

G.10.1.6 Pharmacological management of agitation, aggression and apathy

Mood stabilisers vs placebo

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Agitation: CMAI – lower numbers favour mood stabilisers							
4 (Herrmann 2007, Porsteinsson 2001, Profenno 2005, Tariot 2005)	Not serious	Serious ¹	Not serious	Serious ²	254	MD -0.67 (-3.42, 4.77)	Low
NPI/BPRS subscale agitation/aggression - lower numbers favour mood stabilisers							
2 (Herrmann 2007, Tariot 2005)	Not serious	Serious ¹	Not serious	Very serious ³	172	SMD 0.40 (-0.31, 1.10)	Very low
Neuropsychiatric profile NPI total score - lower numbers favour mood stabilisers							
2 (Herrmann 2007, Profenno 2005)	Not serious	Not serious	Not serious	Not Serious	51	MD 2.87 (1.01, 4.73)	High
Brief Psychiatric Rating scale - lower numbers favour mood stabilisers							
2 (Porsteinsson 2001, Tariot 2005, Olin 2001)	Not serious	Not serious	Not serious	Serious ²	224	MD 0.46 (-1.78, 2.70)	Moderate
Physical Self Maintenance Scale – lower numbers favour mood stabilisers							

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
4 (Porsteinsson 2001, Profenno 2005, Tariot 2005, Olin 2001)	Not serious	Not serious	Not serious	Serious ²	248	MD 0.15 (-0.27, 0.57)	Moderate
Cognition MMSE – higher numbers favours mood stabilisers							
4 (Herrmann; Porsteinsson; Tariot; Olin)	Not serious	Not serious	Not serious	Not serious	273	MD -0.94 (-1.72, -0.17)	High
Any adverse events - lower numbers favour mood stabilisers							
2 (Herrmann 2007, Porsteinsson 2001)	Not serious	Not serious	Not serious	Serious ⁴	83	RR 1.77 (1.19, 2.62)	Moderate
Serious adverse events - lower numbers favour mood stabilisers							
1 (Porsteinsson 2001)	Not serious	N/A	Not serious	Very serious ³	56	RR 1.00 (0.15, 6.61)	Low
<ol style="list-style-type: none"> 1. i^2 value > 40%. 2. Non-significant result. 3. 95% CI crosses two lines of a defined MID interval 4. 95% CI crosses one line of a defined MID interval 							

Cholinesterase inhibitors vs placebo

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Agitation: CMAI – lower numbers favour cholinesterase inhibitors							
1 (Howard 2007)	Not serious	N/A	Not serious	Serious ¹	221	MD 1.35 (-3.85, 6.54)	Moderate
Neuropsychiatric profile NPI total score - lower numbers favour cholinesterase inhibitors							
3 (Holmes 2004, Howard 2007, Mahlberg 2007)	Not serious	Serious ²	Not serious	Serious ¹	317	MD -4.95 (-11.19, 1.29)	Low
Neuropsychiatric profile NPI agitation subscale – lower numbers favour cholinesterase inhibitors							
1 (Mahlberg 2007)	Not serious	N/A	Not serious	Not serious	20	MD -5.20 (-7.95, -2.45)	Moderate
Global assessment SIB - higher numbers favour cholinesterase inhibitors							

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
1 (Howard 2007)	Not serious	N/A	Not serious	Not serious	60	MD 6.75 (1.59, 11.91)	High
NOSGER- higher favours cholinesterase inhibitors							
1 (Mahlberg 2007)	Not serious	N/A	Not serious	Serious ¹	20	MD -6.60 (-23.30, 10.10)	Moderate
Cognition (standardised MMSE) higher favours cholinesterase inhibitors							
1 (Howard 2007)	Not serious	N/A	Not serious	Not serious	113	MD 1.50 (0.15, 2.85)	High
1. Non-significant result. 2. i^2 value > 40%.							

Memantine vs placebo

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Agitation: CMAI – lower numbers favour memantine							
1 (Fox 2012)	Not serious	N/A	Not serious	Serious ¹	149	MD -3.10 (-9.43, 3.23)	Moderate
Neuropsychiatric profile NPI total score - lower numbers favour memantine							
1 (Fox 2012)	Not serious	N/A	Not serious	Not serious	138	MD -9.40 (-15.41, -3.39)	High
Global assessment SIB - higher numbers favour memantine							
1 (Fox 2012)	Not serious	N/A	Not serious	Serious ¹	149	MD 2.40 (-1.81, 6.61)	Moderate
Clinicians global impression of change CGIC - higher numbers favour memantine							
1 (Fox 2012)	Not serious	N/A	Not serious	Serious ¹	149	MD -0.10 (-0.60, 0.40)	Moderate
Cognition (standardised MMSE) – higher numbers favour memantine							
1 (Fox 2012)	Not serious	N/A	Not serious	Serious ¹	149	MD 1.00 (-1.16, 3.16)	Moderate
1. Non-significant result.							

