |        |                    | 01 02 05 1               | 2 5 10 |
| Test for overall effect: Z | = 0.47 (P = | 0.64) |        |       |        |                    | Favours cyp. + hal. Favo | 2 0 10 |

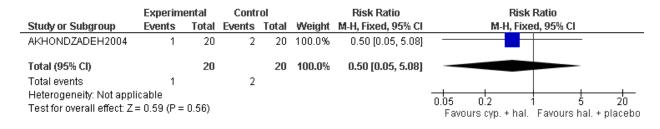
# **Increased appetite**

|                            | Ехрегіт     | ental | Contr  | ol    |        | Risk Ratio         | Risk Ratio                                 |
|----------------------------|-------------|-------|--------|-------|--------|--------------------|--|
| Study or Subgroup          | Events      | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                         |
| AKHONDZADEH2004            | 9           | 20    | 4      | 20    | 100.0% | 2.25 [0.83, 6.13]  |  |
| Total (95% CI)             |             | 20    |        | 20    | 100.0% | 2.25 [0.83, 6.13]  |  |
| Total events               | 9           |       | 4      |       |        |                    |  |
| Heterogeneity: Not appl    | icable      |       |        |       |        |                    | 0.1 0.2 0.5 1 2 5 10                       |
| Test for overall effect: Z | = 1.59 (P = | 0.11) |        |       |        |                    | Favours cyp. + hal. Favours hal. + placebo |

# Morning drowsiness

|                            | Ехрегіт     | ental | Contr  | ol    |        | Risk Ratio         | Risk Ratio                                 |
|----------------------------|-------------|-------|--------|-------|--------|--------------------|--|
| Study or Subgroup          | Events      | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                         |
| AKHONDZADEH2004            | 3           | 20    | 2      | 20    | 100.0% | 1.50 [0.28, 8.04]  |  |
| Total (95% CI)             |             | 20    |        | 20    | 100.0% | 1.50 [0.28, 8.04]  |  |
| Total events               | 3           |       | 2      |       |        |                    |  |
| Heterogeneity: Not appl    | icable      |       |        |       |        |                    | 01 02 05 1 2 5 10                          |
| Test for overall effect: Z | = 0.47 (P = | 0.64) |        |       |        |                    | Favours cyp. + hal. Favours hal. + placebo |

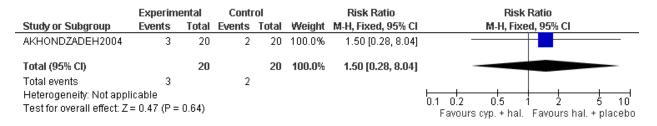
# Day time drowsiness



#### Restlessness

|                            | Experim     | ental | Contr  | ol    |        | Risk Ratio         | Risk Ratio   |
|----------------------------|-------------|-------|--------|-------|--------|--------------------|--|
| Study or Subgroup          | Events      | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI   |
| AKHONDZADEH2004            | 1           | 20    | 4      | 20    | 100.0% | 0.25 [0.03, 2.05]  |  |
| Total (95% CI)             |             | 20    |        | 20    | 100.0% | 0.25 [0.03, 2.05]  |  |
| Total events               | 1           |       | 4      |       |        |                    |  |
| Heterogeneity: Not appl    | licable     |       |        |       |        |                    | 0.05 0.2 1 5 20  |
| Test for overall effect: Z | = 1.29 (P = | 0.20) |        |       |        |                    | 0.05 0.2 1 5 20<br>Favours cyp. + hal. Favours hal. + placek |

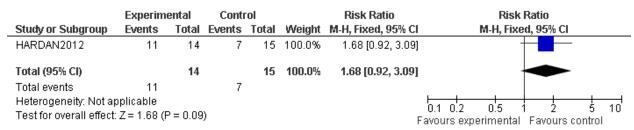
#### **Fatigue**



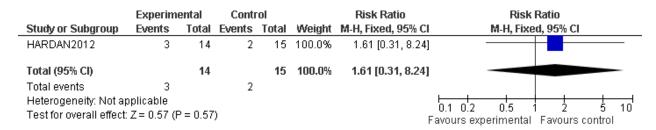
#### 1.33.4 Adverse events associated with antioxidants

Adverse events associated with N-acetylcysteine versus placebo

#### Any gastrointestinal side effect



#### Constipation



#### Nausea

|                         | Experim     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|-------------------------|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixed, 95% Cl                 |
| HARDAN2012              | 6           | 14       | 3      | 15    | 100.0% | 2.14 [0.66, 6.97  | ]                                    |
| Total (95% CI)          |             | 14       |        | 15    | 100.0% | 2.14 [0.66, 6.97  |                                      |
| Total events            | 6           |          | 3      |       |        |                   |                                      |
| Heterogeneity: Not ap   | pplicable   |          |        |       |        |                   | 01 02 05 1 2 5 10                    |
| Test for overall effect | Z = 1.27 (F | P = 0.21 | )      |       |        |                   | Favours experimental Favours control |

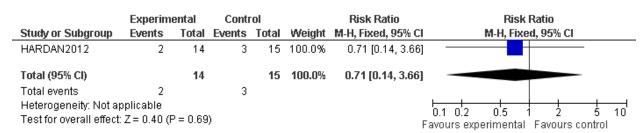
#### Diarrhoea

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C  | M-H, Fixed, 95% CI                   |
| HARDAN2012               | 3           | 14       | 1      | 15    | 100.0% | 3.21 [0.38, 27.40] |                                      |
| Total (95% CI)           |             | 14       |        | 15    | 100.0% | 3.21 [0.38, 27.40] |                                      |
| Total events             | 3           |          | 1      |       |        |                    |                                      |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 0.05 0.2 1 5 20                      |
| Test for overall effect: | Z = 1.07 (F | P = 0.29 | )      |       |        |                    | Favours experimental Favours control |

# **Increased appetite**

|   | Ехрегіт | ental    | Contr  | ol    |        | Risk Ratio          | Risk Ratio   |
|---|---------|----------|--------|-------|--------|---------------------|--|
| Study or Subgroup                                 | Events  | Total    | Events | Total | Weight | M-H, Fixed, 95% CI  | M-H, Fixed, 95% CI                                     |
| HARDAN2012  | 2       | 14       | 0      | 15    | 100.0% | 5.33 [0.28, 102.26] |  |
| Total (95% CI)                                    |         | 14       |        | 15    | 100.0% | 5.33 [0.28, 102.26] |  |
| Total events                                      | 2       |          | 0      |       |        |                     |  |
| Heterogeneity: Not ap<br>Test for overall effect: | •       | P = 0.27 | )      |       |        | F                   | 0.01 0.1 1 10 100 Sayours experimental Fayours control |

# Loss of appetite



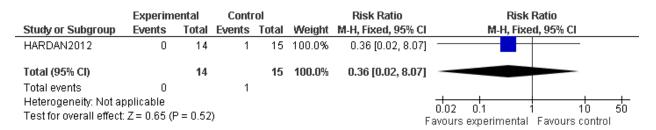
#### Akathisia

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| HARDAN2012               | 1           | 14       | 0      | 15    | 100.0% | 3.20 [0.14, 72.62] |                                      |
| Total (95% CI)           |             | 14       |        | 15    | 100.0% | 3.20 [0.14, 72.62] |                                      |
| Total events             | 1           |          | 0      |       |        |                    |                                      |
| Heterogeneity: Not ap    | pplicable   |          |        |       |        |                    | 0.02 0.1 1 10 50                     |
| Test for overall effect: | Z = 0.73 (F | P = 0.47 | )      |       |        | F                  | Favours experimental Favours control |

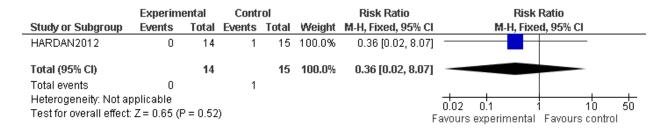
# Increased motor activity

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                 |
| HARDAN2012               | 2           | 14       | 3      | 15    | 100.0% | 0.71 [0.14, 3.66  | 1                                    |
| Total (95% CI)           |             | 14       |        | 15    | 100.0% | 0.71 [0.14, 3.66  |                                      |
| Total events             | 2           |          | 3      |       |        |                   |                                      |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                   | 01 02 05 1 2 5 10                    |
| Test for overall effect: | Z = 0.40 (F | ° = 0.69 | )      |       |        |                   | Favours experimental Favours control |

#### **Tremor**



#### **Dizziness**



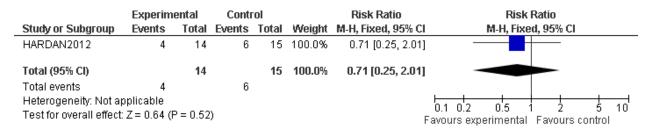
# Excitement/agitation

|                         | Ехрегіт        | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                              |
|-------------------------|----------------|----------|--------|-------|--------|-------------------|---|
| Study or Subgroup       | Events         | Total    | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                    |
| HARDAN2012              | 2              | 14       | 3      | 15    | 100.0% | 0.71 [0.14, 3.66  | i] ———————————————————————————————————— |
| Total (95% CI)          |                | 14       |        | 15    | 100.0% | 0.71 [0.14, 3.66] |   |
| Total events            | 2              |          | 3      |       |        |                   |   |
| Heterogeneity: Not ap   |                |          |        |       |        |                   | 0.1 0.2 0.5 1 2 5 10                    |
| Test for overall effect | : Z = 0.40  (F | r = 0.69 | )      |       |        |                   | Favours experimental Favours control    |

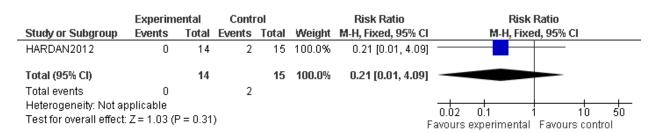
# Depressed affect

|                          | Experimental Contro |          | ol     |       | Risk Ratio | Risk Ratio         |                                     |  |
|--------------------------|---------------------|----------|--------|-------|------------|--------------------|-------------------------------------|--|
| Study or Subgroup        | Events              | Total    | Events | Total | Weight     | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                  |  |
| HARDAN2012               | 1                   | 14       | 0      | 15    | 100.0%     | 3.20 [0.14, 72.62] |                                     |  |
| Total (95% CI)           |                     | 14       |        | 15    | 100.0%     | 3.20 [0.14, 72.62] |                                     |  |
| Total events             | 1                   |          | 0      |       |            |                    |                                     |  |
| Heterogeneity: Not ap    | oplicable           |          |        |       |            |                    | 0.02 0.1 1 10 50                    |  |
| Test for overall effect: | Z = 0.73 (F         | P = 0.47 | )      |       |            |                    | avours experimental Favours control |  |

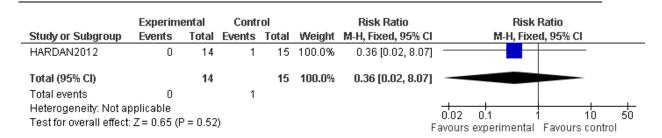
# Nasal congestion



#### **Increased salivation**



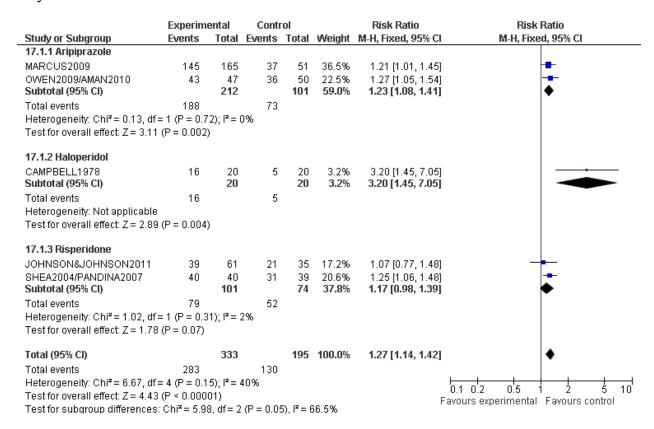
# **Sweating**



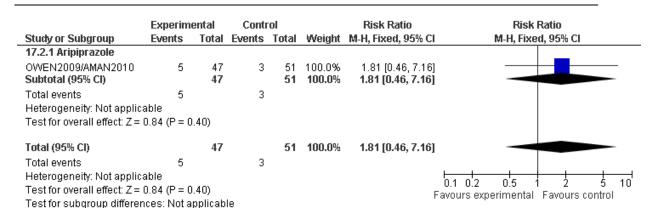
# 1.33.5 Adverse events associated with antipsychotics

Adverse events associated with antipsychotics versus placebo

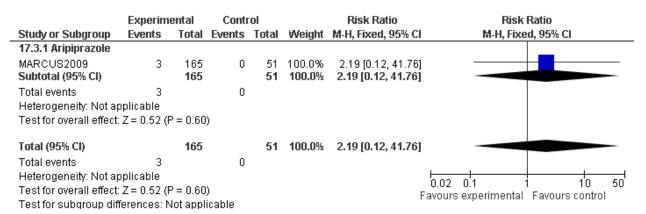
#### Any side effect



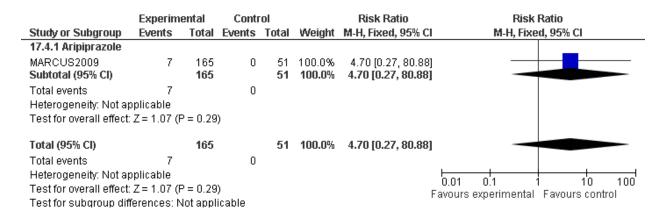
#### Discontinuation due to adverse events



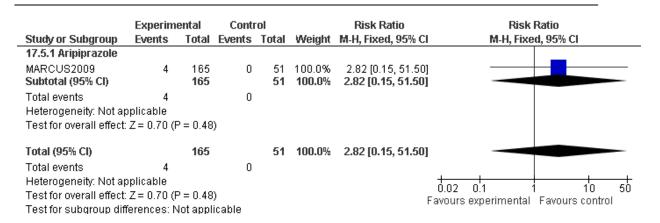
#### Discontinuation due to drooling



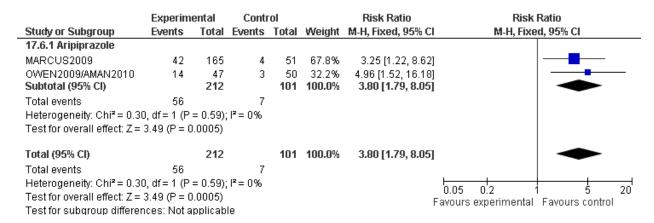
#### Discontinuation due to sedation



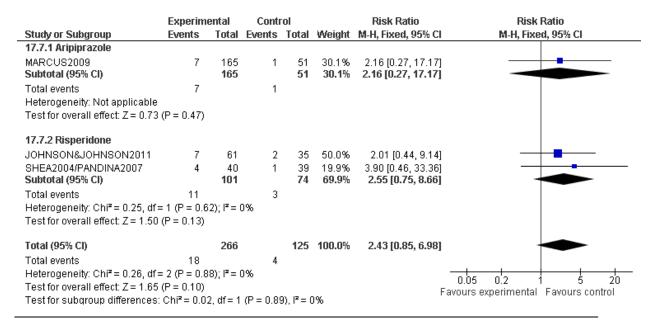
#### Discontinuation due to tremor



#### Clinically relevant (>=7%) weight gain



#### Weight gain

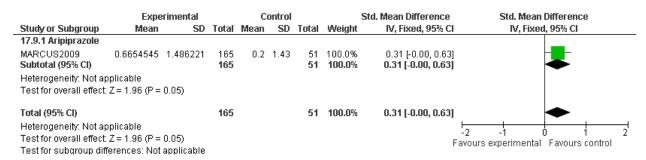


Autism: the management and support of children and young people on the autism spectrum (March 2013)

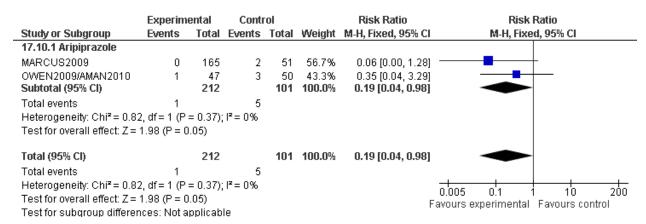
## Weight gain (in kg)

|  | Expe                        | rimental    |                   | C       | ontrol |       |        | Std. Mean Difference | Std. Mean Difference             |
|--|-----------------------------|-------------|-------------------|---------|--------|-------|--------|----------------------|----------------------------------|
| Study or Subgroup                            | Mean                        | SD          | Total             | Mean    | SD     | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                |
| 17.8.1 Aripiprazole                          |                             |             |                   |         |        |       |        |                      |                                  |
| MARCUS2009                                   | 1.3654545                   | 2.224007    | 165               | 0.3     | 2.14   | 51    | 34.1%  |                      | <del>-</del>                     |
| Subtotal (95% CI)                            |                             |             | 165               |         |        | 51    | 34.1%  | 0.48 [0.16, 0.80]    | •                                |
| Heterogeneity: Not applicable                |                             |             |                   |         |        |       |        |                      |                                  |
| Test for overall effect: Z = 2.97            | (P = 0.003)                 |             |                   |         |        |       |        |                      |                                  |
| 17.8.2 Risperidone                           |                             |             |                   |         |        |       |        |                      |                                  |
| JOHNSON&JOHNSON2011                          | 1.8352941                   | 1.694987    | 51                | 0.7     | 1.19   | 33    | 16.7%  | 0.74 [0.29, 1.19]    | <del></del>                      |
| LUBY2006                                     | 2.96                        | 2.53        | 11                | 0.61    | 1.1    | 12    | 4.2%   | 1.18 [0.28, 2.08]    |                                  |
| NAGARAJ2006                                  | 2.81                        | 2.04        | 19                | 1.71    | 1.3    | 20    | 8.2%   | 0.63 [-0.01, 1.28]   | -                                |
| RUPPRISPERIDONE2001                          | 2.7                         | 2.9         | 49                | 0.8     | 2.2    | 52    | 21.1%  | 0.74 [0.33, 1.14]    | _ <del></del>                    |
| SHEA2004/PANDINA2007                         | 2.7                         | 2           | 40                | 1       | 1.6    | 38    | 15.6%  | 0.93 [0.46, 1.40]    |                                  |
| Subtotal (95% CI)                            |                             |             | 170               |         |        | 155   | 65.9%  | 0.80 [0.57, 1.03]    | •                                |
| Heterogeneity: Chi <sup>2</sup> = 1.39, df = | = 4 (P = 0.85);             | $I^2 = 0\%$ |                   |         |        |       |        |                      |                                  |
| Test for overall effect: $Z = 6.86$          | (P < 0.00001)               | )           |                   |         |        |       |        |                      |                                  |
| Total (95% CI)                               |                             |             | 335               |         |        | 206   | 100.0% | 0.69 [0.51, 0.88]    | •                                |
| Heterogeneity: Chi <sup>2</sup> = 3.91, df=  | = 5 (P = 0.56);             | $I^2 = 0\%$ |                   |         |        |       |        | _                    |                                  |
| Test for overall effect: $Z = 7.30$          |                             |             |                   |         |        |       |        | Four                 | -2 -1 0 1 2                      |
| Test for subgroup differences:               | Chi <sup>2</sup> = $2.52.6$ | f=1 (P=0    | .11), <b>[</b> ²: | = 60.3% | 5      |       |        | ravi                 | ours experimental Favours contro |

## BMI change (kg/m-squared)



# Clinically relevant prolactin elevation (above upper limit of normal for age & gender)

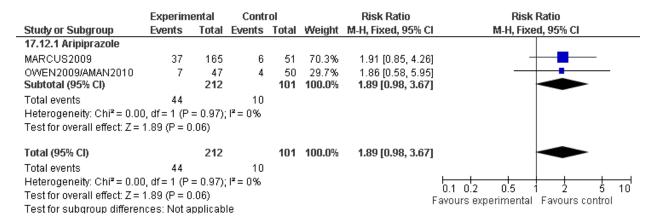


Autism: the management and support of children and young people on the autism spectrum (March 2013)

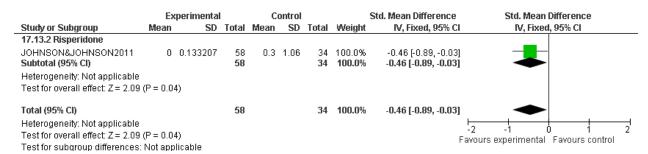
#### Prolactin concentration (ng/ml)

|   | Exp       | eriment  | al                   | C     | ontrol |                 |                         | Std. Mean Difference                           | Std. Mean Difference                              |
|---|-----------|----------|----------------------|-------|--------|-----------------|-------------------------|--|---|
| Study or Subgroup   | Mean      | SD       | Total                | Mean  | SD     | Total           | Weight                  | IV, Fixed, 95% CI                              | IV, Fixed, 95% CI                                 |
| 17.11.1 Risperidone   |           |          |                      |       |        |                 |                         |  |   |
| LUBY2006  | 33.38     | 14.48    | 11                   | 11.11 | 18.74  | 12              | 21.4%                   | 1.27 [0.36, 2.19]                              | <del></del>                                       |
| RUPPRISPERIDONE2001<br>Subtotal (95% CI)                          | 39        | 19.2     | 49<br><b>60</b>      | 10.1  | 8.8    | 52<br><b>64</b> | 78.6%<br><b>100.0</b> % | 1.94 [1.46, 2.42]<br><b>1.80 [1.38, 2.22</b> ] |   |
| Heterogeneity: Chi² = 1.61, d<br>Test for overall effect: Z = 8.3 | ,         |          |                      | %     |        |                 |                         |  |   |
| Total (95% CI)  |           |          | 60                   |       |        | 64              | 100.0%                  | 1.80 [1.38, 2.22]                              | •   |
| Heterogeneity: Chi² = 1.61, d                                     | lf=1 (P=  | 0.21);   | l <sup>2</sup> = 389 | Х.    |        |                 |                         | -  | <del></del>                                       |
| Test for overall effect: $Z = 8.3$                                | 4 (P < 0. | 00001)   |                      |       |        |                 |                         | Far  | -2 -1 U 1 2<br>vours experimental Favours control |
| Test for subgroup difference                                      | s: Not ap | plicable | е                    |       |        |                 |                         | ı a  | vodis experimental il avodis control              |

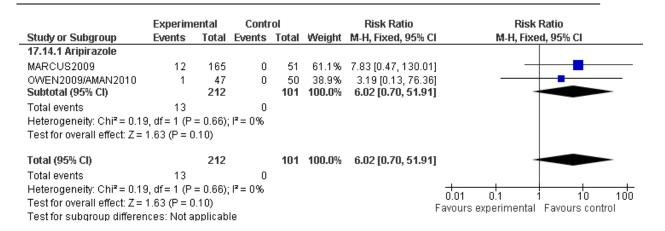
#### Any treatment-emergent extrapyramidal symptom



