APPENDIX 19:

GRADE EVIDENCE PROFILES

1.1 SETTINGS FOR CARE

1.1.1 Community-based teams

Current living training environment compared with developmental group home training environment for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With developmental group home training environment	**With current living**		**Risk with developmental centre group home training environment**	**Risk difference with current living (95% CI)**
ommunity living skills (measured with average number of skills gained across community living skills behavioural domains; better indicated by lower values)											
20 (1 study) 1 year	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	10	10	N/A	N/A	MD -8.90 (8.06 to 9.74)

[1] Non-randomised allocation and non-blind assessment of outcome increased the risk of selection and detection bias.
[2] Extrapolated from adults with a learning disability.
[3] The precision, reliability and validity of the outcome measure were unclear because it was under-specified and the sample size was small.
[4] Due to risk of bias, indirectness and imprecision.

Specialist behaviour therapy team compared with treatment as usual for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With treatment as usual	**With specialist behaviour therapy team**		**Risk with treatment as usual**	**Risk difference with specialist behaviour therapy team (95% CI)**
Challenging behaviour (lethargy/hyperactivity) (measured with Aberrant Behavior Checklist; better indicated by lower values)											
63 (1 study) 6 months	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	31	32	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Challenging behaviour (irritability) (measured with Aberrant Behavior Checklist; better indicated by lower values)											
63 (1 study) 6 months	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	31	32	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Could not extract data for efficacy because median values and interquartile ranges were reported. This may also imply that the data were skewed. Therefore, restricted to analysing the results from this study via narrative review.
[2] Extrapolated from adults with a learning disability.
[3] Due to risk of bias, indirectness and imprecision.

Observational studies of specialist assessment and treatment units for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With specialist assessment and treatment unit**		**Risk with control**	**Risk difference with specialist assessment and treatment unit (95% CI)**
Challenging behaviour (measured with ABS Part II violent behaviour domain; better indicated by lower values)											
16 (1 study) 6 months	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	N/A	16	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Small sample size and ABS data only available for half of the participants. There was also no control group and efficacy data could not be extracted.
[2] Extrapolated from adults with a learning disability.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

Liaison worker compared with treatment as usual for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With treatment as usual	**With liaison worker**		**Risk with treatment as usual**	**Risk difference with liaison worker (95% CI)**
Access to services (measured with number of contacts with services; better indicated by lower values)											
26 (1 study) 9 months	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3,4]	14	12	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Efficacy data could not be extracted.
[2] Extrapolated from adults with a learning disability.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

1.1.2 Residential accommodation and related services

Community housing compared with residential institution for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With community housing	With residential institution		Risk with community housing	Risk difference with residential institution (95% CI)
Residential satisfaction – social life (measured with Satisfaction Questionnaire of Seltzer and Seltzer's [1978] Community Adjustment Scale; better indicated by lower values)											
29 (1 study) 0.1 to 8 years	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	15	14	N/A	N/A	MD 5.80 (3.14 to 8.46)
Residential satisfaction – autonomy (measured with Satisfaction Questionnaire of Seltzer and Seltzer's [1978] Community Adjustment Scale; better indicated by lower values)											
29 (1 study) 0.1 to 8 years	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,5]	15	14	N/A	N/A	MD -1.20 (-2.28 to -0.12)
Residential satisfaction – total (measured with Satisfaction Questionnaire of Seltzer and Seltzer's [1978] Community Adjustment Scale; better indicated by lower values)											
29 (1 study) 0.1 to 8 years	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,5]	15	14	N/A	N/A	MD 5.60 (1.1 to 10.1)
Adaptive behaviour (measured with ABS, VABS or a modified version of the Behaviour Development Survey; better indicated by lower values)											
224 (3 studies) 12 to 48	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊖⊖⊖ VERY	103	121	N/A	N/A	SMD -0.48 (-0.75 to -0.20)

months						LOW[1,2,5]					
Social skills (measured with staff-rated social skills; better indicated by lower values)											
100 (1 study) 30 months	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,5]	50	50	N/A	N/A	MD -5.10 (-14.31 to 4.11)
Quality of life (measured with behavioural observations of quality of life; better indicated by lower values)											
100 (1 study) 30 months	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,5]	50	50	N/A	N/A	MD -12.90 (-16.05 to -9.75)
Activity outside the home (measured with diary self-report on the number of trips outside the home; better indicated by lower values)											
36 (1 study) 18 months	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	18	18	N/A	N/A	MD -3.00 (-6.99 to 0.99)

[1] Non-randomised allocation and non-blind assessment of outcome increases the risk of selection and detection bias.
[2] Extrapolated from adults with a learning disability.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.
[5] Due to risk of bias and indirectness.

Small residential homes compared with an institution for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With institution	**With small residential homes**		**Risk with institution**	**Risk difference with small residential homes (95% CI)**
Quality of life (measured with QoL-Q; better indicated by lower values)											
179 (1 study) Not reported	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3]	76	103	N/A	N/A	MD 11.40 (8.79 to 14.01)
Choice making (measured with Residence Choice Assessment Scale; better indicated by lower values)											
179 (1 study) Not reported	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3]	76	103	N/A	N/A	MD 36.60 (30.89 to 42.31)
Community inclusion (measured with Use of Community Facilities Scale; better indicated by lower values)											
179 (1 study) Not reported	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3]	76	103	N/A	N/A	MD 7.40 (4.86 to 9.94)
Contact with family (measured with frequency of face-to-face visits; better indicated by lower values)											
179 (1 study) Not reported	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3]	76	103	N/A	N/A	MD 0.60 (0.36 to 0.84)

[1] Non-randomised allocation of participants and significant group differences in adaptive/maladaptive behaviour.
[2] Extrapolated from adults with a learning disability.
[3] Due to risk of bias and indirectness.

Dispersed supported living compared with residential homes for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With residential homes	**With dispersed supported living**		**Risk with residential homes**	**Risk difference with dispersed supported living (95% CI)**
Social inclusion (measured with number of community amenities used in past months; better indicated by lower values)											
241 (1 study)	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3]	138	103	N/A	N/A	MD 0.90 (0.43 to 1.37)

[1] Limited data could be extracted from the study because a measure of variation (SD) was only reported for one scale item. Non-randomised allocation and non-blind assessment of outcome also increased the risk of selection and detection bias.
[2] Extrapolated from adults with a learning disability.
[3] Due to risk of bias and indirectness.

Semi-independent apartments compared with group homes for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With semi-independent apartments	**With group homes**		**Risk with semi-independent apartments**	**Risk difference with group home (95% CI)**
Resident satisfaction (measured with Lifestyle Satisfaction Scale; better indicated by lower values)											
204 (1 study) 1 year	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3]	147	57	N/A	N/A	MD -8.72 (-12.61 to -4.83)

[1] There were differences in sample sizes across groups and significant differences in demographic factors found between groups (for example, group home residents were the oldest); participants in independent apartments had the highest mean score for adaptive behaviour and the lowest mean score for challenging behaviour, which were not controlled for in statistical analysis. Non-randomisation and non-blind assessment of outcome also increased the risk of selection and detection bias.
[2] Extrapolated from adults with a learning disability.
[3] Due to risk of bias and indirectness.

Intermediate care placement compared with direct community placement for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With direct community placement	**With intermediate care placement**		**Risk with direct community placement**	**Risk difference with intermediate care placement between institution and community (95% CI)**
Adaptive behaviour (measured with AAMD ABS; better indicated by lower values)											
57 (1 study) 1 year	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3]	39	18	N/A	N/A	MD 5.89 (-12.24 to 24.02)

[1] Discrepancy in sample size between groups. Also, non-randomised allocation and non-blind assessment of outcomes increases the risk of selection and detection bias.
[2] Extrapolated from adults with a learning disability.
[3] Due to risk of bias and indirectness.