Tetrahydrocannabinol vs placebo

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Agitation CMAI – lower numbers favour THC							
1 (van den Elsen 2015)	Not serious	N/A	Not serious	Serious ¹	47	MD 2.80 (-7.43, 13.03)	Moderate
Neuropsychiatric profile NPI total score - lower numbers favour THC							

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
1 (van den Elsen 2015)	Not serious	N/A	Not serious	Serious ¹	47	MD 3.90 (-4.69, 12.49)	Moderate
NPI agitation/aggression subscale – lower numbers favour THC							
1 (van den Elsen 2015)	Not serious	N/A	Not serious	Serious ¹	47	MD 0.10 (-2.30, 2.50)	Moderate
NPI aberrant behaviour subscale – lower numbers favour THC							
1 (van den Elsen 2015)	Not serious	N/A	Not serious	Serious ¹	47	MD -0.10 (-2.45, 2.25)	Moderate
Caregivers Clinical global impression of change CCGIC- higher numbers favour THC							
1 (van den Elsen 2015)	Not serious	N/A	Not serious	Serious ¹	46	MD 0.30 (-0.48, 1.08)	Moderate
Activities of daily living - Barthel index- higher numbers favour THC							
1 (van den Elsen 2015)	Not serious	N/A	Not serious	Serious ¹	46	MD 1.30 (-1.73, 4.33)	Moderate
Quality of life QoL AD – higher numbers favour THC							
1 (van den Elsen 2015)	Not serious	N/A	Not serious	Serious ¹	43	MD -1.60 (-4.47, 1.27)	Moderate
1. Non-significant result.							

Prazosin vs placebo

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
Neuropsychiatric profile NPI total score - lower numbers favour prazosin							
1 (Wang 2008)	Very serious ¹	N/A	Not serious	Serious ²	13	MD -18.00 (-41.93, 5.93)	Very low
Brief Psychiatric rating scale – lower numbers favour prazosin							
1 (Wang 2008)	Very serious ¹	N/A	Not serious	Not serious	13	MD -12.00 (-19.15, -4.85)	Low
Clinicians global impression of change CGIC - higher numbers favour prazosin							
1 (Wang 2008)	Very serious ¹	N/A	Not serious	Not serious	13	MD -1.90 (-3.38, -0.42)	Low
1. Study at high risk of bias.							
2. Non-significant result.							

Dextromethorphan-quinidine vs placebo

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
NPI – lower numbers favour intervention							
1 (Cummings 2015)	Not serious	N/A	Not serious	Not serious	159	MD -5.90 (-11.68, -0.12)	High
NPI agitation/aggression subscale – lower numbers favour intervention							
1 (Cummings 2015)	Not serious	N/A	Not serious	Not serious	159	MD -1.70 (-2.84, -0.56)	High
Depression (Cornell scale) – lower numbers favour intervention							
1 (Cummings 2015)	Not serious	N/A	Not serious	Not serious	141	MD -1.60 (-2.92, -0.28)	High
CGIC – higher numbers favour intervention							
1 (Cummings 2015)	Not serious	N/A	Not serious	Serious ¹	152	MD 1.00 (-1.06, 3.06)	Moderate
MMSE – higher numbers favour intervention							
1 (Cummings 2015)	Not serious	N/A	Not serious	Serious ¹	151	MD 0.70 (-0.41, 1.81)	Moderate
QoL ADS – higher numbers favour intervention							
1 (Cummings 2015)	Not serious	N/A	Not serious	Serious ¹	152	MD 0.40 (-1.42, 2.22)	Moderate
Any adverse events – lower numbers favour intervention							
1 (Cummings 2015)	Not serious	N/A	Not serious	Not serious	279	RR 1.41 (1.12, 1.79)	High
Serious adverse events – lower numbers favour intervention							
1 (Cummings 2015)	Not serious	N/A	Not serious	Serious ¹	279	RR 1.67 (0.65, 4.33)	Moderate
Mortality – lower numbers favour intervention							
1 (Cummings 2015)	Not serious	N/A	Not serious	Very serious ²	279	No deaths in either arm	Low
1. Non-significant result. 2. Relative risk could not be calculated.							

Modafinil vs placebo

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
FrsBe Apathy – lower numbers favour modafinil							
1 (Frakey 2012)	Not serious	N/A	Not serious	Serious ¹	22	MD 7.00 (-2.80, 16.80)	Moderate
DAFS functional assessment – higher numbers favour modafinil							

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
1 (Frakey 2012)	Not serious	N/A	Not serious	Serious ¹	22	MD -3.09 (-12.80, 6.62)	Moderate
Activities of daily living – higher numbers favour modafinil							
1 (Frakey 2012)	Not serious	N/A	Not serious	Serious ¹	22	MD -3.36 (-7.74, 1.02)	Moderate
Zarit carer burden index – lower numbers favour modafinil							
1 (Frakey 2012)	Not serious	N/A	Not serious	Serious ¹	22	MD 0.00 (-12.40, 12.40)	Moderate
1. Non-significant result.							

Donepezil and choline alfoscerate vs donepezil

Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect size (95% CI)	Quality
FrsBe Apathy severity- lower numbers favour donepezil and choline							
1 (Rea 2015)	Not serious	N/A	Not serious	Not serious	113	MD -2.70 (-4.69, -0.71)	High
NPI severity - lower numbers favour donepezil and choline							
1 (Rea 2015)	Not serious	N/A	Not serious	Not serious	113	MD -7.70 (-14.23, -1.17)	High
Frontal Assessment Battery – higher numbers favour donepezil and choline							
1 (Rea 2015)	Not serious	N/A	Not serious	Not serious	113	MD 1.60 (0.48, 2.72)	High
MMSE – higher numbers favour donepezil and choline							
1 (Rea 2015)	Not serious	N/A	Not serious	Not serious	113	MD 2.50 (0.59, 4.41)	High
1 ADAS cog –lower numbers favour donepezil and choline							
1 (Rea 2015)	Not serious	N/A	Not serious	Not serious	113	MD -8.50 (-13.65, -3.35)	High