Biological/pharmacological intervention studies

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
ChEIs and/or memantine						
Amenta et al 2012, 2014 (1, 2) Italy	Donepezil 10 mg/day + choline alphoscerate (cholinergic precursor) 1200 mg/day vs donepezil 10 mg/day + placebo 2 years	General BPSD	• RCT • 113 community-dwelling people with mild-moderate AD associated with vascular damage (67 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores for donepezil + choline alphoscerate at 1 year when compared with baseline ($p < 0.05$), ns at 2 years Significant difference between total NPI scores in favour of donepezil + choline alphoscerate due to significant **increase** in donepezil + placebo group at 1 & 2 years ($p < 0.05$) Insufficient data to calculate ES	Moderate 11
Araki et al 2014 (3) Japan	Memantine titrated to 20 mg/day + donepezil (dose not reported) vs donepezil only 24 weeks	General BPSD	• RCT • 37 outpatients with moderate-severe AD (19 females) • Number table randomisation • Raters not blinded • No post-intervention f/u	NPI	Significant difference between groups in total NPI scores in favour of memantine + donepezil due to **increase** for donepezil only group at 24 weeks ($p < 0.001$, $d = 2.08$)	Moderate 11
Ballard et al 2015 (4) UK	Memantine titrated to 20 mg/day vs antipsychotics: ≥ risperidone 0.5mg, olanzapine 5mg, quetiapine 25mg or haloperidol 0.5mg 24 weeks	General BPSD Agitation	• RCT • 199 care home residents with probable AD & already receiving an antipsychotic (138 females) • Block randomisation, method not reported • Raters blinded • No post-intervention f/u	NPI CMAI	Ns change for either group & ns difference between groups in total CMAI & NPI scores at any time point ES n/a	Strong 14

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Bando et al 2017 (5) Japan	Rivastigmine patch, titrated every 4 weeks in 4.5mg/day increments from 4.5mg to max 18mg/day 24 weeks	Agitation	• Open-label, repeated measures study • 61 outpatients with mild-severe dementia not taking ChEIs or memantine (30 females) • No randomisation • Raters not blinded • No post-intervention f/u	CGBRS restlessness subscale	Significant decrease in CGBRS restlessness subscale scores at 24 weeks when compared with baseline ($p = 0.002$, $d = 0.44$)	Modest 7
Boxer et al 2013 (6) USA	Memantine titrated to 2 x 10mg/day by week 4 vs placebo 26 weeks	General BPSD	• Parallel group RCT • 81 people with bvFTD or semantic dementia recruited from academic dementia research centres (30 females) • Computer-generated block randomisation • Raters blinded • No post-intervention f/u	NPI	Ns difference between groups on total NPI scores at 26 weeks ES n/a	Strong 13
Carotenuto et al 2017 (7) Italy	Donepezil 10 mg/day + choline alphoscerate (cholinergic precursor) 1200 mg/day vs donepezil 10 mg/day + placebo 24 months	General BPSD	• RCT • 113 community-dwelling people with mild-moderate AD (70 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	NPI	Significantly greater decrease in total NPI scores for donepezil + choline alphoscerate when compared with donepezil + placebo ($p < 0.05$, $d = 0.5$)	Moderate 12

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Clerici et al 2012 (8) Italy	Memantine up-titrated weekly by 5mg/day increments to 20 mg/day (10 mg twice daily) 6 months	General BPSD	• Repeated measures study • 297 dementia-unit patients with moderately severe-severe AD not taking ChEIs (229 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI subsyndromes: affect, physical behaviour, psychosis & hypomania	Ns change in total NPI scores for memantine at 6 months when compared with baseline Ns decrease in NPI affect cluster (depression/dysphoria, anxiety, irritability/lability, agitation/aggression) in 30% of patients, NPI physical behaviour cluster (apathy/indifference, aberrant motor behaviour, night-time behaviour, appetite/eating change) in 24% of patients & NPI psychosis cluster (delusions, hallucinations) in 29% of patients with no worsening in any other subsyndrome at 6 months ES n/a	Modest 9
Cumbo et al 2014 (9) Italy	Memantine 20mg/day vs donepezil 10mg/day vs rivastigmine 12mg/day vs galantamine 24mg/day 12 months	General BPSD	• Open-label RCT • 177 community-dwelling people with mild-moderate AD (96 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	NPI BEHAVE-AD	Significant decrease in total NPI & BEHAVE-AD scores for memantine ($p < 0.01$), donepezil ($p = 0.001$) & rivastigmine ($p = 0.030$) at 12 months when compared with baseline, ns change for galantamine Significant decrease in total NPI & BEHAVE-AD scores for memantine (both $p < 0.01$, $d = 0.51$), NPI ($p = 0.011$, $d = 0.54$) & BEHAVE-AD ($p = 0.011$, $d = 0.41$) for donepezil, NPI ($p = 0.030$, $d = 0.55$) & BEHAVE-AD ($p = 0.030$, $d = 0.53$) for rivastigmine at 12 months when compared with baseline, ns change for galantamine	Strong 14

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
D'Onofrio et al 2015 (10) Italy	Rivastigmine patch 4.6mg/day up-titrated if tolerated to 9.5mg/day + 90 minute cognitive stimulation sessions weekly vs rivastigmine patch 4.6mg/day up-titrated if tolerated to 9.5mg/day only 6 months	General BPSD Depression	• RCT • 90 community-dwelling patients with moderate AD (48 females) • Sealed envelope randomisation • Raters not blinded • No post-intervention f/u	NPI HAM-D 21 GDS-SF	Significant decrease in HAM-D 21 ($p < 0.0001$, $d = 2.1$) & GDS-SF depression scores ($p < 0.0001$, $d = 2.3$) & total NPI scores ($p < 0.0001$, $d = 1.8$) for rivastigmine patch + cognitive stimulation at 6 months when compared with baseline, significant decrease in scores on all measures for rivastigmine patch only group ($p < 0.0001$ – $p = 0.003$) Significantly greater decrease in scores on all measures for rivastigmine patch + cognitive stimulation when compared with rivastigmine patch only at 6 months on all measures ($p < 0.0001$) Insufficient data to calculate ES	Strong 13
Dysken et al 2014 (11) USA	Alpha tocopherol (synthetic vitamin E) 2000 IU/day + memantine 20 mg/day vs memantine 20 mg/day maintenance dose + vitamin E 2000 IU/day vs matching placebos Treatment range: 6 months to 4 years	General BPSD	• Multicentre RCT • 613 patients with mild-moderate AD prescribed ChEIs from 14 Veterans Affairs medical centres (19 females) • Permuted block randomisation • Raters blinded • No post-intervention f/u	NPI	Ns difference in total NPI scores between groups post treatment ES n/a	Strong 13
Emre et al 2014 (12) Turkey	Rivastigmine capsule titrated to 6 mg twice daily vs rivastigmine patch titrated to 9.5mg/24 hr 76 weeks	General BPSD	• International multicentre RCT • 583 community-dwelling people with PDD (186 females) • Interactive voice randomisation • Raters blinded • No post-intervention f/u	NPI	Significantly greater decrease in NPI scores for rivastigmine capsules when compared with patches at week 24 ($p = 0.032$, $d = 0.16$) & week 76 ($p = 0.007$, $d = 0.19$)	Strong 14

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Freund-Levi et al 2014a (13) & 2014b (14) Sweden	Galantamine 4mg twice daily week 1 → 8mg twice daily week 2 → 12mg twice daily from week 3 vs risperidone 0.25mg twice daily week 1 → 0.5mg twice daily week 2 → 1mg morning + 0.5mg evening from week 3 12 weeks	General BPSD Agitation	• Open-label RCT • 100 community-dwelling memory clinic patients with various types of moderate dementia admitted to a geropsychiatric ward (67 females) • Sealed envelope randomisation • Raters not blinded • No post-intervention f/u	NPI CMAI	Significant decrease in total NPI scores for galantamine & risperidone at 12 weeks ($p = 0.02$, $d = 1.57$), ns difference between groups Significant decrease in total CMAI agitation scores for risperidone ($p < 0.0005$, $d = 0.65$) & galantamine ($p = 0.008$, $d = 0.40$) at 12 weeks when compared with baseline Significantly greater decrease in total CMAI agitation scores for risperidone when compared with galantamine at 12 weeks ($p = 0.01$, $d = 0.24$)	Strong 13
Gareri et al 2014 (15) Italy	Memantine add-on up-titrated weekly by 5mg/day increments to 20mg/day from week 4+ stable dose donepezil, rivastigmine or galantamine at highest tolerated dose 6 months	General BPSD	• Multicentre repeated measures study • 240 patients with AD from 7 ambulatory dementia centres taking AChEIs (148 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores at 3 & 6 months when compared with baseline ($p = 0.0001$, $d = 0.20$)	Moderate 10
Grossberg et al 2013 (16) USA	Memantine extended-release 28mg/day vs placebo 24 weeks	General BPSD	• RCT • 677 people with moderate-severe AD, the majority were of Hispanic origin (487 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	NPI	Significantly greater decrease in total NPI scores for memantine when compared with placebo ($p = 0.005$, $d = 0.16$)	Strong 13

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Han et al 2012 (17) South Korea	Transdermal rivastigmine patch monotherapy vs rivastigmine patch + memantine 20mg/day 24 weeks	General BPSD	• Open-label multicentre RCT • 146 medical centre patients with mild-moderate probable AD (32 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	NPI	Ns difference between groups for total NPI scores at 24 weeks ES n/a	Moderate 10
Herrmann et al 2013 (18) Canada	Memantine 5mg/day up-titrated in 5 mg weekly increments to 20 mg/day at week 4 vs placebo 24 weeks	General BPSD Agitation	• RCT • 369 community-dwelling people with moderate-severe AD, agitation & aggression (215 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	NPI CMAI	Ns difference between groups for total NPI & CMAI change scores at 24 weeks ES n/a	Moderate 12
Howard et al 2012 (19) UK	Continued donepezil vs discontinued donepezil vs continued donepezil + start memantine vs discontinued donepezil + start memantine (all groups previously treated with donepezil) 52 weeks	General BPSD	• RCT • 295 community-dwelling people with moderate-severe AD (193 females) • Randomisation by minimisation algorithm • Raters blinded • No post-intervention f/u	NPI	Significantly lower total NPI scores for continued donepezil + memantine & discontinued donepezil + memantine when compared with continued & discontinued donepezil only groups ($p = 0.002$, $d = 0.29$) Significantly lower total NPI scores for continued donepezil + memantine when compared with continued donepezil only ($p = 0.006$, $d = 0.37$) Ns difference in total NPI scores between continued & discontinued donepezil only groups	Strong 14

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Ikeda et al 2013 (20) Japan	Donepezil 3mg/day for 2 weeks → 5mg/day for 50 weeks after ≥ 8 weeks wash out period post previous 12 week Donepezil RCT	General BPSD	• Multicentre, open-label repeated measures extension study • 108 neurological-centre patients with probable DLB (67 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Ns decrease in total NPI scores at 52 weeks when compared with baseline ES n/a, although scores indicated a significant decrease at weeks 8 - 40 ($p < 0.05$)	Moderate 10
Ikeda et al 2015 (21) Japan	Donepezil 5-10mg/day vs placebo 12 weeks	General BPSD	• RCT • 142 neurological centre patients with probable DLB (80 females) • Dynamic allocation randomisation • Raters blinded • No post-intervention f/u	NPI	Ns difference in total NPI scores between groups at 12 weeks ES n/a	Strong 13
Ishikawa et al 2016 (22) Japan	Memantine 5mg/day up-titrated weekly to 20mg/day 4 weeks	General BPSD Nocturnal disruption	• Repeated measures study • 12 neuropsychiatric inpatients with mild-moderate AD (8 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI Polysomno-graphy (PSG) AIS	Significant decrease in total NPI scores at 4 weeks when compared with baseline ($p = 0.009$, Hedge's $g = 0.83$) Significant increase in PSG total sleep time minutes ($p = 0.002$, Hedge's $g = 1.24$) & sleep efficiency ($p = 0.002$, Hedge's $g = 1.23$) at 4 weeks when compared with baseline Ns decrease in mean AIS insomnia scores at 4 weeks when compared with baseline, ES n/a	Moderate 10

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Jaidi et al 2018 (23) France	Clinically significant reduction (minimum 20%) in anticholinergic burden vs unadjusted anticholinergic burden during inpatient admission	General BPSD	• Repeated measures study • 125 acute specialised dementia care unit patients with mild-severe dementia (81 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI-NH	Clinically significant reduction in anticholinergic burden significantly associated with significant reduction in total NPI-NH scores ($p = 0.002$, $d = 0.37$)	Moderate 10
Kano et al 2013 (24) Japan	Substudy 1. Donepezil 5 mg/day switched to galantamine up-titrated from 8 to 16mg/day vs donepezil 5 mg/day switched to galantamine 24 mg/day Substudy 2. Donepezil 5mg/day increased to 10 mg/day vs donepezil 5mg/day + memantine up-titrated from 5mg/day to maximum 20 mg/day 28 weeks	Agitation	• 2 open-label RCTs • 67 (substudy 1 - 34, substudy 2 - 33) community-dwelling outpatients with moderate-severe AD (27 females) • Randomisation method not reported • Raters not blinded • No post-intervention f/u	NPI agitation subscale CMAI	1. Ns decrease in total CMAI agitation & NPI agitation subscale scores for donepezil switched to galantamine 16mg & donepezil switched to galantamine 24mg at 28 weeks when compared with baseline, ns difference between groups, ES n/a 2. Significant decrease in total CMAI agitation scores for memantine add-on & increased donepezil at 28 weeks when compared with baseline ($p < 0.05$), insufficient data to calculate ES Significantly greater decrease in total CMAI agitation scores for memantine add-on when compared with increased donepezil at 28 weeks ($p < 0.05$), insufficient data to calculate ES Ns decrease in NPI agitation subscale scores for memantine add-on & increased donepezil at 28 weeks when compared with baseline, ES n/a	Modest 9

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Kazui et al 2017 (25) Japan	Donepezil 3mg/day 2 weeks → 5mg/day 14 weeks	General BPSD Nocturnal disruption	• Open-label repeated measures study • 16 neuropsychological clinic patients with mild-moderate DLB (8 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI Wrist actigraphy	Significant decrease in total NPI scores at 16 weeks when compared with baseline ($p = 0.015$, Hedge's $g = 0.95$) Ns change in total sleep time & sleep efficiency on indices of actigraphy at 16 weeks when compared with baseline, ES n/a	Modest 8
Korucu et al 2018 (26) Turkey	Donepezil 5-10mg/day vs rivastigmine 4.6mg-9.5mg/day 1 month	Anxiety Depression Nocturnal disruption	• Repeated measures study • 35 people with mild-moderate AD (17 females) • No randomisation • Raters not blinded • No post-intervention f/u	BAI CSDD PSQI	Ns change in BAI anxiety, CSDD depression & PSQI sleep quality scores at 1 month when compared with baseline, ns difference between groups ES n/a	Modest 9
Kurz et al 2014 (27) Germany	Memantine extended-release 28mg/day vs placebo 24 weeks	General BPSD	• RCT • 677 community-dwelling people with probable AD (487 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	NPI	Significantly greater decrease in total NPI scores for memantine when compared with placebo at 24 weeks ($p < 0.002$), reported ES small	Moderate 10
Manabe et al 2016 (28) Japan	Donepezil 5-10mg/day administered following relapse in BPSD, including visual hallucinations, despite ongoing donepezil 5 mg/day 4 weeks	Delusions & hallucinations	• Open-label repeated measures study • 24 outpatients with mild-severe DLB (15 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI hallucinations subscale	Significant decrease in NPI hallucinations subscale scores at 4 weeks when compared with baseline ($p < 0.0001$) Insufficient data to calculate ES	Modest 8