Person-centred planning compared with system-centred planning for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With system-centred planning	**With person-centred planning**		**Risk with system-centred planning**	**Risk difference with person-centred planning (95% CI)**
Movement into community (assessed with number of participants moving into community)											
37 (1 study) 3 years	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	5/18 (27.8%)	18/19 (94.7%)	RR 3.41 (1.61 to 7.24)	Study population	
										278 per 1000	669 more per 1000 (from 169 more to 1000 more)
										Moderate	
										N/A	N/A

[1] Allocation was not randomised increasing the risk of selection bias.
[2] Extrapolated from adults with a learning disability.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

Observational studies of the TEACCH approach in a residential setting for adults with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With TEACCH approach in residential setting**		**Risk with control**	**Risk difference with TEACCH approach in residential setting (95% CI)**
Social abilities (measured with staff-report questionnaire [based on VABS] and observation checklist; better indicated by lower values)											
12 (1 study) 6 months	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3]	N/A	12	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Functional communication (measured with staff-report questionnaire [based on VABS] and observation checklist; better indicated by lower values)											
12 (1 study) 6 months	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨀⨀⨀ VERY LOW[1,4]	N/A	12	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Small sample size, no control group and efficacy data could not be extracted.
[2] Small sample size.
[3] Due to risk of bias and imprecision.
[4] Due to risk of bias.

Observational studies of the move from institutional to community settings for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With move from institutional to community settings**		**Risk with control**	**Risk difference with move from institutional to community settings (95% CI)**
Challenging behaviour (measured with MOAS and Problems Questionnaire; better indicated by lower values)											
329 (3 studies) 12 to 24 months	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,,3]	N/A	329	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Quality of Life (measured with QoL-Q; better indicated by lower values)											
29 (1 study) 53 months	Very serious[1]	No serious inconsistency	Serious[2]	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,4,5]	N/A	29	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Family contact (measured with Developmental Disabilities Quality Assurance Questionnaire; better indicated by lower values)											
177 (1 study) 5 years	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3]	N/A	177	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Adaptive behaviour (measured with Part 1 of the AAMD ABS total score; better indicated by lower values)											
32 (1 study) 5.5 years	Very serious[1]	No serious inconsistency	Serious[2]	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,4,5]	N/A	32	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] No control group and efficacy data could not be extracted.
[2] Extrapolated from adults with a learning disability.
[3] Due to risk of bias and indirectness.
[4] Small sample size.
[5] Due to risk of bias, indirectness and imprecision.

Observational studies of the move from more restrictive to less restrictive work or living environments for adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With move from more restrictive to less restrictive work or living environments**		**Risk with control**	**Risk difference with move from more restrictive to less restrictive work or living environments (95% CI)**
Self-determination (measured with Arcs's Self-Determination Scale: Adult Version; better indicated by lower values)											
31 (1 study) 1 year	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3,4]	N/A	31	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Autonomous functioning (measured with Autonomous Functioning Checklist; better indicated by lower values)											
31 (1 study) 1 year	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3,4]	N/A	31	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] No control group and efficacy data could not be extracted.
[2] Extrapolated from adults with a learning disability.
[3] Sample size was small.
[4] Due to risk of bias, indirectness and imprecision.

1.1.3 Clinical care pathways – multidisciplinary teams

Economic evidence profile

Study and country	Limitations	Applicability	Other comments	Incremental[1] cost (£)	Incremental effect (QALYs)	ICER (£/QALY)	Uncertainty[2]
NAO (2009) UK	Potentially serious limitations[3]	Partially applicable[4]	Snapshot approach with annutised costs and outcomes Public sector perspective; costs the NHS reported separately	Per 1000 working-age population: £859 cost to the NHS £215 saving to the public purse	N/A	N/A	For a range of identification rate range achieved by multidisciplinary team 2 to 14%: Cost to the NHS: £752 to £1,181 per 1000 working-age population Cost to public purse: £752 to -£5,370 (saving) per 1000 working-age population

[1] Costs converted to 2010/11 prices using Hospital and Community Health Service.
[2] Costs converted to 2010/11 prices using Hospital and Community Health Service.
[3] Cost analysis; key input parameters based on a survey, local unpublished data and expert opinion.
[4] Perspective broader than NHS and PSS.

1.2 PSYCHOSOCIAL INTERVENTIONS

1.2.1 Behavioural therapies aimed at communication

Natural language teaching compared with analogue language teaching for communication in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With analogue language teaching	**With natural language teaching**		**Risk with analogue language teaching**	**Risk difference with natural language teaching (95% CI)**
Communication (measured with language acquisition measured by number of nouns generalised; better indicated by lower values)											
24 (1 study) 3 months	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2,3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	11.5	11.5	N/A	N/A	SMD -0.71 (-1.55 to 0.13)

[1] Non-randomised and non-blind, so high risk of bias.
[2] Study was designed to compare two alternative treatments and not to determine overall treatment efficacy.
[3] Small sample size.
[4] Due to risk of bias and imprecision.

Observational studies of functional communication skills training in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With functional communication skills training**		**Risk with control**	**Risk difference with functional communication skills training (95% CI)**
Communication (measured with VABS subscale of communication; better indicated by lower values)											
18 (1 study) 18 months	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3]	N/A	18	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational study and could not extract efficacy data.
[2] Small sample size.
[3] Due to risk of bias and imprecision.

1.2.2 Facilitated communication

Observational studies of facilitated communication in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With observational studies of facilitated communication for adults with autism**		**Risk with control**	**Risk difference with observational studies of facilitated communication for adults with autism (95% CI)**
Behavioural and social interaction responses (measured with behavioural observations; better indicated by lower values)											
12 (1 study) 17 weeks	Very serious[1,2]	No serious inconsistency	No serious indirectness	Very serious[3,4]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3,4,5]	N/A	12	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] No control group.
[2] Efficacy data could not be extracted.
[3] Small sample size.
[4] Behavioural observations were non-blind.
[5] Due to risk of bias and imprecision.

1.2.3 Behavioural therapies aimed at behaviour management

Independence training compared with no-treatment control group in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no treatment	With behavioural therapies		Risk with no treatment	Risk difference with behavioural therapies (95% CI)
Activities of daily living (showering) (measured with task-specific checklist for showering; better indicated by lower values)											
72 (1 study) 7 months	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	36	36	N/A	N/A	MD 8.40 (6.99 to 9.81)

[1] No attention-placebo control group, so participants did not receive the same care apart from intervention; also, the study was non-blind so there was a risk of performance and detection bias.
[2] Extrapolated from adults with a learning disability.
[3] The outcome measure was designed specifically for this study and lacks formal assessments of reliability and validity.
[4] Due to risk of bias, indirectness and imprecision.

Observational studies of adaptive skills training in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With behavioural therapies**		**Risk with control**	**Risk difference with behavioural therapies (95% CI)**
Activities of daily living (measured with Behavior Maturity Checklist II-1978 toileting subscale; better indicated by lower values)											
51 (1 study) 10 years	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3]	N/A	51	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational study with no control group and efficacy data could not be extracted.
[2] Extrapolated from adults with a learning disability.
[3] Due to risk of bias and indirectness.

Behavioural weight control compared with no-treatment control in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no treatment	**With behavioural therapies**		**Risk with no treatment**	**Risk difference with behavioural therapies (95% CI)**
Self care (measured with weight loss; better indicated by lower values)											
21 (1 study) 26 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	11	10	N/A	N/A	SMD 0.44 (-0.43 to 1.30)

[1] Control group consisted of drop-outs from the experimental group, so there was high risk for selection bias. The study was also non-randomised and non-blind, increasing the risk of performance and detection bias.
[2] Extrapolated from adults with a learning disability.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

Observational studies of self-instructional pictorial child care manuals in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With behavioural therapies**		**Risk with control**	**Risk difference with behavioural therapies (95% CI)**
Parenting skill (measured with target child-care behaviour checklist; better indicated by lower values)											
10 (1 study) 3 years	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3]	N/A	10	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational study and efficacy data could not be extracted.
[2] Extrapolated from adults with a learning disability.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

1.2.4 Cognitive behavioural therapies

Cognitive behavioural therapies compared with treatment as usual for coexisting conditions in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With treatment as usual	**With cognitive behavioural therapies**		**Risk with treatment as usual**	**Risk difference with cognitive behavioural therapies (95% CI)**
Severity of coexisting condition (OCD) (measured with Y-BOCS severity scale; better indicated by lower values)											
24 (1 study) 16 months	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2]	12	12	N/A	N/A	MD 2.42 (-3.6 to 8.44)

[1] No attention-placebo control group, so participants did not receive the same care apart from intervention; also, the study was non-randomised and non-blind so risk of selection, performance and detection bias.
[2] Small sample size.
[3] Due to risk of bias and imprecision.