## **Extrapyramidal symptoms**



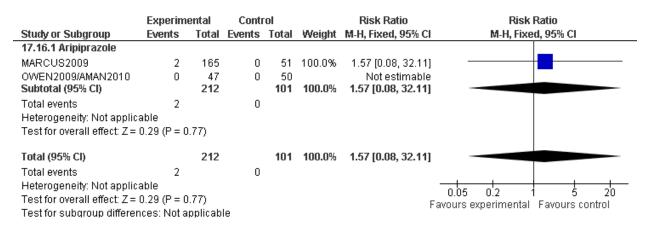
#### Extrapyramidal disorder



#### Fasting glucose (mg/dL) change score

|                                      | Ex       | perimental | I     | Co   | ontro | I     |        | Std. Mean Difference | Std. Mean Difference            |
|--------------------------------------|----------|------------|-------|------|-------|-------|--------|----------------------|---------------------------------|
| Study or Subgroup                    | Mean     | SD         | Total | Mean | SD    | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI               |
| 17.15.1 Risperidone                  |          |            |       |      |       |       |        |                      | _L                              |
| JOHNSON&JOHNSON2011                  | -0.2     | 9.286649   | 46    | -0.4 | 8.2   | 22    | 100.0% | 0.02 [-0.49, 0.53]   | _                               |
| Subtotal (95% CI)                    |          |            | 46    |      |       | 22    | 100.0% | 0.02 [-0.49, 0.53]   | -                               |
| Heterogeneity: Not applicable        |          |            |       |      |       |       |        |                      |                                 |
| Test for overall effect: Z = 0.09 (F | P = 0.90 | 3)         |       |      |       |       |        |                      |                                 |
| Total (95% CI)                       |          |            | 46    |      |       | 22    | 100.0% | 0.02 [-0.49, 0.53]   | •                               |
| Heterogeneity: Not applicable        |          |            |       |      |       |       |        | <u> </u>             | <del></del>                     |
| Test for overall effect: Z = 0.09 (F | P = 0.93 | 3)         |       |      |       |       |        | -2<br>Favou          | rs experimental Favours control |
| Test for subgroup differences: N     | lot app  | licable    |       |      |       |       |        | ravou                | is experimental Favours control |

# Fasting glucose (=>115 mg/dL)



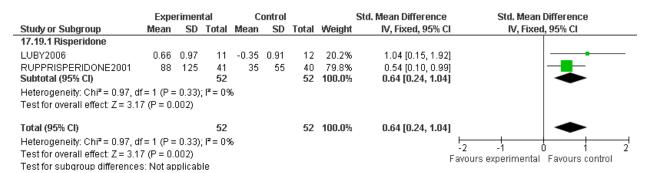
# Fasting triglycerides (=>120 mg/dL for females or 160 mg/dL for males)

|                                       | Experim      | ental    | Conti       | rol   |        | Risk Ratio        | Risk Ratio   |
|---------------------------------------|--------------|----------|-------------|-------|--------|-------------------|--|
| Study or Subgroup                     | Events       | Total    | Events      | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                                 |
| 17.17.1 Aripiprazole                  |              |          |             |       |        |                   |  |
| MARCUS2009                            | 17           | 165      | 2           | 51    | 38.7%  | 2.63 [0.63, 10.99 | ıj <del>  •</del>                                    |
| OWEN2009/AMAN2010                     | 6            | 47       | 5           | 50    | 61.3%  | 1.28 [0.42, 3.90  | )j <del>                                    </del>   |
| Subtotal (95% CI)                     |              | 212      |             | 101   | 100.0% | 1.80 [0.74, 4.35  | i 🔷  |
| Total events                          | 23           |          | 7           |       |        |                   |  |
| Heterogeneity: Chi <sup>2</sup> = 0.6 | 3, df = 1 (P | = 0.43); | $I^2 = 0\%$ |       |        |                   |  |
| Test for overall effect: Z=           | 1.30 (P = 0  | .19)     |             |       |        |                   |  |
| Total (95% CI)                        |              | 212      |             | 101   | 100.0% | 1.80 [0.74, 4.35  |  |
| Total events                          | 23           |          | 7           |       |        |                   |  |
| Heterogeneity: Chi <sup>2</sup> = 0.6 | 3, df = 1 (P | = 0.43); | $I^2 = 0\%$ |       |        |                   | 0.05 0.2 1 5 20                                      |
| Test for overall effect: Z=           | 1.30 (P = 0  | .19)     |             |       |        |                   | 0.05 0.2 1 5 20 Favours experimental Favours control |
| Test for subgroup differer            | nces: Not a  | pplicab  | le          |       |        |                   | i avouis experimental Favouis control                |

#### Insulin resistance (HOMA-IR) change score

|                                   | Expe           | rimental |       | C    | ontrol |       |        | Std. Mean Difference | Std. Mean Difference                  |
|-----------------------------------|----------------|----------|-------|------|--------|-------|--------|----------------------|---------------------------------------|
| Study or Subgroup                 | Mean           | SD       | Total | Mean | SD     | Total | Weight | IV, Fixed, 95% C     | I IV, Fixed, 95% CI                   |
| 17.18.1 Risperidone               |                |          |       |      |        |       |        |                      |                                       |
| JOHNSON&JOHNSON2011               | 0.1813953      | 1.429791 | 43    | 0.36 | 1.59   | 22    | 100.0% | -0.12 [-0.63, 0.40   | n — — —                               |
| Subtotal (95% CI)                 |                |          | 43    |      |        | 22    | 100.0% | -0.12 [-0.63, 0.40   | ] -                                   |
| Heterogeneity: Not applicable     |                |          |       |      |        |       |        |                      |                                       |
| Test for overall effect: Z = 0.45 | (P = 0.65)     |          |       |      |        |       |        |                      |                                       |
| Total (95% CI)                    |                |          | 43    |      |        | 22    | 100.0% | -0.12 [-0.63, 0.40   | 1                                     |
| Heterogeneity: Not applicable     |                |          |       |      |        |       |        |                      | 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 |
| Test for overall effect: Z = 0.45 | (P = 0.65)     |          |       |      |        |       |        |                      | Favours experimental Favours control  |
| Test for subgroup differences:    | Not applicable | le       |       |      |        |       |        |                      | i avouis experimentar Favouis Control |

# Leptin (mg/L) change score



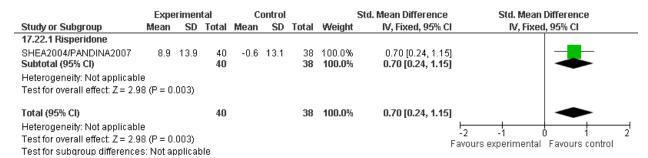
#### Diastolic blood pressure (mm Hg) change scores

|                                    | Expe       | rimer   | ıtal  | Co   | ontro | I     |        | Std. Mean Difference | Std. Mean Difference            |
|------------------------------------|------------|---------|-------|------|-------|-------|--------|----------------------|---------------------------------|
| Study or Subgroup                  | Mean       | SD      | Total | Mean | SD    | Total | Weight | IV, Fixed, 95% CI    | IV, Fixed, 95% CI               |
| 17.20.1 Risperidone                |            |         |       |      |       |       |        |                      |                                 |
| SHEA2004/PANDINA2007               | 0.7        | 9.1     | 40    | -0.7 | 8.8   | 38    | 100.0% | 0.15 [-0.29, 0.60]   | _ <b></b>                       |
| Subtotal (95% CI)                  |            |         | 40    |      |       | 38    | 100.0% | 0.15 [-0.29, 0.60]   | <b>*</b>                        |
| Heterogeneity: Not applicab        | le         |         |       |      |       |       |        |                      |                                 |
| Test for overall effect: $Z = 0.6$ | 68 (P = 0. | 50)     |       |      |       |       |        |                      |                                 |
| Total (95% CI)                     |            |         | 40    |      |       | 38    | 100.0% | 0.15 [-0.29, 0.60]   | •                               |
| Heterogeneity: Not applicab        | le         |         |       |      |       |       |        | <u> </u>             | <del></del>                     |
| Test for overall effect: $Z = 0.6$ | 68 (P = 0. | 50)     |       |      |       |       |        | -2<br>Fouch          | -1 U 1                          |
| Test for subgroup difference       | es: Not ar | polical | ole   |      |       |       |        | Favou                | rs experimental Favours control |

# Systolic blood pressure (mm Hg) change scores

|   | Expe   | rimen | tal             | C    | ontrol |                 |                          | Std. Mean Difference                            | Std. Mean Difference                                |
|---|--------|-------|-----------------|------|--------|-----------------|--------------------------|---|---|
| Study or Subgroup M   | lean   | SD    | Total           | Mean | SD     | Total           | Weight                   | IV, Fixed, 95% CI                               | IV, Fixed, 95% CI                                   |
| 17.21.1 Risperidone   |        |       |                 |      |        |                 |                          |   | _   |
| SHEA2004/PANDINA2007<br>Subtotal (95% CI)   | 4      | 10.4  | 40<br><b>40</b> | -0.7 | 10.7   | 38<br><b>38</b> | 100.0%<br><b>100.0</b> % | 0.44 [-0.01, 0.89]<br><b>0.44 [-0.01, 0.89]</b> |   |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.92 (  | P = 0. | 05)   |                 |      |        |                 |                          |   |   |
| Total (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 1.92 ( Test for subgroup differences: I |        |       | <b>40</b>       |      |        | 38              | 100.0%                   | 0.44 [-0.01, 0.89]                              | -2 -1 0 1 2<br>Favours experimental Favours control |

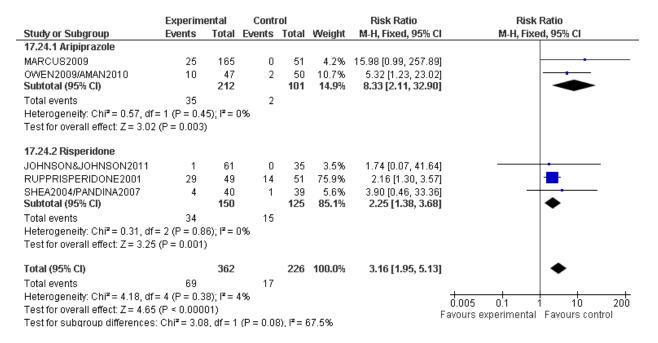
# Pulse (bpm) change score



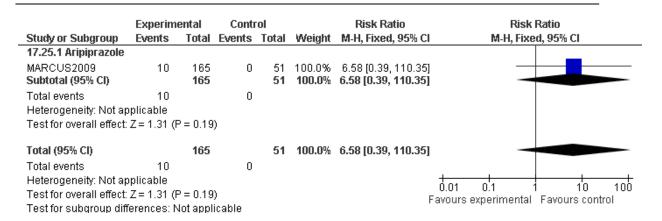
# Somnolence/Drowsiness

|   | Experim       | ental                            | Contr      | ol         |        | Risk Ratio         | Risk Ratio   |
|---|---------------|----------------------------------|------------|------------|--------|--------------------|--|
| Study or Subgroup                           | Events        | Total                            | Events     | Total      | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                                     |
| 17.23.1 Aripiprazole                        |               |                                  |            |            |        |                    |  |
| MARCUS2009                                  | 14            | 165                              | 2          | 51         | 20.1%  | 2.16 [0.51, 9.20]  | <del></del>  |
| OWEN2009/AMAN2010                           | 8             | 47                               | 2          | 50         | 12.8%  | 4.26 [0.95, 19.02] |  |
| Subtotal (95% CI)                           |               | 212                              |            | 101        | 32.9%  | 2.98 [1.07, 8.31]  |  |
| Total events                                | 22            |                                  | 4          |            |        |                    |  |
| Heterogeneity: Chi <sup>z</sup> = 0.41, df: | = 1 (P = 0.5) | $(2); I^2 = I$                   | 0%         |            |        |                    |  |
| Test for overall effect: Z = 2.08           | (P = 0.04)    |                                  |            |            |        |                    |  |
| 17.23.2 Risperidone                         |               |                                  |            |            |        |                    |  |
| JOHNSON&JOHNSON2011                         | 7             | 61                               | 1          | 35         | 8.4%   | 4.02 [0.52, 31.31] |  |
| RUPPRISPERIDONE2001                         | 24            | 49                               | 6          | 51         | 38.7%  | 4.16 [1.86, 9.30]  |  |
| SHEA2004/PANDINA2007                        | 29            | 40                               | 3          | 39         | 20.0%  | 9.43 [3.13, 28.42] |  |
| Subtotal (95% CI)                           |               | 150                              |            | 125        | 67.1%  | 5.71 [3.08, 10.60] | •  |
| Total events                                | 60            |                                  | 10         |            |        |                    |  |
| Heterogeneity: Chi² = 1.50, df:             | = 2 (P = 0.4) | $7); I^2 = I$                    | 0%         |            |        |                    |  |
| Test for overall effect: Z = 5.53           | (P < 0.000    | 01)                              |            |            |        |                    |  |
| Total (95% CI)                              |               | 362                              |            | 226        | 100.0% | 4.81 [2.85, 8.13]  | •  |
| Total events                                | 82            |                                  | 14         |            |        |                    |  |
| Heterogeneity: Chi² = 2.78, df:             | = 4 (P = 0.6  | $(0);  \mathbf{r} = \mathbf{r} $ | 0%         |            |        |                    |  |
| Test for overall effect: Z = 5.88           | (P < 0.000    | 01)                              |            |            |        | -                  | 0.05 0.2 1 5 20<br>ayours experimental Fayours control |
| Test for subgroup differences               | : Chi² = 1.1- | 4, df = 1                        | (P = 0.29) | 3), I² = 1 | 12.2%  | r                  | avours experimental Favours control                    |

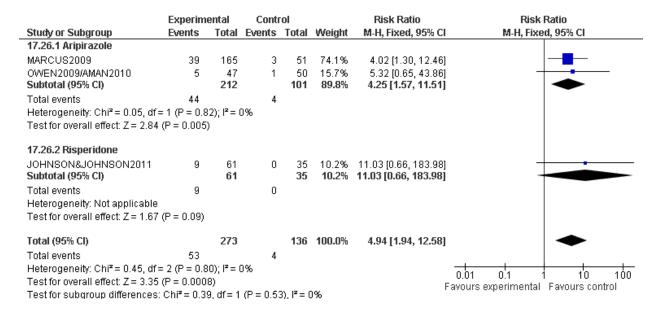
#### **Fatigue**



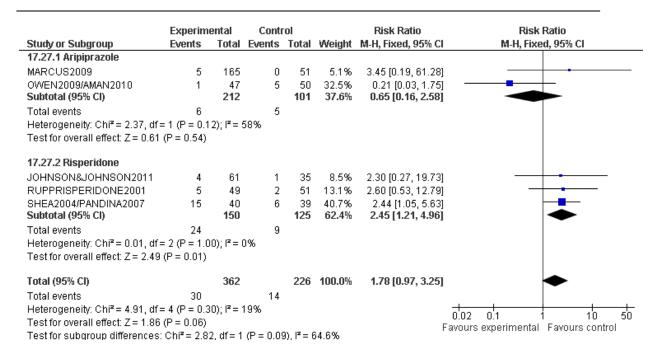
#### Lethargy



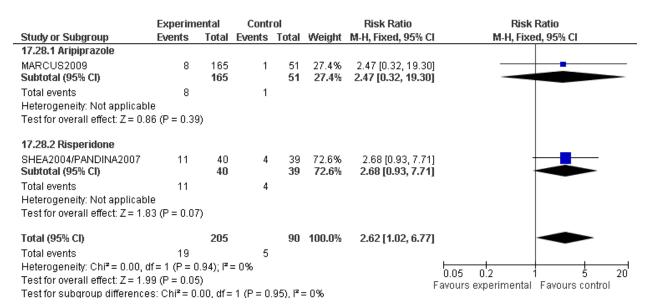
#### Sedation



#### Upper respiratory tract infection



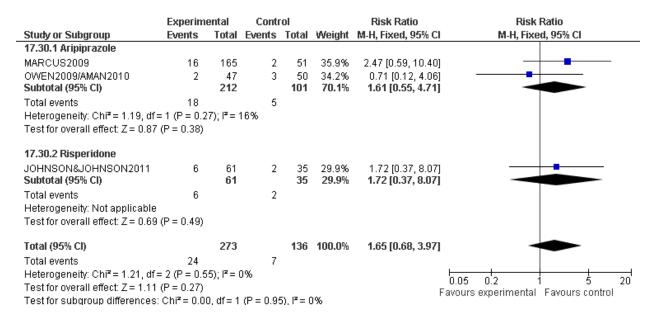
#### Rhinitis/rhinorrhea



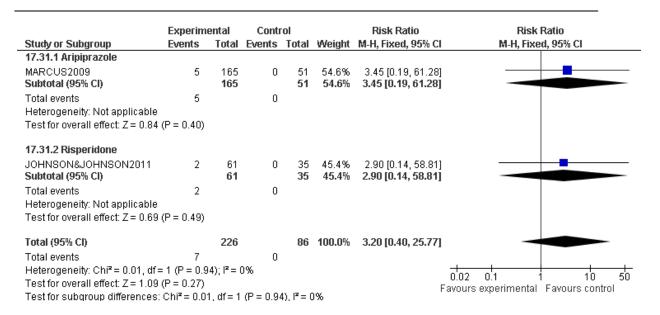
#### Nasal congestion

|   | Experime     | ntal      | Contr | ol               |                        | Risk Ratio                                    | Risk Ratio   |
|---|--------------|-----------|-------|------------------|------------------------|---|--|
| Study or Subgroup   | Events       |           |       |                  | Weight                 | M-H, Fixed, 95% C                             |  |
| 17.29.1 Aripiprazole  |              |           |       |                  |                        |   | i li   |
| MARCUS2009  | 6            | 165       | 1     | 51               | 6.9%                   | 1.85 [0.23, 15.05                             | 5]   |
| OWEN2009/AMAN2010<br>Subtotal (95% CI)  | 3            | 47<br>212 | 1     | 50<br><b>101</b> | 4.4%<br>11.3%          | 3.19 [0.34, 29.62<br><b>2.37 [0.52, 10.77</b> |  |
| Total events  | 9            |           | 2     |                  |                        |   |  |
| Heterogeneity: Chi² = 0.12, df  | = 1 (P = 0.) | 73); l² = | = 0%  |                  |                        |   |  |
| Test for overall effect: $Z = 1.12$   | 2 (P = 0.26) |           |       |                  |                        |   |  |
| 17.29.2 Risperidone   |              |           |       |                  |                        |   |  |
| RUPPRISPERIDONE2001<br>Subtotal (95% CI)  | 25           | 49<br>49  | 20    | 51<br><b>51</b>  | 88.7%<br><b>88.7</b> % | 1.30 [0.84, 2.02<br><b>1.30 [0.84, 2.02</b>   |  |
| Total events<br>Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.18                                      |              |           | 20    |                  |                        |   |  |
| Total (95% CI)  |              | 261       |       | 152              | 100.0%                 | 1.42 [0.92, 2.19                              | ı <b>→</b>   |
| Total events Heterogeneity: Chi <sup>2</sup> = 0.73, df Test for overall effect: Z = 1.60 Test for subgroup differences | ) (P = 0.11) |           |       | 45), l² =        | : 0%                   |   | 0.05 0.2 1 5 20 Favours experimental Favours control |

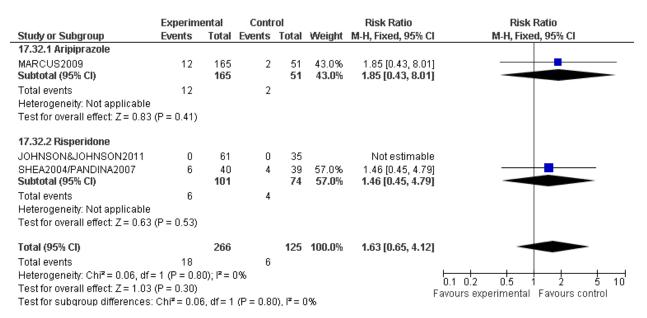
# Nasopharyngitis



#### Nose bleed



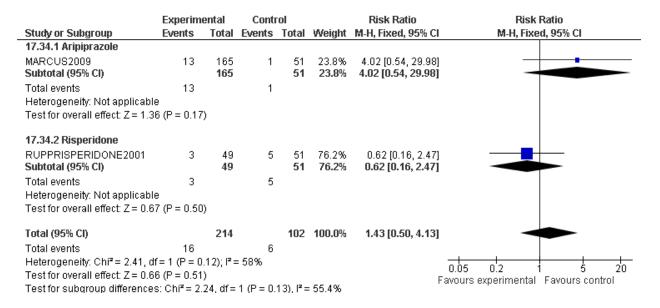
# Coughing



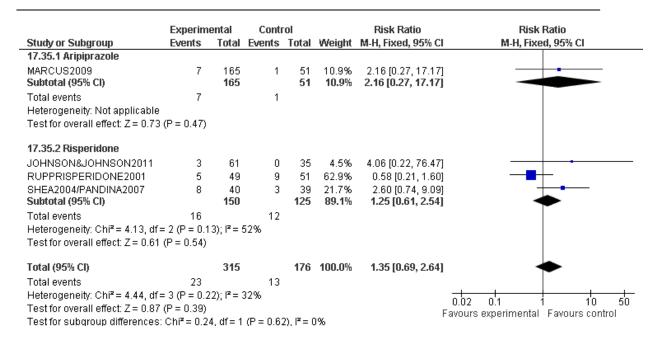
#### **Increased** appetite

|   | Experim                | ental           | Contr      | ol                     |        | Risk Ratio         | Risk Ratio   |
|---|------------------------|-----------------|------------|------------------------|--------|--------------------|--|
| Study or Subgroup                           | Events                 |                 |            |                        | Weight | M-H, Fixed, 95% CI |  |
| 17.33.1 Aripiprazole                        |                        |                 |            |                        |        |                    |  |
| MARCUS2009                                  | 20                     | 165             | 2          | 51                     | 18.6%  | 3.09 [0.75, 12.78] | +  |
| OWEN2009/AMAN2010                           | 7                      | 47              | 5          | 50                     | 29.4%  | 1.49 [0.51, 4.37]  | <del>-   • -</del>                                     |
| Subtotal (95% CI)                           |                        | 212             |            | 101                    | 48.0%  | 2.11 [0.89, 5.01]  |  |
| Total events                                | 27                     |                 | 7          |                        |        |                    |  |
| Heterogeneity: Chi² = 0.68, df=             | = 1 (P = 0.4           | 1); $I^{2} = 0$ | 0%         |                        |        |                    |  |
| Test for overall effect: $Z = 1.69$         | (P = 0.09)             |                 |            |                        |        |                    |  |
| 17.33.2 Risperidone                         |                        |                 |            |                        |        |                    |  |
| JOHNSON&JOHNSON2011                         | 16                     | 61              | 2          | 35                     | 15.4%  | 4.59 [1.12, 18.80] |  |
| RUPPRISPERIDONE2001                         | 12                     | 49              | 2          | 51                     | 11.9%  | 6.24 [1.47, 26.48] | I  |
| SHEA2004/PANDINA2007                        | 9                      | 40              | 4          | 39                     | 24.6%  | 2.19 [0.74, 6.54]  |  |
| Subtotal (95% CI)                           |                        | 150             |            | 125                    | 52.0%  | 3.83 [1.84, 8.01]  | •  |
| Total events                                | 37                     |                 | 8          |                        |        |                    |  |
| Heterogeneity: Chi <sup>2</sup> = 1.50, df= | = 2 (P = 0.4)          | $7); I^2 = 0$   | 0%         |                        |        |                    |  |
| Test for overall effect: $Z = 3.58$         | (P = 0.000)            | 3)              |            |                        |        |                    |  |
| Total (95% CI)                              |                        | 362             |            | 226                    | 100.0% | 3.01 [1.73, 5.24]  | •  |
| Total events                                | 64                     |                 | 15         |                        |        |                    |  |
| Heterogeneity: Chi² = 3.29, df=             | = 4 (P = 0.5           | 1); $I^2 = 0$   | 0%         |                        |        |                    | 0.05 0.2 1 5 2   |
| Test for overall effect: $Z = 3.89$         | (P = 0.000)            | 1)              |            |                        |        | 1                  | 0.05 0.2 1 5 2<br>Favours experimental Favours control |
| Test for subgroup differences:              | Chi <sup>2</sup> = 1.0 | 6, df = 1       | (P = 0.30) | $0),  \mathbf{r}  = 0$ | 3.0%   | ſ                  | ravouis expeninental ravouis contion                   |