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Matsuzono et al 2015a (29) Japan	Rivastigmine 4.5mg/day up-titrated to 18mg/day vs donepezil 3mg/day up-titrated to 5 or 10mg/day 12 months	General BPSD Apathy Depression	• Retrospective clinical cohort study • 145 dementia clinic patients with moderate AD (95 females), 58 assessed for general BPSD, 76 for apathy, 77 for depression • No randomisation • Raters blinded • No post-intervention f/u	GDS AS ABS	Ns change in total NPI, GDS depression & AS apathy scores for rivastigmine or donepezil at 12 months; ns difference between groups Significantly greater decrease in total ABS change scores for rivastigmine in severe BPSD subgroup (n = 14) when compared with mild BPSD subgroup (n = 12) at 3 months ($p < 0.01$), ns at 12 months ES n/a	Modest 9
Matsuzono et al 2015b (30) Japan	Substudy 1. Memantine monotherapy 5-20mg/day Substudy 2. Memantine treatment in any manner i.e. monotherapy or any combination of memantine + other ChEIs grouped according to high or low MMSE scores Substudy 3. Memantine treatment in any manner grouped according to high or low ABS scores 12 months	General BPSD Apathy Depression	• Retrospective clinical cohort study • Substudy 1. 38 people with mild-moderate dementia (25 females) Substudy 2. 163 people with mild-severe dementia (86 females) Substudy 3. 71 people with mild-severe dementia (number of females not reported) • No randomisation • Raters not blinded • No post-intervention f/u	ABS AS GDS	1. Significant decrease in total ABS scores for memantine monotherapy at 6 months ($p < 0.01$) when compared with baseline, ns at 12 months 2. Significant decrease in global ABS scores for those in memantine in any manner group with MMSE ≥ 15 at 6 months ($p < 0.01$) & 12 months ($p < 0.05$) when compared with baseline 3. Significant decrease in total ABS scores for memantine in any manner group with severe BPSD (n = 41) at 6 months ($p < 0.01$) & 12 months ($p < 0.05$) when compared with baseline Insufficient data to calculate ES Ns change in GDS depression & AS apathy scores at 12 months for any group in any study, ES n/a	Moderate 10

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Matsuzono et al 2015c (31) Japan	Memantine 5-20mg/day vs donepezil 3-10mg/day vs galantamine 8-24 mg/day vs rivastigmine 4.5-18 mg/day 12 months	General BPSD Apathy Depression	• Retrospective clinical cohort study • 373 people aged ≥75 years with AD on ChEI monotherapy (240 females) • No randomisation • Raters blinded • No post-intervention f/u	ABS AS GDS	Ns change in GDS depression & AS apathy scores at 12 months for any group Significant decrease in total ABS scores at 3 months ($p < 0.05$) & 6 months ($p < 0.01$) for memantine & at 3 months for rivastigmine ($p < 0.01$), all ns at 12 months ES n/a	Moderate 10
Matsuzono et al 2015d (32) Japan	Donepezil only for 6 months → donepezil + memantine 5-20 mg for 12 months vs galantamine only for 6 months → galantamine + memantine 5-20 mg for 12 months	General BPSD Apathy Depression	• Retrospective clinical cohort study • 114 people with AD (73 females) • No randomisation • Raters blinded • No post-intervention f/u	GDS AS ABS	Ns change in total ABS BPSD, GDS depression or AS apathy scores with addition of memantine in donepezil or galantamine group at 12 months when compared with baseline, ES n/a Donepezil + memantine significantly better at maintaining apathy scores at 12 months & total ABS BPSD scores at 6 months after addition of memantine, when compared with galantamine + memantine ($p < 0.05$), insufficient data to calculate ES Older cohort subgroup (age >75, n = 89) showed significant decrease in ABS scores & significant **increase** in AS apathy scores for galantamine + memantine at 12 months when compared with baseline ($p < 0.05$)	Moderate 10
Miranda et al 2015 (33) Brazil	ChEIs: donepezil 5-10mg/day or galantamine 16-24mg/day or rivastigmine 6-12mg/day 12 months	General BPSD Depression	• Observational, naturalistic repeated measures study • 129 outpatients with mild-moderate AD or AD + CVD (67 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI CSDD	Significant decrease in CSDD depression scores for all ChEIs at 12 months when compared with baseline ($p < 0.01$), insufficient data to calculate ES Ns difference in total NPI scores at 12 months when compared with baseline, ES n/a Patients with mild dementia & those who were 'good responders' at 3 months remained good responders to ChEIs at 12 months	Modest 9

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Naharci et al 2015 (34) Turkey	Donepezil 5 & 10 mg/day or galantamine 8, 16 & 24 mg/day or rivastigmine 5cm^2 & 10cm^2 patch up-titrated over 2 or 4 weeks to maximum tolerated dose 6 months	Nocturnal disruption	• Observational, repeated measures study • 87 outpatients with mild-moderate AD or mixed dementia (33 females) • No randomisation • Raters not blinded • No post-intervention f/u	PSQI	Significant improvement in PSQI sleep quality for galantamine group at 6 months when compared with baseline (p = 0.028), ns change for donepezil & rivastigmine Significantly greater improvement in PSQI sleep quality for galantamine when compared with donepezil (p = 0.008, d = 1.3) & rivastigmine (p = 0.040, d = 0.8) at 6 months	Modest 8
Nakamura et al 2014 (35) Japan	Memantine 5 mg/day up-titrated by 5 mg/week to 20mg/day vs placebo 24 weeks	General BPSD	• Pooled analysis of 2 RCTs • 633 outpatients with moderate-severe AD (424 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	BEHAVE-AD	Significantly greater decrease in total BEHAVE-AD scores for memantine when compared with placebo at 12 weeks (p = 0.0005) & 24 weeks (p = 0.013) Insufficient data to calculate ES	Moderate 12
Nakano et al 2015 (36) Japan	Galantamine newly introduced or switched from other ChEIs up-titrated from 8mg/day to 24mg/day over 12 weeks 24 months	General BPSD Depression Apathy	• Retrospective repeated measures study • 279 very old people with mild-severe AD (170 females) • No randomisation • Raters blinded • No post-intervention f/u	ABS GDS AS	Ns change in total ABS BPSD, GDS depression & AS apathy scores at 24 months ES n/a	Moderate 11
Nakayama et al 2017 (37) Japan	Galantamine 4mg twice daily up-titrated at 4 week intervals to 8mg twice daily then 12mg twice daily 12 weeks	General BPSD	• Prospective study • 50 people with mild AD & naïve to ChEIs (20 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Ns difference in total NPI scores at 12 weeks ES n/a	Modest 8

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Oh et al 2015 (38) South Korea	Rivastigmine titrated to stable maintenance dose: mean transdermal dose 6.1 ± 2.3mg/day (20 patients) & oral dose 8.0 ± 1.7mg/day (3 patients) 24 weeks	General BPSD	• Open-label, repeated measures study • 23 outpatients with moderate PDD prescribed antiparkinsonian medication (12 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores at 24 weeks when compared with baseline ($p = 0.049$, $d = 0.26$)	Moderate 10
Ohta et al 2017 (39) Japan	ChEI switch: donepezil to galantamine (D→G), donepezil to rivastigmine (D→R), galantamine to donepezil (G→D), galantamine to rivastigmine (G→R), rivastigmine to donepezil (R→D), rivastigmine to galantamine (R→G) 6 months before drug switch & 6 months after	General BPSD Apathy Depression	• Retrospective, repeated measures chart review • 171 patients with mild-moderate AD & with a switch in ChEI medication • No randomisation • Raters not blinded • No post-intervention f/u	ABS AS GDS	Significant **increase** in total ABS scores for R→D ($p = 0.043$) at 6 months post switch when compared with time of drug switch, significant decrease in ABS scores for G→D ($p = 0.042$) & G→R ($p = 0.035$) at 3 months but not 6 months, ns change in ABS scores for D→G, D→R & R→G at 6 months Ns change in GDS depression & AS apathy scores for any group at 6 months post switch ES n/a	Moderate 10
Peters et al 2015 (40) Germany	Memantine 20mg/day + galantamine-controlled release (CR) 24mg/day vs galantamine-CR 24mg/day + placebo 52 weeks	General BPSD	• RCT • 226 community-dwelling, antidementia drug-naïve people with probable mild-moderate AD (144 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	NPI	Ns change in total NPI scores at 52 weeks when compared with baseline for either group, ns difference between groups ES n/a	Strong 13

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Rea et al 2015 (41) Italy	Donepezil 10 mg/day + choline alphoscerate (precursor cholinergic drug) 1,200 mg/day vs donepezil 10 mg/day + placebo 24 months	Apathy	• RCT • 113 community dwelling people with mild-moderate AD & apathy (60 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	NPI apathy subscale	Significantly greater decrease in NPI apathy subscale scores for donepezil + choline alphoscerate when compared with donepezil only at 24 months ($p < 0.05$, $d = 0.42$)	Moderate 11
Richarz et al 2014 (42) Germany	Galantamine 8mg/day up-titrated to 16 or 24mg/day 36 months	General BPSD	• Multicentre open-label, repeated measures study • 75 community-dwelling people with mild AD (41 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores at 12 months ($p < 0.05$) when compared with baseline; ns change at 3 years ES n/a	Modest 9
Spalletta et al 2013 (43) Italy	Rivastigmine patch 4.6 mg/day increased to 9.5 mg/day at 3 months 6 months	Depression	• Open-label, repeated measures study • 50 outpatients with mild AD & major depressive episode from 5 memory clinics (31 females) • No randomisation • Raters not blinded • No post-intervention f/u	CERAD dysphoria subscale	Significant decrease in CERAD dysphoria subscale scores at 6 months ($p = 0.006$, $d = 0.31$) Significant decrease in frequency of major depressive episodes at 6 months (62%) when compared with 100% at baseline ($p < 0.0001$)	Modest 9
Spalletta et al 2014 (44) Italy	Switch from non-rivastigmine oral ChEI (donepezil or galantamine) to rivastigmine patch vs switch from rivastigmine patch to non-rivastigmine oral ChEI 6 months	Depression Apathy	• Observational, repeated measures study • 423 outpatients with mild-moderate AD from 38 memory clinics (256 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI apathy & depression subscales	Significant decrease in NPI depression subscale scores for switch from oral ChEI to rivastigmine patch at 6 months when compared with switch from rivastigmine patch to oral ChEI ($p = 0.019$), insufficient data to calculate ES, ns change in NPI depression subscale frequency scores at 6 months when compared with baseline, ES n/a Ns change in apathy subscale scores at 6 months	Moderate 11

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Suzuki et al 2013 (45) Japan	Memantine 5mg up-titrated by 5 mg 2nd weekly to 10-20mg/day added to stable dose of psychotropic drugs with aim to reduce psychotropic drug dosages wherever possible vs continued stable dose of psychotropic drugs 16 weeks	General BPSD Psychotropic drug use	• Open-label, repeated measures study • 38 inpatients with severe AD (32 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores for memantine group ($p < 0.005$, $d = 0.4$) & continued psychotropic drugs ($p < 0.005$) at 16 weeks when compared with baseline, ns difference between groups Significantly lower risperidone equivalent dose ($p = 0.0036$), diazepam equivalent dose ($p = 0.0012$) & sodium valproate ($p = 0.0069$) for memantine group at 24 weeks when compared with continued psychotropics group	Modest 9
Suzuki et al 2014 (46) Japan	Donepezil treatment discontinuation due to persistent symptoms or financial reasons vs control group not concomitantly taking ChEIs 16 weeks	General BPSD Antipsychotic drug use	• Flexible-dose, open-label repeated measures study • 44 psychiatry inpatients with severe AD (37 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI Chart review	Significant decrease in total NPI scores for both groups at 16 weeks when compared with baseline, donepezil discontinuation ($p < 0.005$, $d = 0.08$), ns difference between groups Significantly greater decrease in risperidone equivalent dose for donepezil discontinuation when compared with control group ($p = 0.04$)	Modest 9
Wilkinson et al 2012 (47) France, Germany Switzerland UK	Memantine up-titrated to target dose 20 mg/day vs placebo 52 weeks	General BPSD	• RCT • 277 outpatients with moderate AD from 31 specialist clinics (158 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	NPI	Ns change in total NPI scores at 52 weeks when compared with baseline, ns difference between groups ES n/a	Strong 13

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Yatabe et al 2013 (48) Japan	Donepezil dose escalation from 5mg/day to 10mg/day 8 weeks	General BPSD	• Repeated measures study • 27 community-dwelling people with mild-moderate AD taking donepezil 5mg/day ≥ 3 months (21 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Ns change in total NPI scores 8 weeks after dose escalation when compared with baseline ES n/a	Modest 9
Yoon et al 2017 (49) South Korea	Rivastigmine patch monotherapy 5cm^2 4 weeks → 10cm^2 4 weeks maintained at highest tolerated patch size for remainder of study vs rivastigmine patch 5cm^2 4 weeks → 10cm^2 4 weeks + memantine initiated after 8 weeks at 5mg/day increased weekly to target dose 20mg/day 24 weeks	Agitation Aggression	• Open-label, randomised study • 147 outpatients with mild-moderate AD & agitation (114 females) • Randomisation method not reported • Raters not blinded • No post-intervention f/u	Korean CMAI	Factor analyses indicated 2 symptom clusters: factor A aggressive agitated behaviours & factor B nonaggressive agitated behaviours Significantly greater decrease in total CMAI agitation ($p = 0.043$, $d = 0.42$) & factor B scores ($p = 0.022$, $d = 0.34$) for monotherapy group when compared with combination rivastigmine + memantine at 24 weeks, ns change in factor A aggressive agitated behaviours scores Significant decrease in CMAI factor B scores in monotherapy group only at 24 weeks when compared with baseline ($p = 0.043$, $d = 0.18$) Significant **increase** in total CMAI agitation scores ($p = 0.04$, $d = 0.15$) & factor B scores ($p = 0.027$, $d = 0.23$) for combination rivastigmine + memantine at 24 weeks when compared with baseline	Moderate 11
Zhang et al 2015 (50) China	Memantine 10mg x 2/day vs donepezil 10mg/day 24 weeks	General BPSD	• RCT • 167 people with mild-moderate AD (101 females) • Method of randomisation not reported • Raters blinded • No post-intervention f/u	NPI	Significant decrease in in total NPI scores for memantine ($p < 0.001$, $d = 0.56$) & donepezil ($p < 0.001$, $d = 0.32$) groups at 24 weeks when compared with baseline, ns difference between groups in total NPI scores	Moderate 12