Cognitive behavioural therapies compared with treatment as usual for anti-victimisation skills in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With treatment as usual	**With cognitive behavioural therapies**		**Risk with treatment as usual**	**Risk difference with cognitive behavioural therapies (95% CI)**
Anti-victimisation skills (measured with Self Social Interpersonal Decision Making Scale and the Protective Behaviour Skills Evaluation; better indicated by lower values)											
80 (3 studies[1]) 3 to 9 weeks	Serious[2]	No serious inconsistency	Serious[3]	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[2,3,4,5]	40	40	N/A	N/A	SMD 1.07 (0.58 to 1.56)
Anti-victimisation skills (assessed with: bullying victimisation rates)											
38 (1 study) 3 months	Serious[2]	No serious inconsistency	Serious[3]	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[2,3,6]	7/18 (38.9%)	5/20 (25%)	RR 0.64 (0.25 to 1.67)	Study population	
										389 per 1000	140 fewer per 1000 (from 292 fewer to 261 more)
										Moderate	
										389 per 1000	140 fewer per 1000 (from 292 fewer to 261 more)

[1] Two RCTs (KHEMKA2000, KHEMKA2005) and one quasi-experimental study (MAZZUCCHELLI2001) combined.
[2] No attention-placebo control group, so participants did not receive the same care apart from intervention; also, the study was non-blind so there was a risk of performance and detection bias.
[3] Extrapolated from adults with a learning disability.
[4] The precision of the outcome measures for KHEMKA2000 and KHEMKA2005 was unclear.
[5] Due to risk of bias, indirectness and imprecision.
[6] Due to risk of bias and indirectness.

Cognitive behavioural therapies compared with waitlist control or treatment as usual for anger management in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With waitlist control or treatment as usual	**With cognitive behavioural therapies**		**Risk with waitlist control or treatment as usual control**	**Risk difference with cognitive behavioural therapies (95% CI)**
Anger management (measured with DPI, Anger Inventory and Provocation Inventory; better indicated by lower values)											
169 (3 studies) 4 to 9 months	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3]	70	99	N/A	N/A	MD -0.59 (-0.9 to -0.27)

[1] No attention-placebo control group, so participants did not receive same care apart from intervention; also, the study was non-randomised and non-blind so there was a risk of selection, performance and detection bias.
[2] Extrapolated from adults with a learning disability.
[3] Due to risk of bias and indirectness.

Cognitive behavioural therapies for anger management in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With cognitive behavioural therapies**		**Risk with control**	**Risk difference with cognitive behavioural therapies (95% CI)**
Anger management (measured with aggressive gestures on the videotaped role-play test and Anger Inventory for Mentally Retarded Adults; better indicated by lower values)											
65 (2 studies) 19 to 27 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3]	N/A	65	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational studies and could not extract efficacy data.
[2] Extrapolated from adults with a learning disability.
[3] The precision of the outcome measure in BENSON1996 was unclear.
[4] Due to risk of bias, indirectness and imprecision.

1.2.5 Leisure programmes

Leisure programmes compared with waitlist control in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With waitlist control	**With leisure programmes**		**Risk with control**	**Risk difference with leisure programme compared with waitlist control in adults with autism (95% CI)**
Quality of life (measured with QoL-Q – Spanish version; better indicated by lower values)											
71 (1 study) 1 year	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨀ MODERATE[1,2]	34	37	N/A	N/A	MD 8.33 (5.21 to 11.45 SD)
Emotion recognition (measured with the Facial Discrimination Battery – Spanish version – recognition of emotion subscale; better indicated by lower values)											
40 (1 study) 1 year	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	20	20	N/A	N/A	MD 12.77 (2.12 to 23.42)

[1] No attention-placebo control group, which increased the risk of performance bias.
[2] Small sample size.
[3] Due to risk of bias.
[4] Due to risk of bias and imprecision.

1.2.6 Social learning interventions

Emotion recognition training compared with treatment as usual in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With treatment as usual	**With emotion recognition training**		**Risk with treatment as usual**	**Risk difference with emotion recognition training (95% CI)**
Emotion recognition (measured with The Cambridge Mindreading (CAM) Face-Voice Battery: Face task; better indicated by lower values)											
40 (1 study) 15 weeks	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Undetected	⊕⊕⊖⊖ LOW[1,2]	22	18	N/A	N/A	MD 2.70 (-2.27 to 7.67)

[1] No attention-placebo control group, so participants did not receive same care apart from intervention; also, the study was non-blind so there was risk of performance and detection bias.
[2] Small sample size.
[3] Due to risk of bias and imprecision.

Observational studies of social skills group interventions in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With social skills group interventions**		**Risk with control**	**Risk difference with social skills group (95% CI)**
Social interaction (measured with EQ and role-play 'party' scenario; better indicated by lower values)											
23 (2 studies) 8 to 52 weeks	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3]	N/A	23	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational study and could not extrapolate efficacy data.
[2] Small sample size.
[3] Due to risk of bias and imprecision.

Social skills group interventions compared with waitlist control in adolescents with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With waitlist control	**With social skills group interventions**		**Risk with waitlist control**	**Risk difference with social skills group (95% CI)**
Social interaction (measured with TASSK; better indicated by lower values)											
33 (1 study) 24 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	16	17	N/A	N/A	MD 6.30 (4.32 to 8.28)

[1] No attention-placebo control group, so participants did not receive same care apart from intervention; also, the study was non-blind so there was a risk of performance and detection bias.
[2] Extrapolated from adolescents with autism.
[3] Sample size was small.
[4] Due to risk of bias, indirectness and imprecision.

Observational studies of social skills groups for adolescents with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With social skills group**		**Risk with control**	**Risk difference with social skills group (95% CI)**
Social interaction (measured with blind-expert video rating and social responsiveness/social skills rating scales; better indicated by lower values)											
49 (3 studies) 2.5 to 11 months	Serious[1]	Serious[2]	Serious[3]	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4,5]	N/A	49	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Challenging behaviour (measured with Aberrant Behavior Checklist – Irritability subscale; better indicated by lower values)											
30 (1 study) 12 weeks	Serious[1]	No serious inconsistency	Serious[3]	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,3,4]	N/A	30	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational studies and efficacy data could not be extracted.
[2] HERBRECHT2009 and WEBB2004 found no significant treatment effects, while TSE2007 found a significant treatment effect (effect size 0.39).
[3] Extrapolated from adolescents with autism.
[4] Sample size was small.
[5] Due to risk of bias, inconsistency, indirectness and imprecision.
[6] Due to risk of bias, indirectness and imprecision.

Social skills group interventions compared with treatment as usual in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With treatment as usual	**With social skills group interventions**		**Risk with treatment as usual**	**Risk difference with social skills group (95% CI)**
Challenging behaviour (measured with Part 2 of the AAMD ABS; better indicated by lower values)											
44 (1 study) 10 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	24	20	N/A	N/A	MD -2.03 (-11.79 to 7.73)

[1] No attention-placebo control group, so participants did not receive same care apart from intervention; also, the study was non-blind so there was a risk of performance and detection bias.
[2] Extrapolated from adults with a learning disability.
[3] Sample size was small.
[4] Due to risk of bias, indirectness and imprecision.

1.2.7 Supported employment programmes

Supported employment programmes compared with sheltered workshop programmes in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With sheltered workshop programmes	**With supported employment programmes**		**Risk with sheltered workshop programmes**	**Risk difference with supported employment programmes (95% CI)**
Autistic behaviours (measured with CARS; better indicated by lower values)											
51 (1 study) 3 years	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2]	26	25	N/A	N/A	MD -6.07 (-10.09 to -2.05)
Quality of life (measured with Quality of Life Survey; better indicated by lower values)											
51 (1 study) 3 years	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3]	26	25	N/A	N/A	MD 5.20 (2.69 to 7.71)

[1] Group allocation not randomised.
[2] Sample size figures varied throughout the paper with no explanation as to the changing values. The sample sizes used for analysis were selected from the demographic table, but it is not clear if this assumption was valid or correct.
[3] Due to risk of bias and imprecision.