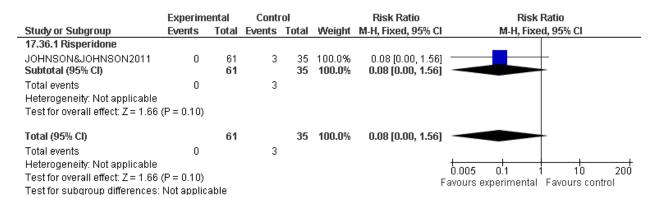
#### Decreased appetite



# Abdominal pain/Stomachache



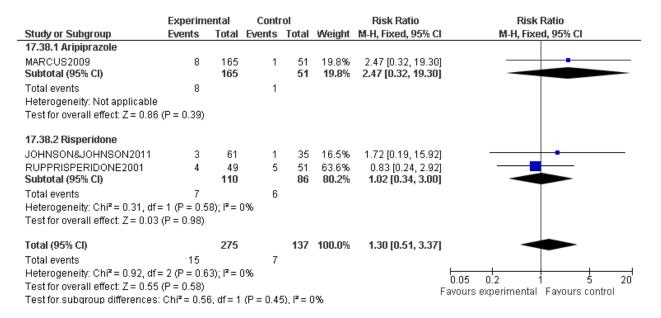
#### Abdominal discomfort



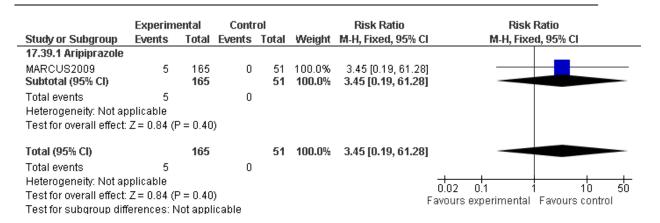
#### Vomiting

|   | Ехрегіт                | ental           | Contr      | ol         |        | Risk Ratio         | Risk Ratio  |
|---|------------------------|-----------------|------------|------------|--------|--------------------|---|
| Study or Subgroup                           | Events                 | Total           | Events     | Total      | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                                      |
| 17.37.1 Aripiprazole                        |                        |                 |            |            |        |                    |   |
| MARCUS2009                                  | 22                     | 165             | 4          | 51         | 21.5%  | 1.70 [0.61, 4.71]  | <del>  •</del>  |
| OWEN2009/AMAN2010                           | 7                      | 47              | 2          | 50         | 6.8%   | 3.72 [0.81, 17.03] | +   |
| Subtotal (95% CI)                           |                        | 212             |            | 101        | 28.3%  | 2.19 [0.95, 5.03]  |   |
| Total events                                | 29                     |                 | 6          |            |        |                    |   |
| Heterogeneity: Chi <sup>2</sup> = 0.71, df: | = 1 (P = 0.4)          | $0); I^{z} = I$ | 0%         |            |        |                    |   |
| Test for overall effect: Z = 1.84           | (P = 0.07)             |                 |            |            |        |                    |   |
| 17.37.2 Risperidone                         |                        |                 |            |            |        |                    |   |
| JOHNSON&JOHNSON2011                         | 4                      | 61              | 2          | 35         | 8.9%   | 1.15 [0.22, 5.95]  |   |
| RUPPRISPERIDONE2001                         | 16                     | 49              | 12         | 51         | 41.4%  | 1.39 [0.73, 2.63]  | <del>                                     </del>        |
| SHEA2004/PANDINA2007                        | 6                      | 40              | 6          | 39         | 21.4%  | 0.97 [0.34, 2.76]  |   |
| Subtotal (95% CI)                           |                        | 150             |            | 125        | 71.7%  | 1.23 [0.74, 2.07]  | · • • • • • • • • • • • • • • • • • • •                 |
| Total events                                | 26                     |                 | 20         |            |        |                    |   |
| Heterogeneity: Chi² = 0.33, df:             | = 2 (P = 0.8           | 5); l² = t      | 0%         |            |        |                    |   |
| Test for overall effect: $Z = 0.80$         | (P = 0.42)             |                 |            |            |        |                    |   |
| Total (95% CI)                              |                        | 362             |            | 226        | 100.0% | 1.50 [0.97, 2.34]  | •   |
| Total events                                | 55                     |                 | 26         |            |        |                    |   |
| Heterogeneity: Chi² = 2.25, df:             | = 4 (P = 0.6           | 9); l² = 1      | 0%         |            |        |                    | 0.05 0.2 1 5 20   |
| Test for overall effect: $Z = 1.82$         | (P = 0.07)             |                 |            |            |        | 1                  | 0.05 0.2 1 5 20<br>Favours experimental Favours control |
| Test for subgroup differences               | Chi <sup>2</sup> = 1.3 | 1, df = 1       | (P = 0.25) | 5), I² = 3 | 23.6%  | '                  | aroulo expellitettat il aroulo collitot                 |

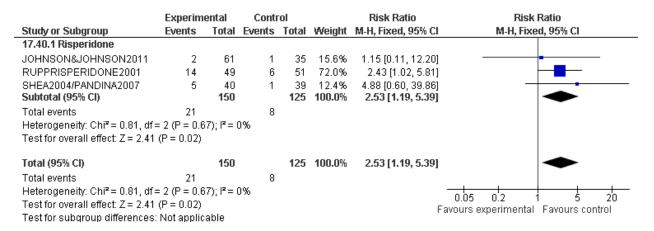
#### Nausea



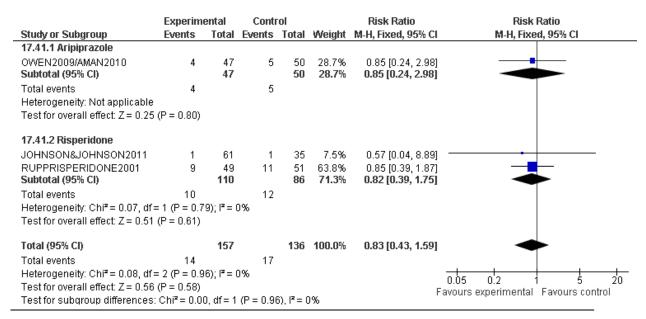
#### Gastroenteritis viral



### Constipation

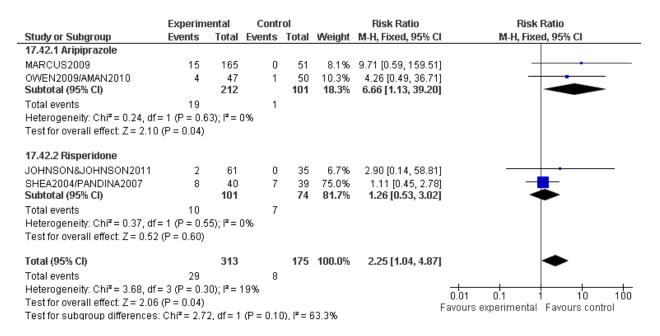


#### Diarrhoea

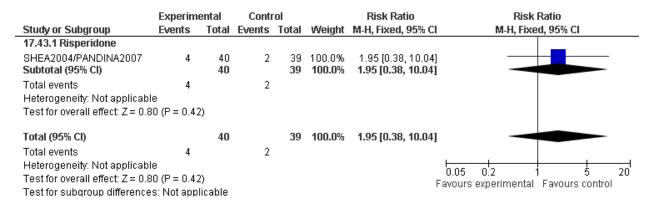


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#### **Fever**



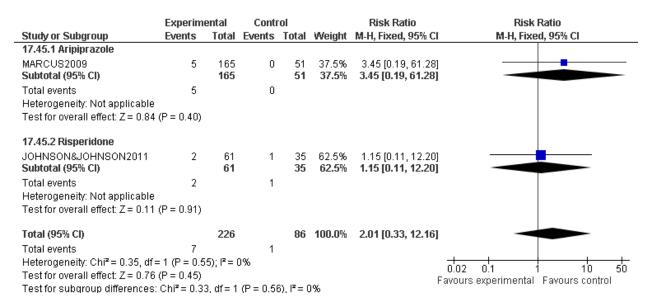
#### Influenza-like symptoms



#### Insomnia

|  | Favours experi                 | mental     | Contr                   | ol              |                        | Risk Ratio                                    | Risk Ratio   |
|--|--------------------------------|------------|-------------------------|-----------------|------------------------|---|--|
| Study or Subgroup                            | Events                         | Total      | Events                  | Total           | Weight                 | M-H, Fixed, 95% CI                            | M-H, Fixed, 95% CI                                       |
| 17.44.1 Aripiprazole                         |                                |            |                         |                 |                        |   |  |
| OWEN2009/AMAN2010<br>Subtotal (95% Cl)       | 3                              | 47<br>47   | 4                       | 50<br><b>50</b> | 13.9%<br><b>13.9</b> % | 0.80 [0.19, 3.38]<br><b>0.80 [0.19, 3.38]</b> |  |
| Total events                                 | 3                              |            | 4                       |                 |                        |   |  |
| Heterogeneity: Not applicable                |                                |            |                         |                 |                        |   |  |
| Test for overall effect: Z = 0.31            | (P = 0.76)                     |            |                         |                 |                        |   |  |
| 17.44.2 Risperidone                          |                                |            |                         |                 |                        |   |  |
| JOHNSON&JOHNSON2011                          | 0                              | 61         | 2                       | 35              | 11.4%                  | 0.12 [0.01, 2.35]                             | · · · · · · · · · · · · · · · · · · ·                    |
| RUPPRISPERIDONE2001                          | 7                              | 49         | 15                      | 51              | 52.8%                  | 0.49 [0.22, 1.09]                             | <del></del>  |
| SHEA2004/PANDINA2007                         | 6                              | 40         | 6                       | 39              | 21.8%                  | 0.97 [0.34, 2.76]                             |  |
| Subtotal (95% CI)                            |                                | 150        |                         | 125             | 86.1%                  | 0.56 [0.31, 1.03]                             | •  |
| Total events                                 | 13                             |            | 23                      |                 |                        |   |  |
| Heterogeneity: Chi <sup>z</sup> = 2.26, df = | 2 (P = 0.32); I <sup>z</sup> = | 11%        |                         |                 |                        |   |  |
| Test for overall effect: Z = 1.87            | (P = 0.06)                     |            |                         |                 |                        |   |  |
| Total (95% CI)                               |                                | 197        |                         | 175             | 100.0%                 | 0.59 [0.34, 1.04]                             | •  |
| Total events                                 | 16                             |            | 27                      |                 |                        |   |  |
| Heterogeneity: Chi <sup>2</sup> = 2.40, df = | 3 (P = 0.49); I <sup>z</sup> = | 0%         |                         |                 |                        |   | 0.01 0.1 1 10 10   |
| Test for overall effect: Z = 1.83            | (P = 0.07)                     |            |                         |                 |                        | ı   | 0.01 0.1 1 10 10<br>Favours experimental Favours control |
| Test for subgroup differences:               | $Chi^2 = 0.19, df = 1$         | I(P = 0.6) | 6), I <sup>z</sup> = 09 | 6               |                        | '   | avodio experimental Tavodio control                      |

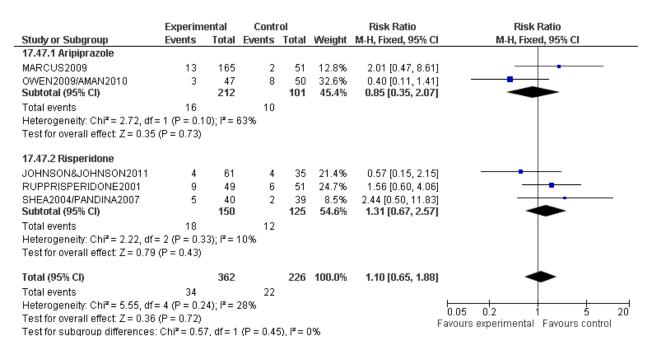
### Hypersomnia



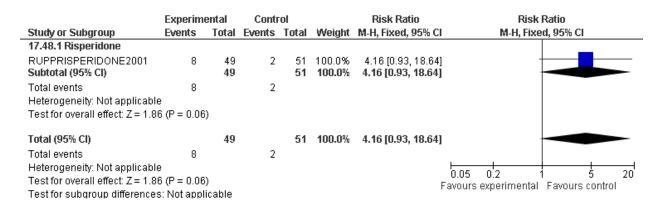
### Sleep problems

|                                    | Experim      | ental  | Contr  | ol    |        | Risk Ratio        | Risk Ratio   |
|------------------------------------|--------------|--------|--------|-------|--------|-------------------|--|
| Study or Subgroup                  | Events       | Total  | Events | Total | Weight | M-H, Fixed, 95% ( | CI M-H, Fixed, 95% CI                                    |
| 17.46.1 Risperidone                |              |        |        |       |        |                   |  |
| RUPPRISPERIDONE2001                | 11           | 49     | 9      | 51    | 100.0% | 1.27 [0.58, 2.80  | 0] —   |
| Subtotal (95% CI)                  |              | 49     |        | 51    | 100.0% | 1.27 [0.58, 2.80  | oj 🔷   |
| Total events                       | 11           |        | 9      |       |        |                   |  |
| Heterogeneity: Not applicabl       | e            |        |        |       |        |                   |  |
| Test for overall effect: $Z = 0.6$ | 0 (P = 0.55  | )      |        |       |        |                   |  |
| Total (95% CI)                     |              | 49     |        | 51    | 100.0% | 1.27 [0.58, 2.80  | 0]   |
| Total events                       | 11           |        | 9      |       |        |                   |  |
| Heterogeneity: Not applicabl       | e            |        |        |       |        |                   | 104 012 015 4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1        |
| Test for overall effect: $Z = 0.6$ | i0 (P = 0.55 | )      |        |       |        |                   | 0.1 0.2 0.5 1 2 5 1 Favours experimental Favours control |
| Test for subgroup difference       | s: Not appl  | icable |        |       |        |                   | ravours experimental ravours control                     |

#### Headache

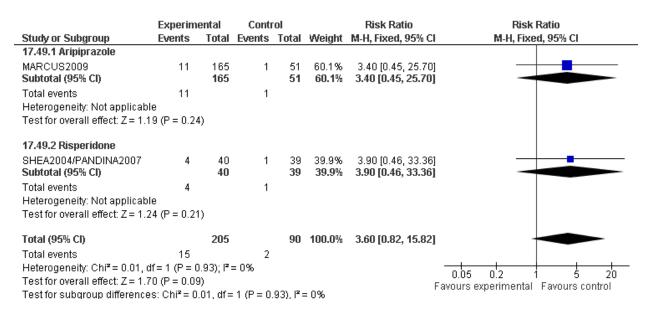


#### **Dizziness**

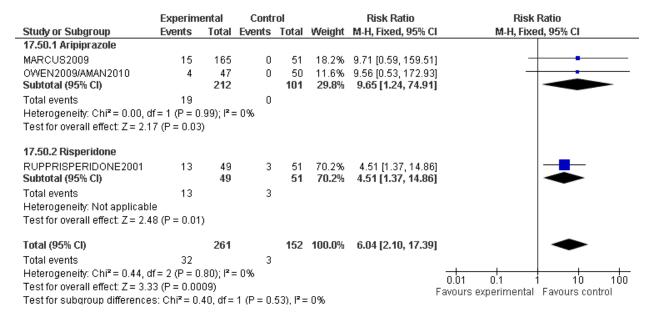


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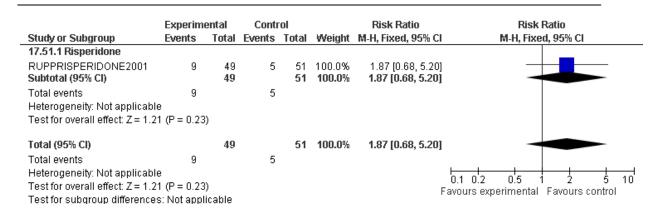
#### **Increased salivation**



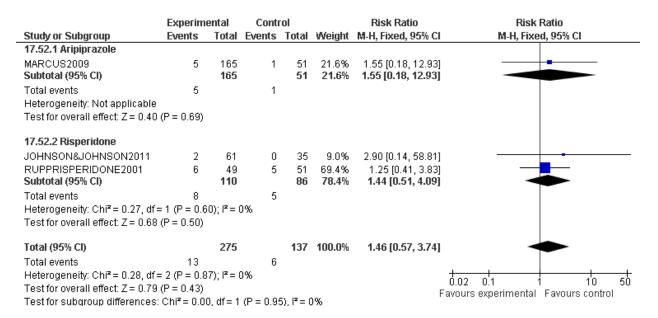
### **Drooling**



#### Dry mouth



#### **Increased thirst**



# Tachycardia

|   | Experim       | ental                   | Conti  | ol              |                         | Risk Ratio                                      | Risk Ratio   |
|---|---------------|-------------------------|--------|-----------------|-------------------------|---|--|
| Study or Subgroup                         | Events        | Total                   | Events | Total           | Weight                  | M-H, Fixed, 95% C                               | I M-H, Fixed, 95% CI                                   |
| 17.53.1 Risperidone                       |               |                         |        |                 |                         |   |  |
| RUPPRISPERIDONE2001                       | 6             | 49                      | 1      | 51              | 65.9%                   | 6.24 [0.78, 50.01                               | 1  |
| SHEA2004/PANDINA2007<br>Subtotal (95% CI) | 5             | 40<br><b>89</b>         | 0      | 39<br><b>90</b> | 34.1%<br><b>100.0</b> % | 10.73 [0.61, 187.79<br><b>7.77 [1.45, 41.72</b> |  |
| Total events                              | 11            |                         | 1      |                 |                         |   |  |
| Heterogeneity: Chi² = 0.09, o             | f = 1 (P = 0) | ).76); l² :             | = 0%   |                 |                         |   |  |
| Test for overall effect: $Z = 2.3$        | 39 (P = 0.02  | 2)                      |        |                 |                         |   |  |
| Total (95% CI)                            |               | 89                      |        | 90              | 100.0%                  | 7.77 [1.45, 41.72                               |  |
| Total events                              | 11            |                         | 1      |                 |                         |   |  |
| Heterogeneity: Chi² = 0.09, o             | f=1 (P=0      | ).76); l <sup>z</sup> : | = 0%   |                 |                         |   | 004 04 40 400  |
| Test for overall effect: $Z = 2.3$        | 39 (P = 0.02  | 2)                      |        |                 |                         |   | 0.01 0.1 1 10 100 Favours experimental Favours control |
| Test for subgroup difference              | s: Not ann    | licable                 |        |                 |                         |   | ravouis experimental ravouis contion                   |

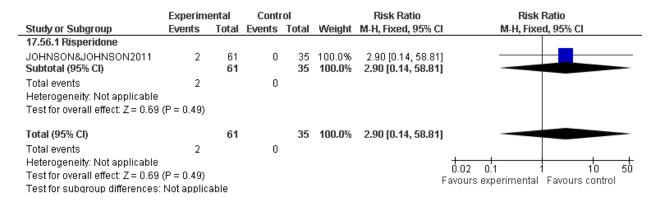
### Anorexia

|  | Experime    | ental           | Contr  | ol              |                          | Risk Ratio                                     | Risk Ratio  |
|--|-------------|-----------------|--------|-----------------|--------------------------|--|---|
| Study or Subgroup  | Events      | Total           | Events | Total           | Weight                   | M-H, Fixed, 95% C                              | CI M-H, Fixed, 95% CI                                   |
| 17.54.1 Risperidone  |             |                 |        |                 |                          |  |   |
| SHEA2004/PANDINA2007<br>Subtotal (95% CI)  | 4           | 40<br><b>40</b> | 1      | 39<br><b>39</b> | 100.0%<br><b>100.0</b> % | 3.90 [0.46, 33.36<br><b>3.90 [0.46, 33.3</b> 6 |   |
| Total events<br>Heterogeneity: Not applicabl<br>Test for overall effect: Z = 1.2                           |             | )               | 1      |                 |                          |  |   |
| Total (95% CI)   |             | 40              |        | 39              | 100.0%                   | 3.90 [0.46, 33.36                              | 5]  |
| Total events  Heterogeneity: Not applicabl  Test for overall effect: Z = 1.2  Test for subgroup difference | 4 (P = 0.21 | _               | 1      |                 |                          |  | 0.05 0.2 1 5 20<br>Favours experimental Favours control |

# **Anxiety**

|  | Ехрегіте | ental           | Contr  | ol              |                          | Risk Ratio                                   | Risk Ratio                           |
|--|----------|-----------------|--------|-----------------|--------------------------|--|--------------------------------------|
| Study or Subgroup  | Events   | Total           | Events | Total           | Weight                   | M-H, Fixed, 95% (                            | CI M-H, Fixed, 95% CI                |
| 17.55.1 Risperidone  |          |                 |        |                 |                          |  | _                                    |
| RUPPRISPERIDONE2001<br>Subtotal (95% CI)   | 12       | 49<br><b>49</b> | 10     | 51<br><b>51</b> | 100.0%<br><b>100.0</b> % | 1.25 [0.59, 2.62<br><b>1.25 [0.59, 2.6</b> 2 |                                      |
| Total events<br>Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.59 |          | )               | 10     |                 |                          |  |                                      |
| Total (95% CI)   |          | 49              |        | 51              | 100.0%                   | 1.25 [0.59, 2.62                             | 21                                   |
| Total events   | 12       |                 | 10     |                 |                          |  |                                      |
| Heterogeneity: Not applicable  | !        |                 |        |                 |                          |  | 0.1 0.2 0.5 1 2 5 10                 |
| Test for overall effect: Z = 0.59 Test for subgroup differences                    |          | ,               |        |                 |                          |  | Favours experimental Favours control |

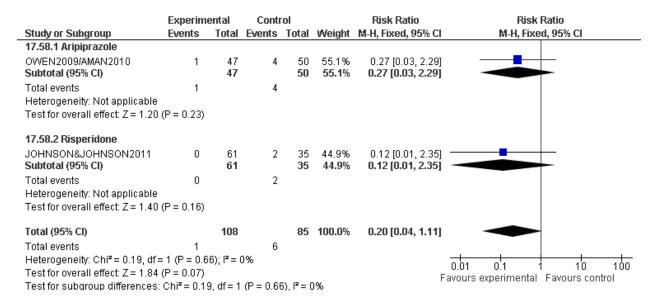
# Depression



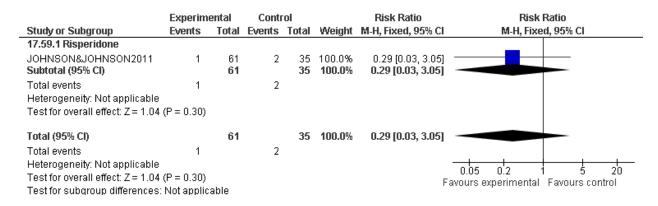
### Apathy

|   | Experime    | ental           | Contr  | ol              |                          | Risk Ratio   | Risk Ratio   |
|---|-------------|-----------------|--------|-----------------|--------------------------|--|--|
| Study or Subgroup   | Events      | Total           | Events | Total           | Weight                   | M-H, Fixed, 95% (                                  | CI M-H, Fixed, 95% CI                                  |
| 17.57.1 Risperidone   |             |                 |        |                 |                          |  |  |
| SHEA2004/PANDINA2007<br>Subtotal (95% CI)   | 5           | 40<br><b>40</b> | 0      | 39<br><b>39</b> | 100.0%<br><b>100.0</b> % | 10.73 [0.61, 187.79<br><b>10.73 [0.61, 187.7</b> 9 |  |
| Total events<br>Heterogeneity: Not applicabl<br>Test for overall effect: Z = 1.6                        |             | )               | 0      |                 |                          |  |  |
| Total (95% CI)  |             | 40              |        | 39              | 100.0%                   | 10.73 [0.61, 187.79                                | 9]   |
| Total events Heterogeneity: Not applicabl Test for overall effect: Z = 1.6 Test for subgroup difference | 3 (P = 0.10 | •               | 0      |                 |                          |  | 0.01 0.1 1 10 100 Favours experimental Favours control |