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Zhang et al 2016 (51) China	Rivastigmine patch 9.5mg/day vs rivastigmine capsule 6mg 2 x daily 24 weeks	General BPSD	• RCT • 501 community-dwelling people with moderate-severe AD (279 females) • Interactive voice randomisation • Raters blinded • No post-intervention f/u	NPI-12	Ns decrease in total NPI-12 scores for both groups at 24 weeks when compared with baseline, ns difference between groups ES n/a	Strong 13
Analgesic medications						
Blytt et al 2018a (52) & Blytt et al 2018b (53) Norway	Paracetamol 3g/day (for those not already on pain treatment) or transdermal buprenorphine 10ug/h/7days (for those already on pain treatment) vs placebo tablets or transdermal patches Study a 1 week Study b 13 weeks	Nocturnal disruption	• Multicentre RCT • 106 residents with dementia & depression from 47 RACSs (80 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	Sleep parameters: total sleep time, sleep efficiency, sleep onset latency, wake after onset, early morning awakening & number of wake bouts	Study a: significant improvement in total sleep time (p = 0.003, d = 0.25), sleep onset latency (p = 0.047, d = 0.27) & early morning awakening (p = 0.043, d = 0.22) for active treatment group when compared with placebo at 1 week Study b: ns difference between active pain treatment & placebo at 13 weeks, ES n/a	Moderate 12
Erdal et al 2018 (54) Norway	Paracetamol maximum 3g/day vs placebo or buprenorphine maximum 10 µg/hour vs placebo 13 weeks	Depression	• Multicentre RCT • 162 residents with dementia from 47 RACSs (122 females) • Computer-generated block randomisation • Raters blinded • No post-intervention f/u	CSDD	Ns change in CSDD depression scores for either analgesic treatment at 13 weeks when compared with baseline, ns difference between groups ES n/a	Strong 13

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Hamina et al 2018 (55) Finland	Opioid initiation vs matched cohort with no opioid initiation & 30 day period prior to opioid initiation compared with 30 day period 6 months post-initiation	Psychotropic drug use	• Quasi-experimental, repeated measures study • 6,652 community-dwelling people with AD (4,546 females) • Not randomised • Raters not blinded • No post-intervention f/u	Finnish Prescription Register	Ns decrease in antipsychotic & benzodiazepine & related drug use for opioid initiation when compared with no opioid initiation Ns decrease in antipsychotic (0.3 percentage points) & benzodiazepine & related drug use (0.4 percentage points) per month after opioid initiation for 6 months ES n/a	Modest 8
Husebo et al 2014a (56), 2014b (57) & Habiger et al 2016 (58) Norway	Stepwise pain management protocol: paracetamol ≤ 3g daily, extended-release morphine ≤ 20mg daily, buprenorphine ≤ 10µg daily &/or pregabaline ≤ 300mg daily according to assessed pain needs vs usual care 8 weeks	General BPSD Agitation Aggression Depression Delusions	• Cluster RCT • 352 residents from 18 RACSs with moderate-severe dementia (262 females) • Computer-generated randomisation • Raters blinded • 4 week post-intervention f/u	CMAI 3 factor groups NPI-NH depression subscale NPI delusions subscale NPI agitation cluster: agitation/ aggression, disinhibition, irritability & aberrant motor behaviour	Significant decrease in CMAI verbally agitated behaviour factor ($p < 0.001$, $d = 0.30$), physically non-aggressive behaviour factor ($p = 0.008$, $d = 0.18$) & aggressive behaviour factor ($p = 0.037$, $d = 0.13$) change scores for pain management protocol when compared with usual care at 8 weeks, scores increased at 4 week f/u (significance not reported) Significantly greater decrease in NPI depression subscale scores for pain management protocol when compared with usual care at 8 weeks ($p = 0.025$, reported ES = 0.3), effect maintained at 4 week f/u (significance not reported) Significant decrease in total NPI scores for pain management protocol when compared with usual care at 8 weeks ($p < 0.001$, $d = 0.39$) Continued next page	Moderate 12

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Husebo et al 2014a (56), 2014b (57) & Habiger et al 2016 (58) cont.					Significant decrease in NPI agitation cluster scores for pain management protocol when compared with usual care at 8 weeks for total population ($p < 0.001$, $d = 0.34$) & in subgroup with ≥ 1 symptom of agitation at baseline ($n = 265$, $p < 0.001$, $d = 0.42$) Ns change in NPI delusions subscale scores for pain management protocol in total population but significant decrease in subgroup with ≥ 1 symptom of psychosis at baseline for pain management protocol when compared with usual care at 8 weeks ($n = 154$, $p = 0.034$, $d = 0.24$)	
Petro et al 2016 (59) Italy	Oxycodone/naloxone initiated at low doses 5/2.5mg/day or twice daily increased to maximum 20/10mg twice daily 45 days	General BPSD	• Open-label repeated measures study • 53 patients with mild-moderate cognitive impairment & moderate-severe chronic pain from RACSs & AD centres (35 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores for oxycodone/naloxone at 45 days when compared with baseline ($p < 0.0001$, $d = 0.82$) Significant decrease in proportion of patients with moderate-severe total NPI scores (≥50) from 39.6% at baseline to 11.3% at 45 days ($p = 0.001$, Relative Risk = 28.5%, odds ratio = 2.4)	Modest 9
Traditional medicines						
Fujii et al 2018 (60) USA	Gamma-oryzanol (rice bran lipids) 50mg twice daily vs usual care 4 weeks	General BPSD	• RCT • 69 psychiatric hospital patients with moderate AD, VaD or LBD (38 females) • Random number table randomisation • Raters blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores for γ-oryzanol group at 4 weeks when compared with baseline ($p < 0.01$, $d = 0.58$), ns change for usual care	Moderate 11

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Furukawa et al 2017 (61) Japan	Yokukansan 2.5 g x 3 daily vs placebo for 4 weeks followed by Yokukansan 2.5 g x 3 daily for all patients 8 weeks	General BPSD	• Multicentre, open-label RCT • 145 patients with mild-moderate AD from 22 clinics, hospitals & RACSs (84 females) • Block randomisation, method not reported • Rater blinding not reported • No post-intervention f/u	NPI-Q	Significant decrease in total NPI-Q scores for Yokukansan & placebo (both $p < 0.001$) groups at 4, 8 & 12 weeks, ns difference between groups ES n/a	Strong 13
Herrschaft et al 2012 (62) Germany	EGb 761 dry extract from ginkgo biloba leaves 240mg/day vs placebo 24 weeks	General BPSD	• Multicentre RCT • 410 outpatients with mild-moderate AD or VaD from 17 psychiatry or neurology clinics (279 females) • Computer-generated block randomisation • Raters blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores for ginko at 24 weeks when compared with baseline ($p < 0.001$, $d = 0.64$) Significantly greater decrease in total NPI scores for ginko when compared with placebo at 24 weeks ($p < 0.001$, $d = 0.36$)	Strong 14
Iwasaki et al 2012 (63) Japan	Yokukansan traditional Japanese medicine 2.5g x 3 daily 4 weeks	General BPSD	• Multicentre, open-label repeated measures study • 63 in-or outpatients with DLB from 15 hospitals (33 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores at 4 weeks when compared with baseline ($p < 0.001$, $d = 0.78$)	Moderate 11
Kudoh et al 2016 (64) Japan	7.5mg Ninjin'yoeito (NYT) extract traditional Japanese medicine + donepezil 5mg/day vs donepezil 5mg/day only 2 years	Depression	• Open-label, nonrandomised study • 23 clinic outpatients with mild-moderate AD taking donepezil ≥ 8 months (15 females) • No randomisation • Raters blinded • No post-intervention f/u	NPI	Significant decrease in NPI depression subscale scores for NYT + donepezil when compared with donepezil only at 24 months ($p < 0.05$, $d = 0.3$) Significant decrease in median NPI depression subscale scores for NYT + donepezil at 6, 12 & 18 months when compared with baseline ($p < 0.01$), ns at 24 months	Moderate 11

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Nagata et al 2012 (65) Japan	Yokukansan traditional Japanese medicine 2.5g x 3 daily 4 weeks	General BPSD	• Open-label, repeated measures study • 13 people with mild-moderate VaD (4 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores at 4 weeks when compared with baseline ($p < 0.05$, Hedge's $g = 0.60$)	Modest 9
Pan et al 2014 (66) China	Shen-Zhi-Ling (SZL) traditional Chinese medicine oral liquid vs placebo 20 weeks	General BPSD	• RCT • 98 people with moderate AD (36 females) • Randomisation method not reported • Raters blinded • 5 week post-intervention f/u	BEHAVE-AD NPI Actigraphy to assess BPSD severity	Significantly delayed development of BPSD per evening & nocturnal actigraphy for SZL at 20 weeks when compared with baseline ($p < 0.05$, $d = 0.04$) Ns difference between groups in total BEHAVE-AD & NPI scores at any timepoint or at 5 week f/u, ES n/a	Moderate 11
Sadhu et al 2014 (67) India	Polyherbal tablets x 2 daily: extracts of Bacopa monnieri 450mg/day + Hippophae rhamnoides 250mg/day + Dioscorea bulbifera 250mg/day vs donepezil 20mg/day 12 months	Depression	• RCT • 123 community-dwelling people with severe AD (number of females not reported) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	GDS	Significant decrease in GDS depression scores for polyherbal formulation when compared with donepezil group at 12 months ($p < 0.0001$, $d = 0.82$)	Moderate 12
Sumiyoshi et al 2013 (68) Japan	7.5g Yokukansan powder + ongoing antipsychotic treatment 4 weeks	General BPSD	• Open-label, repeated measures study • 11 patients with moderate-severe AD or VaD & chronic renal failure on haemodialysis (4 females) • No randomisation • Raters blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores for YKS period when compared with baseline ($p = 0.007$, Hedge's $g = 1.32$)	Moderate 10

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Atypical antipsychotics						
Ballard et al 2018 (69) UK	Pimavanserin 17mg/ x 2 daily vs placebo after 3 weeks washout in those taking other antipsychotic medication 12 weeks	Delusions & hallucinations Agitation	• Multicentre RCT • 181 residents with moderate-severe AD & psychotic symptoms severe enough to warrant treatment with antipsychotic from 133 RACSs (144 females) • Computer-generated block randomisation • Raters blinded • No post-intervention f/u	NPI-NH hallucinations + delusions subscales CMAI-SF	Significantly greater decrease in mean NPI–NH psychosis scores for pimavanserin at week 6 when compared with baseline (p = 0.045, d = 0.32), ns at week 12 Significant greater decrease in mean NPI–NH psychosis scores in subgroup with severe psychotic symptoms (baseline NPI-NH psychosis score ≥12) for pimavanserin at week 6 when compared with baseline (n = 57, p = 0.011, d = -0.73), ns at week 12 Ns difference between groups for CMAI agitation & total NPI scores, ES n/a	Strong 13
De Deyn et al 2012 (70) Belgium	Quetiapine extended release (XR) vs immediate release (IR) 50 mg/day increased to 100 mg/day by day 4, then flexible dose 50-300 mg/day by day 8 6 weeks	General BPSD Agitation	• RCT • 109 RACS residents with AD, prescribed antipsychotic medication for psychosis &/or agitation • Block randomisation, method not reported • Raters blinded • No post-intervention f/u	NPI–NH CMAI	Ns change in total NPI & CMAI scores for both groups at 6 weeks ES n/a	Moderate 11

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Devanand et al 2012 (71) USA	Phase A: open-label risperidone 16 weeks → responders with significant decrease in total NPI core scores randomised to phase B: 1. risperidone continued 32 weeks vs 2. risperidone 16 weeks→ placebo 16 weeks vs 3. 32 weeks placebo	General BPSD	• Multicentre, discontinuation RCT • 110 risperidone responders with mild AD & psychosis, agitation or aggression • Randomisation method not reported • Raters blinded • No post-intervention f/u	NPI core score: sum delusions, hallucinations, agitation/ aggression subscales	Significantly greater risk of relapse (≥ 5 points or 30% increase in NPI core score at end of phase A) for group 3 than groups 1 & 2 at week 16 ($p < 0.004$) Significantly greater risk of relapse for group 2 than group 1 at week 32 ($p < 0.02$) Insufficient data to calculate ES	Strong 13
Fujii et al 2019 (72) USA	A. non-psychotropics: anxiolytics, ChEIs, antidepressants, anti-epileptics, tiapride hydrochloride, yi-gan san &/or gamma-orizanol vs B. psychotropics: chlorpromazine, levomepromazine, risperidone, olanzapine &/or quetiapine 6 weeks	General BPSD	• Repeated measures study • 48 psychiatric hospital inpatients with moderate AD, VaD or DLB (number of females not reported) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores for group A ($p < 0.01$, $d = 1.66$) & group B ($p < 0.01$, $g = 2.3$), ns difference between groups	Modest 9

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Grossberg et al 2020 (73) USA	Study 1: fixed doses brexpiprazole 2mg/day, brexpiprazole 1mg/day vs placebo 12 weeks Study 2: flexible doses brexpiprazole 0.5−2mg/day vs placebo 12 weeks	Agitation	• Multicentre RCT • 433 in study 1 (239 females), 270 in study 2 (130 females) community- or care facility-dwelling people with probable AD & agitation • Stratified computer-generated randomisation • Raters blinded • No post-intervention f/u	CMAI	Study 1: significantly greater decrease in CMAI scores for brexpiprazole 2mg/day at 12 weeks when compared with placebo (p = 0.040, d = -0.25), ns difference between brexpiprazole 1mg/day & placebo groups Study 2: ns change in CMAI scores for brexpiprazole 0.5−2 mg/day, post hoc analysis indicated significant decrease for those titrated to 2mg/day (p = 0.012, d = -0.19)	Strong 13
Teodorescu et al 2018 (74) Romania	Clozapine up-titrated from 6.25mg/day or 12.5mg/day to mean dose 59.16 mg/day (SD ±40.48) used as last resort for refractory BPSD ie lack of or insufficient response to trials of at least 2 antipsychotics	Restraint Psychotropic drug use	• Retrospective chart review • 27 hospital inpatients with moderate-severe dementia admitted for aggression, agitation or psychosis (9 females) • No randomisation • Raters not blinded • No post-intervention f/u	Psychotropic drug use during admission Episodes of physical restraint	Significant decrease in concomitant psychotropic drug use after clozapine initiation when compared with prior (p < 0.01) Significant decrease in physical restraint episodes after clozapine initiation when compared with prior (p < 0.05) Insufficient data to calculate ES	Moderate 12
Teranishi et al 2013 (75) Japan	Risperidone 0.5-2.0mg/day vs yokukansan 2.7-7.5g/day vs fluvoxamine 25-200mg/day 8 weeks	General BPSD	• RCT • 82 psychiatric hospital inpatients with moderate AD, VaD or DLB (51 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores for risperidone (p < 0.001, d = 0.61), yokukansan (p < 0.001, d = 0.61) & fluvoxamine (p < 0.001, d = 0.68) groups at 8 weeks when compared with baseline, ns difference between groups	Moderate 12