Supported employment programmes compared with waitlist control in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With waitlist control	**With supported employment programmes**		**Risk with waitlist control**	**Risk difference with supported employment programmes (95% CI)**
Executive function (measured with 'Stockings of Cambridge' (SOC) Planning Task from CANTAB; better indicated by lower values)											
44 (1 study) 30 months	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2,3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	22	22	N/A	N/A	MD -2.75 (-4.41 to -1.09)

[1] Group allocation not randomised.
[2] Sample size not reported for each group. Analysis based on an assumption of equal numbers in each group, but may be invalid.
[3] Sample size was small.
[4] Due to risk of bias and imprecision.

Economic evidence profile for supported employment programmes

Study and country, or review	Limitations	Applicability	Other comments	Incremental cost (£)[5]	Incremental effect (QALYs)	ICER (£/QALY)	Uncertainty
Mawhood and Howlin (1999), UK	Potentially serious limitations[6]	Directly applicable	Quasi-experimental parallel group controlled trial Only intervention costs of employment support – intervention costs of control group not estimated Measure of outcome: probability of employment	£13,018	0.38	£34,258	Not reported
Economic analysis for this guideline	Minor limitations[7]	Directly applicable	Decision-tree followed by Markov model Time horizon: 8 years *Costs considered:* Main analysis: intervention costs Secondary analysis 1: intervention and accommodation costs Secondary analysis 2: intervention and NHS/PSS costs Measure of outcome: QALY	Main analysis: £157 Secondary analysis 1: -£1,117 Secondary analysis 2: -£611	0.11	Main analysis: £1,467 per QALY Secondary analyses: supported employment dominant	One-way sensitivity analysis (main analysis): 50% change in supported employment intervention cost: £15,190 per QALY to supported employment dominant. 50% change in standard care intervention cost: supported employment dominant to £15,452 per QALY. Threshold analysis (main analysis): minimum risk ratio of supported employment versus standard care required for the intervention to be cost-effective: 1.45 (upper NICE threshold); 1.59 (lower NICE threshold). Probabilistic sensitivity analysis: probability that the intervention is cost-effective at the lower NICE threshold. Main analysis: 77.5% Secondary analysis 1: 80.4% Secondary analysis 2: 80.8%

[5] Costs uplifted to 2011 UK pounds using the UK Hospital and Community Health Service inflation index.
[6] Short time horizon; only intervention costs of supported employment considered; resource use or costs of control not estimated.
[7] Efficacy data based on quasi-experimental parallel group controlled trial; time horizon was 8 years; cost data based on published sources; national unit costs used; probabilistic sensitivity analysis conducted.

Supported employment programmes compared with treatment as usual in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control group	**With supported employment programmes**		**Risk with control group**	**Risk difference with supported employment programmes (95% CI)**
Job placements (assessed with number of participants in work)											
50 (1 study) 2 years	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[1,2]	5/20 (25%)	19/30 (63.3%)	RR 2.53 (1.13 to 5.67)	Study population	
										250 per 1000	382 more per 1000 (from 32 more to 1000 more)
										Moderate	
										250 per 1000	382 more per 1000 (from 32 more to 1000 more)

[1] Group allocation not randomised.
[2] Due to risk of bias.

Observational studies of supported employment programmes in adults with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With supported employment programmes**		**Risk with control**	**Risk difference with supported employment programmes (95% CI)**
Job placements (measured with number of participants in work; better indicated by lower values)											
89 (1 study) 1 year	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[1,2]	N/A	89	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] No control group and efficacy data could not be extracted.
[2] Due to risk of bias.

1.2.8 Support for families, partners and carers

Coping skills training programme compared with treatment as usual for mothers of adolescents with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With treatment as usual	**With coping skills training programme**		**Risk with treatment as usual**	**Risk difference with coping skills training programme (95% CI)**
Social support (measured with Coping Strategy Indicator; better indicated by lower values)											
20 (1 study) 4 weeks	Very serious[1,2,3]	No serious inconsistency	No serious indirectness	Serious[4]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4,5]	10	10	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Hopelessness (measured with Beck Hopelessness Scale; better indicated by lower values)											
20 (1 study) 4 weeks	Very serious[1,2,3]	No serious inconsistency	No serious indirectness	Serious[4]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4,5]	10	10	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Group allocation not randomised.
[2] Efficacy data could not be extracted.
[3] Short duration of follow-up.
[4] Small sample size.
[5] Due to risk of bias and imprecision.

Psychoeducational group permanency planning programme compared with treatment as usual for mothers of adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With treatment as usual	**With psychoeducation group permanency planning programme**		**Risk with treatment as usual**	**Risk difference with psychoeducation group permanency planning programme (95% CI)**
Knowledge and awareness about planning (measured with cluster based on standardised and original scales; better indicated by lower values)											
27 (1 study) 6 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	14	13	N/A	N/A	SMD -0.99 (-1.79 to -0.19)
Competence and confidence to plan (measured with cluster based on standardised and original scales; better indicated by lower values)											
27 (1 study) 6 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	14	13	N/A	N/A	SMD -1.36 (-2.20 to -0.53)

Appraisals of the planning process (measured with cluster based on standardised and original scales; better indicated by lower values)											
27 (1 study) 6 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	14	13	N/A	N/A	SMD -0.61 (-1.39 to 0.1)
Intermediate planning behaviours (measured with cluster based on standardised and original scales; better indicated by lower values)											
27 (1 study) 6 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	14	13	N/A	N/A	SMD -0.49 (-1.25 to 0.28)
Residential and legal planning (measured with cluster based on standardised and original scales; better indicated by lower values)											
27 (1 study) 6 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	14	13	N/A	N/A	SMD -1.02 (-1.82 to -0.21)

[1] Non-blind allocation, administration and assessment; randomisation methods were unclear; it was not clear if the control group received the same care apart from the intervention; there was also a relatively short duration of follow-up, and concerns regarding the reliability and validity of outcome measures.
[2] Extrapolated from adults with a learning disability.
[3] Small sample size and group N were not clear (assumed N = 13 in experimental and N = 14 in control, but it was not clear if this assumption is correct).
[4] Due to risk of bias, indirectness and imprecision.

1.3 BIOMEDICAL INTERVENTIONS

1.3.1 Antipsychotics: grade profiles

Risperidone compared with placebo for behaviour management in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With risperidone**		**Risk with placebo**	**Risk difference with risperidone (95% CI)**
Challenging behaviour (measured with Aberrant Behavior Checklist and SIB-Q (Aggression); better indicated by lower values)											
66 (2 studies) 12 to 22 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⊕⊕⊕⊖ MODERATE[1,2]	33	33	N/A	N/A	SMD -0.79 (-1.29 to -0.28)
Autistic behaviours (measured with Ritvo-Freeman Real-life Rating Scale; better indicated by lower values)											
31 (1 study) 12 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⊕⊕⊕⊖ MODERATE[1,2]	16	15	N/A	N/A	SMD -0.72 (-1.45 to 0.01)
Core autism symptom (repetitive behaviour) (measured with Y-BOCS; better indicated by lower values)											
31 (1 study) 12 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⊕⊕⊕⊖ MODERATE[1,2]	16	15	N/A	N/A	SMD -0.94 (-1.68 to -0.19)
Symptom severity or improvement (measured with CGI scale; better indicated by lower values)											
31 (1 study) 12 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⊕⊕⊕⊖ MODERATE[1,2]	16	15	N/A	N/A	SMD -1.40 (-2.18 to -0.61)

[1] Sample size was small.
[2] Due to imprecision.