# Aggression

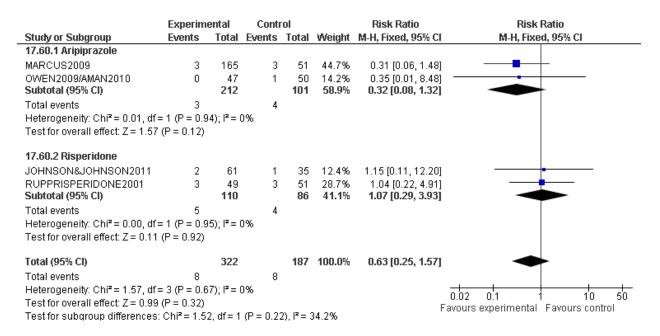


### Agitation

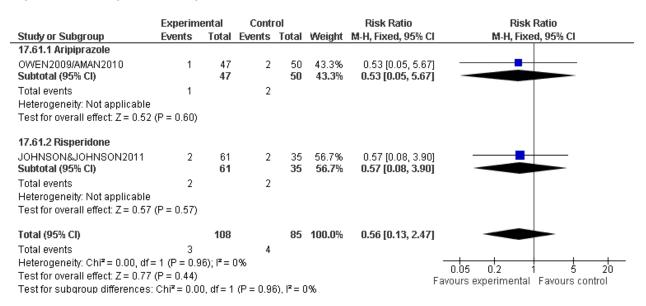


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#### Restlessness



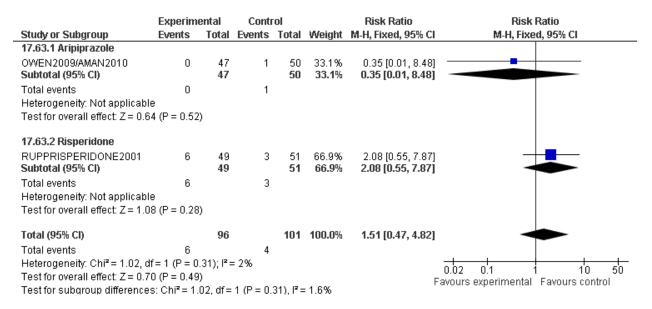
### Psychomotor hyperactivity



### Tremor

|  | Ехрегіте     | ntal            | Contr  | ol               |                        | Risk Ratio  | Risk Ratio   |
|--|--------------|-----------------|--------|------------------|------------------------|---|--|
| Study or Subgroup  | Events       |                 | Events |                  | Weight                 | M-H, Fixed, 95% CI                                |  |
| 17.62.1 Aripirazole  |              |                 |        |                  |                        |   |  |
| MARCUS2009   | 17           | 165             | 0      | 51               | 27.9%                  | 10.96 [0.67, 179.19]                              | -  |
| OWEN2009/AMAN2010<br>Subtotal (95% CI)   | 4            | 47<br>212       | 0      | 50<br><b>101</b> | 17.7%<br><b>45.6</b> % | 9.56 [0.53, 172.93]<br><b>10.42 [1.33, 81.48]</b> |  |
| Total events   | 21           |                 | 0      |                  |                        |   |  |
| Heterogeneity: Chi² = 0.00, d<br>Test for overall effect: Z = 2.2  |              |                 | = 0%   |                  |                        |   |  |
| 17.62.2 Risperidone  |              |                 |        |                  |                        |   |  |
| RUPPRISPERIDONE2001  | 7            | 49              | 1      | 51               | 35.9%                  | 7.29 [0.93, 57.07]                                | <del></del>  |
| SHEA2004/PANDINA2007<br>Subtotal (95% CI)  | 4            | 40<br><b>89</b> | 0      | 39<br><b>90</b>  | 18.5%<br><b>54.4</b> % | 8.78 [0.49, 157.85]<br><b>7.79 [1.46, 41.70]</b>  |  |
| Total events   | 11           |                 | 1      |                  |                        |   |  |
| Heterogeneity: Chi² = 0.01, d<br>Test for overall effect: Z = 2.4  | •            |                 | = 0%   |                  |                        |   |  |
| Total (95% CI)   |              | 301             |        | 191              | 100.0%                 | 8.99 [2.40, 33.64]                                | •  |
| Total events Heterogeneity: Chi <sup>z</sup> = 0.06, d Test for overall effect: Z = 3.2 Test for subgroup difference | 6 (P = 0.00° | 1)              |        | 83), l²=         | : 0%                   | ı   | 0.01 0.1 1 10 10<br>Favours experimental Favours control |

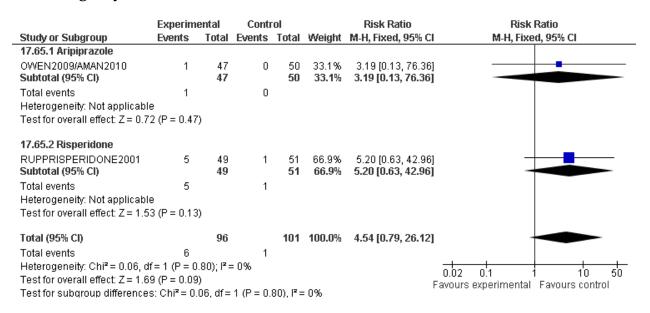
# Dyskinesia/Hyperkinesia



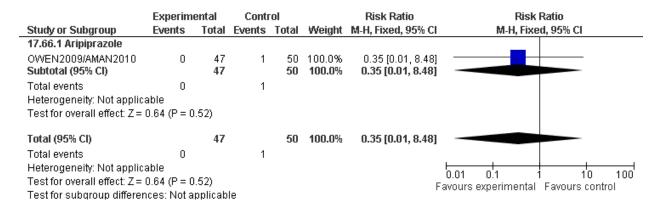
#### Hypokinesia

|  | Experimental       | Contr  | ol    |        | Risk Ratio        | Risk Ratio   |
|--|--------------------|--------|-------|--------|-------------------|--|
| Study or Subgroup                            | Events Total       | Events | Total | Weight | M-H, Fixed, 95% C | CI M-H, Fixed, 95% CI                                |
| 17.64.1 Aripiprazole                         |                    |        |       |        |                   |  |
| OWEN2009/AMAN2010                            | 1 47               | 0      | 50    | 100.0% | 3.19 [0.13, 76.38 | 6]   |
| Subtotal (95% CI)                            | 47                 |        | 50    | 100.0% | 3.19 [0.13, 76.36 | 5]   |
| Total events                                 | 1                  | 0      |       |        |                   |  |
| Heterogeneity: Not applic                    | able               |        |       |        |                   |  |
| Test for overall effect: Z=                  | 0.72 (P = 0.47)    |        |       |        |                   |  |
| Total (95% CI)                               | 47                 |        | 50    | 100.0% | 3.19 [0.13, 76.36 | 3]   |
| Total events                                 | 1                  | 0      |       |        |                   |  |
| Heterogeneity: Not applic                    | able               |        |       |        |                   | 002 04 4 40 5  |
| Test for overall effect: Z = 0.72 (P = 0.47) |                    |        |       |        |                   | 0.02 0.1 1 10 5 Favours experimental Favours control |
| Test for subgroup differen                   | nces: Not applicab | le     |       |        |                   | ravouis experimental ravouis continu                 |

### Muscle rigidity

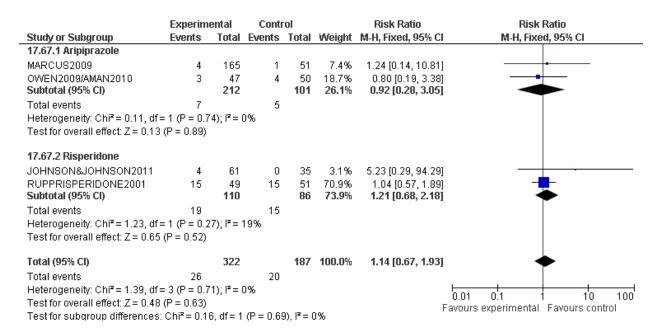


#### Muscle spasms

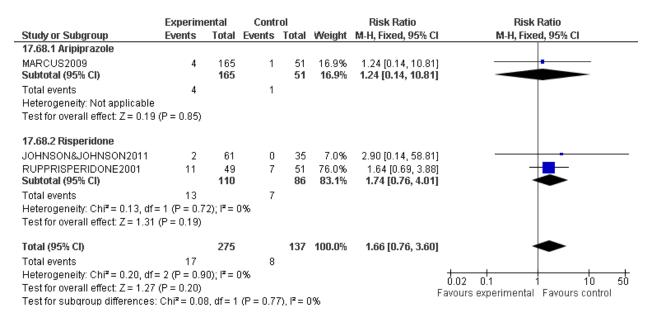


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#### **Enuresis**



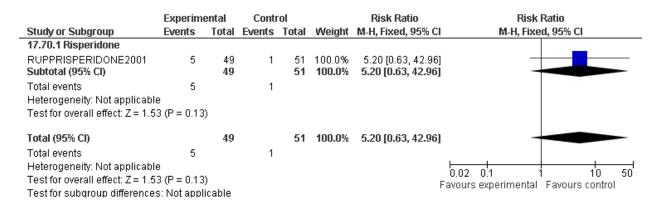
#### Skin irritation/Rash



#### Earache/Ear infection

|                                     | Ехрегіт       | ental          | Contr  | ol    |        | Risk Ratio                           | Risk Ratio                            |
|-------------------------------------|---------------|----------------|--------|-------|--------|--------------------------------------|---------------------------------------|
| Study or Subgroup                   | Events        | Total          | Events | Total | Weight | M-H, Fixed, 95% C                    | CI M-H, Fixed, 95% CI                 |
| 17.69.1 Risperidone                 |               |                |        |       |        |                                      |                                       |
| JOHNSON&JOHNSON2011                 | 2             | 61             | 0      | 35    | 13.9%  | 2.90 [0.14, 58.81                    | 1]                                    |
| RUPPRISPERIDONE2001                 | 2             | 49             | 4      | 51    | 86.1%  | 0.52 [0.10, 2.71                     | 1]                                    |
| Subtotal (95% CI)                   |               | 110            |        | 86    | 100.0% | 0.85 [0.22, 3.30                     | 0]                                    |
| Total events                        | 4             |                | 4      |       |        |                                      |                                       |
| Heterogeneity: Chi² = 0.98, df      | = 1 (P = 0.3) | $(2); I^2 = 0$ | 0%     |       |        |                                      |                                       |
| Test for overall effect: Z = 0.23   | (P = 0.82)    |                |        |       |        |                                      |                                       |
| Total (95% CI)                      |               | 110            |        | 86    | 100.0% | 0.85 [0.22, 3.30                     | 01                                    |
| Total events                        | 4             |                | 4      |       |        |                                      |                                       |
| Heterogeneity: Chi² = 0.98, df      | = 1 (P = 0.3) | (2); $I^2 = 0$ | 0%     |       |        |                                      | 0.02 0.1 1 10 50                      |
| Test for overall effect: $Z = 0.23$ |               |                |        |       |        | Favours experimental Favours control |                                       |
| Test for subgroup differences       | : Not applic  | able           |        |       |        |                                      | i avouis experimental Favouis control |

#### Sore throat



# Adverse events associated with low dose antipsychotics versus placebo

# Any side effect

|                                     | Ехрегіте    | ental                  | Contr      | ol              |                        | Risk Ratio                                     | Risk Ratio                           |
|-------------------------------------|-------------|------------------------|------------|-----------------|------------------------|--|--------------------------------------|
| Study or Subgroup                   | Events      | Total                  | Events     | Total           | Weight                 | M-H, Fixed, 95% C                              | M-H, Fixed, 95% CI                   |
| 18.1.1 Aripiprazole (5mg/day)       |             |                        |            |                 |                        |  |                                      |
| MARCUS2009<br>Subtotal (95% CI)     | 46          | 52<br><b>52</b>        | 37         | 51<br><b>51</b> | 65.8%<br><b>65.8</b> % | 1.22 [1.00, 1.48]<br><b>1.22 [1.00, 1.48</b> ] |                                      |
| Total events                        | 46          |                        | 37         |                 |                        |  |                                      |
| Heterogeneity: Not applicable       |             |                        |            |                 |                        |  |                                      |
| Test for overall effect: Z = 1.99 ( | P = 0.05    |                        |            |                 |                        |  |                                      |
| 18.1.2 Risperidone (0.125-0.17      | /5mg/day)   |                        |            |                 |                        |  |                                      |
| JOHNSON&JOHNSON2011                 | 12          | 30                     | 21         | 35              | 34.2%                  | 0.67 [0.40, 1.12]                              |                                      |
| Subtotal (95% CI)                   |             | 30                     |            | 35              | 34.2%                  | 0.67 [0.40, 1.12]                              | <b>→</b>                             |
| Total events                        | 12          |                        | 21         |                 |                        |  |                                      |
| Heterogeneity: Not applicable       |             |                        |            |                 |                        |  |                                      |
| Test for overall effect: Z = 1.54 ( | P = 0.12    |                        |            |                 |                        |  |                                      |
| Total (95% CI)                      |             | 82                     |            | 86              | 100.0%                 | 1.03 [0.84, 1.26]                              | •                                    |
| Total events                        | 58          |                        | 58         |                 |                        |  |                                      |
| Heterogeneity: Chi² = 5.60, df =    | 1 (P = 0.0) | 2); I <sup>2</sup> = 8 | 32%        |                 |                        |  | 01 02 05 1 2 5 10                    |
| Test for overall effect: Z = 0.30 ( | P = 0.77    |                        |            |                 |                        |  |                                      |
| Test for subgroup differences:      | Chi² = 4.62 | 2, df = 1              | (P = 0.03) | $3),  l^2 = 7$  | 78.3%                  |  | Favours experimental Favours control |

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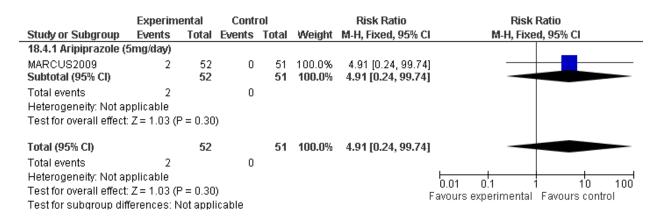
### Discontinuation due to sedation

|                         | Experim      | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                             |
|-------------------------|--------------|----------|--------|-------|--------|-------------------|--|
| Study or Subgroup       | Events       | Total    | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                   |
| 18.2.1 Aripiprazole (   | 5mg/day)     |          |        |       |        |                   |  |
| MARCUS2009              | 1            | 52       | 0      | 51    | 100.0% | 2.94 [0.12, 70.61 |  |
| Subtotal (95% CI)       |              | 52       |        | 51    | 100.0% | 2.94 [0.12, 70.61 |  |
| Total events            | 1            |          | 0      |       |        |                   |  |
| Heterogeneity: Not a    | pplicable    |          |        |       |        |                   |  |
| Test for overall effect | Z = 0.67 (F  | P = 0.51 | )      |       |        |                   |  |
| Total (95% CI)          |              | 52       |        | 51    | 100.0% | 2.94 [0.12, 70.61 | 1                                      |
| Total events            | 1            |          | 0      |       |        |                   |  |
| Heterogeneity: Not a    | pplicable    |          |        |       |        |                   | 0.01 0.1 1 10 100                      |
| Test for overall effect | Z = 0.67 (F  | P = 0.51 | )      |       |        |                   | Favours experimental Favours control   |
| Test for subgroup dit   | fferences: N | lot appl | icable |       |        |                   | r avours experimental T avours control |

# Discontinuation due to drooling

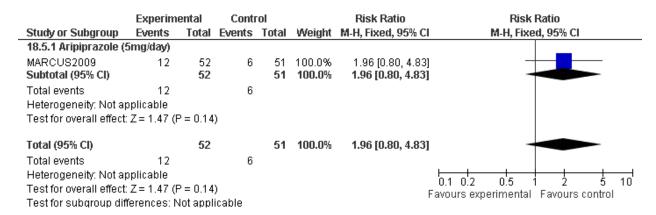
|   | Ехрегіт     | ental           | Contr  | ol              |                          | Risk Ratio                                     | Risk Ratio   |
|---|-------------|-----------------|--------|-----------------|--------------------------|--|--|
| Study or Subgroup   | Events      | Total           | Events | Total           | Weight                   | M-H, Fixed, 95% C                              | I M-H, Fixed, 95% CI                                   |
| 18.3.1 Aripiprazole (   | 5mg/day)    |                 |        |                 |                          |  |  |
| MARCUS2009<br>Subtotal (95% CI)   | 1           | 52<br><b>52</b> | 0      | 51<br><b>51</b> | 100.0%<br><b>100.0</b> % | 2.94 [0.12, 70.61<br><b>2.94 [0.12, 70.6</b> 1 |  |
| Total events Heterogeneity: Not ap  | •           | 0.54            | . 0    |                 |                          |  |  |
| Test for overall effect:  | Z = 0.67 (F | ′= 0.51         | )      |                 |                          |  |  |
| Total (95% CI)  |             | 52              |        | 51              | 100.0%                   | 2.94 [0.12, 70.61                              |  |
| Total events<br>Heterogeneity: Not ap<br>Test for overall effect:<br>Test for subgroup diff | Z = 0.67 (F |                 | •      |                 |                          |  | 0.01 0.1 1 10 100 Favours experimental Favours control |

#### Discontinuation due to tremor

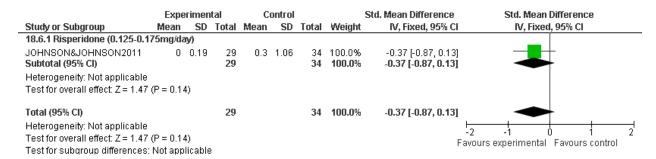


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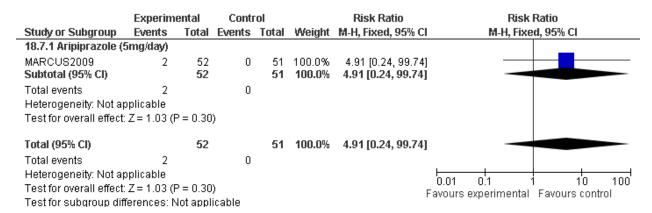
#### Any treatment-emergent extrapyramidal symptoms



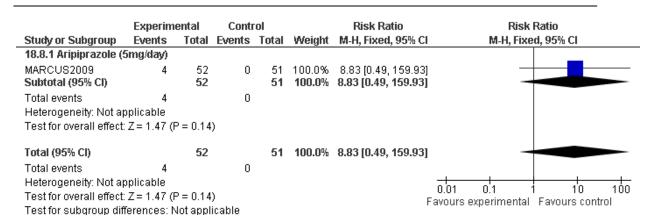
### **Extrapyramidal symptoms**



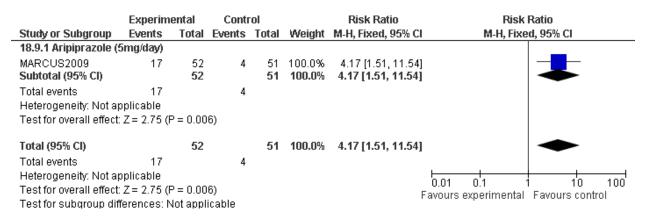
### Extrapyramidal disorder



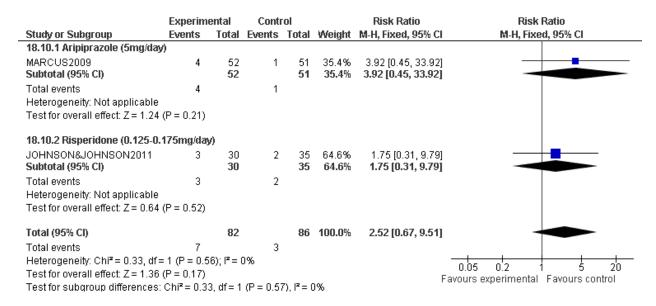
#### **Tremor**



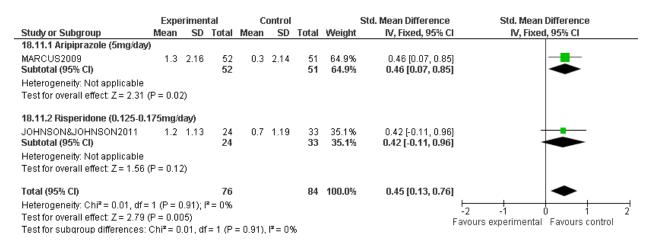
### Clinically relevant (>=7%) weight gain



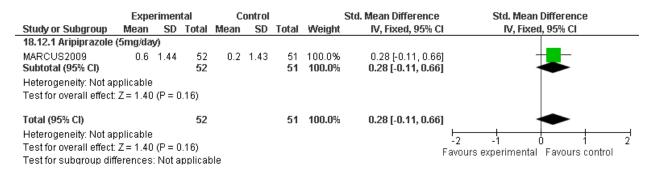
### Weight gain



# Weight gain (in kg)



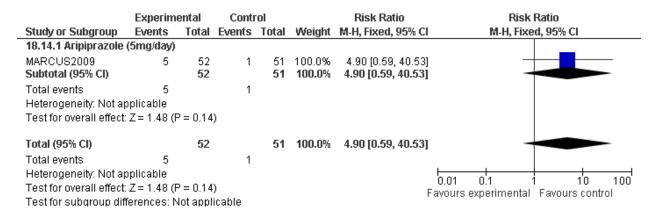
### BMI change (kg/m-squared)