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Antidepressants						
An et al 2017 (76) South Korea	Escitalopram up-titrated from 5mg/day to maximum dose 15mg/day vs placebo 12 weeks	Depression	• RCT • 84 community-dwelling people with moderate AD & depression (48 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	GDS CSDD NPI depression subscale	Ns change in NPI, GDS, & CSDD depression scores, ns difference between groups at 12 weeks ES n/a	Moderate 11
Banerjee et al 2013 (77) See Zuidersma et al 2019 below for secondary analysis UK	Sertraline 150mg/day vs mirtazapine 45mg/day vs placebo 39 weeks	Depression	• RCT • 326 community-dwelling, old-age psychiatry service outpatients with probable AD & depression (221 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	CSDD	Ns change in CSDD depression scores for sertraline & mirtazapine at 39 weeks when compared with baseline, ns difference between groups ES n/a	Strong 15
Bergh et al 2012 (78) Norway	Discontinuation of SSRIs: escitalopram, citalopram, sertraline or paroxetine vs continued treatment 25 weeks	Depression General BPSD	• Multicentre RCT • 128 residents with mild-severe AD, VaD or AD/VaD & no depressive disorder from 52 RACSs (96 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	CSDD NPI	Significant increase in CSDD depression scores for discontinuation group at 25 weeks ($p = 0.003$, $d = 0.38$) Ns increase in total NPI scores for discontinuation group when compared with continuation group at 25 weeks, ES = 0.53	Strong 13

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Choe et al 2015 (79) Korea	Escitalopram 20 mg/day vs placebo 52 weeks	General BPSD Depression	• RCT • 74 dementia clinic patients with mild-to-moderate AD, without major depression (28 females) • Web-based block randomisation • Raters blinded • No post-intervention f/u	NPI CSDD	Significantly greater decrease in CSDD depression scores for escitalopram when compared with placebo at 28 weeks (p = 0.035), ns at 52 weeks Ns change in total NPI scores ES n/a	Strong 13
Herrmann et al 2012 (80) Canada	Citalopram 10 mg/day up-titrated by 10 mg/week to maximum 40 mg/day on basis of tolerability 6 weeks	General BPSD	• Open-label, repeated measures study • 15 memory clinic outpatients with mild-moderate FTD (6 females) • No randomisation • Raters blinded • No post-intervention f/u	NPI FBI	Significant decrease in total NPI scores at 6 weeks when compared with baseline (p = 0.004) Significant decrease in total FBI scores over 6 weeks when compared with baseline (p = 0.001) Insufficient data to calculate ES	Moderate 12
Huang et al 2015 (81) USA	Initiation of antipsychotic or antidepressant treatment after no prior use in previous 6 months 3 months	General BPSD	• Retrospective cohort study • 3,696 long stay RACS residents with AD & related dementias (2,674 females) • 5% random sample of 2006-2009 data, method not reported • Raters not blinded • No post-intervention f/u	Medicare Minimum Data Set: verbally or physically abusive behaviour or socially inappropriate/ disruptive behaviours	Decrease in number & frequency of behaviour symptoms in 51.1% of those treated with antipsychotics & 48.1% of those treated with antidepressants after 3 months, ns difference between groups ES n/a	Modest 9
Mokhber et al 2014 (82) Iran	Desipramine 25-150mg 3 x day vs sertraline 25-50mg day vs venlafaxine 37.5–150mg 2 x day 12 weeks	Depression	• RCT • 59 people with moderate AD & major depressive disorder (25 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	HAM-D	Significant decrease in HAM-D depression scores for sertraline at 12 weeks when compared with baseline (p < 0.05), insufficient data to calculate ES Ns change in HAM-D depression scores for desipramine & venlafaxine at 12 weeks when compared with baseline, ES n/a	Moderate 11

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Porsteinsson et al 2014 (83) & Leonpacher et al 2016 (84) For additional information see Rosenberg et al 2015 (85) Canada/USA	Citalopram 30 mg/day + psychosocial intervention: crisis management + educational materials + counselling vs placebo + psychosocial intervention 9 weeks	General BPSD Agitation Aggression	• Multicentre RCT • 186 community-dwelling people with mild-severe probable AD & agitation (85 females) • Stratified randomisation, method not reported • Raters blinded • No post-intervention f/u	NBRS CMAI NPI agitation/ aggression subscale NBRS agitation subscale	Significant decrease in NBRS agitation (p = 0.04, d = 0.12), CMAI agitation (p = 0.008, d = 0.15) & total NPI scores (p = 0.01, d = 0.25) for citalopram + psychosocial intervention when compared with placebo + psychosocial intervention Ns change in NBRS agitation subscale scores at 9 weeks, ns difference between groups, ES n/a Ns difference in NPI agitation/aggression subscale scores between groups at 9 weeks, ES n/a	Moderate 12
Scoralick et al 2017 (86) Brazil	Mirtazapine 15 mg/day vs placebo 2 weeks	Nocturnal disruption	• RCT • 24 community-dwelling people with mild-severe AD & sleep disorders (18 females) • Randomisation via true number service • Raters blinded • No post-intervention f/u	Actigraphy	Ns change in duration or efficiency of nocturnal sleep for mirtazapine at 2 weeks when compared with placebo Significant increase in daytime total sleep for mirtazapine when compared with placebo at 2 weeks (p = 0.046) ES n/a	Moderate 12
Zhou et al 2019 (87) China	Memantine 20mg/day target dose + citalopram 10 mg/day up-titrated to 30 mg/day over 2 weeks vs memantine 20mg/day target dose + placebo 12 weeks	General BPSD	• RCT • 80 mental health centre outpatients & inpatients with moderate AD (47 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores for both groups at 12 weeks when compared with baseline (p < 0.05) Significantly greater decrease in total NPI scores for memantine + citalopram when compared with memantine + placebo (p < 0.05, d = -1.21)	Moderate 11

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Zuidersma et al 2019 (88) Secondary analysis of Banerjee et al 2013 above UK	Sertraline 50mg/day up-titrated to 100mg at 2 weeks → dose adjusted according to CSDD score at 4 weeks: if ≥ 4 dose increased to maximum 150mg/day. If CSDD ≤ 4, readministered at 8 weeks, if ≥ 4 dose increased to maximum vs mirtazapine 15mg up-titrated to 30mg at 2 weeks → dose adjusted according to CSDD score at 4 weeks: if ≥ 4 dose increased to maximum mirtazapine 45mg/day. If CSDD ≤ 4, readministered at 8 weeks, if ≥ 4 dose increased to maximum vs placebo 39 weeks	Depression	• RCT • 326 community-dwelling, old-age psychiatry service outpatients with probable AD & depression (221 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	CSDD	Significant decrease in CSDD depression scores for mirtazapine when compared with baseline at 13 weeks in subgroup with relatively severe psychological/affective symptoms, pessimism, low self-esteem & absence of sleep problems (n = 91, p = 0.019, d = 0.72) Ns change for sertraline, ns at week 39	Strong 13
Psychostimulants						
Frakey et al 2012 (89) USA	Modafinil 100mg/day week 1 → 200mg/day remaining 7 weeks + ChEIs vs placebo + ChEIs 8 weeks	Apathy	• RCT • 23 psychiatric hospital outpatients with mild-moderate AD & apathy (number of females not reported) • Simple random sampling • Raters blinded • No post-intervention f/u	FrSBe apathy	Significant decrease in FrSBe apathy scores for both groups at 8 weeks when compared with baseline (p < 0.001), ns difference between groups ES n/a	Moderate 12

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Lapid et al 2017 (90) USA	Armodafinil 150mg/day for 4 weeks → 250mg/day 8 weeks	Nocturnal disruption General BPSD	• Open-label, repeated measures study • 20 outpatients with hypersomnia associated with mild-moderate DLB (4 females) • No randomisation • Raters not blinded • No post-intervention f/u	ESS MWT NPI	Significantly improved ESS scores ($p < 0.001$) & MWT wakefulness ($p = 0.003$) at 12 weeks when compared with baseline Significant decrease in total NPI scores at 12 weeks when compared with baseline ($p = 0.003$) Insufficient data to calculate ES	Modest 8
Padala et al 2018 (91) USA	Methylphenidate 5 mg up-titrated to 10mg/ 2 x day at 2 weeks until 12 weeks then dose tapered to 5mg/ 2 x day for 3 days & ceased vs placebo 12 weeks	Apathy Depression	• RCT • 60 male, community-dwelling veterans with mild AD • Block randomisation by sealed envelopes • Raters blinded • No post-intervention f/u	AES-C CSDD	Significantly greater decrease in AES-C apathy scores for methylphenidate when compared with placebo at 4 weeks ($p = 0.006$), 8 weeks ($p < 0.001$) & 12 weeks ($p < 0.001$, $d = 1.39$) Significantly greater improvement in CSDD depression scores for methylphenidate when compared with placebo at 12 weeks ($p = 0.004$, $d = 0.75$)	Moderate 12
Rosenberg et al 2013 (92) See Lanctot et al 2014 (93) for secondary analysis USA	Methylphenidate 5 mg twice daily up-titrated to 10 mg twice daily if tolerated vs placebo 6 weeks	Apathy	• Multicentre RCT • 60 community- or RACS-dwelling people with mild-moderate AD & apathy (37 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	AES NPI apathy subscale	Significantly greater decrease in NPI apathy subscale scores for methylphenidate group at 6 weeks when compared with placebo ($p = 0.02$) based on model estimate of treatment effect, insufficient data to calculate ES Ns change in AES apathy scores at 6 weeks when compared with placebo, ns correlation between AES change scores & any attention measures for methylphenidate or placebo group, ES n/a	Strong 13

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
THC/Cannabinoids						
Herrmann et al 2019 (94) Canada	Nabilone 1-2 mg/day for 6 weeks vs placebo for 6 weeks with 1 week washout between phases	Agitation General BPSD	• Crossover RCT • 39 geriatric psychiatry clinic patients & RACS residents with AD & agitation (9 females) • Computer-generated block randomisation • Raters blinded • No post-intervention f/u	CMAI NPI-NH	Significant decrease in CMAI agitation scores ($p = 0.003$, $d = 0.52$) & total NPI scores ($p = 0.004$, $d = 0.49$) for nabilone group when compared with placebo at 14 weeks	Strong 14
Shelef et al 2016 (95) Israel	Medical cannabis oil THC 2.5 - 7.5mg 2 x day added to usual medication regime 4 weeks	General BPSD	• Open-label, repeated measures study • 11 geriatric psychiatry inpatients with moderate-severe AD (5 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Significant decrease in total NPI scores at 4 weeks when compared with baseline ($p < 0.01$, Hedge's $g = 1.76$)	Modest 8
Van den Elsen et al 2015a (96) Netherlands	Tetrahydrocannabinol (THC) 1.5mg 3 x day vs placebo 3 weeks	General BPSD Agitation	• Multicentre RCT • 50 community- or RACS-dwelling people with moderate AD, VaD or mixed dementia (25 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	NPI CMAI	Significant decrease in total NPI scores for both groups at 3 weeks ($p < 0.05$), ns difference between groups Ns change in CMAI agitation scores at 3 weeks for THC ES n/a	Moderate 12

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Van den Elsen et al 2015b (97) Netherlands	6 x 2 week treatment blocks: tetrahydrocannabinol (THC) 0.75mg twice daily vs placebo for 3 days → 4 day washout (blocks 1-3) & THC 1.5mg twice daily vs placebo for 3 days → 4 day washout (blocks 4-6)	General BPSD Agitation	• Multicentre, crossover RCT • 22 community-dwelling people with mild-moderate AD, VaD or mixed dementia (7 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	NPI CMAI	Ns change in total NPI & CMAI agitation scores for low-dose & high-dose THC when compared with placebo at 12 weeks Total NPI & CMAI scores **increased** in both groups over study period ES n/a	Strong 15
Woodward et al 2014 (98) USA	Dronabinol mean dose 7.03mg/day in addition to psychoactive medication treatment 7 days	General BPSD Nocturnal disruption Resistance to care	• Open-label, repeated measures chart review • 40 acute neuropsychiatric unit inpatients with severe & different types of dementia admitted for BPSD (28 females) • No randomisation • Raters not blinded • No post-intervention f/u	PAS PAS resisting care domain Observed sleep	Significant decrease in total PAS agitation scores ($p < 0.0001$, $d = 1.10$) & PAS resisting care scores ($p < 0.0001$) at 7 days when compared with baseline Ns change in number of observed nighttime awakenings during treatment period, increased observed sleep duration approached significance ($p = 0.06$), ES n/a	Moderate 11
Other pharmacological/biological treatments						
Adrait et al 2017 (99) France	Active hearing aids vs inactive hearing aids first 6 months → active hearing aids for both groups second 6 months	General BPSD	• Multicentre, semi-crossover RCT • 51 community-dwelling people with mild-moderate AD (29 females) • Randomisation according to order of inclusion • Raters blinded • No post-intervention f/u	NPI	Ns change in total NPI scores for active hearing aids at 12 months ES n/a	Moderate 12

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Bowen et al 2015 (100) USA	Leuprolide acetate (synthetic gonadotropin-releasing hormone) 11.25 mg vs 22.5 mg vs placebo by 3 monthly injections 48 weeks	General BPSD	• RCT • 109 community-dwelling females with mild-moderate AD • Stratified randomisation • Raters blinded • No post-intervention f/u	NPI	Ns difference between groups in total NPI scores at 48 weeks ES n/a	Strong 13
Butchart et al 2015 (101) UK	Subcutaneous etanercept (autoimmune drug) 50mg/week vs placebo 24 weeks	General BPSD Depression	• RCT • 41 people with mild-moderate AD (16 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	NPI CSDD	Ns difference between groups in total NPI & CSDD scores at 24 weeks ES n/a	Strong 14
Castagna et al 2016 (102) Italy	Rivastigmine patch + citicoline (cholinergic supplement) 1000 mg/day vs rivastigmine patch only 9 months	General BPSD Depression	• Repeated measures controlled study • 174 outpatients with moderate AD or mixed dementia on highest tolerated dosage of rivastigmine patch ≥ 6 months (124 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI GDS-SF	Significant decrease in total NPI scores for rivastigmine + citicoline when compared with rivastigmine only at 9 months ($p = 0.000$, $d = 0.78$) Significant decrease in GDS-SF depression scores for both groups at 9 months ($p = 0.028$), difference between groups not reported, insufficient data to calculate ES	Moderate 11
Cummings et al 2015 (103) USA	Dextromethorphan-quinidine 30/10mg twice daily vs placebo 10 weeks	Agitation Aggression	• Multicentre RCT • 220 people with mild-severe AD & agitation (126 females) • Interactive web response, block randomisation • Raters blinded • No post-intervention f/u	NPI agitation/ aggression subscale	Significant decrease in NPI agitation /aggression subscale scores for dextromethorphan-quinidine at 10 weeks when compared with baseline ($p < 0.001$), significantly greater decrease for dextromethorphan-quinidine when compared with placebo group ($p < .001$) Insufficient data to calculate ES	Strong 13