Risperidone compared with placebo for behaviour management in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With risperidone**		**Risk with placebo**	**Risk difference with risperidone (95% CI)**
Challenging behaviour (measured with Aberrant Behavior Checklist score [challenging behaviour]; better indicated by lower values)											
58 (1 study) 26 weeks	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊕⊖⊖ LOW[1,2,3]	29	29	N/A	N/A	MD -4.77 (-18.38 8.84)
Aggression (measured with MOAS; better indicated by lower values)											
58 (1 study) 26 weeks	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊕⊖⊖ LOW[1,2,3]	29	29	N/A	N/A	MD 0.58 (-4.90 to 6.06)
Symptom severity or improvement (measured with CGI Scale; better indicated by lower values)											
132 (2 studies) 4 to 26 weeks	Serious[1]	Serious[4]	Very serious[2,5]	No serious imprecision	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4,5]	66	66	N/A	N/A	SMD -0.30 (-0.64 to 0.04)
Quality of life (measured with QoL-Q; better indicated by lower values)											
58 (1 study) 26 weeks	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊕⊖⊖ LOW[1,2,3]	29	29	N/A	N/A	MD 2.88 (-2.56 to 8.32)

Challenging behaviour (narrative reporting) (measured with Aberrant Behavior Checklist total score; better indicated by lower values)											
38 (1 study) 8 weeks	Serious[6]	No serious inconsistency	Serious[2]	Serious[7]	Undetected	⊕⊖⊖⊖ VERY LOW[2,6,7,8]	19	19	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Symptom severity or improvement (narrative reporting) (measured with CGI scale; better indicated by lower values)											
38 (1 study) 8 weeks	Serious[6]	No serious inconsistency	Serious[2]	Serious[7]	Undetected	⊕⊖⊖⊖ VERY LOW[2,6,7,8]	19	19	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Data were skewed in TYRER2008.
[2] Extrapolated from a learning disabilities population.
[3] Due to risk of bias and indirectness.
[4] GAGIANO2005 found significant differences whereas TYRER2008 did not.
[5] Participants in GAGIANO2005 had coexisting conditions including conduct disorder, disruptive behaviour disorder, intermittent explosive disorder, oppositional defiant disorder and antisocial personality disorder.
[6] The data reported does not allow for a calculation of effect size.
[7] Small sample size.
[8] Due to risk of bias, indirectness and imprecision.

Open-label risperidone for behaviour management in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With open-label risperidone**		**Risk with control**	**Risk difference with open-label risperidone (95% CI)**
Challenging behaviour (narrative reporting) (measured with Aberrant Behavior Checklist; better indicated by lower values)											
24 (1 study) 76.4 days	Very serious[1]	No serious inconsistency	Very serious[2,3]	Serious[4]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4,5]	N/A	24	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Symptom severity/outcome (narrative reporting) (measured with CGI scale; better indicated by lower values)											
24 (1 study) 76.4 days	Very serious[1]	No serious inconsistency	Very serious[2,3]	Serious[4]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4,5]	N/A	24	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Quality of life (measured with Composite Autonomic Symptom Scale modified version; better indicated by lower values)											
24 (1 study) 76.4 days	Very serious[1]	No serious inconsistency	Very serious[2,3]	Serious[4]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4,5]	N/A	24	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational study with open-label treatment; data extracted did not allow for calculation of effect sizes.
[2] Extrapolated from adults with a learning disability.
[3] Learning disabilities populations also have coexisting psychiatric conditions including epilepsy and organic behaviour disorder.
[4] Small sample size.
[5] Due to risk of bias, indirectness and imprecision.

Haloperidol compared with placebo for behaviour management in adults with autism

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With haloperidol**		**Risk with placebo**	**Risk difference with haloperidol (95% CI)**
Autistic behaviours (measured with CARS; better indicated by lower values)											
33 (1 study) 21 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	16	17	N/A	N/A	MD -2.70 (-7.19 to 1.79)
Side effects (measured with DOTES; better indicated by lower values)											
33 (1 study) 21 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	16	17	N/A	N/A	MD -1.50 (-0.28 to 3.28)

[1] High risk of attrition bias due to higher dropout as a consequence of side effects in the haloperidol group.
[2] Sample was of adolescents with autism.
[3] Sample size was small.
[4] Due to risk of bias, indirectness and imprecision.

Haloperidol compared with placebo for behaviour management in adults with a learning disability

Quality assessment							Summary of findings				
No. of participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With haloperidol**		**Risk with placebo**	**Risk difference with haloperidol (95% CI)**
Challenging behaviour (measured with Aberrant Behavior Checklist; better indicated by lower values)											
57 (1 study) 26 weeks	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊕⊖⊖ LOW[1,2,3]	29	28	N/A	N/A	MD -4.30 (-19.30 to 10.70)
Aggression (measured with MOAS; better indicated by lower values)											
57 (1 study) 26 weeks	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊕⊖⊖ LOW[1,2,3]	29	28	N/A	N/A	MD -4.12 (-8.53 to 0.29)
Symptom severity or improvement (measured with CGI-I; better indicated by lower values)											
57 (1 study) 26 weeks	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊕⊖⊖ LOW[1,2,3]	29	28	N/A	N/A	MD -0.88 (-1.57 to -0.19)
Quality of life (measured with QoL-Q; better indicated by lower values)											
57 (1 study) 26 weeks	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	⊕⊕⊖⊖ LOW[1,2,3]	29	28	N/A	N/A	MD -1.87 (-7.38 to 3.64)

[1] Data were skewed in TYRER2008.
[2] Extrapolated from adults with a learning disability.
[3] Due to risk of bias and indirectness.

Zuclopenthixol compared with placebo for behaviour management in adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With zuclopenthixol**		**Risk with placebo**	**Risk difference with zuclopenthixol (95% CI)**
Challenging behaviour (aggression)											
39 (1 study) 18 weeks	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	1/20 (5%)	7/19 (36.8%)	RR 7.37 (1.2 to 16.85)	Study population	
										50 per 1000	319 more per 1000 (from 10 more to 793 more)
										Moderate	
										50 per 1000	319 more per 1000 (from 10 more to 793 more)
Challenging behaviour (irritability) change from baseline (measured with NOSIE-30; better indicated by lower values)											
85 (1 study) 12 weeks	Serious[4]	No serious inconsistency	Very serious[1,5]	No serious imprecision	Undetected	⨁⨀⨀⨀ VERY LOW[1,4,5,6]	40	45	N/A	N/A	MD -2.20 (-3.86 to -0.54)

Symptom severity or improvement (endpoint data) (assessed with: CGA derived from the CGI scale)											
43 (1 study) 18 weeks	Serious[4]	No serious inconsistency	Very serious[1,5]	Serious[2]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,4,5,7]	1/19 (5.3%)	5/24 (20.8%)	RR 3.96 (0.51 to 13.47)	Study population	
										53 per 1000	156 more per 1000 (from 26 fewer to 656 more)
										Moderate	
										50 per 1000	148 more per 1000 (from 25 fewer to 624 more)
Symptom severity or improvement (change from baseline) (measured with CGI scale; better indicated by lower values)											
85 (1 study) 12 weeks	Serious[4]	No serious inconsistency	Very serious[1,5]	No serious imprecision	Undetected	⨁⨀⨀⨀ VERY LOW[1,4,5,6]	40	45	N/A	N/A	MD 0.70 (0.25 to 1.15)

[1] Extrapolated from a learning disabilities population.
[2] Sample size was small.
[3] Due to indirectness and imprecision.
[4] Higher attrition rate in the placebo group.
[5] Study was very old.
[6] Due to risk of bias and indirectness.
[7] Due to risk of bias, indirectness and imprecision.

Prothipendyl compared with placebo for behaviour management in adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With prothipendyl**		**Risk with placebo**	**Risk difference with prothipendyl (95% CI)**
Symptom severity or improvement (assessed with: Clinical Observation Rating Scale)											
39 (1 study) 16 weeks	Serious[1]	No serious inconsistency	Very serious[2,3]	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4,5]	9/19 (47.4%)	16/20 (80%)	RR 1.69 (1.04 to 1.99)	Study population	
										474 per 1000	327 more per 1000 (from 19 more to 469 more)
										Moderate	
										50 per 1000	35 more per 1000 (from 2 more to 49 more)

[1] Pre-trial differences between experimental and control groups in IQ.
[2] Extrapolated from adults with a learning disability.
[3] Study was very old.
[4] Sample size was small.
[5] Due to risk of bias, indirectness and imprecision.