### **Increased** appetite

|   | Experime       | ental             | Conti      | ol              |                         | Risk Ratio                                       | Risk Ratio                             |
|---|----------------|-------------------|------------|-----------------|-------------------------|--|--|
| Study or Subgroup                             | Events         | Total             | Events     | Total           | Weight                  | M-H, Fixed, 95% C                                | l M-H, Fixed, 95% Cl                   |
| 18.13.1 Aripiprazole (5mg/day                 | )              |                   |            |                 |                         |  |  |
| MARCUS2009<br>Subtotal (95% CI)               | 10             | 52<br><b>52</b>   | 2          | 51<br><b>51</b> | 52.2%<br><b>52.2</b> %  | 4.90 [1.13, 21.29<br><b>4.90 [1.13, 21.29</b> ]  |  |
| Total events<br>Heterogeneity: Not applicable | 10             |                   | 2          |                 |                         |  |  |
| Test for overall effect: $Z = 2.12$           | (P = 0.03)     |                   |            |                 |                         |  |  |
| 18.13.2 Risperidone (0.125-0.1                | 175mg/day      | )                 |            |                 |                         |  |  |
| JOHNSON&JOHNSON2011<br>Subtotal (95% CI)      | 5              | 30<br><b>30</b>   | 2          | 35<br><b>35</b> | 47.8%<br>4 <b>7.8</b> % | 2.92 [0.61, 13.96]<br><b>2.92 [0.61, 13.96</b> ] |  |
| Total events<br>Heterogeneity: Not applicable | 5              |                   | 2          |                 |                         |  |  |
| Test for overall effect: $Z = 1.34$           | (P = 0.18)     |                   |            |                 |                         |  |  |
| Total (95% CI)                                |                | 82                |            | 86              | 100.0%                  | 3.95 [1.36, 11.51]                               |  |
| Total events                                  | 15             |                   | 4          |                 |                         |  |  |
| Heterogeneity: Chi² = 0.23, df =              | 1 (P = 0.6     | 3); <b>I²</b> = I | 0%         |                 |                         |  | 0.05 0.2 1 5 2                         |
| Test for overall effect: $Z = 2.52$           | (P = 0.01)     |                   |            |                 |                         |  | Favours experimental Favours control   |
| Test for subgroup differences:                | $Chi^2 = 0.23$ | 3, df = 1         | (P = 0.64) | $4),   ^2 = 0$  | 0%                      |  | 1 avours experimental 1 avours control |

### Decreased appetite



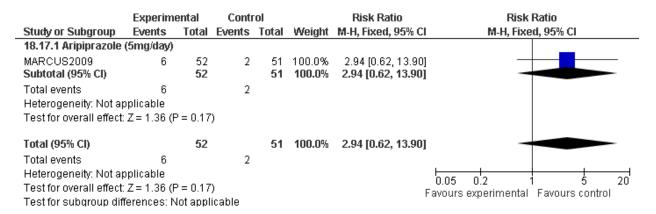
### Fasting Glucose (mg/dL) (Change Score)

|   | Expe      | erimer | ıtal            | Co   | ntro | l               | !                        | Std. Mean Difference                            | Std. Mean Difference              |
|---|-----------|--------|-----------------|------|------|-----------------|--------------------------|---|-----------------------------------|
| Study or Subgroup   | Mean      | SD     | Total           | Mean | SD   | Total           | Weight IV, Fixed, 95% C  |   | IV, Fixed, 95% CI                 |
| 18.15.1 Risperidone (0.125-0.                                     | 175mg/d   | lay)   |                 |      |      |                 |                          |   |                                   |
| JOHNSON&JOHNSON2011<br>Subtotal (95% CI)                          | -0.1      | 8.81   | 23<br><b>23</b> | -0.4 | 8.2  | 22<br><b>22</b> | 100.0%<br><b>100.0</b> % | 0.03 [-0.55, 0.62]<br><b>0.03 [-0.55, 0.62]</b> | -                                 |
| Heterogeneity: Not applicable Test for overall effect: $Z = 0.12$ | (P = 0.91 | 1)     |                 |      |      |                 |                          |   |                                   |
| Total (95% CI)<br>Heterogeneity: Not applicable                   |           |        | 23              |      |      | 22              | 100.0%                   | 0.03 [-0.55, 0.62]                              | 2 1 0 1 2                         |
| Test for overall effect: Z = 0.12 Test for subgroup differences:  | ,         |        |                 |      |      |                 |                          | Fav   | ours experimental Favours control |

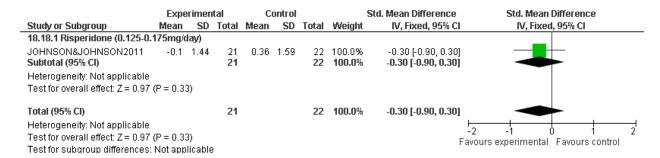
# Fasting glucose (=>115 mg/dL)

|                          | Experime    | ental | Conti  | rol   |        | Risk Ratio         | Risk Ratio           |  |  |  |
|--------------------------|-------------|-------|--------|-------|--------|--------------------|----------------------|--|--|--|
| Study or Subgroup        | Events      | Total | Events | Total | Weight | M-H, Fixed, 95% CI | I M-H, Fixed, 95% CI |  |  |  |
| 18.16.1 Aripiprazole     | (5mg/day)   |       |        |       |        |                    |                      |  |  |  |
| MARCUS2009               | 0           | 52    | 0      | 51    |        | Not estimable      | e l                  |  |  |  |
| Subtotal (95% CI)        |             | 52    |        | 51    |        | Not estimable      | e                    |  |  |  |
| Total events             | 0           |       | 0      |       |        |                    |                      |  |  |  |
| Heterogeneity: Not ap    | oplicable   |       |        |       |        |                    |                      |  |  |  |
| Test for overall effect: | Not applica | able  |        |       |        |                    |                      |  |  |  |
| Total (95% CI)           |             | 52    |        | 51    |        | Not estimable      | e                    |  |  |  |
| Total events             | 0           |       | 0      |       |        |                    |                      |  |  |  |
| Heterogeneity: Not ap    | oplicable   |       |        |       |        |                    | - to - do - do - d   |  |  |  |
|                          | Not applica |       |        |       |        |                    | 0.01 0.1 1 10 1      |  |  |  |

### Fasting triglycerides (=>120 mg/dL for females or 160 mg/dL for males)



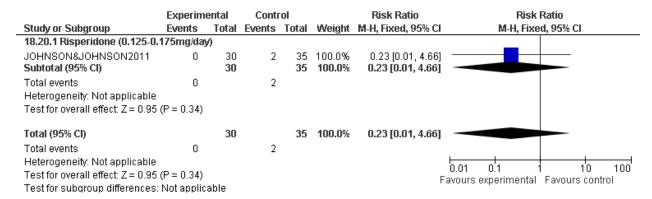
### Insulin Resistance (HOMA-IR) (Change Score)



### Aggression

|   | Experime        | ental           | Control      |                 | Risk Ratio<br>Weight M-H, Fixed, 95% Cl |   | Risk Ratio   |  |  |
|---|-----------------|-----------------|--------------|-----------------|---|---|--|--|--|
| Study or Subgroup   | Events          | Total           | Events Total |                 |   |   | I M-H, Fixed, 95% CI                                 |  |  |
| 18.19.1 Risperidone (0.125-0.1  | 175mg/day       | 0               |              |                 |   |   | _  |  |  |
| JOHNSON&JOHNSON2011<br>Subtotal (95% Cl)  | 0               | 30<br><b>30</b> | 2            | 35<br><b>35</b> | 100.0%<br><b>100.0</b> %                | 0.23 [0.01, 4.66<br><b>0.23 [0.01, 4.66</b> |  |  |  |
| Total events<br>Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.95                          | 0<br>(P = 0.34) |                 | 2            |                 |   |   |  |  |  |
| Total (95% CI)  |                 | 30              |              | 35              | 100.0%                                  | 0.23 [0.01, 4.66                            |  |  |  |
| Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.95 Test for subgroup differences: |                 | -1-1-           | 2            |                 |   |   | 0.02 0.1 1 10 5 Favours experimental Favours control |  |  |

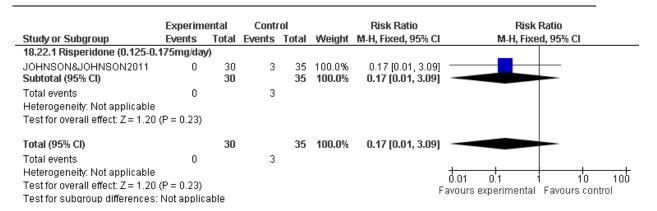
# Agitation



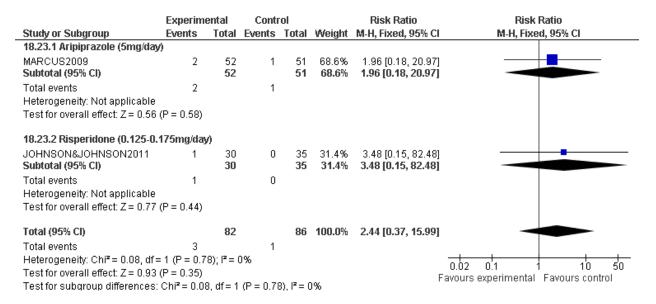
# Depression

|   | Ехрегіт     | ental           | Conti  | rol             |        | Risk Ratio                             | Risk Ratio  |
|---|-------------|-----------------|--------|-----------------|--------|--|---|
| Study or Subgroup   | Events      | Total           | Events | Total           | Weight | M-H, Fixed, 95% C                      | l M-H, Fixed, 95% Cl                                      |
| 18.21.1 Risperidone (0.125-0.   | 175mg/day   | 0               |        |                 |        |  |   |
| JOHNSON&JOHNSON2011<br>Subtotal (95% Cl)  | 0           | 30<br><b>30</b> | 0      | 35<br><b>35</b> |        | Not estimable<br><b>Not estimabl</b> e | - I   |
| Total events<br>Heterogeneity: Not applicable<br>Test for overall effect: Not appl                          | 0<br>icable |                 | 0      |                 |        |  |   |
| Total (95% CI)  |             | 30              |        | 35              |        | Not estimable                          |   |
| Total events Heterogeneity: Not applicable Test for overall effect: Not appl Test for subgroup differences: |             | able            | 0      |                 |        |  | 0.01 0.1 1 10 100<br>Favours experimental Favours control |

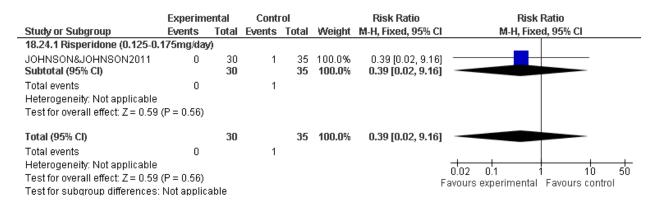
### Abdominal discomfort



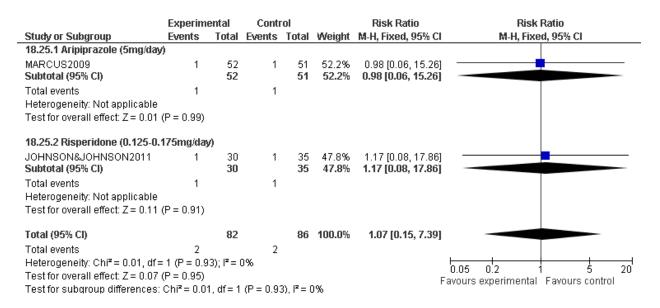
#### Abdominal pain (upper)



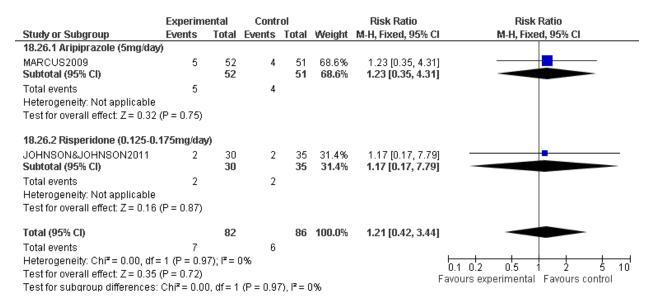
#### Constipation



#### Nausea



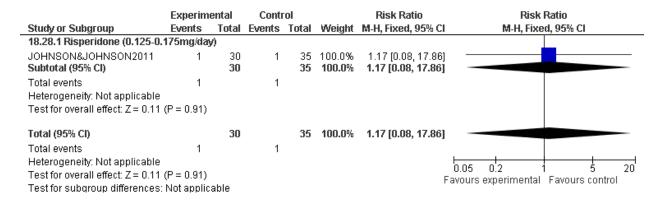
### Vomiting



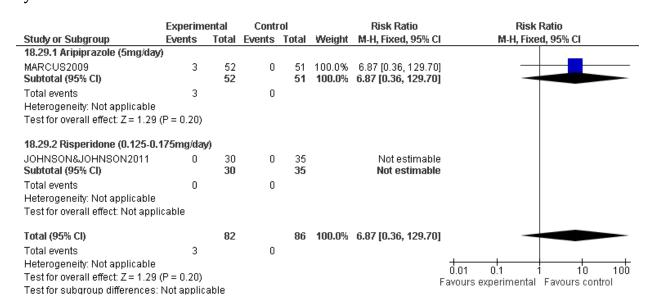
#### Gastroenteritis viral

|                         | Experimental |          | Contr         | ol    |        | Risk Ratio         | Risk Ratio  |
|-------------------------|--------------|----------|---------------|-------|--------|--------------------|---|
| Study or Subgroup       | Events       | Total    | <b>Events</b> | Total | Weight | M-H, Fixed, 95% C  | l M-H, Fixed, 95% Cl                                  |
| 18.27.1 Aripiprazole    | (5mg/day)    |          |               |       |        |                    |   |
| MARCUS2009              | 1            | 52       | 0             | 51    | 100.0% | 2.94 [0.12, 70.61] | 1   |
| Subtotal (95% CI)       |              | 52       |               | 51    | 100.0% | 2.94 [0.12, 70.61] |   |
| Total events            | 1            |          | 0             |       |        |                    |   |
| Heterogeneity: Not a    | pplicable    |          |               |       |        |                    |   |
| Test for overall effect | Z = 0.67 (F  | P = 0.51 | )             |       |        |                    |   |
| Total (95% CI)          |              | 52       |               | 51    | 100.0% | 2.94 [0.12, 70.61] |   |
| Total events            | 1            |          | 0             |       |        |                    |   |
| Heterogeneity: Not a    | pplicable    |          |               |       |        |                    |   |
| Test for overall effect | Z = 0.67 (F  | 9 = 0.51 | )             |       |        |                    | 0.02 0.1 1 10 50 Favours experimental Favours control |
| Test for subgroup dif   | fferences: N | lot appl | icable        |       |        |                    | ravouis experimental ravouis control                  |

#### Diarrhoea



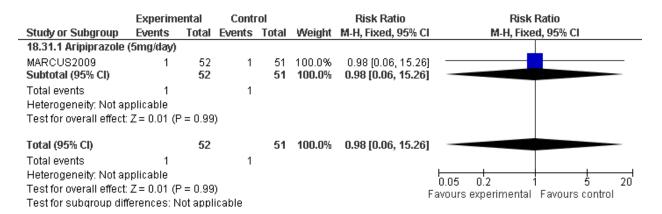
### **Pyrexia**



# Drooling

|                                 | Ехрегіт        | ental           | Conti  | rol             |                          | Risk Ratio                                     | Risk Ratio                             |
|---------------------------------|----------------|-----------------|--------|-----------------|--------------------------|--|--|
| Study or Subgroup               | Events         | Total           | Events | Total           | Weight                   | M-H, Fixed, 95% C                              | I M-H, Fixed, 95% CI                   |
| 18.30.1 Aripiprazole            | (5mg/day)      |                 |        |                 |                          |  |  |
| MARCUS2009<br>Subtotal (95% CI) | 2              | 52<br><b>52</b> | 0      | 51<br><b>51</b> | 100.0%<br><b>100.0</b> % | 4.91 [0.24, 99.74<br><b>4.91 [0.24, 99.7</b> 4 | ·                                      |
| Total events                    | 2              |                 | 0      |                 |                          |  |  |
| Heterogeneity: Not a            | pplicable      |                 |        |                 |                          |  |  |
| Test for overall effect         | t: Z = 1.03 (F | P = 0.30        | )      |                 |                          |  |  |
| Total (95% CI)                  |                | 52              |        | 51              | 100.0%                   | 4.91 [0.24, 99.74                              |  |
| Total events                    | 2              |                 | 0      |                 |                          |  |  |
| Heterogeneity: Not a            | pplicable      |                 |        |                 |                          |  | 0.01 0.1 1 10 10                       |
| Test for overall effect         | t: Z = 1.03 (F | P = 0.30        | )      |                 |                          |  | Favours experimental Favours control   |
| Test for subgroup dit           | fferences: N   | lot appl        | icable |                 |                          |  | 1 avours experimental 1 avours control |

#### **Increased salivation**

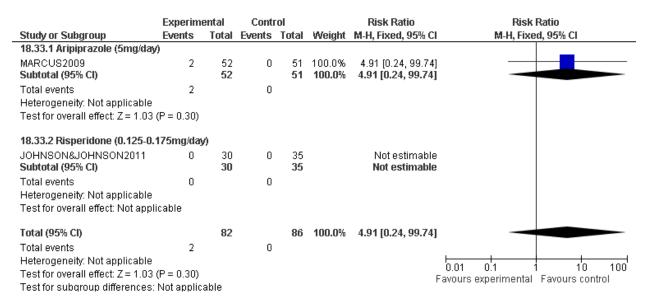


### **Thirst**

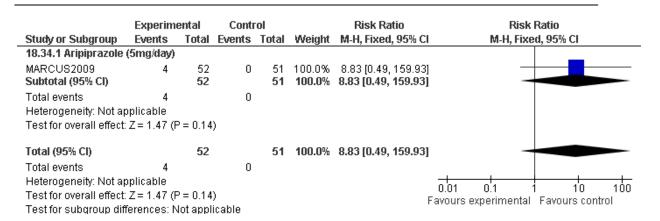
#### DRAFT GUIDELINE

|                                     | Experime   | ental | Contr  | ol    |        | Risk Ratio         | Risk Ratio                            |
|-------------------------------------|------------|-------|--------|-------|--------|--------------------|---------------------------------------|
| Study or Subgroup                   | Events     | Total | Events | Total | Weight | M-H, Fixed, 95% C  | l M-H, Fixed, 95% Cl                  |
| 18.32.1 Aripiprazole (5mg/day       | 0          |       |        |       |        |                    |                                       |
| MARCUS2009                          | 3          | 52    | 1      | 51    | 100.0% | 2.94 [0.32, 27.36  | 1 —                                   |
| Subtotal (95% CI)                   |            | 52    |        | 51    | 100.0% | 2.94 [0.32, 27.36] |                                       |
| Total events                        | 3          |       | 1      |       |        |                    |                                       |
| Heterogeneity: Not applicable       |            |       |        |       |        |                    |                                       |
| Test for overall effect: $Z = 0.95$ | (P = 0.34) |       |        |       |        |                    |                                       |
| 18.32.2 Risperidone (0.125-0.       | 175mg/day  | 0     |        |       |        |                    |                                       |
| JOHNSON&JOHNSON2011                 | 0          | 30    | 0      | 35    |        | Not estimable      |                                       |
| Subtotal (95% CI)                   |            | 30    |        | 35    |        | Not estimable      | 9                                     |
| Total events                        | 0          |       | 0      |       |        |                    |                                       |
| Heterogeneity: Not applicable       |            |       |        |       |        |                    |                                       |
| Test for overall effect: Not appl   | icable     |       |        |       |        |                    |                                       |
| Total (95% CI)                      |            | 82    |        | 86    | 100.0% | 2.94 [0.32, 27.36] |                                       |
| Total events                        | 3          |       | 1      |       |        |                    |                                       |
| Heterogeneity: Not applicable       |            |       |        |       |        |                    | 0.01 0.1 1 10 100                     |
| Test for overall effect: $Z = 0.95$ | (P = 0.34) |       |        |       |        |                    | Favours experimental Favours control  |
| Test for subgroup differences:      | Not applie | able  |        |       |        |                    | i avours experimental Favours control |

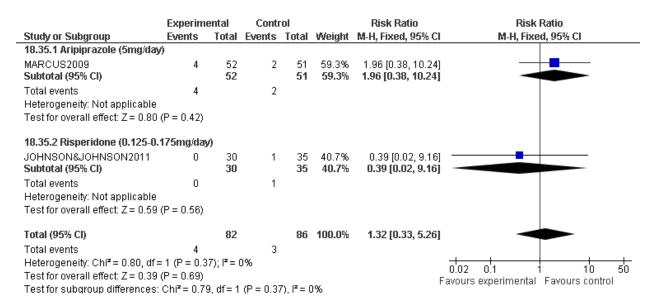
### **Fatigue**



# Lethargy



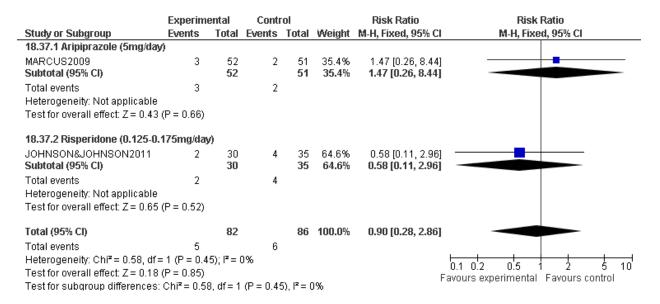
#### Somnolence



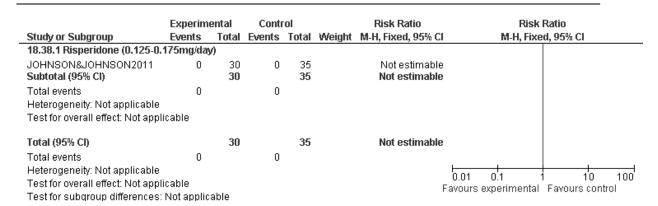
#### Sedation

| tio Risk Ratio                       |
|--------------------------------------|
| 95% CI M-H, Fixed, 95% CI            |
|                                      |
| , 10.25]<br>, <b>10.25</b> ]         |
|                                      |
|                                      |
|                                      |
| , 82.48]<br>, <b>82.48</b> ]         |
|                                      |
|                                      |
| 4, 9.62]                             |
|                                      |
| 0.02 0.1 1 10 50                     |
| Favours experimental Favours control |
|                                      |