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Cummings et al 2016 (104) USA	Bexarotene (lymphoma drug) 75 mg twice daily days 1–7 → 150 mg twice daily days 8–28 vs placebo 4 weeks	General BPSD	• RCT • 20 people with mild-moderate AD (13 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	NPI	Ns difference in total NPI scores between groups at 4 weeks ES n/a	Strong 13
Finger et al 2015 (105) Canada	Intranasal oxytocin 24, 48 or 72 IU twice daily divided into 3 sprays per nostril over 10 minute intervals to maximize absorption vs saline spray placebo 1 week	General BPSD Apathy	• RCT • 23 people with mild-moderate bvFTD or semantic dementia (12 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	AES NPI	Ns change in total AES & NPI scores for intranasal oxytocin when compared with placebo at 1 week ES n/a	Moderate 12
Gareri et al 2017 (106) Italy	Citicoline (cholinergic supplement) 1000mg/day + ChEI (donepezil, rivastigmine or galantamine) vs ChEI only 9 months	General BPSD Depression	• Multicentre controlled study • 448 community-dwelling people with moderate dementia from 7 centres (273 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI GDS-SF	Ns change in GDS-SF depression & total NPI scores for Citicoline + ChEI at 9 months when compared with baseline, ns difference between groups ES n/a	Moderate 11
Henderson et al 2015 (107) USA	Raloxifene (osteoporosis drug) 120mg/day vs placebo 12 months	General BPSD	• RCT • 42 community-dwelling females with mild-moderate AD • Randomisation by random number generator • Raters blinded • No post-intervention f/u	NPI	Ns difference in total NPI scores between groups at 12 months ES n/a	Strong 13

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Herring et al 2020 (108) USA	Suvorexant 10-20mg/night (orexin receptor antagonist) vs placebo 4 weeks	Nocturnal disruption General BPSD	• RCT • 285 community-dwelling people with mild-moderate AD & insomnia (186 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	Total sleep time recorded at sleep laboratory NPI Clinician's Global Impression of Insomnia Severity	Significantly greater improvement in total sleep time for suvorexant at week 4 when compared with placebo ($p < 0.01$, $d = 0.39$) Significantly greater improvement in Clinician's Global Impression of Insomnia Severity for suvorexant at 4 weeks when compared with placebo ($p = 0.010$, $d = 0.18$) Ns difference in total NPI scores between groups at 4 weeks, ES n/a	Strong 13
Kim et al 2014 (109) Korea	Varenicline (nicotine addiction drug) 0.5mg/day 7 days → 0.5mg twice daily 7 days → 1 mg twice daily 4 weeks vs placebo 6 weeks	General BPSD	• Multicentre, crossover RCT • 48 outpatients with mild-moderate AD (42 females) • Block randomisation, method not reported • Raters blinded • No post-intervention f/u	NPI	Ns difference in total NPI scores between groups at 6 weeks Significant decrease in total NPI scores for varenicline in those with moderate AD at 6 weeks ($n = 14$, $p = 0.0275$) ES n/a	Moderate 12
Kwok et al 2013 (110) HK	30 mins acupuncture treatment sessions applied on 6 meridian points provided by experienced Chinese Medicine practitioner twice weekly x 6 weeks vs wait-list control period (no sham acupuncture) for 6 weeks	Nocturnal disruption	• Repeated measures study • 22 community-dwelling people with dementia & sleep disturbance (16 females) • No randomisation • Raters blinded • No post-intervention f/u	Sleep parameters by wrist actigraphy: resting time, total sleep time, sleep onset latency, sleep efficiency, wake after sleep onset	Significantly greater resting time (total time in bed) ($p < 0.05$, $d = 0.94$) & total sleep time ($p < 0.05$, $d = 0.83$) for acupuncture treatment period when compared with wait-list period at 12 weeks Ns change in other sleep parameters, ES n/a	Modest 9

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Morales-Delgado et al 2018 (111) Mexico	Melatonin 5mg/night vs placebo 8 weeks	Nocturnal disruption General BPSD Depression	• RCT • 40 outpatients with mild-moderate dementia & sleep alteration (24 females) • Block computer-generated randomisation • Raters blinded • No post-intervention f/u	PSQI NPI GDS	Ns difference in PSQI sleep quality, total NPI & GDS depression scores between groups ES n/a	Moderate 12
Nave et al 2017 (112) Switzerland	Sembragiline (monoamine oxidase B inhibitor) add-on 1mg vs 5mg daily vs placebo 52 weeks	General BPSD Apathy	• Multicentre RCT • 542 people with moderate AD taking acetylcholinesterase inhibitors (AChEI) or AChEI + memantine from 12 counties (340 females) • Randomisation method not reported • Raters blinded • 12 week post-intervention f/u	BEHAVE-AD-Frequency-Weighted Severity Scale (FW) AES	Significantly less development of total BEHAVE-AD-FW scores for sembragiline 1mg ($p = 0.014$, $d = 0.28$) & 5mg ($p = 0.019$, $d = 0.27$) at 52 weeks when compared with placebo, ns change at 12 week f/u Ns difference in total AES apathy scores between groups, ES n/a	Strong 13
Pardini et al 2015 (113) Italy	Switch from Souvenaid nutraceutical compound 125 ml/day to placebo vs switch from placebo to Souvenaid 125 ml/day 24 weeks	General BPSD	• Crossover RCT • 26 community-dwelling people with bvFTD taking memantine (number of females not reported) • Computer-generated randomisation • Raters blinded • 3 month post-intervention f/u for switch from Souvenaid to placebo group	NPI	Significant decrease in total NPI scores for Souvenaid periods when compared with placebo periods ($p < 0.001$, $d = 4.9$), NPI scores returned to baseline when treatment discontinued	Modest 9

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Pirker-Kees et al 2019 (114) Austria	Stable psychotropic drug monotherapy with SSRI, trazodone, atypical neuroleptics or benzodiazepines vs no psychotropic drugs 12 months	General BPSD	• Observational, repeated measures study • 149 community-dwelling people with mild-moderate dementia (69 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI	Ns difference between groups in total NPI scores at 12 months ES n/a	Moderate 11
Remington et al 2015 (115) USA	Nutraceutical formulation 2 tablets/day: folic acid, alpha-tocopherol, adenosyl methionine, N-acetyl cysteine, acetyl-L-carnitine vs placebo 3-6 months	General BPSD	• RCT with open-label extension • 106 community- or RACS-dwelling patients with mild-moderate AD (number of females not reported) • Simple randomisation • Raters blinded • No post-intervention f/u	NPI	Ns decrease in total NPI scores for nutraceutical formulation at 3 & 6 months when compared with baseline, ns difference between groups ES n/a	Moderate 12
Suzuki & Gen 2015 (116) Japan	Lamotrigine 12.5 mg/day (antiepileptic, mood stabiliser) increased by 12.5 mg at 3 & 6 weeks as needed to maximum 25-100 mg/day + other psychotropics reduced where possible vs usual medications 16 weeks	General BPSD	• Open-label observational study • 40 RACS residents with severe AD (36 females) • No randomisation • No post-intervention f/u	NPI	Ns difference in total NPI scores between groups at 16 weeks ES n/a	Modest 7

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Wade et al 2014 (117) UK, USA	Prolonged-release melatonin 2mg/night vs placebo 24 weeks	Nocturnal disruption	• RCT • 80 outpatients with mild-moderate AD (41 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	PSQI	Significant decrease in total PSQI scores for melatonin group at 24 weeks when compared with baseline (p = 0.004, d = 0.59), ns change for placebo Significant decrease in PSQI sleep efficiency scores for melatonin when compared with placebo at 24 weeks (p = 0.017, d = 0.72)	Strong 14
Brain Stimulation Therapies						
Acharya et al 2015 (118) USA	Inpatient acute Electroconvulsive therapy (ECT) course: sessions administered 3 x weekly or less frequently if clinically indicated over 4 weeks	Agitation Depression	• Naturalistic, repeated measures study • 23 inpatients with different types of dementia from 2 hospitals (14 females) • No randomisation • Raters not blinded • No post-intervention f/u	CMAI-SF NPI CSDD	Significant decrease in total CMAI agitation scores after 12 ECT treatments &/or at discharge when compared with baseline (p = 0.012, n = 8) Significant decrease in total NPI scores at discharge after 12 ECT treatments &/or at discharge when compared with baseline (p < 0.001, n = 8) Ns change in CSDD depression scores Insufficient data to calculate ES	Modest 8
Ahmed et al 2012 (119) Egypt	Bilateral repetitive transcranial magnetic stimulation (rTMS) applied over right dorsolateral prefrontal cortex immediately followed by left: 2000 pulses/day high frequency (20 Hz) vs low frequency (1 Hz) daily x 5 consecutive days	Depression	• RCT • 45 community-dwelling people with mild-severe AD (29 females) • Randomisation method not reported • Raters blinded • 1 & 3 month post-intervention f/u	GDS	Significantly greater decrease in total GDS depression scores for high frequency (20 Hz) rTMS when compared with low frequency (1 Hz) & sham groups at 3 month f/u (p = 0.04 for 20Hz vs 1 Hz, Hedge's g = 0.10, p = 0.0001 for 20 Hz vs sham, Hedge's g = 0.63) at 5 days & 1 & 3 month f/u Time x group interaction effects: 20 Hz group tended to improve more than 1 Hz & sham groups at all time points, insufficient data to calculate ES	Strong 13

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Alcala-Lozano et al 2018 (120) Mexico	Repetitive transcranial magnetic stimulation (rTMS): simple applied over left dorsolateral prefrontal cortex only 1500 total pulses/day vs complex protocol applied over 6 regions of interest 1500 total pulses/day (5 Hz) x 21 consecutive days	General BPSD	• Repeated measures study • 19 community-dwelling people with mild-moderate AD (11 females) • Randomisation method not reported • Rater blinding not reported • 4 week post-intervention f/u	NPI	Significant decrease in total NPI scores for both groups at 21 days & 4 week f/u ($p < 0.001$), ns difference between groups Insufficient data to calculate ES	Modest 9
Bromundt et al 2019 (121) Switzerland	Exposure to individually timed dawn-dusk simulation over bedhead providing naturalistically contoured twilight signals for 7-8 weeks during fall/winter vs period without dawn-dusk simulation control for 8 weeks	Depression Agitation Nocturnal disruption	• Crossover, repeated measures study • 20 RACS residents with mild-severe different types of dementia (17 females) • No randomisation • Raters not blinded • No post-intervention f/u	CMAI VAS NOSGER mood subscale Rest-activity rhythms & sleep parameters recorded by wrist actimetry	Ns change in CMAI agitation or VAS & NOSGER mood scores for dawn-dusk simulation Ns change in sleep parameters & rest-activity rhythms for dawn-dusk simulation ES n/a	Modest 7
Elder et al 2019 (122) UK	2 consecutive 20 minute sessions of active transcranial direct current stimulation (tDCS) separated by 30-min break administered by trained technician vs placebo tDCS delivered according to same protocol 4 consecutive days	Delusions & hallucinations	• RCT • 40 community- or RACS-dwelling people with moderate-severe LBD or PDD & visual hallucinations (9 females) • Computer-generated randomisation • Raters blinded • 1 & 3 month post-intervention f/u	NPI hallucinations subscale	Ns change in NPI hallucinations subscale change scores for active tDCS when compared with placebo tDCS at 5 days & 1 & 3 month f/u ES n/a	Moderate 12

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Ferrucci et al 2018 (123) Italy	5 consecutive daily sessions x 20 min anodal transcranial direct current stimulation (tDCS) 2mA intensity over frontotemporal cortex bilaterally vs similar schedule sham treatment	General BPSD	• Crossover RCT • 12 people with mild-moderate FTD (5 females) • Randomisation method not reported • Raters blinded • 4 week post-intervention f/u	NPI	Significant decrease in post-hoc total NPI scores immediately after tDCS (p = 0.008, d = 2.59), at 2 days post-intervention (p = 0.05, d = 1.76) & at 4 week f/u (p = 0.08, d = 1.85) when compared with baseline, ns difference between groups	Modest 9
Figueiro et al 2014 (124) USA	Low-level 'bluish-white' lighting designed to deliver high circadian stimulation ≤ 1 hour/day 4 weeks	Depression Agitation Nocturnal disruption	• Repeated measures study • 14 residents with AD & related dementias from 8 RACSs (9 females) • No randomisation • Raters not blinded • 4 week post-intervention f/u	PSQI CSDD CMAI Daysimeter device	Significant improvement in total PSQI score (p = 0.01, g = 1.27), sleep efficiency (p = 0.03, g = 0.23) & total sleep time (p = 0.03, g = 0.25) at 4 weeks when compared with baseline, ns at 4 week post-intervention f/u Significant decrease in CSDD depression scores at 4 weeks when compared with baseline (p = 0.03, g = 1.07), ns at 4 week post-intervention f/u Significant decrease in CMAI agitation scores at 4 weeks (p = 0.037, g = 0.99) & 4 week post-intervention f/u (p = 0.03) when compared with baseline	Modest 8

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Figueiro et al 2019 (125) USA	Tailored, active lighting providing high circadian stimulus vs low circadian stimulus lighting below threshold for circadian system activation, delivery method varied according to where participants spent most of their day 4 weeks	Depression Agitation Nocturnal disruption	• Crossover RCT • 46 RACS & assisted-living facility residents with mild-severe dementia & sleep problems (30 females) • Block randomisation, method not reported • Raters not blinded • No post-intervention f/u	PSQI CSDD CMAI Actigraphy	Significant improvement in PSQI sleep quality scores for high stimulus periods at 4 weeks when compared with baseline ($p < 0.001$, $d = 0.81$) & when change scores compared with low stimulus periods ($p < 0.05$), insufficient data to calculate ES Significant decrease in CSDD depression scores for high stimulus periods at 4 weeks when compared with baseline ($p = 0.04$, $d = 58$) & when change scores compared with low stimulus periods ($p = 0.049$, $d = -0.43$) Significantly greater decrease in CMAI agitation scores for high stimulus periods post intervention when compared with low stimulus periods ($p = 0.015$, $d = -0.53$), ns change post-intervention for high stimulus periods when compared with baseline	Moderate 12
Friedman et al 2012 (126) USA	30 mins light boxes: bright white light (~4,200 lux) vs dim red light (~90 lux) daily starting within 30 minutes of rising + 50 mins sleep hygiene therapy via phone 2 weeks	Nocturnal disruption	• Repeated measures study • 54 community-dwelling people with mild-moderate memory impairment (23 females) • Randomisation method not reported • Raters not blinded • No post-intervention f/u	Wrist actigraphy	Significantly greater decrease in time in bed & total sleep time for bright white light when compared with dim red light at 2 weeks ($p < 0.05$) which were associated with sleep worsening ES n/a	Modest 9
Khedr et al 2019 (127) Egypt	20mins per side active transcranial direct current stimulation (tDCS) vs sham tDCS 5 x weekly 2 weeks	Depression	• RCT • 46 clinic outpatients with mild-moderate AD (18 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	CSDD	Significantly greater decrease in CSDD depression scores for active tDCS when compared with sham tDCS at 2 weeks ($p = 0.001$, $d = 0.7$) Significant decrease in CSDD depression scores for both active tDCS ($p = 0.01$, $d = 1.7$) & sham tDCS ($p = 0.02$, $d = 1.0$) when compared with baseline	Moderate 12