Pipamperone compared with placebo for behaviour management in adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With pipamperone**		**Risk with placebo**	**Risk difference with pipamperone (95% CI)**
Challenging behaviour (narrative reporting) (measured with Experiment-specific Behaviour Checklist; better indicated by lower values)											
20 (1 study) 4 months	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	10	10	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Data reported did not allow for calculation of effect size.
[2] Extrapolated from a learning disabilities population.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

Cis(z)-clopenthixol compared with haloperidol for behaviour management in adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With haloperidol	**With Cis(z)-clopenthixol**		**Risk with haloperidol**	**Risk difference with Cis(z)-clopenthixol (95% CI)**
Symptom severity or improvement (assessed with: CGI scale)											
98 (1 study) 12 weeks	No serious risk of bias	No serious inconsistency	Very serious[1,2]	No serious imprecision	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	7/49 (14.3%)	24/49 (49%)	RR 3.43 (1.86 to 5.02)	Study population	
										143 per 1000	347 more per 1000 (from 123 more to 574 more)
										Moderate	
										143 per 1000	347 more per 1000 (from 123 more to 575 more)
Side effects (assessed with: CGI scale)											
98 (1 study) 12 weeks	No serious risk of bias	No serious inconsistency	Very serious[1,2]	No serious imprecision	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	39/49 (79.6%)	33/49 (67.3%)	RR 0.85 (0.57 to 1.05)	Study population	
										796 per 1000	119 fewer per 1000 (from 342 fewer to 40 more)
										Moderate	
										796 per 1000	119 fewer per 1000 (from 342 fewer to 40 more)

[1] Extrapolated from a learning disabilities population.
[2] Study was very old. [3] Due to indirectness.

Open-label olanzapine for behaviour management in adults with a learning disability

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With Open-label olanzapine**		**Risk with control**	**Risk difference with Open-label olanzapine (95% CI)**
Challenging behaviour (narrative reporting) (measured with Aberrant Behavior Checklist; better indicated by lower values)											
16 (1 study) 8 weeks	Very serious[1]	No serious inconsistency	Very serious[2,3]	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4,5]	N/A	16	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Symptom severity/outcome (narrative reporting) (measured with CGI scale; better indicated by lower values)											
16 (2 studies) 8 to 11 weeks	Very serious[1]	No serious inconsistency	Very serious[2,3]	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4,5]	N/A	16	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational studies with open-label treatment and data extracted did not allow for calculation of effect sizes.
[2] Extrapolated from adults with a learning disability.
[3] Learning disabilities population also have coexisting psychiatric conditions including disruptive behaviour disorder, attention-deficit/hyperactivity disorder, oppositional defiant disorder, stereotypic movement disorder, conduct disorder, impulse control disorder, epilepsy and organic behaviour disorder.
[4] Small sample size.
[5] Due to risk of bias, indirectness and imprecision.

1.3.2 Anticonvulsants

Valproate compared with placebo for behaviour management in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With valproate**		**Risk with placebo**	**Risk difference with valproate (95% CI)**
Challenging behaviour (irritability) (measured with Aberrant Behavior Checklist – Irritability and CGI-Irritability; better indicated by lower values)											
57 (2 studies) 8 to 12 weeks	No serious risk of bias	Serious[1]	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	25	32	N/A	N/A	SMD -0.05 (-0.58 to 0.48)
Challenging behaviour (irritability) (assessed with: CGI-Irritability)											
27 (1 study) 12 weeks	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊕⊖⊖ LOW[2,3,5]	1/11 (9.1%)	10/16 (62.5%)	RR 6.87 (1.59 to 10.36)	Study population	
										91 per 1000	534 more per 1000 (from 54 more to 851 more)
										Moderate	
										91 per 1000	534 more per 1000 (from 54 more to 852 more)

Challenging behaviour (aggression) (measured with Parent Overt Aggression Scale; better indicated by lower values)											
30 (1 study) 8 weeks	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊕⊖⊖ LOW[2,3,5]	14	16	N/A	N/A	MD 0.14 (-2.93 to 3.21)
Symptom severity or improvement (measured with CGI-I scale; better indicated by lower values)											
30 (1 study) 8 weeks	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊕⊖⊖ LOW[2,3,5]	14	16	N/A	N/A	MD -0.37 (-0.97 to 0.23)
Side effects (assessed with: checklist derived from *Physicians' Desk Reference*, 1997)											
30 (1 study) 8 weeks	No serious risk of bias	No serious inconsistency	Serious	Serious[3]	Undetected	⊕⊕⊖⊖ LOW[3,5]	11/14 (78.6%)	15/16 (93.8%)	RR 1.19 (0.73 to 1.26)	Study population	
										786 per 1000	149 more per 1000 (from 212 fewer to 204 more)
										Moderate	
										786 per 1000	149 more per 1000 (from 212 fewer to 204 more)

[1] HELLINGS2005 found a negative response and HOLANDER2010 found a positive response for valproate on Aberrant Behavior Checklist irritability scores.
[2] Extrapolation from children with autism.
[3] Small sample sizes.
[4] Due to inconsistency, indirectness and imprecision.
[5] Due to indirectness and imprecision.

Lamotrigine compared with placebo for behaviour management in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With lamotrigine		Risk with placebo	Risk difference with lamotrigine (95% CI)
Autistic behaviours (narrative reporting) (measured with CARS; better indicated by lower values)											
28 (1 study) 18 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	14	14	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Challenging behaviour (narrative reporting) (measured with Aberrant Behavior Checklist – Irritability; better indicated by lower values)											
28 (1 study) 18 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	14	14	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Efficacy data could not be extracted.
[2] Extrapolated from children with autism.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

Open-label topiramate for behaviour management in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With open-label topiramate**		**Risk with control**	**Risk difference with open-label topiramate (95% CI)**
Challenging behaviour (narrative reporting) (measured with CPS – Conduct subscale; better indicated by lower values)											
15 (1 study[1]) 25 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3]	N/A	15	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational case series and efficacy data could not be extracted.
[2] Extrapolated from children with autism.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

1.3.3 Drugs affecting cognition

Donepezil hydrochloride compared with placebo for behaviour management in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With donepezil hydrochloride**		**Risk with placebo**	**Risk difference with donepezil hydrochloride (95% CI)**
Autistic behaviours (measured with modified parent-completed CARS; better indicated by lower values)											
34 (1 study) 6 weeks	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	17	17	N/A	N/A	MD 0.40 (-4.88 to 5.68)

[1] Extrapolated from children with autism.
[2] Small sample size.
[3] Due to indirectness and imprecision.

Amantadine hydrochloride compared with placebo for behaviour management in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With amantadine hydrochloride**		**Risk with placebo**	**Risk difference with amantadine hydrochloride (95% CI)**
Challenging behaviour (irritability) (assessed with: Aberrant Behavior Checklist – parent-completed)											
38 (1 study) 5 weeks	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	7/19 (36.8%)	9/19 (47.4%)	RR 1.29 (0.60 to 2.74)	Study population	
										368 per 1000	107 more per 1000 (from 147 fewer to 641 more)
										Moderate	
										368 per 1000	107 more per 1000 (from 147 fewer to 640 more)

[1] Extrapolated from children with autism.
[2] Small sample size.
[3] Due to indirectness and imprecision.

Open-label memantine for behaviour management in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With memantine**		**Risk with control**	**Risk difference with memantine (95% CI)**
Core symptoms of autism (social-communication difficulties) (measured with CGI-I – Language); better indicated by lower values)											
151 (1 study) 9 months	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	N/A	151	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Challenging behaviour (measured with CGI-I Behaviour Scale and Abberant Behaviour Checklist – Irritability subscale; better indicated by lower values)											
165 (2 studies) 6 to 8 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	N/A	165	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Symptom severity or improvement (measured with CGI-S; better indicated by lower values)											
32 (2 studies) 8 to 19 weeks	Very serious[1]	Serious[4]	Serious[2]	Serious[5]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,5,6,7]	N/A	32	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] No control group and efficacy data could not be extracted.
[2] Extrapolated from children with autism.
[3] CGI scale usually used to rate symptom severity or improvement and it was not clear whether the scale is precise enough to evaluate and differentiate language and behaviour scores as used in this study.
[4] Due to risk of bias, indirectness and imprecision.
[5] ERICKSON2007 reports large treatment effect and OWLEY2006 reports non-significant treatment effect.
[6] Small sample size.
[7] Due to risk of bias, inconsistency, indirectness and imprecision.