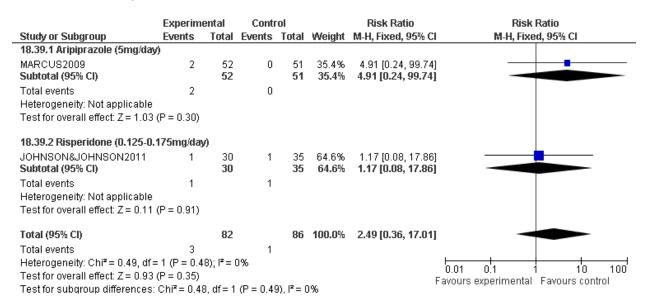
#### Headache



#### Ear infection



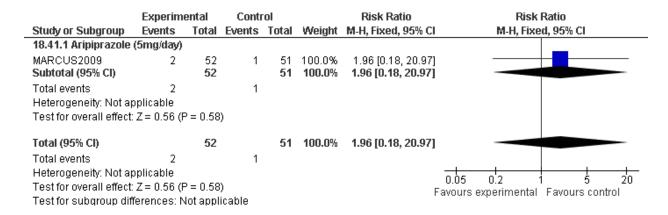
# Upper respiratory tract infection



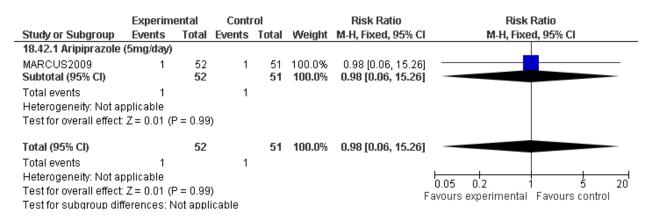
#### Cough

|   | Experime    | ental           | Contr  | ol              |                          | Risk Ratio                                       | Risk Ratio                               |
|---|-------------|-----------------|--------|-----------------|--------------------------|--|--|
| Study or Subgroup   | Events      | Total           | Events | Total           | Weight                   | M-H, Fixed, 95% C                                | l M-H, Fixed, 95% Cl                     |
| 18.40.1 Aripiprazole (5mg/day   | 9           |                 |        |                 |                          |  | <u></u>                                  |
| MARCUS2009<br>Subtotal (95% Cl)   | 8           | 52<br><b>52</b> | 2      | 51<br><b>51</b> | 100.0%<br><b>100.0</b> % | 3.92 [0.87, 17.59]<br><b>3.92 [0.87, 17.59</b> ] |  |
| Total events<br>Heterogeneity: Not applicable                                       | 8           |                 | 2      |                 |                          |  |  |
| Test for overall effect: $Z = 1.79$   | (P = 0.07)  |                 |        |                 |                          |  |  |
| 18.40.2 Risperidone (0.125-0.   | 175mg/day   | 0               |        |                 |                          |  |  |
| JOHNSON&JOHNSON2011<br>Subtotal (95% CI)  | 0           | 30<br><b>30</b> | 0      | 35<br><b>35</b> |                          | Not estimable<br><b>Not estimable</b>            |  |
| Total events<br>Heterogeneity: Not applicable<br>Test for overall effect: Not appli | 0<br>icable |                 | 0      |                 |                          |  |  |
| Total (95% CI)  |             | 82              |        | 86              | 100.0%                   | 3.92 [0.87, 17.59]                               |  |
| Total events  | 8           | -               | 2      |                 | 2001011                  | 2.22 [0.01, 11.00]                               |  |
| Heterogeneity: Not applicable   |             |                 |        |                 |                          |  | 0.05 0.2 1 5 20                          |
| Test for overall effect: $Z = 1.79$   | (P = 0.07)  |                 |        |                 |                          |  | Favours experimental Favours control     |
| Test for subgroup differences:  | Not applic  | able            |        |                 |                          |  | i avodio experimental il avodio colliloi |

#### Rhinorrhea

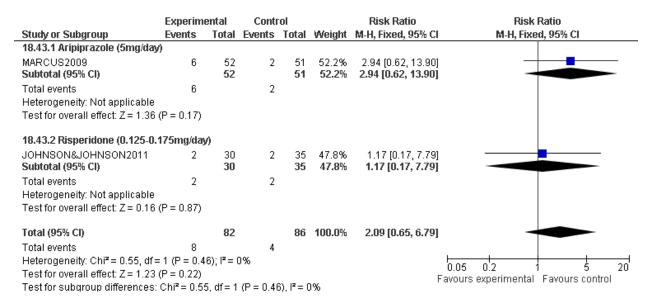


### Nasal congestion



Autism: the management and support of children and young people on the autism spectrum (March 2013)

# Nasopharyngitis

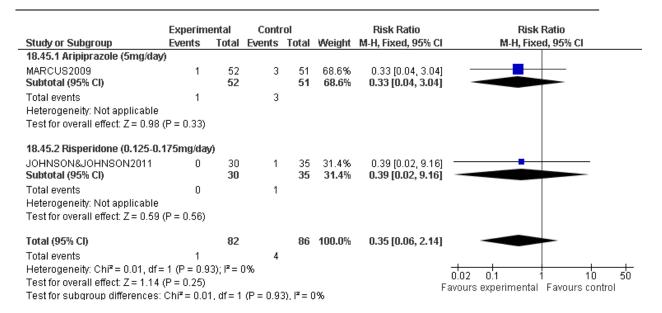


#### Nose bleed

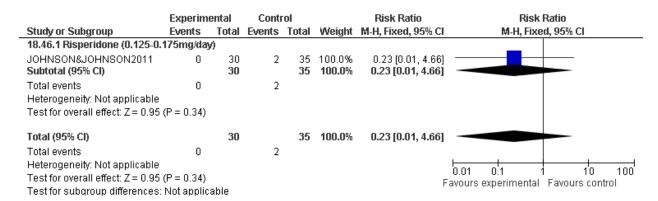
|   | Ехрегіте   | ental           | Contr  | ol              |        | Risk Ratio                            | Risk R                            | atio                     |
|---|------------|-----------------|--------|-----------------|--------|---------------------------------------|-----------------------------------|--------------------------|
| Study or Subgroup   | Events     | Total           | Events | Total           | Weight | M-H, Fixed, 95% CI                    | M-H, Fixed,                       | 95% CI                   |
| 18.44.1 Aripiprazole (5mg/day   | )          |                 |        |                 |        |                                       |                                   |                          |
| MARCUS2009<br>Subtotal (95% CI)   | 0          | 52<br><b>52</b> | 0      | 51<br><b>51</b> |        | Not estimable<br>Not estimable        |                                   |                          |
| Total events<br>Heterogeneity: Not applicable<br>Test for overall effect: Not appli                                   | 0<br>cable |                 | 0      |                 |        |                                       |                                   |                          |
| 18.44.2 Risperidone (0.125-0.1  | 175mg/day  | 0               |        |                 |        |                                       |                                   |                          |
| JOHNSON&JOHNSON2011<br>Subtotal (95% Cl)  | 0          | 30<br><b>30</b> | 0      | 35<br><b>35</b> |        | Not estimable<br><b>Not estimable</b> | I                                 |                          |
| Total events<br>Heterogeneity: Not applicable<br>Test for overall effect: Not appli                                   | 0<br>cable |                 | 0      |                 |        |                                       |                                   |                          |
| Total (95% CI)  |            | 82              |        | 86              |        | Not estimable                         |                                   |                          |
| Total events<br>Heterogeneity: Not applicable<br>Test for overall effect: Not appli<br>Test for subgroup differences: |            | able            | 0      |                 |        |                                       | 0.01 0.1 1 Favours experimental F | 10 100<br>avours control |

#### Akathisia

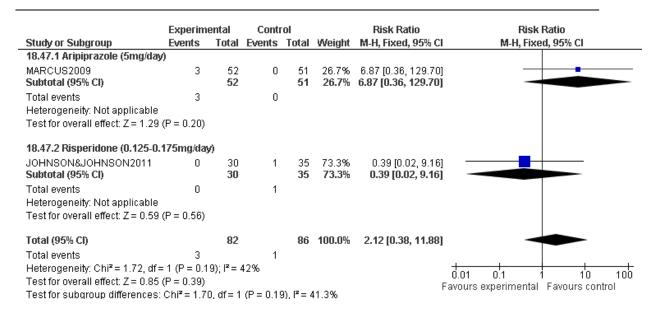
#### DRAFT GUIDELINE



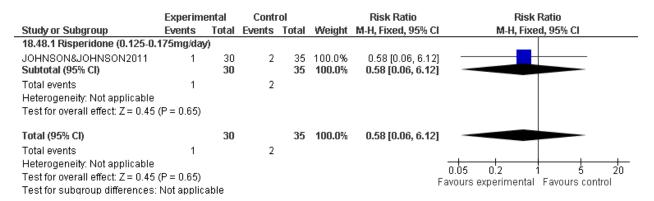
#### Insomnia



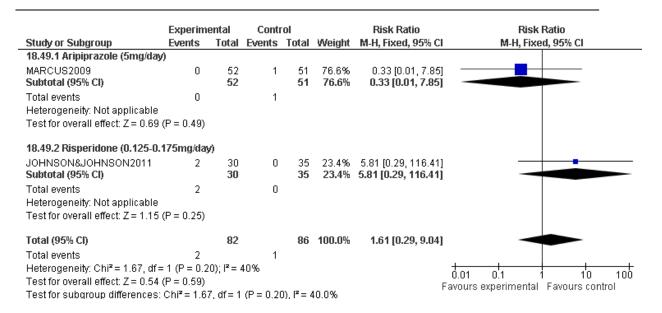
### Hypersomnia



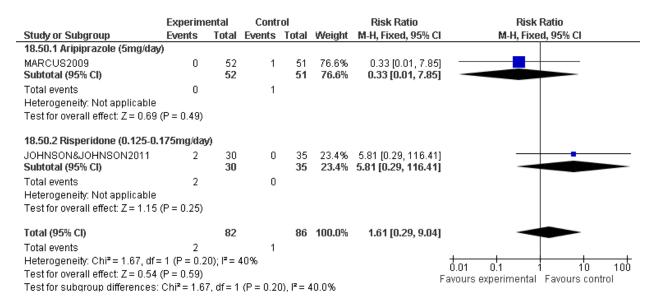
#### Psychomotor hyperactivity



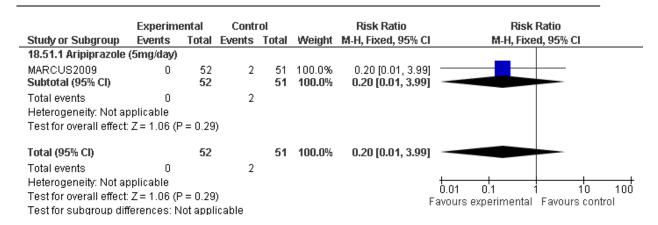
#### **Enuresis**



### Rash



### Clinically relevant prolactin elevation (above upper limit of normal)

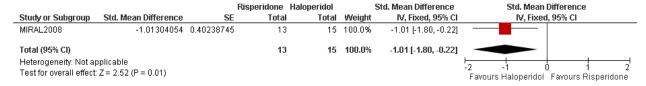


### Adverse events associated with risperidone versus placebo

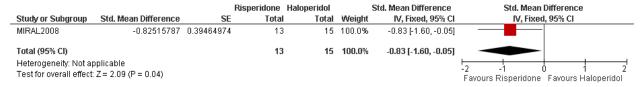
#### Treatment-emergent extrapyramidal symptoms

|   | Risp | Risperidone Haloperidol |       | ol   |      | Std. Mean Difference | Std. Mean Difference |                      |  |  |
|---|------|-------------------------|-------|------|------|----------------------|----------------------|----------------------|--|--|
| Study or Subgroup                                 | Mean | SD                      | Total | Mean | SD   | Total                | Weight               | IV, Fixed, 95% CI    | IV, Fixed, 95% CI                                      |  |
| MIRAL2008   | 0.15 | 0.38                    | 13    | 1.27 | 1.75 | 15                   | 100.0%               | -0.83 [-1.61, -0.05] |  |  |
| Total (95% CI)                                    |      |                         | 13    |      |      | 15                   | 100.0%               | -0.83 [-1.61, -0.05] |  |  |
| Heterogeneity: Not ap<br>Test for overall effect: |      |                         | 1.04) |      |      |                      |                      |                      | -2 -1 0 1 2<br>Favours Risperidone Favours Haloperidol |  |

### Prolactin (change score)



# Liver problems (change in alanine transaminase [ALT])



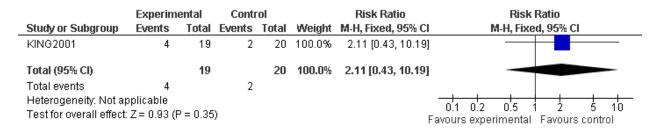
#### 1.33.6 Adverse events associated with antivirals

Adverse events associated with amantadine hydrochloride versus placebo

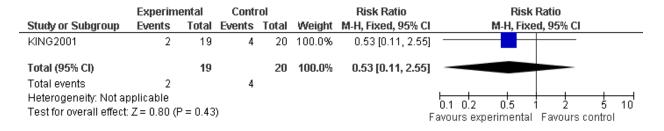
#### Any adverse event

|  | Experim | Contr | Control |       | Risk Ratio | Risk Ratio        |                                      |  |
|--|---------|-------|---------|-------|------------|-------------------|--------------------------------------|--|
| Study or Subgroup                              | Events  | Total | Events  | Total | Weight     | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                 |  |
| KING2001                                       | 14      | 19    | 14      | 20    | 100.0%     | 1.05 [0.71, 1.56  | · -                                  |  |
| Total (95% CI)                                 |         | 19    |         | 20    | 100.0%     | 1.05 [0.71, 1.56  | ı <b>→</b>                           |  |
| Total events                                   | 14      |       | 14      |       |            |                   |                                      |  |
| Heterogeneity: Not applicable                  |         |       |         |       |            |                   | 0.1 0.2 0.5 1 2 5 10                 |  |
| Test for overall effect: $Z = 0.26$ (P = 0.80) |         |       |         |       |            |                   | Favours experimental Favours control |  |

#### Insomnia



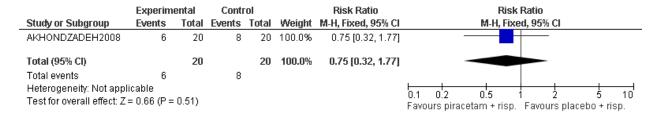
#### Antisocial behaviour



# 1.33.7 Adverse events associated with cognitive enhancers

Adverse events associated with piracetam and risperidone versus placebo and risperidone

# Any treatment-emergent extrapyramidal symptom



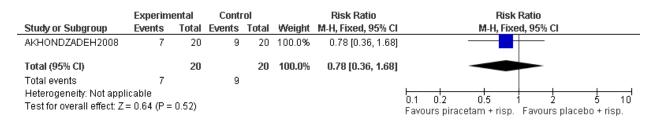
### Constipation

|   | Experim | ental | Contr  | rol   |        | Risk Ratio         | Risk Ratio   |
|---|---------|-------|--------|-------|--------|--------------------|--|
| Study or Subgroup                                     | Events  | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI   |
| AKHONDZADEH2008                                       | 4       | 20    | 3      | 20    | 100.0% | 1.33 [0.34, 5.21]  |  |
| Total (95% CI)  |         | 20    |        | 20    | 100.0% | 1.33 [0.34, 5.21]  |  |
| Total events  | 4       |       | 3      |       |        |                    |  |
| Heterogeneity: Not appl<br>Test for overall effect: Z |         | 0.68) |        |       |        |                    | 0.1 0.2 0.5 1 2 5 10 Favours piracetam + risp. Favours placebo + risp. |

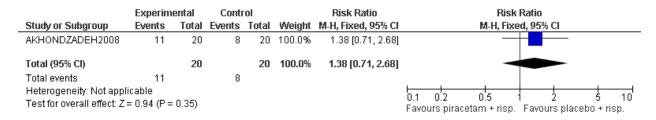
#### Nervousness

|  | Experim | ental | Conti  | rol   |        | Risk Ratio         | Risk Ratio  |
|--|---------|-------|--------|-------|--------|--------------------|---|
| Study or Subgroup                              | Events  | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                                |
| AKHONDZADEH2008                                | 1       | 20    | 2      | 20    | 100.0% | 0.50 [0.05, 5.08]  |   |
| Total (95% CI)                                 |         | 20    |        | 20    | 100.0% | 0.50 [0.05, 5.08]  |   |
| Total events                                   | 1       |       | 2      |       |        |                    |   |
| Heterogeneity: Not applicable                  |         |       |        |       |        |                    | 0.05 0.2 1 5 20                                   |
| Test for overall effect: $Z = 0.59$ (P = 0.56) |         |       |        |       |        |                    | Favours piracetam + risp. Favours placebo + risp. |

# Day time drowsiness



### Morning drowsiness



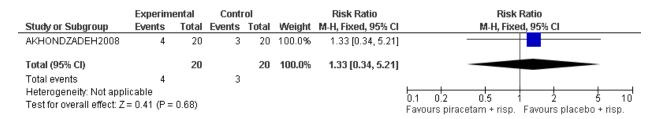
# **Increased appetite**

|                            | Ехрегіт     | ental | Conti  | rol   |        | Risk Ratio         | Risk Ratio  |
|----------------------------|-------------|-------|--------|-------|--------|--------------------|---|
| Study or Subgroup          | Events      | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                                |
| AKHONDZADEH2008            | 7           | 20    | 6      | 20    | 100.0% | 1.17 [0.48, 2.86]  |   |
| Total (95% CI)             |             | 20    |        | 20    | 100.0% | 1.17 [0.48, 2.86]  |   |
| Total events               | 7           |       | 6      |       |        |                    |   |
| Heterogeneity: Not appl    |             |       |        |       |        |                    | 01 02 05 1 2 5 10                                 |
| Test for overall effect: Z | = 0.34 (P = | 0.74) |        |       |        |                    | Favours piracetam + risp. Favours placebo + risp. |

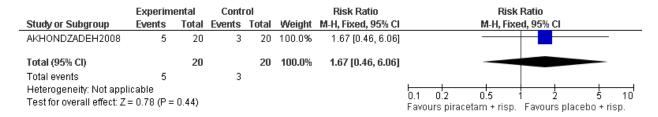
## Loss of appetite

|   | Ехрегіт | ental | Conti  | ol    | Risk Ratio |                    | Risk Ratio   |
|---|---------|-------|--------|-------|------------|--------------------|--|
| Study or Subgroup                                     | Events  | Total | Events | Total | Weight     | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI   |
| AKHONDZADEH2008                                       | 1       | 20    | 1      | 20    | 100.0%     | 1.00 [0.07, 14.90] |  |
| Total (95% CI)  |         | 20    |        | 20    | 100.0%     | 1.00 [0.07, 14.90] |  |
| Total events  | 1       |       | 1      |       |            |                    |  |
| Heterogeneity: Not appl<br>Test for overall effect: Z |         | 1.00) |        |       |            |                    | 0.1 0.2 0.5 1 2 5 10 Favours piracetam + risp. Favours placebo + risp. |

# Dry mouth



## **Fatigue**



## 1.33.8 Adverse events associated with melatonin

Adverse events associated with melatonin versus placebo

## Coughing

|                         | Ехрегіт      | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                        |
|-------------------------|--------------|----------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup       | Events       | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012            | 6            | 30       | 13     | 33    | 100.0% | 0.51 [0.22, 1.17]  | <del></del>                       |
| Total (95% CI)          |              | 30       |        | 33    | 100.0% | 0.51 [0.22, 1.17]  |                                   |
| Total events            | 6            |          | 13     |       |        |                    |                                   |
| Heterogeneity: Not ap   | pplicable    |          |        |       |        |                    | 01 02 05 1 2 5 10                 |
| Test for overall effect | Z = 1.60 (8) | P = 0.11 | )      |       |        |                    | Favours Melatonin Favours Placebo |

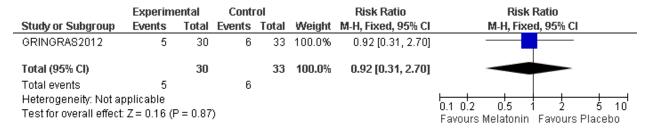
# Mood swings

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                        |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012             | 7           | 30       | 6      | 33    | 100.0% | 1.28 [0.49, 3.39]  |                                   |
| Total (95% CI)           |             | 30       |        | 33    | 100.0% | 1.28 [0.49, 3.39]  |                                   |
| Total events             | 7           |          | 6      |       |        |                    |                                   |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 01 02 05 1 2 5 10                 |
| Test for overall effect: | Z = 0.50 (F | P = 0.61 | )      |       |        |                    | Favours Melatonin Favours Placebo |

# Vomiting

|                          | Experim     | ental    | Contr  | ol lo |        | Risk Ratio         | Risk Ratio                        |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012             | 7           | 30       | 7      | 33    | 100.0% | 1.10 [0.44, 2.77]  |                                   |
| Total (95% CI)           |             | 30       |        | 33    | 100.0% | 1.10 [0.44, 2.77]  |                                   |
| Total events             | 7           |          | 7      |       |        |                    |                                   |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 01 02 05 1 2 5 10                 |
| Test for overall effect: | Z = 0.20 (F | ° = 0.84 | )      |       |        |                    | Favours Melatonin Favours Placebo |

# Increased excitability



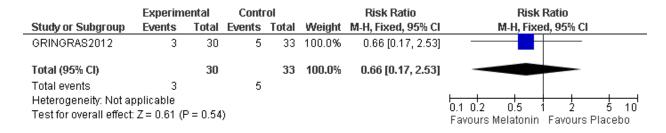
## Headache

|                         | Ехрегіт     | ental    | Contr  | rol   |        | Risk Ratio         | Risk Ratio                        |
|-------------------------|-------------|----------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012            | 2           | 30       | 2      | 33    | 100.0% | 1.10 [0.17, 7.33]  |                                   |
| Total (95% CI)          |             | 30       |        | 33    | 100.0% | 1.10 [0.17, 7.33]  |                                   |
| Total events            | 2           |          | 2      |       |        |                    |                                   |
| Heterogeneity: Not as   | pplicable   |          |        |       |        |                    | 01 02 05 1 2 5 10                 |
| Test for overall effect | Z = 0.10 (F | P = 0.92 | )      |       |        |                    | Favours Melatonin Favours Placebo |

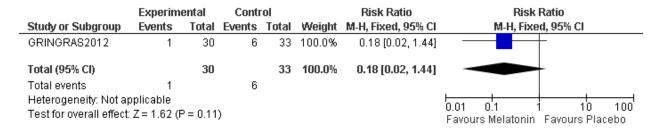
#### Rash

|                          | Experim     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                        |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012             | 4           | 30       | 3      | 33    | 100.0% | 1.47 [0.36, 6.03]  |                                   |
| Total (95% CI)           |             | 30       |        | 33    | 100.0% | 1.47 [0.36, 6.03]  |                                   |
| Total events             | 4           |          | 3      |       |        |                    |                                   |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 01 02 05 1 2 5 10                 |
| Test for overall effect: | Z = 0.53 (F | P = 0.60 | )      |       |        |                    | Favours Melatonin Favours Placebo |

#### Somnolence



## **Fatigue**



## Hypothermia

|                         | Ехрегіт      | ental    | Contr  | rol   |        | Risk Ratio         | Risk Ratio                        |
|-------------------------|--------------|----------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup       | Events       | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012            | 1            | 30       | 2      | 33    | 100.0% | 0.55 [0.05, 5.76]  |                                   |
| Total (95% CI)          |              | 30       |        | 33    | 100.0% | 0.55 [0.05, 5.76]  |                                   |
| Total events            | 1            |          | 2      |       |        |                    |                                   |
| Heterogeneity: Not ap   | pplicable    |          |        |       |        |                    | 0.05 0.2 1 5 20                   |
| Test for overall effect | Z = 0.50 (8) | P = 0.62 | )      |       |        |                    | Favours Melatonin Favours Placebo |

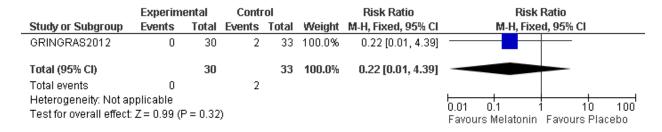
# **Increased activity**

|                          | Experim     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                        |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012             | 3           | 30       | 3      | 33    | 100.0% | 1.10 [0.24, 5.04]  |                                   |
| Total (95% CI)           |             | 30       |        | 33    | 100.0% | 1.10 [0.24, 5.04]  |                                   |
| Total events             | 3           |          | 3      |       |        |                    |                                   |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 01 02 05 1 2 5 10                 |
| Test for overall effect: | Z = 0.12 (F | P = 0.90 | )      |       |        |                    | Favours Melatonin Favours Placebo |