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Konis et al 2018 (128) USA	Socialisation in daylit room vs socialisation indoors under electrical lighting without daylight 8-10am daily 12 weeks	Depression General BPSD	• Nonrandomised cluster study • 83 residents from 8 residential care communities with dementia (56 females) • No randomisation • Raters not blinded • No post-intervention f/u	CSDD NPI-NH	Significantly greater decrease in CSDD depression scores for daylit room when compared with electrical lighting group at 12 weeks ($p = 0.01$, $d = 0.53$) Ns change in total NPI scores at 12 weeks, ES n/a	Modest 9
Munch et al 2017 (129) Switzerland	Dynamic lighting: fluorescent warm white (2700K) + cold white (6500K) ceiling lights vs warm-white conventional lighting 8 weeks during fall/ winter	Agitation Nocturnal disruption	• Between-subject study design • 89 residents with severe dementia from 9 RACS wards (58 females) • No randomisation • Raters not blinded • No post-intervention f/u	CMAI Sleep efficiency via activity watch	Ns difference in CMAI agitation scores between groups but significantly higher agitation scores for men ($n = 31$) when compared with women at 8 weeks ($p = 0.006$), ES n/a Ns difference in sleep efficiency between groups at 8 weeks	Moderate 10
Nguyen et al 2017 (130) France	Repetitive transcranial magnetic stimulation (rTMS) over R & L prefrontal cortex, R & L parietal cortex, Broca's & Wernicke's areas + cognitive training of increasing difficulty 5 x weekly 5 weeks	Apathy	• Prospective study • 10 community-dwelling people with moderate AD (5 females) • No randomisation • Raters not blinded • 6 month post-intervention f/u	IA	Significant decrease in IA apathy scores at 5 weeks ($p < 0.05$, $d = 0.88$) & 6 month f/u ($p < 0.05$, $d = 1.1$) when compared with baseline	Modest 9

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Onega et al 2016 (131) & Onega et al 2018 (132) USA	30 mins exposure 27 inches from bright light delivering 10,000 lux of light or low-level light delivering 250 lux of light, twice daily x 5 days weekly vs placebo light exposure control group 8 weeks	Depression Agitation	• Mixed-model, repeated measures study • 60 RACS residents with mild-severe dementia (43 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	DSAOA DMAS-17 CSDD CMAI PAS BARS	Significantly greater decrease in DSAOA ($p < 0.001$, $d = 2.17$), DMAS-17 ($p < 0.001$, $d = 1.97$) & CSDD ($p < 0.001$, $d = 1.91$) depression scores for bright light exposure at 8 weeks when compared with placebo Significantly greater decrease in CMAI-Frequency ($p < 0.001$, $d = 0.76$), CMAI-Disruptiveness ($p < 0.001$, $d = 0.82$), PAS ($p = 0.017$, $\eta_p^2 = 0.095$) & BARS ($p = 0.007$, $\eta_p^2 = 0.120$) agitation scores for bright light exposure at 8 weeks when compared with placebo	Moderate 11
Padala et al 2018 (133) USA	Repetitive transcranial magnetic stimulation (rTMS) 3000 pulses at 10 Hz 4secs duration with 26secs intervention interval vs sham rTMS treatment 5 days/week 4 weeks	Apathy	• RCT • 20 outpatients with mild-moderate AD & apathy (2 females) • Computer-generated randomisation • Raters blinded • 4 & 8 week post-intervention f/u	AES-C	Significantly greater decrease in mean AES-C apathy change scores for rTMS when compared with sham treatment at 4 weeks ($p = 0.002$, $d = 1.57$) Significance not maintained at 4 or 8 week f/u	Strong 13
Rabey et al 2013 (134) Israel	Repetitive transcranial magnetic stimulation + cognitive training (*rTMS-COG*) 1-4 COG tasks + 1300 pulses/day (5 Hz) 5 x weekly x 6 weeks, 3 brain regions → biweekly sessions x 3 months vs sham treatment	General BPSD	• RCT • 15 community-dwelling people with mild-moderate AD (5 females) • Randomisation method not reported • Raters blinded • No post-intervention f/u	NPI	Ns decrease in total NPI scores for *rTMS-COG* at 6 weeks & 4.5 months when compared with baseline, ns increase for sham treatment ES n/a	Modest 8

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Sekiguchi et al 2017 (135) Japan	1 hour bright light therapy sessions at eye level 0.5 m from patient, within 45^0 visual field equal to approximately 5000 lx of full spectrum light daily 2 weeks	Nocturnal disruption	• Repeated measures case-series • 17 community- or RACS-dwelling people with AD, VaD or LBD (6 females) • No randomisation • Raters not blinded • No post-intervention f/u	NPI-NH sleep subscale	Ns decrease in sleep disturbance in 4 AD participants with shorter duration of illness &/or mild-moderate disease only ES n/a	Modest 7
Sloane et al 2015 (136) USA	13,000K blue-white compact fluorescent light in lamps added to participant's home in area where they spent most of their time from usual awakening time until 6pm for 6 weeks vs 2700K yellow-white compact fluorescent light control in same lamps over same times for 6 weeks separated by 4-week washout	Depression Nocturnal disruption	• Crossover RCT • 17 community-dwelling people with mild-severe dementia & disturbed sleep (11 females) & their carers • Stratified permuted block randomisation • Raters not blinded • No post-intervention f/u	CSDD PSQI MOS sleep scale Sleep quality via wrist actigraphy	Significant decrease in CSDD depression scores for blue-white light when compared with usual light (p = 0.011), ns when compared with yellow-white light control period Significant improvement in PSQI sleep efficiency scores for blue-white light when compared with usual light (p = 0.045), ns when compared with yellow-white light control period Ns change in other sleep measures Insufficient data to calculate ES	Moderate 10
Suemoto et al 2014 (137) Brazil	6 sessions repetitive transcranial direct current stimulation (tDCS) vs sham tDCS 2 weeks	Apathy Depression General BPSD	• RCT • 40 community-dwelling people with moderate AD (28 females) • Computer-generated randomisation • Raters blinded • No post-intervention f/u	SAS CSDD NPI	Ns difference in SAS apathy, CSDD depression & total NPI scores between groups at 2 weeks ES n/a	Strong 13

Author/ Country	Intervention trialled	BPSD reported in the *Guide*	Study design/Follow-up	Relevant outcome measures	Significance ES n/a: where outcomes are nonsignificant, ES is reported as not applicable	Quality rating
Ujkaj et al 2012 (138) USA	Electroconvulsive Therapy (ECT) in addition to psychoactive medication treatment, frequency & duration based on tolerance & clinical response, mean number of treatments 9	Agitation Psychotropic drug use	• Retrospective systematic chart review • 16 geriatric neuropsychiatry unit inpatients with mild-severe different types of dementia admitted for BPSD (15 females) • No randomisation • Raters not blinded • No post-intervention f/u	PAS	Significant decrease in total PAS agitation scores at 4 weeks when compared with baseline ($p < 0.001$, ES = 1.5) Ns decrease in number of psychotropic drugs prescribed at 4 weeks when compared with baseline, ES n/a	Moderate 10
Wahnschaffe et al 2017 (139) Germany	Dynamic lighting system in RACS common room featuring bright light with higher blue light proportions during daytime hours + low light intensity without blue light during evening & night 4 weeks	Agitation	• Repeated measures study • 12 RACS residents with different types of dementia (7 females) • Raters not blinded • No randomisation • No post-intervention f/u	CMAI	Significant decrease in total CMAI scores at 4 weeks when compared with baseline ($p = 0.043$, $d = 0.45$)	Modest 9
Wu et al 2015 (140) China	Low dose risperidone + 20Hz repetitive transcranial direct current stimulation rTMS (applied over left dorsolateral prefrontal cortex) 5 x weekly vs low dose risperidone + sham rTMS 4 weeks	General BPSD	• RCT • 54 mental health hospital inpatients with mild-moderate AD (31 females) • Randomisation by random number table • Raters blinded • No post-intervention f/u	BEHAVE-AD	Significant decrease in total BEHAVE-AD scores for risperidone + rTMS group when compared with risperidone + sham group ($p < 0.001$, $d = 0.68$) 19 (73.1%) patients receiving rTMS showed a decrease in BPSD compared to 11 (42.3%) in sham group	Moderate 12

References

1. Amenta F, Carotenuto A, Fasanaro AM, Rea R, Traini E. The ASCOMALVA (Association between the Cholinesterase Inhibitor Donepezil and the Cholinergic Precursor Choline Alphoscerate in Alzheimer's Disease) Trial: interim results after two years of treatment. Journal of Alzheimer's Disease. 2014;42 Suppl 3:S281-8.
2. Amenta F, Carotenuto A, Fasanaro AM, Rea R, Traini E. The ASCOMALVA trial: association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alphoscerate in Alzheimer's disease with cerebrovascular injury: interim results. Journal of the neurological sciences. 2012;322(1):96-101.
3. Araki T, Wake R, Miyaoka T, Kawakami K, Nagahama M, Furuya M, et al. The effects of combined treatment of memantine and donepezil on Alzheimer's Disease patients and its relationship with cerebral blood flow in the prefrontal area. Int J Geriatr Psychiatry. 2014;29(9):881-9.
4. Ballard C, Thomas A, Gerry S, Yu LM, Aarsland D, Merritt C, et al. A double-blind randomized placebo-controlled withdrawal trial comparing memantine and antipsychotics for the long-term treatment of function and neuropsychiatric symptoms in people with Alzheimer's disease (MAIN-AD). Journal of the American Medical Directors Association. 2015;16(4):316-22.
5. Bando N, Nakamura Y. Preliminary evidence that rivastigmine-induced inhibition of serum butyrylcholinesterase activity improves behavioral symptoms in Japanese patients with Alzheimer's disease. Geriatrics & gerontology international. 2017;17(9):1306-12.
6. Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, et al. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. The Lancet Neurology. 2013;12(2):149-56.
7. Carotenuto A, Rea R, Traini E, Fasanaro AM, Ricci G, Manzo V, et al. The Effect of the Association between Donepezil and Choline Alphoscerate on Behavioral Disturbances in Alzheimer's Disease: Interim Results of the ASCOMALVA Trial. Journal of Alzheimer's Disease. 2017;56(2):805-15.
8. Clerici F, Vanacore N, Elia A, Spila-Alegiani S, Pomati S, Da Cas R, et al. Memantine effects on behaviour in moderately severe to severe Alzheimer's disease: A post-marketing surveillance study. Neurological Sciences. 2012;33(1):23-31.
9. Cumbo E, Ligori LD. Differential effects of current specific treatments on behavioral and psychological symptoms in patients with alzheimer's disease: A 12-month, randomized, open-label trial. Journal of Alzheimer's Disease. 2014;39(3):477-85.
10. D'Onofrio G, Sancarlo D, Addante F, Ciccone F, Cascavilla L, Paris F, et al. A pilot randomized controlled trial evaluating an integrated treatment of rivastigmine transdermal patch and cognitive stimulation in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 2015;30(9):965-75.
11. Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. JAMA. 2014;311(1):33-44.
12. Emre M, Poewe W, De Deyn PP, Barone P, Kulisevsky J, Pourcher E, et al. Long-term safety of rivastigmine in parkinson disease dementia: an open-label, randomized study. Clinical Neuropharmacology. 2014;37(1):9-16.
13. Freund-Levi Y, Bloniecki V, Auestad B, Backstrom ACT, Larksater M, Aarsland D. Galantamine versus risperidone for agitation in people with dementia: A randomized, twelve-week, single-center study. Dementia and Geriatric Cognitive Disorders. 2014;38(3-4):234-44.
14. Freund-Levi Y, Jedenius E, Tysen-Backstrom AC, Larksater M, Wahlund LO, Eriksdotter M. Galantamine versus risperidone treatment of neuropsychiatric symptoms in patients with probable dementia: an open randomized trial. American Journal of Geriatric Psychiatry. 2014;22(4):341-8.
15. Gareri P, Putignano D, Castagna A, Cotroneo AM, De Palo G, Fabbo A, et al. Retrospective study on the benefits of combined Memantine and cholinEsterase inhibitor treatMent in AGEd Patients affected with Alzheimer's Disease: the MEMAGE study. Journal of Alzheimer's Disease. 2014;41(2):633-40.