Open-label galantamine for behaviour management in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With galantamine**		**Risk with control**	**Risk difference with galantamine (95% CI)**
Challenging behaviour (measured with Aberrant Behavior Checklist – Irritability subscale; better indicated by lower values)											
13 (1 study) 12 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3,4]	N/A	13	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Autistic Behaviours (measured with CPRS Autism Factor; better indicated by lower values)											
13 (1 study) 12 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3,4]	N/A	13	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Symptom severity or improvement (measured with CGI-S; better indicated by lower values)											
13 (1 study) 12 weeks	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3,4]	N/A	13	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] No control group and efficacy data could not be extracted.
[2] Extrapolated from children with autism.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

1.3.4 Adrenocorticotrophic hormones

Adrenocorticotrophic hormone (ORG 2766) compared with placebo for behaviour management in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With adrenocorticotrophic hormone (ORG 2766)**		**Risk with placebo**	**Risk difference with adrenocorticotrophic hormone (ORG 2766) (95% CI)**
Challenging behaviour (social withdrawal) (assessed with: Aberrant Behavior Checklist)											
47 (1 study) 6 weeks	Serious[1]	Serious[2]	Serious[3]	Serious[4]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4,5]	4/18 (22.2%)	10/29 (34.5%)	RR 1.55 (0.57 to 4.22)	**Study population**	
										222 per 1000	122 more per 1000 (from 96 fewer to 716 more)
										Moderate	
										222 per 1000	122 more per 1000 (from 95 fewer to 715 more)
Challenging behaviour (social isolation) (measured with GAP; better indicated by lower values)											
20 (1 study) 36 weeks	No serious risk of bias	Serious[2]	Serious[3]	Serious[4]	Undetected	⊕⊖⊖⊖ VERY LOW[2,3,4,5]	10	10	N/A	N/A	SMD -0.92 (-1.82 to -0.02)

Symptom severity or improvement (measured with CGI; better indicated by lower values)											
69 (2 studies) 6 to 36 weeks	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	Undetected	⊕⊕⊖⊖ LOW[1,3,6]	29	40	N/A	N/A	SMD -0.97 (-1.48 to -0.45)

[1] Randomisation methods were unclear in BUITELAAR1996 (authors state 'randomised in principle' and there was a trend for group differences in age and CARS score at baseline).
[2] BUITELAAR1992 found statistically significant treatment effects for challenging behaviour as measured by social isolation on the GAP, whereas BUITELAAR1996 found no significant differences for social withdrawal as measured by Aberrant Behavior Checklist.
[3] Extrapolated from children with autism.
[4] Small sample size.
[5] Due to risk of bias, inconsistency, indirectness and imprecision.
[6] Due to risk of bias, inconsistency, indirectness.

1.3.5 Secretin

Secretin compared with placebo for autistic behaviours in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With secretin**		**Risk with placebo**	**Risk difference with secretin (95% CI)**
Core autistic symptom of social-communication difficulties (measured with Communication and Symbolic Behaviour Scale and PLS-3; better indicated by lower values)											
157 (2 studies) 3 to 8 weeks	Serious[1]	Serious[2]	Serious[3]	No serious imprecision	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3]	79	78	N/A	N/A	SMD -0.29 (-0.77 to 0.2)
Autistic behaviours (measured with CARS and Real Life Ritvo Behaviour Scale; better indicated by lower values)											
86 (2 studies) 3 to 8 weeks	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	Undetected	⊕⊕⊖⊖ LOW[1,3,5]	43	43	N/A	N/A	SMD -0.24 (-0.67 to 0.18)
Challenging behaviour (measured with Parent-completed GBRS; better indicated by lower values)											
62 (1 study) 8 weeks	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	Undetected	⊕⊕⊖⊖ LOW[1,3,5]	31	31	N/A	N/A	SMD -0.14 (-0.64 to 0.36)

[1] For LEVY2003 there was a significant difference between the groups in baseline CARS total score.
[2] The studies found modest but non-significant effect sizes in different directions.
[3] Extrapolated from children with autism.
[4] Due to risk of bias, inconsistency, indirectness.
[5] Due to risk of bias and indirectness.

1.3.6 Melatonin

Open-label melatonin for insomnia in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With melatonin**		**Risk with control**	**Risk difference with melatonin (95% CI)**
Sleep patterns (measured with ActiGraph; better indicated by lower values)											
15 (1 study) 5 weeks	Very serious[1,2]	No serious inconsistency	Serious[3]	Serious[2]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3]	N/A	15	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Open-label study with no control group and efficacy data could not be extracted.
[2] Small sample size.
[3] Extrapolated from children with autism.
[4] Due to risk of bias, indirectness and imprecision.

1.3.7 Stimulants

Methylphenidate compared with placebo for coexisting hyperactivity in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With methylphenidate		Risk with placebo	Risk difference with methylphenidate (95% CI)
Hyperactivity (measured with Aberrant Behavior Checklist – Hyperactivity subscale (parent-report); better indicated by lower values)											
62 (1 study) 5 weeks	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	Undetected	⊕⊕⊕⊖ MODERATE[1,3]	30	32	N/A	N/A	MD -8.80 (-13.72 to -3.88)
Social interaction (initiating joint attention) (measured with JAMES; Better indicated by lower values)											
34 (1 study) 5 weeks	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	Undetected	⊕⊕⊖⊖ LOW[1,2,4]	17	17	N/A	N/A	MD 6.50 (-2.85 to 15.85)
Repetitive behaviour (measured with CY-BOCS-PDD; better indicated by lower values)											
63 (1 study) 5 weeks	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	Undetected	⊕⊕⊕⊖ MODERATE[1,3]	31	32	N/A	N/A	MD -0.92 (-2.82 to 0.98)

[1] Extrapolated from children with autism.
[2] Small sample size.
[3] Due to indirectness.
[4] Due to indirectness and imprecision.

1.3.8 Antidepressants

Clomipramine compared with placebo for autistic behaviours in adolescents with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With clomipramine**		**Risk with control**	**Risk difference with clomipramine compared with placebo for behaviour management in adults with autism (95% CI)**
Autistic behaviours (measured with CARS; better indicated by lower values)											
32 (1 study) 21 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	16	16	N/A	N/A	MD -1.60 (-7.07 to 3.87)
Side effects (global) (measured with DOTES; better indicated by lower values)											
32 (1 study) 21 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	16	16	N/A	N/A	MD 1.20 (-0.45 to 2.85)

[1] Risk of attrition bias due to high drop-out in the clomipramine group.
[2] Sample includes children and adolescents with autism, and mean age was 16 years.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

Fluvoxamine compared with placebo for autistic behaviours in adults with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With fluvoxamine		Risk with control	Risk difference with fluvoxamine compared with placebo for behaviour management in adults with autism (95% CI)
Core autistic symptom (repetitive behaviour) (measured with Y-BOCS; better indicated by lower values)											
30 (1 study) 12 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1,2]	Undetected	⊕⊕⊖⊖ LOW[1,2,3]	15	15	N/A	N/A	MD -8.20 (-13.92 to -2.48)
Autistic behaviours (measured with Ritvo-Freeman Real-Life Rating Scale; better indicated by lower values)											
30 (1 study) 21 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⊕⊕⊕⊖ MODERATE[1,3]	15	15	N/A	N/A	SMD -0.82 (-1.56 to -0.07)
Challenging behaviour (aggression) change from baseline (measured with Brown Aggression Scale; better indicated by lower values)											
30 (1 study) 21 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⊕⊕⊕⊖ MODERATE[1,3]	15	15	N/A	N/A	SMD -0.92 (-1.68 to -0.17)

Maladaptive behaviour (change from baseline) (measured with VABS; better indicated by lower values)											
30 (1 study) 21 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⊕⊕⊕⊖ MODERATE[1,3]	15	15	N/A	N/A	SMD -1.61 (-2.43 to -0.79)
Symptom severity or improvement (dichotomous) (assessed with: CGI scale)											
30 (1 study) 21 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⊕⊕⊕⊖ MODERATE[1,3]	0/15 (0%)	8/15 (53.3%)	RR 17 (1.07 to 270.41)	Study population	
										0 per 1000	N/A
										Moderate	
										0 per 1000	N/A
Symptom severity or improvement (continuous) (measured with CGI scale; better indicated by lower values)											
30 (1 study) 21 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Undetected	⊕⊕⊕⊖ MODERATE[1,3]	15	15	N/A	N/A	SMD -1.94 (-2.8 to -1.07)

[1] Small sample size.
[2] Y-BOCS valid and reliable for assessing severity of obsessive–compulsive symptoms in individuals with OCD, but reliability and validity for assessing repetitive thoughts in autism was unknown.
[3] Due to imprecision.