#### Nausea

|                          | Experim     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                        |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012             | 1           | 30       | 2      | 33    | 100.0% | 0.55 [0.05, 5.76]  |                                   |
| Total (95% CI)           |             | 30       |        | 33    | 100.0% | 0.55 [0.05, 5.76]  |                                   |
| Total events             | 1           |          | 2      |       |        |                    |                                   |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 0.05 0.2 1 5 20                   |
| Test for overall effect: | Z = 0.50 (F | P = 0.62 | )      |       |        |                    | Favours Melatonin Favours Placebo |

## **Dizziness**



## **Breathlessness**

|                         | Ехрегіт      | ental | Contr  | ol    |        | Risk Ratio         | Risk Ratio                        |     |
|-------------------------|--------------|-------|--------|-------|--------|--------------------|-----------------------------------|-----|
| Study or Subgroup       | Events       | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |     |
| GRINGRAS2012            | 0            | 30    | 0      | 33    |        | Not estimable      |                                   |     |
| Total (95% CI)          |              | 30    |        | 33    |        | Not estimable      |                                   |     |
| Total events            | 0            |       | 0      |       |        |                    |                                   |     |
| Heterogeneity: Not as   | oplicable    |       |        |       |        |                    | 01 02 05 1 2 5 1                  | 111 |
| Test for overall effect | : Not applic | able  |        |       |        |                    | Favours Melatonin Favours Placebo |     |

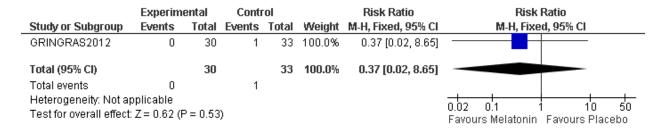
# Hung-over feeling

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                        |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012             | 1           | 30       | 0      | 33    | 100.0% | 3.29 [0.14, 77.82] |                                   |
| Total (95% CI)           |             | 30       |        | 33    | 100.0% | 3.29 [0.14, 77.82] |                                   |
| Total events             | 1           |          | 0      |       |        |                    |                                   |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                    | 0.02 0.1 1 10 50                  |
| Test for overall effect: | Z = 0.74 (F | P = 0.46 | )      |       |        |                    | Favours Melatonin Favours Placebo |

#### **Tremor**

|                          | Experim    | ental | Contr  | ol    |        | Risk Ratio         | Risk Ratio                        |
|--------------------------|------------|-------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup        | Events     | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012             | 0          | 30    | 0      | 33    |        | Not estimable      |                                   |
| Total (95% CI)           |            | 30    |        | 33    |        | Not estimable      |                                   |
| Total events             | 0          |       | 0      |       |        |                    |                                   |
| Heterogeneity: Not ap    | plicable   |       |        |       |        |                    | 01 02 05 1 2 5 10                 |
| Test for overall effect: | Not applic | able  |        |       |        |                    | Favours Melatonin Favours Placebo |

## Seizures



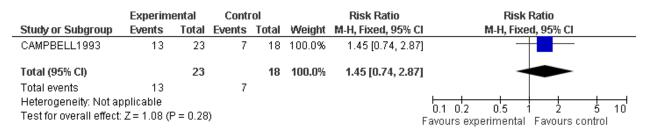
## Other

|                         | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                        |
|-------------------------|-------------|----------|--------|-------|--------|--------------------|-----------------------------------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                |
| GRINGRAS2012            | 15          | 30       | 20     | 33    | 100.0% | 0.82 [0.53, 1.30]  |                                   |
| Total (95% CI)          |             | 30       |        | 33    | 100.0% | 0.82 [0.53, 1.30]  | •                                 |
| Total events            | 15          |          | 20     |       |        |                    |                                   |
| Heterogeneity: Not as   | oplicable   |          |        |       |        |                    | 01 02 05 1 2 5 10                 |
| Test for overall effect | Z = 0.84 (F | P = 0.40 | )      |       |        |                    | Favours Melatonin Favours Placebo |

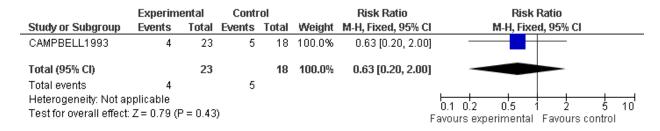
# 1.33.9 Adverse events associated with opioid antagonists

Adverse events associated with naltrexone versus placebo

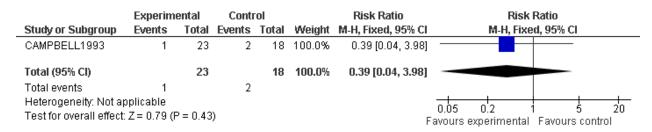
## Any side effect



## Aggressiveness



#### Self-injurious behaviour



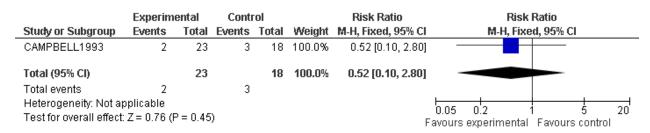
## Hyperactivity

|                         | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio  |
|-------------------------|-------------|----------|--------|-------|--------|--------------------|---|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI  |
| CAMPBELL1993            | 2           | 23       | 3      | 18    | 100.0% | 0.52 [0.10, 2.80]  |   |
| Total (95% CI)          |             | 23       |        | 18    | 100.0% | 0.52 [0.10, 2.80]  |   |
| Total events            | 2           |          | 3      |       |        |                    |   |
| Heterogeneity: Not ap   | oplicable   |          |        |       |        |                    | 0.05 0.2 1 5 20   |
| Test for overall effect | Z = 0.76 (F | P = 0.45 | )      |       |        | ı                  | - 0.05 - 0.2 - 1 5 - 20<br>Favours experimental Favours control |

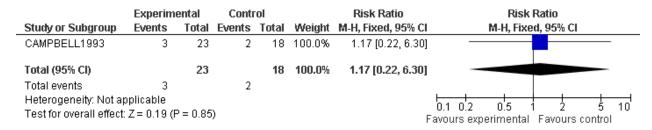
## Temper tantrums

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| CAMPBELL1993             | 2           | 23       | 1      | 18    | 100.0% | 1.57 [0.15, 15.92] |                                      |
| Total (95% CI)           |             | 23       |        | 18    | 100.0% | 1.57 [0.15, 15.92] |                                      |
| Total events             | 2           |          | 1      |       |        |                    |                                      |
| Heterogeneity: Not ap    | •           |          |        |       |        |                    | 0.05 0.2 1 5 20                      |
| Test for overall effect: | Z = 0.38 (F | P = 0.71 | )      |       |        | F                  | Favours experimental Favours control |

## Stereotypies



# **Irritability**



## Decreased verbal production (transient)

|                          | Ехрегіт     | ental    | Contr  | ol    | Risk Ratio |                    | Risk Ratio                          |
|--------------------------|-------------|----------|--------|-------|------------|--------------------|-------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight     | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                  |
| CAMPBELL1993             | 1           | 23       | 0      | 18    | 100.0%     | 2.38 [0.10, 55.06] |                                     |
| Total (95% CI)           |             | 23       |        | 18    | 100.0%     | 2.38 [0.10, 55.06] |                                     |
| Total events             | 1           |          | 0      |       |            |                    |                                     |
| Heterogeneity: Not ap    | plicable    |          |        |       |            |                    | 0.02 0.1 1 10 50                    |
| Test for overall effect: | Z = 0.54 (F | P = 0.59 | )      |       |            | F                  | avours experimental Favours control |

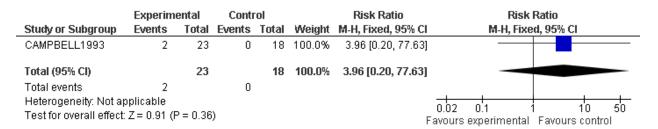
# Slight sleepiness

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                          |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|-------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% Cl                  |
| CAMPBELL1993             | 1           | 23       | 0      | 18    | 100.0% | 2.38 [0.10, 55.06] |                                     |
| Total (95% CI)           |             | 23       |        | 18    | 100.0% | 2.38 [0.10, 55.06] |                                     |
| Total events             | 1           |          | 0      |       |        |                    |                                     |
| Heterogeneity: Not as    | oplicable   |          |        |       |        |                    | 0.02 0.1 1 10 50                    |
| Test for overall effect: | Z = 0.54 (F | P = 0.59 | )      |       |        | F                  | avours experimental Favours control |

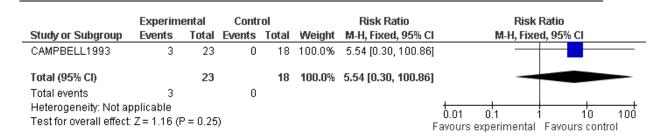
# Falling asleep

|                          | Experim     | ental    | Control |       |        | Risk Ratio        | Risk Ratio                           |
|--------------------------|-------------|----------|---------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events  | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixed, 95% Cl                 |
| CAMPBELL1993             | 2           | 23       | 0       | 18    | 100.0% | 3.96 [0.20, 77.63 |                                      |
| Total (95% CI)           |             | 23       |         | 18    | 100.0% | 3.96 [0.20, 77.63 |                                      |
| Total events             | 2           |          | 0       |       |        |                   |                                      |
| Heterogeneity: Not as    | oplicable   |          |         |       |        |                   | 0.02 0.1 1 10 50                     |
| Test for overall effect: | Z = 0.91 (F | P = 0.36 | )       |       |        |                   | Favours experimental Favours control |

## Decreased appetite



## Vomiting



## 1.33.10 Adverse events associated with SNRIs

## Adverse events associated with atomoxetine versus placebo

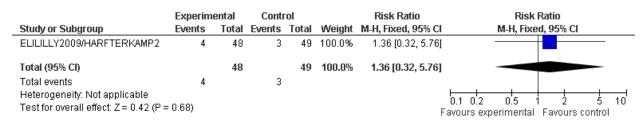
## Any adverse event

|   | Ехрегіт | ental | Contr  | ol    |        | Risk Ratio        | Risk Ratio  |
|---|---------|-------|--------|-------|--------|-------------------|---|
| Study or Subgroup   | Events  | Total | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                                      |
| ELILILLY2009/HARFTERKAMP2   | 39      | 48    | 32     | 49    | 100.0% | 1.24 [0.97, 1.59  | 1   |
| Total (95% CI)  |         | 48    |        | 49    | 100.0% | 1.24 [0.97, 1.59  | 1 ◆   |
| Total events  | 39      |       | 32     |       |        |                   |   |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.75 (P = | 0.08)   |       |        |       |        |                   | 0.1 0.2 0.5 1 2 5 10 Favours experimental Favours control |

#### Discontinuation due to adverse events

|  | Ехрегіт | ental | Contr  | ol    |        | Odds Ratio        | Odds Ratio                           |
|--|---------|-------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup  | Events  | Total | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                 |
| ELILILLY2009/HARFTERKAMP2  | 1       | 48    | 0      | 49    | 100.0% | 3.13 [0.12, 78.66 | 1                                    |
| Total (95% CI)   |         | 48    |        | 49    | 100.0% | 3.13 [0.12, 78.66 |                                      |
| Total events   | 1       |       | 0      |       |        |                   |                                      |
| Heterogeneity: Not applicable Test for overall effect: Z = 0.69 (P = 0 | 1.40\   |       |        |       |        |                   | 0.005 0.1 1 10 200                   |
| restror overall effect. Z = 0.08 (F = t                                | 3.49)   |       |        |       |        |                   | Favours experimental Favours control |

# Abdominal pain



# Upper abdominal pain

|  | Ехрегіт | ental | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--|---------|-------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup                      | Events  | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| ELILILLY2009/HARFTERKAMP2              | 9       | 48    | 3      | 49    | 100.0% | 3.06 [0.88, 10.63] |                                      |
| Total (95% CI)                         |         | 48    |        | 49    | 100.0% | 3.06 [0.88, 10.63] |                                      |
| Total events                           | 9       |       | 3      |       |        |                    |                                      |
| Heterogeneity: Not applicable          |         |       |        |       |        |                    | 01 02 05 1 2 5 10                    |
| Test for overall effect: Z = 1.76 (P = | 0.08)   |       |        |       |        |                    | Favours experimental Favours control |

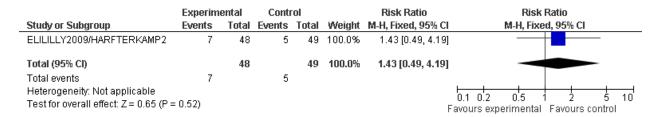
## Diarrhoea

|   | Ехрегіт | ental | Contr  | ol    |        | Risk Ratio        | Risk                             | Ratio     |
|---|---------|-------|--------|-------|--------|-------------------|----------------------------------|-----------|
| Study or Subgroup   | Events  | Total | Events | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixe                      | d, 95% CI |
| ELILILLY2009/HARFTERKAMP2   | 1       | 48    | 3      | 49    | 100.0% | 0.34 [0.04, 3.16  |                                  |           |
| Total (95% CI)  |         | 48    |        | 49    | 100.0% | 0.34 [0.04, 3.16] |                                  |           |
| Total events  | 1       |       | 3      |       |        |                   |                                  |           |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.95 (P = | 0.34)   |       |        |       |        |                   | 0.05 0.2<br>Favours experimental | 5 20      |

## Nausea

|   | Ехрегіт | ental | Conti  | rol   |        | Risk Ratio         | Risk Ratio                           |
|---|---------|-------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup   | Events  | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| ELILILLY2009/HARFTERKAMP2   | 14      | 48    | 4      | 49    | 100.0% | 3.57 [1.27, 10.08] |                                      |
| Total (95% CI)  |         | 48    |        | 49    | 100.0% | 3.57 [1.27, 10.08] |                                      |
| Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.41 (P = | - 0.02\ |       | 4      |       |        |                    | 0.1 0.2 0.5 1 2 5 10                 |
| 1621 (L - 574)  | - 0.02) |       |        |       |        |                    | Favours experimental Favours control |

## Vomiting



# **Fatigue**

|  | Experime | ental | Conti  | rol   |        | Risk Ratio        | Risk Ratio                           |
|--|----------|-------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup                      | Events   | Total | Events | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixed, 95% Cl                 |
| ELILILLY2009/HARFTERKAMP2              | 11       | 48    | 4      | 49    | 100.0% | 2.81 [0.96, 8.21  | 1                                    |
| Total (95% CI)                         |          | 48    |        | 49    | 100.0% | 2.81 [0.96, 8.21  |                                      |
| Total events                           | 11       |       | 4      |       |        |                   |                                      |
| Heterogeneity: Not applicable          |          |       |        |       |        |                   | 0.1 0.2 0.5 1 2 5 10                 |
| Test for overall effect: Z = 1.89 (P = | : 0.06)  |       |        |       |        |                   | Favours experimental Favours control |

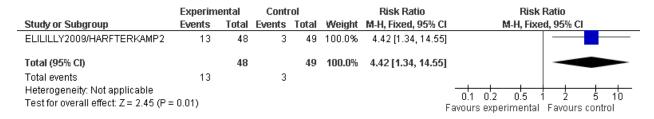
# **Pyrexia**

|  | Ехрегіт | ental | Contr  | ol    |        | Risk Ratio        | Risk                 | Ratio           |    |
|--|---------|-------|--------|-------|--------|-------------------|----------------------|-----------------|----|
| Study or Subgroup  | Events  | Total | Events | Total | Weight | M-H, Fixed, 95% C | M-H, Fixe            | ed, 95% CI      |    |
| ELILILLY2009/HARFTERKAMP2  | 0       | 48    | 3      | 49    | 100.0% | 0.15 [0.01, 2.75  |                      |                 |    |
| Total (95% CI)   |         | 48    |        | 49    | 100.0% | 0.15 [0.01, 2.75] |                      |                 |    |
| Total events   | 0       |       | 3      |       |        |                   |                      |                 |    |
| Heterogeneity: Not applicable Test for overall effect: Z = 1,29 (P = 1 | 0.20)   |       |        |       |        |                   | 0.01 0.1             |                 | 00 |
| 1631101 Overall ellect. 2 = 1.23 (1 = 1                                | 0.20)   |       |        |       |        |                   | Favours experimental | Favours control |    |

#### Influenza

|  | Experim | ental | Contr  | ol    |        | Risk Ratio         | Risk                 | Ratio     |
|--|---------|-------|--------|-------|--------|--------------------|----------------------|-----------|
| Study or Subgroup                      | Events  | Total | Events | Total | Weight | M-H, Fixed, 95% C  | I M-H, Fixe          | d, 95% CI |
| ELILILLY2009/HARFTERKAMP2              | 3       | 48    | 0      | 49    | 100.0% | 7.14 [0.38, 134.69 | )] —                 |           |
| Total (95% CI)                         |         | 48    |        | 49    | 100.0% | 7.14 [0.38, 134.69 | 1 -                  |           |
| Total events                           | 3       |       | 0      |       |        |                    |                      |           |
| Heterogeneity: Not applicable          |         |       |        |       |        |                    | 1<br>0 01 0 1        | 10 100    |
| Test for overall effect: Z = 1.31 (P = | 0.19)   |       |        |       |        |                    | Favours experimental |           |

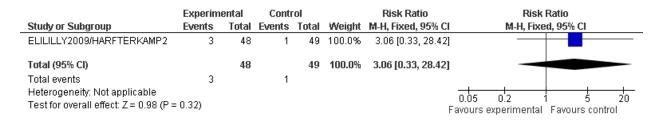
# Deceased appetite



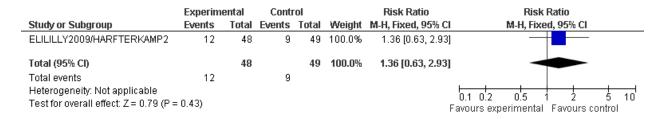
## Myalgia

|  | Experime | ental | Contr  | ol    |        | Risk Ratio         | Risk                 | Ratio      |
|--|----------|-------|--------|-------|--------|--------------------|----------------------|------------|
| Study or Subgroup                      | Events   | Total | Events | Total | Weight | M-H, Fixed, 95% C  | I M-H, Fixe          | ed, 95% CI |
| ELILILLY2009/HARFTERKAMP2              | 3        | 48    | 0      | 49    | 100.0% | 7.14 [0.38, 134.69 | )] —                 |            |
| Total (95% CI)                         |          | 48    |        | 49    | 100.0% | 7.14 [0.38, 134.69 | 1 -                  |            |
| Total events                           | 3        |       | 0      |       |        |                    |                      |            |
| Heterogeneity: Not applicable          |          |       |        |       |        |                    | 1<br>0 01 0 1        | 1 10 100   |
| Test for overall effect: Z = 1.31 (P = | 0.19)    |       |        |       |        |                    | Favours experimental |            |

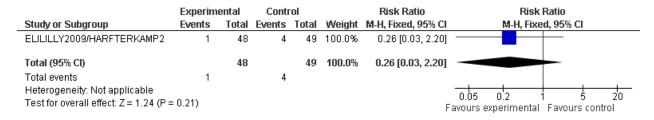
#### **Dizziness**



#### Headache



## Psychomotor hyperactivity



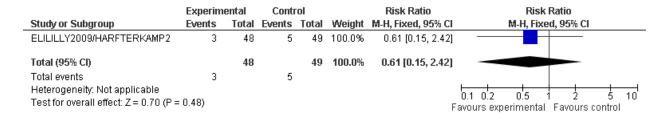
## Aggression

|  | Experime | ental | Conti  | rol   |        | Risk Ratio        | Risk Ratio                           |
|--|----------|-------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup                      | Events   | Total | Events | Total | Weight | M-H, Fixed, 95% C | l M-H, Fixed, 95% Cl                 |
| ELILILLY2009/HARFTERKAMP2              | 2        | 48    | 3      | 49    | 100.0% | 0.68 [0.12, 3.89] |                                      |
| Total (95% CI)                         |          | 48    |        | 49    | 100.0% | 0.68 [0.12, 3.89] |                                      |
| Total events                           | 2        |       | 3      |       |        |                   |                                      |
| Heterogeneity: Not applicable          |          |       |        |       |        |                   | 01 02 05 1 2 5 1                     |
| Test for overall effect: Z = 0.43 (P = | 0.67)    |       |        |       |        |                   | Favours experimental Favours control |

## Early morning awakening

|   | Ехрегіт | ental | Contr  | ol    |        | Risk Ratio          | Risk                              | Ratio                |            |
|---|---------|-------|--------|-------|--------|---------------------|-----------------------------------|----------------------|------------|
| Study or Subgroup   | Events  | Total | Events | Total | Weight | M-H, Fixed, 95% C   | 1 M-H, Fixe                       | d, 95% CI            |            |
| ELILILLY2009/HARFTERKAMP2   | 5       | 48    | 0      | 49    | 100.0% | 11.22 [0.64, 197.60 | - J                               |                      |            |
| Total (95% CI)  |         | 48    |        | 49    | 100.0% | 11.22 [0.64, 197.60 | ] -                               |                      |            |
| Total events  | 5       |       | 0      |       |        |                     |                                   |                      |            |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.65 (P = | 0.10)   |       |        |       |        |                     | 0.005 0.1<br>Favours experimental | 1 10<br>Favours cont | 200<br>rol |

#### Initial insomnia

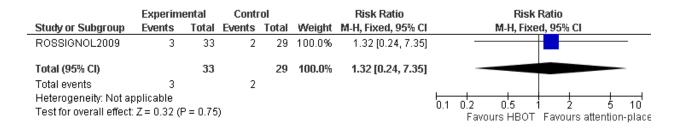


# 1.34ADVERSE EVENTS ASSOCIATED WITH BIOMEDICAL INTERVENTIONS

# 1.34.1 Adverse events associated with medical procedures

Adverse events associated with HBOT versus attention-placebo

## Any adverse event



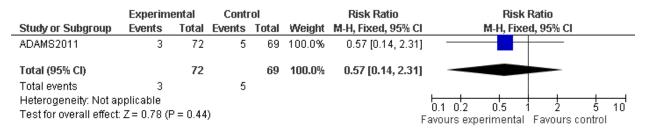
### Minor-grade ear barotrauma

|                             | Ехрегіт        | ental | Conti  | rol   |        | Risk Ratio        | Risk                 | Ratio      |
|-----------------------------|----------------|-------|--------|-------|--------|-------------------|----------------------|------------|
| Study or Subgroup           | Events         | Total | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixe          | ed, 95% CI |
| SAMPANTHAVIVAT2012          | 11             | 29    | 3      | 29    | 100.0% | 3.67 [1.14, 11.79 | ]                    |            |
| Total (95% CI)              |                | 29    |        | 29    | 100.0% | 3.67 [1.14, 11.79 | ]                    |            |
| Total events                | 11             |       | 3      |       |        |                   |                      |            |
| Heterogeneity: Not applica  | able           |       |        |       |        |                   | 0.05 0.2             | 1 5 20     |
| Test for overall effect: Z= | 2.18 (P = 0.1) | .03)  |        |       |        |                   | Favours experimental |            |

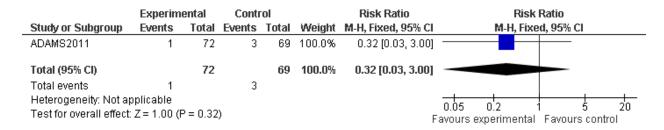
## 1.34.2 Adverse events associated with nutritional interventions

Adverse events associated with multivitamin/mineral supplement versus placebo

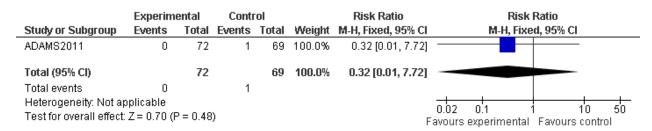
#### Discontinuation due to adverse events