16. Grossberg GT, Manes F, Allegri RF, Gutierrez-Robledo LM, Gloger S, Xie L, et al. The safety, tolerability, and efficacy of once-daily memantine (28 mg): A multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. CNS Drugs. 2013;27(6):469-78.
17. Han HJ, Kim BC, Lee JY, Ryu SH, Na HR, Yoon SJ, et al. Response to rivastigmine transdermal patch or memantine plus rivastigmine patch is affected by apolipoprotein E genotype in Alzheimer patients. Dement Geriatr Cogn Disord. 2012;34(3-4):167-73.
18. Herrmann N, Gauthier S, Boneva N, Lemming OM. A randomized, double-blind, placebo-controlled trial of memantine in a behaviorally enriched sample of patients with moderate-to-severe Alzheimer's disease. International Psychogeriatrics. 2013;25(06):919-27.
19. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med. 2012;366(10):893-903.
20. Ikeda M, Mori E, Kosaka K, Iseki E, Hashimoto M, Matsukawa N, et al. Long-term safety and efficacy of donepezil in patients with dementia with Lewy bodies: results from a 52-week, open-label, multicenter extension study. Dement Geriatr Cogn Disord. 2013;36(3-4):229-41.
21. Ikeda M, Mori E, Matsuo K, Nakagawa M, Kosaka K. Donepezil for dementia with Lewy bodies: A randomized, placebo-controlled, confirmatory phase III trial. Alzheimer's Research and Therapy. 2015;7(4).
22. Ishikawa I, Shinno H, Ando N, Mori T, Nakamura Y. The effect of memantine on sleep architecture and psychiatric symptoms in patients with Alzheimer's disease. Acta Neuropsychiatrica. 2016;28(3):157-64.
23. Jaïdi Y, Nonnonhou V, Kanagaratnam L, Bertholon LA, Badr S, Noël V, et al. Reduction of the Anticholinergic Burden Makes It Possible to Decrease Behavioral and Psychological Symptoms of Dementia. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2018;26(3):280-8.
24. Kano O, Ito H, Takazawa T, Kawase Y, Murata K, Iwamoto K, et al. Clinically meaningful treatment responses after switching to galantamine and with addition of memantine in patients with Alzheimer's disease receiving donepezil. Neuropsychiatr Dis Treat. 2013;9:259-65.
25. Kazui H, Adachi H, Kanemoto H, Yoshiyama K, Wada T, Tokumasu Nomura K, et al. Effects of donepezil on sleep disturbances in patients with dementia with Lewy bodies: An open-label study with actigraphy. Psychiatry Research. 2017;251:312-8.
26. Korucu O, Demiryurek BE, Morkavuk G, Korucu AA. The effect of cholinesterase inhibitors on sleep in the patients with Alzheimer's disease: An observational prospective study. Psychiatry and Clinical Psychopharmacology. 2018;28(1):14-8.
27. Kurz A, Grimmer T. Efficacy of memantine hydrochloride once-daily in Alzheimer's disease. Expert Opinion on Pharmacotherapy. 2014;15(13):1955-60.
28. Manabe Y, Ino T, Yamanaka K, Kosaka K. Increased dosage of donepezil for the management of behavioural and psychological symptoms of dementia in dementia with Lewy bodies. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 2016;16(3):202-8.
29. Matsuzono K, Sato K, Kono S, Hishikawa N, Ohta Y, Yamashita T, et al. Clinical Benefits of Rivastigmine in the Real World Dementia Clinics of the Okayama Rivastigmine Study (ORS). Journal of Alzheimer's Disease. 2015;48(3):757-63.
30. Matsuzono K, Yamashita T, Ohta Y, Hishikawa N, Koike M, Sato K, et al. Clinical Benefits of Memantine Treatment for Alzheimer's Disease in the Okayama Memantine Study II (OMS II). Journal of Alzheimer's Disease. 2015;47(2):487-93.
31. Matsuzono K, Yamashita T, Ohta Y, Hishikawa N, Sato K, Kono S, et al. Clinical Benefits for Older Alzheimer's Disease Patients: Okayama Late Dementia Study (OLDS). Journal of Alzheimer's Disease. 2015;46(3):687-93.
32. Matsuzono K, Hishikawa N, Ohta Y, Yamashita T, Deguchi K, Nakano Y, et al. Combination Therapy of Cholinesterase Inhibitor (Donepezil or Galantamine) plus Memantine in the Okayama Memantine Study. Journal of Alzheimer's Disease. 2015;45(3):771-80.
33. Miranda LF, Gomes KB, Silveira JN, Pianetti GA, Byrro RM, Peles PR, et al. Predictive factors of clinical response to cholinesterase inhibitors in mild and moderate Alzheimer's disease and mixed dementia: a one-year naturalistic study. Journal of Alzheimer's Disease. 2015;45(2):609-20.
34. Naharci MI, Ozturk A, Yasar H, Cintosun U, Kocak N, Bozoglu E, et al. Galantamine improves sleep quality in patients with dementia. Acta Neurologica Belgica. 2015;115(4):563-8.

35. Nakamura Y, Kitamura S, Homma A, Shiosakai K, Matsui D. Efficacy and safety of memantine in patients with moderate-to-severe Alzheimer's disease: results of a pooled analysis of two randomized, double-blind, placebo-controlled trials in Japan. Expert Opinion on Pharmacotherapy. 2014;15(7):913-25.
36. Nakano Y, Matsuzono K, Yamashita T, Ohta Y, Hishikawa N, Sato K, et al. Long-Term Efficacy of Galantamine in Alzheimer's Disease: The Okayama Galantamine Study (OGS). Journal of Alzheimer's Disease. 2015;47(3):609-17.
37. Nakayama S, Suda A, Nakanishi A, Motoi Y, Hattori N. Galantamine Response Associates with Agitation and the Prefrontal Cortex in Patients with Alzheimer's Disease. Journal of Alzheimer's Disease. 2017;57(1):267-73.
38. Oh YS, Kim JS, Lee PH. Effect of Rivastigmine on Behavioral and Psychiatric Symptoms of Parkinson's Disease Dementia. J Mov Disord. 2015;8(2):98-102.
39. Ohta Y, Darwish M, Hishikawa N, Yamashita T, Sato K, Takemoto M, et al. Therapeutic effects of drug switching between acetylcholinesterase inhibitors in patients with Alzheimer's disease. Geriatrics & gerontology international. 2017;17(11):1843-8.
40. Peters O, Fuentes M, Joachim LK, Jessen F, Luckhaus C, Kornhuber J, et al. Combined treatment with memantine and galantamine-CR compared with galantamine-CR only in antidementia drug naïve patients with mild-to-moderate Alzheimer's disease. Alzheimer's & dementia (New York, N Y). 2015;1(3):198-204.
41. Rea R, Carotenuto A, Traini E, Fasanaro AM, Manzo V, Amenta F. Apathy Treatment in Alzheimer's Disease: Interim Results of the ASCOMALVA Trial. Journal of Alzheimer's Disease. 2015;48(2):377-83.
42. Richarz U, Gaudig M, Rettig K, Schauble B. Galantamine treatment in outpatients with mild Alzheimer's disease. Acta Neurologica Scandinavica. 2014;129(6):382-92.
43. Spalletta G, Gianni W, Giubilei F, Casini AR, Sancesario G, Caltagirone C, et al. Rivastigmine patch ameliorates depression in mild AD: preliminary evidence from a 6-month open-label observational study. Alzheimer Dis Assoc Disord. 2013;27(3):289-91.
44. Spalletta G, Caltagirone C, Padovani A, Sorbi S, Attar M, Colombo D, et al. Cognitive and affective changes in mild to moderate Alzheimer's disease patients undergoing switch of cholinesterase inhibitors: A 6-month observational study. PLoS ONE. 2014;9(2).
45. Suzuki H, Inoue Y, Nishiyama A, Mikami K, Gen K. Clinical efficacy and changes in the dosages of concomitantly used psychotropic drugs in memantine therapy in Alzheimer's disease with behavioral and psychological symptoms on dementia. Therapeutic Advances in Psychopharmacology. 2013;3(3):123-8.
46. Suzuki H, Inoue Y, Mikami K, Gen K. The influence and changes in the dosages of concomitantly used psychotropic drugs associated with the discontinuation of donepezil in severe Alzheimer's disease with behavioral and psychological symptoms on dementia: A preliminary open-label trial. Therapeutic Advances in Psychopharmacology. 2014;4(1):37-42.
47. Wilkinson D, Windfeld K, Colding-Jorgensen E. Safety and efficacy of idalopirdine, a 5-HT6 receptor antagonist, in patients with moderate Alzheimer's disease (LADDER): a randomised, double-blind, placebo-controlled phase 2 trial. The Lancet Neurology. 2014;13(11):1092-9.
48. Yatabe Y, Hashimoto M, Kaneda K, Honda K, Ogawa Y, Yuuki S, et al. Efficacy of increasing donepezil in mild to moderate Alzheimer's disease patients who show a diminished response to 5mg donepezil: A preliminary study. Psychogeriatrics. 2013;13(2):88-93.
49. Yoon SJ, Choi SH, Na HR, Park KW, Kim EJ, Han HJ, et al. Effects on agitation with rivastigmine patch monotherapy and combination therapy with memantine in mild to moderate Alzheimer's disease: a multicenter 24-week prospective randomized open-label study (the Korean EXelon Patch and combination with mEmantine Comparative Trial study). Geriatrics & gerontology international. 2017;17(3):494-9.
50. Zhang N, Wei C, Du H, Shi FD, Cheng Y. The Effect of Memantine on Cognitive Function and Behavioral and Psychological Symptoms in Mild-to-Moderate Alzheimer's Disease Patients. Dementia & Geriatric Cognitive Disorders. 2015;40(1-2):85-93.
51. Zhang ZX, Hong Z, Wang YP, He L, Wang N, Zhao ZX, et al. Rivastigmine Patch in Chinese Patients with Probable Alzheimer's disease: A 24-week, Randomized, Double-Blind Parallel-Group Study Comparing Rivastigmine Patch (9.5 mg/24 h) with Capsule (6 mg Twice Daily). CNS Neuroscience & Therapeutics. 2016;22(6):488-96.

52. Blytt KM, Bjorvatn B, Husebo B, Flo E. Effects of pain treatment on sleep in nursing home patients with dementia and depression: A multicenter placebo-controlled randomized clinical trial. Int J Geriatr Psychiatry. 2018;33(4):663-70.
53. Blytt KM, Husebo B, Flo E, Bjorvatn B. Long-Term Pain Treatment Did Not Improve Sleep in Nursing Home Patients with Comorbid Dementia and Depression: A 13-Week Randomized Placebo-Controlled Trial. Front Psychol. 2018;9:134.
54. Erdal A, Flo E, Aarsland D, Ballard C, Slettebo DD, Husebo BS. Efficacy and Safety of Analgesic Treatment for Depression in People with Advanced Dementia: Randomised, Multicentre, Double-Blind, Placebo-Controlled Trial (DEP.PAIN.DEM). Drugs & aging. 2018;35(6):545-58.
55. Hamina A, Lavikainen P, Tanskanen A, Tolppanen AM, Tiihonen J, Hartikainen S, et al. Impact of opioid initiation on antipsychotic and benzodiazepine and related drug use among persons with Alzheimer's disease. Int Psychogeriatr. 2018;30(7):947-56.
56. Husebo BS, Ballard C, Cohen-Mansfield J, Seifert R, Aarsland D. The response of agitated behavior to pain management in persons with dementia. American Journal of Geriatric Psychiatry. 2014;22(7):708-17.
57. Husebo BS, Ballard C, Fritze F, Sandvik RK, Aarsland D. Efficacy of pain treatment on mood syndrome in patients with dementia: a randomized clinical trial. Int J Geriatr Psychiatry. 2014;29(8):828-36.
58. Habiger TF, Flo E, Achterberg WP, Husebo BS. The Interactive Relationship between Pain, Psychosis, and Agitation in People with Dementia: Results from a Cluster-Randomised Clinical Trial. Behavioural Neurology. 2016;2016:7036415.
59. Petrò E, Ruffini E, Cappuccio M, Guerini V, Belotti G, Fascendini S, et al. Low-dose oral prolonged-release oxycodone/naloxone for chronic pain in elderly patients with cognitive impairment: an efficacy-tolerability pilot study. Neuropsychiatr Dis Treat. 2016;12:559-69.
60. Fujii M, Butler JP, Sasaki H. Gamma-oryzanol for behavioural and psychological symptoms of dementia. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 2018;18(2):151-2.
61. Furukawa K, Tomita N, Uematsu D, Okahara K, Shimada H, Ikeda M, et al. Randomized double-blind placebo-controlled multicenter trial of Yokukansan for neuropsychiatric symptoms in Alzheimer's disease. Geriatr Gerontol Int. 2017;17(2):211-8.
62. Herrschaft H, Nacu A, Likhachev S, Sholomov I, Hoerr R, Schlaefke S. Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: a randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. J Psychiatr Res. 2012;46(6):716-23.
63. Iwasaki K, Kosaka K, Mori H, Okitsu R, Furukawa K, Manabe Y, et al. Improvement in delusions and hallucinations in patients with dementia with Lewy bodies upon administration of yokukansan, A traditional Japanese medicine. Psychogeriatrics. 2012;12(4):235-41.
64. Kudoh C, Arita R, Honda M, Kishi T, Komatsu Y, Asou H, et al. Effect of ninjin'yoeito, a Kampo (traditional Japanese) medicine, on cognitive impairment and depression in patients with Alzheimer's disease: 2 years of observation. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 2016;16(2):85-92.
65. Nagata K, Yokoyama E, Yamazaki T, Takano D, Maeda T, Takahashi S, et al. Effects of yokukansan on behavioral and psychological symptoms of vascular dementia: an open-label trial. Phytomedicine. 2012;19(6):524-8.
66. Pan W, Wang Q, Kwak S, Song Y, Qin B, Wang M, et al. Shen-zhi-ling oral liquid improves behavioral and psychological symptoms of dementia in Alzheimer's disease. Evidence-Based Complementary & Alternative Medicine: eCAM. 2014;2014:913687.
67. Sadhu A, Upadhyay P, Agrawal A, Ilango K, Karmakar D, Singh GP, et al. Management of cognitive determinants in senile dementia of Alzheimer's type: therapeutic potential of a novel polyherbal drug product. Clinical Drug Investigation. 2014;34(12):857-69.
68. Sumiyoshi H, Mantani A, Nishiyama S, Fujiwaki S, Ohta S, Masuda Y, et al. Yokukansan treatment of chronic renal failure patients receiving hemodialysis, with behavioral and psychological symptoms of dementia: an open-label study. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2013;21(11):1082-5.
69. Ballard C, Banister C, Khan Z, Cummings J, Demos G, Coate B, et al. Evaluation of the safety, tolerability, and efficacy of pimavanserin versus placebo in patients with Alzheimer's disease psychosis: a phase 2, randomised, placebo-controlled, double-blind study. Lancet Neurology. 2018;17(3):213-22.

70. De Deyn PP, Eriksson H, Svensson H. Tolerability of extended-release quetiapine fumarate compared with immediate-release quetiapine fumarate in older patients with Alzheimer's disease with symptoms of psychosis and/or agitation: a randomised, double-blind, parallel-group study. Int J Geriatr Psychiatry. 2012;27(3):296-304.
71. Devanand DP, Mintzer J, Schultz SK, Andrews HF, Sultzer DL, de la Pena D, et al. Relapse Risk after Discontinuation of Risperidone in Alzheimer's Disease. New England Journal of Medicine. 2012;367(16):1497-507.
72. Fujii M, Butler JP, Sasaki H. Antipsychotic drug use and favourable natures of emotional functions in patients with dementia. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 2019;19(4):320-4.
73. Grossberg GT, Kohegyi E, Mergel V, Josiassen MK, Meulien D, Hobart M, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled Trials. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2020;28(4):383-400.
74. Teodorescu A, Dima L, Ifteni P, Rogozea LM. Clozapine for Treatment-Refractory Behavioral Disturbance in Dementia. American Journal of Therapeutics. 2018;25(3):e320-e5.
75. Teranishi M, Kurita M, Nishino S, Takeyoshi K, Numata Y, Sato T, et al. Efficacy and tolerability of risperidone, yokukansan, and fluvoxamine for the treatment of behavioral and psychological symptoms of dementia: A blinded, randomized trial. Journal of Clinical Psychopharmacology. 2013;33(5):600-7.
76. An H, Choi B, Park KW, Kim DH, Yang DW, Hong CH, et al. The Effect of Escitalopram on Mood and Cognition in Depressive Alzheimer's Disease Subjects. Journal of Alzheimer's disease : JAD. 2017;55(2):727-35.
77. Banerjee S, Hellier J, Romeo R, Dewey M, Knapp M, Ballard C, et al. Study of the use of antidepressants for depression in dementia: The HTA-SADD trial- A multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine. Health Technology Assessment. 2013;17(7):1-43.
78. Bergh S, Selbaek G, Engedal K. Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial. BMJ (Clinical research ed). 2012;344:e1566.
79. Choe YM, Kim KW, Jhoo JH, Ryu SH, Seo EH, Sohn BK, et al. Multicenter, randomized, placebo-controlled, double-blind clinical trial of escitalopram on the progression-delaying effects in Alzheimer's disease. Int J Geriatr Psychiatry. 2016;31(7):731-9.
80. Herrmann N, Black SE, Chow T, Cappell J, Tang-Wai DF, Lanctot KL. Serotonergic function and treatment of behavioral and psychological symptoms of frontotemporal dementia. The American Journal of Geriatric Psychiatry. 2012;20(9):789-97.
81. Huang TY, Wei YJ, Moyo P, Harris I, Lucas JA, Simoni-Wastila L. Treated Behavioral Symptoms and Mortality in Medicare Beneficiaries in Nursing Homes with Alzheimer's Disease and Related Dementias. Journal of the American Geriatrics Society. 2015;63(9):1757-65.
82. Mokhber N, Abdollahian E, Soltanifar A, Samadi R, Saghebi A, Haghighi MB, et al. Comparison of sertraline, venlafaxine and desipramine effects on depression, cognition and the daily living activities in Alzheimer patients. Pharmacopsychiatry. 2014;47(4-5):131-40.
83. Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, et al. Effect of citalopram on agitation in Alzheimer disease: The CitAD randomized clinical trial. JAMA - Journal of the American Medical Association. 2014;311(7):682-91.
84. Leonpacher AK, Peters ME, Drye LT, Makino KM, Newell JA, Devanand DP, et al. Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia: Evidence From the CitAD Study. American Journal of Psychiatry. 2016;173(5):473-80.
85. Rosenberg PB, Drye LT, Porsteinsson AP, Pollock BG, Devanand DP, Frangakis C, et al. Change in agitation in Alzheimer's disease in the placebo arm of a nine-week controlled trial. International Psychogeriatrics. 2015;27(12):2059-67.
86. Scoralick FM, Louzada LL, Quintas JL, Naves JO, Camargos EF, Nobrega OT. Mirtazapine does not improve sleep disorders in Alzheimer's disease: results from a double-blind, placebo-controlled pilot study. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 2017;17(2):89-96.
87. Zhou T, Wang J, Xin C, Kong L, Wang C. Effect of memantine combined with citalopram on cognition of BPSD and moderate Alzheimer's disease: A clinical trial. Experimental and therapeutic medicine. 2019;17(3):1625-30.