Open-label fluoxetine for behaviour management in adolescents with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With open-label fluoxetine for behaviour management in adults with autism**		**Risk with control**	**Risk difference with open-label fluoxetine for behaviour management in adults with autism (95% CI)**
Symptom severity or improvement (measured with CGI scale; better indicated by lower values)											
23 (1 study) 189 days	Very serious[1]	No serious inconsistency	Very serious[2,3]	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4,5]	N/A	23	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Compulsive behaviour (measured with CGI scale; better indicated by lower values)											
23 (1 study) 189 days	Very serious[1]	No serious inconsistency	Very serious[2,3]	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4,5]	N/A	23	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] No control group and efficacy data could not be extracted.
[2] The mean age was above 15 years, but this was predominantly a child and adolescent sample.
[3] Participants also had coexisting psychiatric disorders.
[4] Small sample size.
[5] Due to risk of bias, indirectness and imprecision.

Open-label sertraline for autistic behaviours in adults with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With open-label sertraline for behaviour management in adults with autism**		**Risk with control**	**Risk difference with open-label sertraline for behaviour management in adults with autism (95% CI)**
Core autistic symptom (repetitive behaviour) (measured with Y-BOCS; better indicated by lower values)											
37 (1 study) 12 weeks	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,,3]	N/A	37	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Autistic behaviours (measured with Ritvo-Freeman Real-Life Rating Scale; better indicated by lower values)											
37 (1 study) 12 weeks	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,3,4]	N/A	37	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Maladaptive behaviour (measured with VABS; better indicated by lower values)											
37 (1 study) 12 weeks	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,3,4]	N/A	37	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Symptom severity or improvement (measured with CGI-I; better indicated by lower values)											
37 (1 study) 12 weeks	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	Undetected	⨁⊖⊖⊖ VERY LOW[1,3,4]	N/A	37	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] No control group and efficacy data could not be extracted.
[2] Y-BOCS scale valid and reliable for assessing severity of obsessive–compulsive symptoms in individuals with OCD, but reliability and validity for assessing repetitive thoughts in autism was unknown.
[3] Due to risk of bias and imprecision.
[4] Small sample size.

1.3.9 Restrictive diets, vitamins, minerals and supplements

Gluten- and casein-free diet compared with treatment as usual for autistic behaviours in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With treatment as usual	**With gluten- and casein-free diet**		**Risk with treatment as usual**	**Risk difference with gluten- and casein-free diet (95% CI)**
Autistic behaviours (social isolation and bizarre behaviours) (measured with Diagnosis of Psychotic Behaviour in Children; better indicated by lower values)											
20 (1 study) 1 year	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	10	10	N/A	N/A	MD -5.60 (-9.04 to -2.16)

[1] Risk of performance bias because it was unclear if the intervention groups received the same care apart from treatment; also, participants receiving care and individuals administering care were not blind to group allocation.
[2] Extrapolated from children with autism.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

Open-label ketogenic diet for autistic behaviours in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With ketogenic diet**		**Risk with control**	**Risk difference with ketogenic diet (95% CI)**
Autistic behaviours (measured with CARS; better indicated by lower values)											
30 (1 study) 6 months	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	N/A	30	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational study with no control group, so there was high potential for bias and it was not possible to extract efficacy data.
[2] Extrapolated from children with autism.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

L-carnosine compared with placebo for autistic behaviours in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With L-carnosine**		**Risk with placebo**	**Risk difference with L-carnosine (95% CI)**
Autistic behaviours (measured with CARS; better indicated by lower values)											
31 (1 study) 8 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	17	14	N/A	N/A	MD -4.01 (-9.03 to 1.01)
Symptom improvement (measured with CGI-I; better indicated by higher values)											
31 (1 study) 8 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⊖⊖⊖ VERY LOW[1,2,3,4]	17	14	N/A	N/A	MD -2.14 (-0.99 to 5.27)

[1] Baseline group differences in autistic behaviours as measured by the GARS.
[2] Extrapolated from children with autism.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

Micronutrients compared with standard medication for autistic behaviours in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With standard medication	**With micronutrients**		**Risk with standard medication**	**Risk difference with micronutrient (95% CI)**
Autistic behaviours (measured with CARS; better indicated by lower values)											
88 (1 study[1]) 3 to 98 months	Serious[2]	No serious inconsistency	Serious[3]	No serious imprecision	Undetected	⨁⨀⨀⨀ VERY LOW[2,3,4]	44	44	N/A	N/A	MD -0.50 (-5.62 to 6.62)
Challenging behaviour (irritability) (measured with Aberrant Behavior Checklist; better indicated by lower values)											
88 (1 study[1]) 3 to 98 months	Serious[2]	No serious inconsistency	Serious[3]	No serious imprecision	Undetected	⨁⨀⨀⨀ VERY LOW[2,3,4]	44	44	N/A	N/A	MD -7.40 (-9.91 to -4.89)
Symptom severity (measured with CGI-S; better indicated by lower values)											
88 (1 study[1]) 3 to 98 months	Serious[2]	No serious inconsistency	Serious[3]	No serious imprecision	Undetected	⨁⨀⨀⨀ VERY LOW[2,3,4]	44	44	N/A	N/A	MD -1.38 (-2.04 to -0.72)

[1] Case-control.
[2] This was a non-randomised and non-blinded study so there is a high risk of bias.
[3] Extrapolated from children with autism.
[4] Due to risk of bias, indirectness

Open-label iron supplementation for coexisting sleep problems in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With iron supplement**		**Risk with control**	**Risk difference with iron supplement (95% CI)**
Sleep patterns (measured with Restless Sleep score; better indicated by lower values)											
33 (1 study) 8 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3,4]	N/A	33	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Challenging behaviour (measured with CGI-I; better indicated by lower values)											
33 (1 study) 8 weeks	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⨁⨀⨀⨀ VERY LOW[1,2,3,4]	N/A	33	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] Observational study with no control group, no blinding and a high attrition rate, so there was potential for bias. It was also not possible to extract efficacy data.
[2] Extrapolated from children with autism.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.

Open-label magnesium-vitamin B6 supplementation for core autistic symptoms in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With magnesium-vitamin B6		Risk with control	Risk difference with magnesium-vitamin B6 (95% CI)
Core symptom of autism (social-interaction and communication difficulties, stereotyped behaviour) (measured with DSM-IV clinical evaluation; better indicated by lower values)											
33 (1 study) 24 months	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4]	N/A	33	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted
Symptom severity or improvement (measured with BSE; better indicated by lower values)											
11 (1 study) 14 weeks	Very serious[1,4]	No serious inconsistency	Very serious[2]	Serious[3]	Undetected	⊕⊖⊖⊖ VERY LOW[1,2,3,4,5]	N/A	11	N/A	Efficacy data could not be extracted	Efficacy data could not be extracted

[1] No control group results in high risk of bias and efficacy data could not be extracted.
[2] Extrapolated from children with autism.
[3] Small sample size.
[4] Due to risk of bias, indirectness and imprecision.
[5] Sample selected for their previous sensitivity to the treatment.

Digestive enzyme supplementation compared with placebo for behaviour management in children with autism

Quality assessment							Summary of findings				
Participants (No. of studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With digestive enzyme supplementation**		**Risk with placebo**	**Risk difference with digestive enzyme supplementation (95% CI)**
Core symptom of autism (social-communication difficulties) (measured with Language Development Survey Vocabulary score; better indicated by lower values)											
43 (1 study) 6 months	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	22	21	N/A	N/A	MD 1.36 (-15.74 to 18.46)
Gastrointestinal symptoms (measured with Parent-rated Additional Rating Scale gastrointestinal symptoms subscale; better indicated by lower values)											
43 (1 study) 6 months	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	22	21	N/A	N/A	MD 0.18 (-0.27 to 0.63)
Challenging behaviour (measured with Parent-rated Global Behaviour Rating Scale; better indicated by higher values)											
43 (1 study) 6 months	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	Undetected	⨁⨁⨀⨀ LOW[1,2,3]	22	21	N/A	N/A	MD 0.14 (-0.19 to 0.47)

[1] Extrapolated from children with autism.
[2] Small sample size.
[3] Due to indirectness and imprecision.