#### Discontinuation due to diarrhoea



## Discontinuation due to increased stimming



## Discontinuation due to behaviour problems

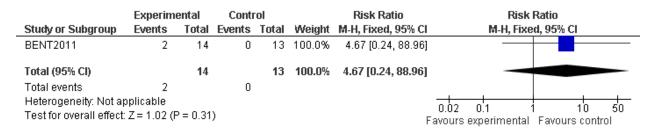
|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| ADAMS2011                | 2           | 72       | 1      | 69    | 100.0% | 1.92 [0.18, 20.66] |                                      |
| Total (95% CI)           |             | 72       |        | 69    | 100.0% | 1.92 [0.18, 20.66] |                                      |
| Total events             | 2           |          | 1      |       |        |                    |                                      |
| Heterogeneity: Not as    | oplicable   |          |        |       |        |                    | 0.05 0.2 1 5 20                      |
| Test for overall effect: | Z = 0.54 (F | P = 0.59 | )      |       |        | F                  | Favours experimental Favours control |

# Adverse events associated with omega-3 fatty acids versus placebo

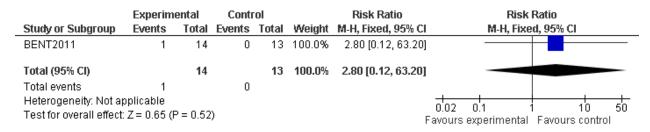
## Any adverse event

|                          | Ехрегіт     | ental    | Contr  | rol   |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| BENT2011                 | 5           | 14       | 4      | 13    | 100.0% | 1.16 [0.40, 3.41]  |                                      |
| Total (95% CI)           |             | 14       |        | 13    | 100.0% | 1.16 [0.40, 3.41]  |                                      |
| Total events             | 5           |          | 4      |       |        |                    |                                      |
| Heterogeneity: Not ap    | oplicable   |          |        |       |        |                    | 01 02 05 1 2 5 10                    |
| Test for overall effect: | Z = 0.27 (F | P = 0.79 | )      |       |        |                    | Favours experimental Favours control |

#### Rash



# Upper respiratory infection



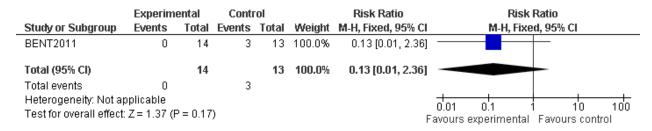
#### Nose bleeds

|                          | Experimental Control |       |        | Risk Ratio | Risk Ratio                           |                    |                    |
|--------------------------|----------------------|-------|--------|------------|--------------------------------------|--------------------|--------------------|
| Study or Subgroup        | Events               | Total | Events | Total      | Weight                               | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| BENT2011                 | 1                    | 14    | 0      | 13         | 100.0%                               | 2.80 [0.12, 63.20] |                    |
| Total (95% CI)           |                      | 14    |        | 13         | 100.0%                               | 2.80 [0.12, 63.20] |                    |
| Total events             | 1                    |       | 0      |            |                                      |                    |                    |
| Heterogeneity: Not ap    | oplicable            |       |        |            |                                      |                    | 0.02 0.1 1 10 50   |
| Test for overall effect: | )                    |       |        |            | Favours experimental Favours control |                    |                    |

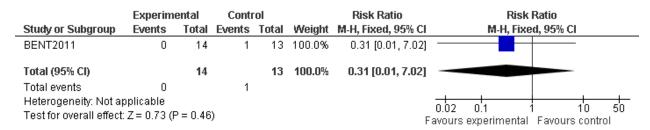
## **GI** symptoms

|                          | Experimental Control |       |        | ol    |        | Risk Ratio                           | Risk Ratio         |
|--------------------------|----------------------|-------|--------|-------|--------|--------------------------------------|--------------------|
| Study or Subgroup        | Events               | Total | Events | Total | Weight | M-H, Fixed, 95% CI                   | M-H, Fixed, 95% CI |
| BENT2011                 | 1                    | 14    | 0      | 13    | 100.0% | 2.80 [0.12, 63.20]                   |                    |
| Total (95% CI)           |                      | 14    |        | 13    | 100.0% | 2.80 [0.12, 63.20]                   |                    |
| Total events             | 1                    |       | 0      |       |        |                                      |                    |
| Heterogeneity: Not ap    | oplicable            |       |        |       |        |                                      | 0.02 0.1 1 10 50   |
| Test for overall effect: | P = 0.52             | )     |        |       | ı      | Favours experimental Favours control |                    |

# Hyperactivity

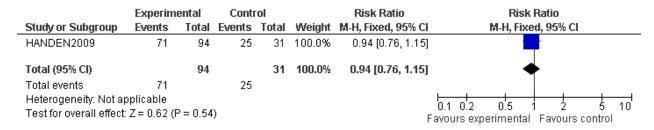


## Self-stimulatory behaviour

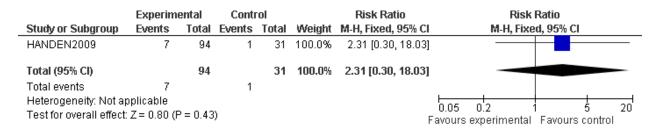


# Adverse events associated with immunoglobulin (dosages combined) versus placebo

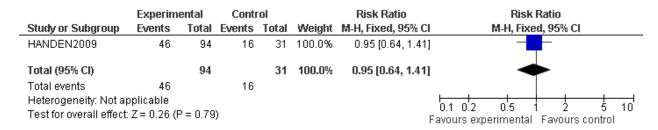
## Any side effect



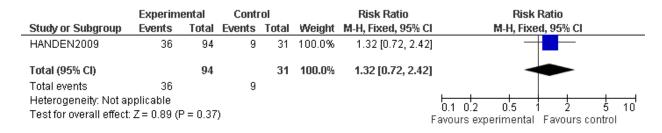
#### Discontinuation due to adverse events



#### Infections or infestations



#### Gastrointestinal disorders



Autism: the management and support of children and young people on the autism spectrum (March 2013)

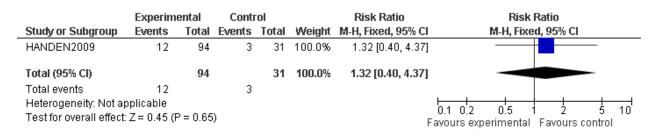
## Psychiatric disorders

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| HANDEN2009               | 17          | 94       | 6      | 31    | 100.0% | 0.93 [0.40, 2.16]  |                                      |
| Total (95% CI)           |             | 94       |        | 31    | 100.0% | 0.93 [0.40, 2.16]  |                                      |
| Total events             | 17          |          | 6      |       |        |                    |                                      |
| Heterogeneity: Not ap    | oplicable   |          |        |       |        |                    | 01 02 05 1 2 5 10                    |
| Test for overall effect: | Z = 0.16 (F | P = 0.87 | )      |       |        | ſ                  | Favours experimental Favours control |

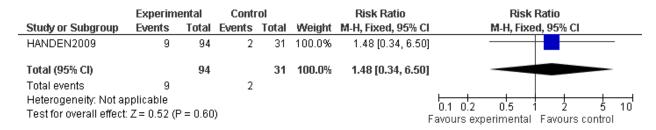
## Respiratory, thoracic or mediastinal disorders

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                          |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|-------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                  |
| HANDEN2009               | 15          | 94       | 4      | 31    | 100.0% | 1.24 [0.44, 3.45]  |                                     |
| Total (95% CI)           |             | 94       |        | 31    | 100.0% | 1.24 [0.44, 3.45]  |                                     |
| Total events             | 15          |          | 4      |       |        |                    |                                     |
| Heterogeneity: Not ap    | oplicable   |          |        |       |        |                    | 01 02 05 1 2 5 10                   |
| Test for overall effect: | Z = 0.41 (F | P = 0.68 | )      |       |        | F                  | avours experimental Favours control |

#### Skin or subcutaneous tissue disorders



## General disorders or administration site conditions



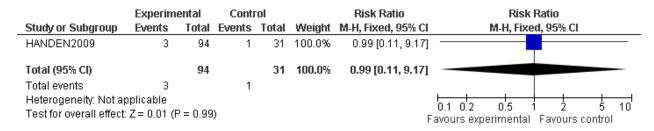
## Nervous system disorders

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                   |
| HANDEN2009               | 7           | 94       | 0      | 31    | 100.0% | 5.05 [0.30, 86.01] |                                      |
| Total (95% CI)           |             | 94       |        | 31    | 100.0% | 5.05 [0.30, 86.01] |                                      |
| Total events             | 7           |          | 0      |       |        |                    |                                      |
| Heterogeneity: Not ap    | oplicable   |          |        |       |        |                    | 0.02 0.1 1 10 50                     |
| Test for overall effect: | Z = 1.12 (F | P = 0.26 | )      |       |        |                    | Favours experimental Favours control |

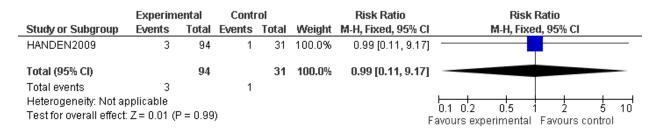
## Injury, poisoning or procedural complications

|                          | Ехрегіт     | ental    | Conti  | ol    |        | Risk Ratio         | Risk Ratio                          |
|--------------------------|-------------|----------|--------|-------|--------|--------------------|-------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                  |
| HANDEN2009               | 5           | 94       | 1      | 31    | 100.0% | 1.65 [0.20, 13.58] |                                     |
| Total (95% CI)           |             | 94       |        | 31    | 100.0% | 1.65 [0.20, 13.58] |                                     |
| Total events             | 5           |          | 1      |       |        |                    |                                     |
| Heterogeneity: Not as    | oplicable   |          |        |       |        |                    | 0.05 0.2 1 5 20                     |
| Test for overall effect: | Z = 0.46 (F | P = 0.64 | )      |       |        | F                  | avours experimental Favours control |

# Investigations



#### Metabolism or nutrition disorders



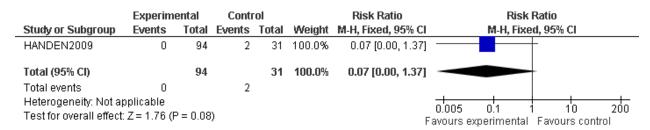
## Eye disorders

|                         | Experim     | ental    | Contr  | ol    |        | Risk Ratio         | Risk Ratio                           |
|-------------------------|-------------|----------|--------|-------|--------|--------------------|--------------------------------------|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C  | l M-H, Fixed, 95% Cl                 |
| HANDEN2009              | 3           | 94       | 0      | 31    | 100.0% | 2.36 [0.13, 44.42] |                                      |
| Total (95% CI)          |             | 94       |        | 31    | 100.0% | 2.36 [0.13, 44.42] |                                      |
| Total events            | 3           |          | 0      |       |        |                    |                                      |
| Heterogeneity: Not a    |             |          |        |       |        |                    | 0.02 0.1 1 10 50                     |
| Test for overall effect | Z = 0.57 (F | P = 0.57 | ")     |       |        |                    | Favours experimental Favours control |

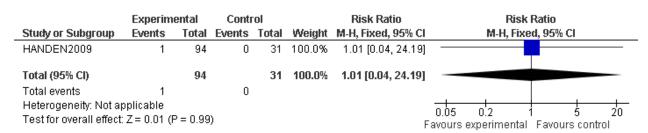
## Blood or lymphatic system disorders

|                          | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                           |
|--------------------------|-------------|----------|--------|-------|--------|-------------------|--------------------------------------|
| Study or Subgroup        | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | M-H, Fixed, 95% CI                   |
| HANDEN2009               | 1           | 94       | 1      | 31    | 100.0% | 0.33 [0.02, 5.12] |                                      |
| Total (95% CI)           |             | 94       |        | 31    | 100.0% | 0.33 [0.02, 5.12] |                                      |
| Total events             | 1           |          | 1      |       |        |                   |                                      |
| Heterogeneity: Not ap    | plicable    |          |        |       |        |                   | 0.02 0.1 1 10 50                     |
| Test for overall effect: | Z = 0.79 (F | P = 0.43 | )      |       |        |                   | Favours experimental Favours control |

## Renal or urinary disorders



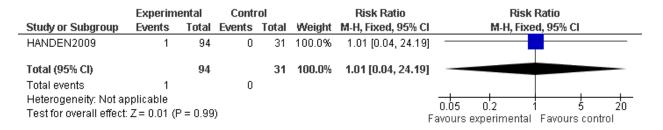
## Ear or labyrinth disorders



## Immune system disorders

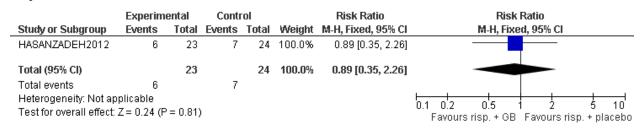
|                         | Ехрегіт     | ental    | Contr  | ol    |        | Risk Ratio        | Risk Ratio                              |
|-------------------------|-------------|----------|--------|-------|--------|-------------------|---|
| Study or Subgroup       | Events      | Total    | Events | Total | Weight | M-H, Fixed, 95% C | I M-H, Fixed, 95% CI                    |
| HANDEN2009              | 1           | 94       | 0      | 31    | 100.0% | 1.01 [0.04, 24.19 | n — — — — — — — — — — — — — — — — — — — |
| Total (95% CI)          |             | 94       |        | 31    | 100.0% | 1.01 [0.04, 24.19 |   |
| Total events            | 1           |          | 0      |       |        |                   |   |
| Heterogeneity: Not ap   | pplicable   |          |        |       |        |                   | 0.05 0.2 1 5 20                         |
| Test for overall effect | Z = 0.01 (F | P = 0.99 | )      |       |        |                   | Favours experimental Favours control    |

#### Vascular disorders

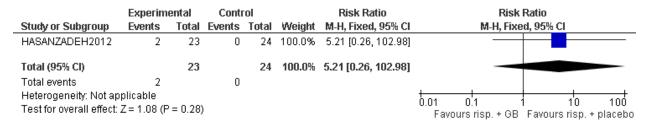


# Adverse events associated with ginkgo biloba and risperidone versus placebo and risperidone

## Day time drowsiness



## Morning drowsiness



# Constipation

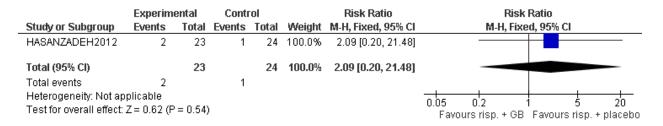
#### DRAFT GUIDELINE

|                          | Experim     | ental   | Contr  | ol    |        | Risk Ratio         | Risk Ratio                                 |
|--------------------------|-------------|---------|--------|-------|--------|--------------------|--|
| Study or Subgroup        | Events      | Total   | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI                         |
| HASANZADEH2012           | 3           | 23      | 3      | 24    | 100.0% | 1.04 [0.23, 4.65]  |  |
| Total (95% CI)           |             | 23      |        | 24    | 100.0% | 1.04 [0.23, 4.65]  |  |
| Total events             | 3           |         | 3      |       |        |                    |  |
| Heterogeneity: Not ap    | plicable    |         |        |       |        |                    | 01 02 05 1 2 5 10                          |
| Test for overall effect: | Z = 0.06 (P | = 0.96) | ı      |       |        |                    | Favours risp. + GB Favours risp. + placebo |

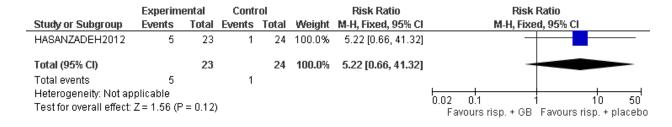
#### **Dizziness**

|   | Ехрегіт | ental   | Contr  | ol    |        | Risk Ratio         | Risk Ratio  |
|---|---------|---------|--------|-------|--------|--------------------|---|
| Study or Subgroup                                   | Events  | Total   | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI  |
| HASANZADEH2012                                      | 1       | 23      | 3      | 24    | 100.0% | 0.35 [0.04, 3.11]  |   |
| Total (95% CI)                                      |         | 23      |        | 24    | 100.0% | 0.35 [0.04, 3.11]  |   |
| Total events  | 1       |         | 3      |       |        |                    |   |
| Heterogeneity: Not ap<br>Test for overall effect: . | •       | = 0.34) | )      |       |        |                    | 0.05 0.2 1 5 20<br>Favours risp. + GB Favours risp. + placebo |

#### Slow movement



#### Nervousness



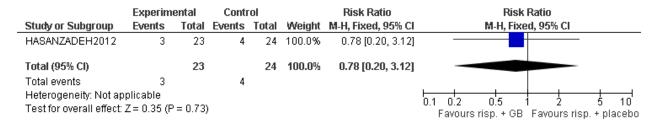
#### Restlessness

|   | Experim | ental   | Contr  | ol    |        | Risk Ratio         | Risk Ratio   |
|---|---------|---------|--------|-------|--------|--------------------|--|
| Study or Subgroup                                 | Events  | Total   | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI   |
| HASANZADEH2012                                    | 3       | 23      | 5      | 24    | 100.0% | 0.63 [0.17, 2.33]  |  |
| Total (95% CI)                                    |         | 23      |        | 24    | 100.0% | 0.63 [0.17, 2.33]  |  |
| Total events                                      | 3       |         | 5      |       |        |                    |  |
| Heterogeneity: Not ap<br>Test for overall effect: |         | = 0.48) | )      |       |        |                    | 0.1 0.2 0.5 1 2 5 10<br>Favours risp. + GB Favours risp. + placebo |

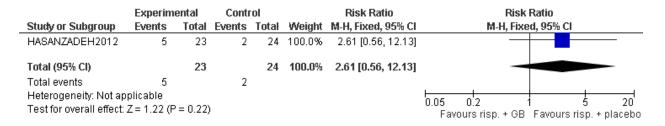
## **Increased appetite**

|   | Experime | ental   | Contr  | ol    |        | Risk Ratio         | Risk Ratio   |
|---|----------|---------|--------|-------|--------|--------------------|--|
| Study or Subgroup                                   | Events   | Total   | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI   |
| HASANZADEH2012                                      | 6        | 23      | 10     | 24    | 100.0% | 0.63 [0.27, 1.44]  |  |
| Total (95% CI)                                      |          | 23      |        | 24    | 100.0% | 0.63 [0.27, 1.44]  |  |
| Total events  | 6        |         | 10     |       |        |                    |  |
| Heterogeneity: Not ap<br>Test for overall effect: 2 | •        | = 0.27) | ı      |       |        |                    | 0.1 0.2 0.5 1 2 5 10<br>Favours risp. + GB Favours risp. + placebo |

## Loss of appetite



## **Fatigue**



#### Diarrhoea

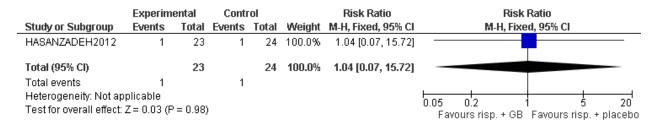
#### DRAFT GUIDELINE

|   | Experim | ental   | Contr  | ol    |        | Risk Ratio         | Risk Ratio   |
|---|---------|---------|--------|-------|--------|--------------------|--|
| Study or Subgroup                                 | Events  | Total   | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% CI   |
| HASANZADEH2012                                    | 3       | 23      | 3      | 24    | 100.0% | 1.04 [0.23, 4.65]  |  |
| Total (95% CI)                                    |         | 23      |        | 24    | 100.0% | 1.04 [0.23, 4.65]  |  |
| Total events                                      | 3       |         | 3      |       |        |                    |  |
| Heterogeneity: Not ap<br>Test for overall effect: |         | = 0.96) | )      |       |        |                    | 0.1 0.2 0.5 1 2 5 10<br>Favours risp. + GB Favours risp. + placebo |

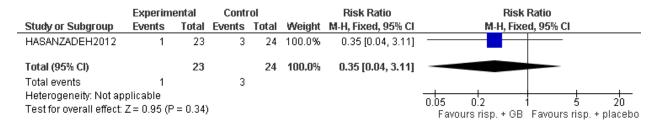
#### **Twitches**

|   | Ехрегіт | ental     | Conti  | ol    |        | Risk Ratio          | Risk Ratio         |
|---|---------|-----------|--------|-------|--------|---------------------|--------------------|
| Study or Subgroup                                 | Events  | Total     | Events | Total | Weight | M-H, Fixed, 95% CI  | M-H, Fixed, 95% CI |
| HASANZADEH2012                                    | 3       | 23        | 0      | 24    | 100.0% | 7.29 [0.40, 133.82] |                    |
| Total (95% CI)                                    |         | 23        |        | 24    | 100.0% | 7.29 [0.40, 133.82] |                    |
| Total events                                      | 3       |           | 0      |       |        |                     |                    |
| Heterogeneity: Not ap<br>Test for overall effect: | •       | 9 = 0.18) | )      |       |        |                     | 0.01               |

## Dry mouth



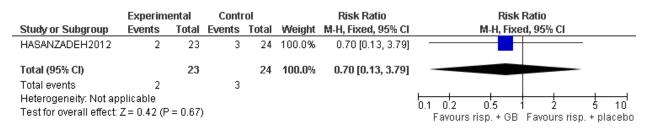
## Trouble swallowing



## Sore throat/tongue

|                               | Experimental |       | Control |       |        | Risk Ratio                                 | Risk Ratio         |
|-------------------------------|--------------|-------|---------|-------|--------|--|--------------------|
| Study or Subgroup             | Events       | Total | Events  | Total | Weight | M-H, Fixed, 95% CI                         | M-H, Fixed, 95% CI |
| HASANZADEH2012                | 1            | 23    | 5       | 24    | 100.0% | 0.21 [0.03, 1.65]                          |                    |
| Total (95% CI)                |              | 23    |         | 24    | 100.0% | 0.21 [0.03, 1.65]                          |                    |
| Total events                  | 1            |       | 5       |       |        |  |                    |
| Heterogeneity: Not applicable |              |       |         |       |        |  | 0.05 0.2 1 5 20    |
| Test for overall effect:      | = 0.14)      | )     |         |       |        | Favours risp. + GB Favours risp. + placebo |                    |

## Abdominal pain



# Adverse events associated with gluten-free and casein-free diet versus treatment as usual

|  | Experimental |       | Control |       | Risk Ratio |                   |   | Risk Ratio     |                  |                  |             |         |
|--|--------------|-------|---------|-------|------------|-------------------|---|----------------|------------------|------------------|-------------|---------|
| Study or Subgroup  | Events       | Total | Events  | Total | Weight     | M-H, Fixed, 95% C | 1 |                | M-H, Fix         | ed, 95% CI       |             |         |
| WHITELEY2010   | 0            | 38    | 0       | 34    |            | Not estimable     | Э |                |                  |                  |             |         |
| Total (95% CI)   |              | 38    |         | 34    |            | Not estimable     | 9 |                |                  |                  |             |         |
| Total events   | 0            |       | 0       |       |            |                   |   |                |                  |                  |             |         |
| Heterogeneity: Not applicable<br>Test for overall effect: Not applicable |              |       |         |       |            |                   |   | 0.2<br>irs ext | 0.5<br>perimenta | 1 2<br>I Favours | 5<br>contro | 10<br>I |