88. Zuidersma M, Chua KC, Hellier J, Voshaar RO, Banerjee S. Sertraline and Mirtazapine Versus Placebo in Subgroups of Depression in Dementia: Findings From the HTA-SADD Randomized Controlled Trial. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2019;27(9):920-31.
89. Frakey LL, Salloway S, Buelow M, Malloy P. A randomized, double-blind, placebo-controlled trial of modafinil for the treatment of apathy in individuals with mild-to-moderate Alzheimer's disease. J Clin Psychiatry. 2012;73(6):796-801.
90. Lapid MI, Kuntz KM, Mason SS, Aakre JA, Lundt ES, Kremers W, et al. Efficacy, Safety, and Tolerability of Armodafinil Therapy for Hypersomnia Associated with Dementia with Lewy Bodies: A Pilot Study. Dementia & Geriatric Cognitive Disorders. 2017;43(5-6):269-80.
91. Padala PR, Padala KP, Lensing SY, Ramirez D, Monga V, Bopp MM, et al. Methylphenidate for Apathy in Community-Dwelling Older Veterans With Mild Alzheimer's Disease: A Double-Blind, Randomized, Placebo-Controlled Trial. Am J Psychiatry. 2018;175(2):159-68.
92. Rosenberg PB, Lanctot KL, Drye LT, Herrmann N, Scherer RW, Bachman DL, et al. Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: a randomized, placebo-controlled trial. J Clin Psychiatry. 2013;74(8):810-6.
93. Lanctot KL, Chau SA, Herrmann N, Drye LT, Rosenberg PB, Scherer RW, et al. Effect of methylphenidate on attention in apathetic AD patients in a randomized, placebo-controlled trial. International Psychogeriatrics. 2014;26(2):239-46.
94. Herrmann N, Ruthirakuhan M, Gallagher D, Verhoeff N, Kiss A, Black SE, et al. Randomized Placebo-Controlled Trial of Nabilone for Agitation in Alzheimer's Disease. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2019;27(11):1161-73.
95. Shelef A, Barak Y, Berger U, Paleacu D, Tadger S, Plopsky I, et al. Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study. Journal of Alzheimer's Disease. 2016;51(1):15-9.
96. van den Elsen GA, Ahmed AI, Verkes RJ, Kramers C, Feuth T, Rosenberg PB, et al. Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: A randomized controlled trial. Neurology. 2015;84(23):2338-46.
97. van den Elsen GA, Ahmed AI, Verkes RJ, Feuth T, van der Marck MA, Olde Rikkert MG. Tetrahydrocannabinol in Behavioral Disturbances in Dementia: A Crossover Randomized Controlled Trial. American Journal of Geriatric Psychiatry. 2015;23(12):1214-24.
98. Woodward MR, Harper DG, Stolyar A, Forester BP, Ellison JM. Dronabinol for the treatment of agitation and aggressive behavior in acutely hospitalized severely demented patients with noncognitive behavioral symptoms. American Journal of Geriatric Psychiatry. 2014;22(4):415-9.
99. Adrait A, Perrot X, Nguyen MF, Gueugnon M, Petitot C, Collet L, et al. Do Hearing Aids Influence Behavioral and Psychological Symptoms of Dementia and Quality of Life in Hearing Impaired Alzheimer's Disease Patients and Their Caregivers? Journal of Alzheimer's disease : JAD. 2017;58(1):109-21.
100. Bowen RL, Perry G, Xiong C, Smith MA, Atwood CS. A clinical study of lupron depot in the treatment of women with Alzheimer's disease: preservation of cognitive function in patients taking an acetylcholinesterase inhibitor and treated with high dose lupron over 48 weeks. Journal of Alzheimer's Disease. 2015;44(2):549-60.
101. Butchart J, Brook L, Hopkins V, Teeling J, Puntener U, Culliford D, et al. Etanercept in Alzheimer disease: A randomized, placebo-controlled, double-blind, phase 2 trial.[Erratum appears in Neurology. 2015 Dec 8;85(23):2084; PMID: 26644054]. Neurology. 2015;84(21):2161-8.
102. Castagna A, Cotroneo AM, Ruotolo G, Gareri P. The CITIRIVAD Study: CITIcoline plus RIVAstigmine in Elderly Patients Affected with Dementia Study. Clinical Drug Investigation. 2016;36(12):1059-65.
103. Cummings JL, Lyketsos CG, Peskind ER, Porsteinsson AP, Mintzer JE, Scharre DW, et al. Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia: A Randomized Clinical Trial. JAMA. 2015;314(12):1242-54.
104. Cummings JL, Zhong K, Kinney JW, Heaney C, Moll-Tudla J, Joshi A, et al. Double-blind, placebo-controlled, proof-of-concept trial of bexarotene Xin moderate Alzheimer's disease. Alzheimer's Research & Therapy. 2016;8:4.
105. Finger EC, MacKinley J, Blair M, Oliver LD, Jesso S, Tartaglia MC, et al. Oxytocin for frontotemporal dementia: a randomized dose-finding study of safety and tolerability. Neurology. 2015;84(2):174-81.

106. Gareri P, Castagna A, Cotroneo AM, Putignano D, Conforti R, Santamaria F, et al. The Citicholinage Study: Citicoline Plus Cholinesterase Inhibitors in Aged Patients Affected with Alzheimer's Disease Study. Journal of Alzheimer's Disease. 2017;56(2):557-65.
107. Henderson VW, Ala T, Sainani KL, Bernstein AL, Stephenson BS, Rosen AC, et al. Raloxifene for women with Alzheimer disease: A randomized controlled pilot trial. Neurology. 2015;85(22):1937-44.
108. Herring WJ, Ceesay P, Snyder E, Bliwise D, Budd K, Hutzelmann J, et al. Polysomnographic assessment of suvorexant in patients with probable Alzheimer's disease dementia and insomnia: a randomized trial. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2020;16(3):541-51.
109. Kim SY, Choi SH, Rollema H, Schwam EM, McRae T, Dubrava S, et al. Phase II crossover trial of varenicline in mild-to-moderate Alzheimer's disease. Dementia & Geriatric Cognitive Disorders. 2014;37(3-4):232-45.
110. Kwok T, Leung PC, Wing YK, Ip I, Wong B, Ho DWH, et al. The effectiveness of acupuncture on the sleep quality of elderly with dementia: A within-subjects trial. Clinical Interventions in Aging. 2013;8:923.
111. Morales-Delgado R, Cámara-Lemarroy CR, Salinas-Martínez R, Gámez-Treviño D, Arredondo-Jaime A, Hernández-Maldonado E, et al. A randomized placebo-controlled trial evaluating the effect of melatonin on sleep quality in patients with mild-moderate dementia. Eur Geriatr Med. 2018;9(4):449-54.
112. Nave S, Doody RS, Boada M, Grimmer T, Savola JM, Delmar P, et al. Sembragiline in Moderate Alzheimer's Disease: Results of a Randomized, Double-Blind, Placebo-Controlled Phase II Trial (MAyflOwer RoAD). Journal of Alzheimer's Disease. 2017;58(4):1217-28.
113. Pardini M, Serrati C, Guida S, Mattei C, Abate L, Massucco D, et al. Souvenaid reduces behavioral deficits and improves social cognition skills in frontotemporal dementia: A proof-of-concept Study. Neurodegenerative Diseases. 2015;15(1):58-62.
114. Pirker-Kees A, Dal-Bianco P, Schmidt R. Effects of psychotropic medication on cognition, caregiver burden, and neuropsychiatric symptoms in Alzheimer's disease over 12 months: Results from a prospective registry of dementia in Austria (PRODEM). Journal of Alzheimer's Disease. 2019;71(2):623-30.
115. Remington R, Bechtel C, Larsen D, Samar A, Doshanjh L, Fishman P, et al. A Phase II Randomized Clinical Trial of a Nutritional Formulation for Cognition and Mood in Alzheimer's Disease. Journal of Alzheimer's Disease. 2015;45(2):395-405.
116. Suzuki H, Gen K. Clinical efficacy of lamotrigine and changes in the dosages of concomitantly used psychotropic drugs in Alzheimer's disease with behavioural and psychological symptoms of dementia: a preliminary open-label trial. Psychogeriatrics. 2015;15(1):32-7.
117. Wade AG, Farmer M, Harari G, Fund N, Laudon M, Nir T, et al. Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-month, randomized, placebo-controlled, multicenter trial. Clinical Interventions In Aging. 2014;9:947-61.
118. Acharya D, Harper DG, Achtyes ED, Seiner SJ, Mahdasian JA, Nykamp LJ, et al. Safety and utility of acute electroconvulsive therapy for agitation and aggression in dementia. Int J Geriatr Psychiatry. 2015;30(3):265-73.
119. Ahmed MA, Darwish ES, Khedr EM, El Serogy YM, Ali AM. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. J Neurol. 2012;259(1):83-92.
120. Alcalá-Lozano R, Morelos-Santana E, Cortés-Sotres JF, Garza-Villarreal EA, Sosa-Ortiz AL, González-Olvera JJ. Similar clinical improvement and maintenance after rTMS at 5 Hz using a simple vs. complex protocol in Alzheimer's disease. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation. 2018;11(3):625-7.
121. Bromundt V, Wirz-Justice A, Boutellier M, Winter S, Haberstroh M, Terman M, et al. Effects of a dawn-dusk simulation on circadian rest-activity cycles, sleep, mood and well-being in dementia patients. Exp Gerontol. 2019;124:110641.
122. Elder GJ, Colloby SJ, Firbank MJ, McKeith IG, Taylor JP. Consecutive sessions of transcranial direct current stimulation do not remediate visual hallucinations in Lewy body dementia: a randomised controlled trial. Alzheimers Res Ther. 2019;11(1):9.
123. Ferrucci R, Mrakic-Sposta S, Gardini S, Ruggiero F, Vergari M, Mameli F, et al. Behavioral and neurophysiological effects of transcranial direct current stimulation (tDCS) in fronto-temporal dementia. Frontiers in Behavioral Neuroscience. 2018;12.
124. Figueiro MG, Plitnick BA, Lok A, Ejones GE, Higgins P, Rhornick TR, et al. Tailored lighting intervention improves measures of sleep, depression, and agitation in persons with Alzheimer's disease and related dementia living in long-term care facilities. Clinical Interventions in Aging. 2014;9:1527-37.

125. Figueiro MG, Plitnick B, Roohan C, Sahin L, Kalsher M, Rea MS. Effects of a Tailored Lighting Intervention on Sleep Quality, Rest-Activity, Mood, and Behavior in Older Adults With Alzheimer Disease and Related Dementias: A Randomized Clinical Trial. J Clin Sleep Med. 2019;15(12):1757-67.
126. Friedman L, Spira AP, Hernandez B, Mather C, Sheikh J, Ancoli-Israel S, et al. Brief morning light treatment for sleep/wake disturbances in older memory-impaired individuals and their caregivers. Sleep medicine. 2012;13(5):546-9.
127. Khedr EM, Salama RH, Abdel Hameed M, Abo Elfetoh N, Seif P. Therapeutic Role of Transcranial Direct Current Stimulation in Alzheimer Disease Patients: Double-Blind, Placebo-Controlled Clinical Trial. Neurorehabilitation & Neural Repair. 2019;33(5):384-94.
128. Konis K, Mack WJ, Schneider EL. Pilot study to examine the effects of indoor daylight exposure on depression and other neuropsychiatric symptoms in people living with dementia in long-term care communities. Clinical Interventions In Aging. 2018;13:1071-7.
129. Munch M, Schmieder M, Bieler K, Goldbach R, Fuhrmann T, Zumstein N, et al. Bright Light Delights: Effects of Daily Light Exposure on Emotions, Restactivity Cycles, Sleep and Melatonin Secretion in Severely Demented Patients. Current Alzheimer Research. 2017;14(10):1063-75.
130. Nguyen JP, Suarez A, Kemoun G, Meignier M, Le Saout E, Damier P, et al. Repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease. Neurophysiologie Clinique. 2017;47(1):47-53.
131. Onega LL, Pierce TW, Epperly L. Effect of Bright Light Exposure on Depression and Agitation in Older Adults with Dementia. Issues Ment Health Nurs. 2016;37(9):660-7.
132. Onega LL, Pierce TW, Epperly L. Bright Light Therapy to Treat Depression in Individuals with Mild/Moderate or Severe Dementia. Issues in Mental Health Nursing. 2018;39(5):370-3.
133. Padala PR, Padala KP, Lensing SY, Jackson AN, Hunter CR, Parkes CM, et al. Repetitive transcranial magnetic stimulation for apathy in mild cognitive impairment: A double-blind, randomized, sham-controlled, cross-over pilot study. Psychiatry Research. 2018;261:312-8.
134. Rabey JM, Dobronevsky E, Aichenbaum S, Gonen O, Marton RG, Khaigrekht M. Repetitive transcranial magnetic stimulation combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: a randomized, double-blind study. Journal of neural transmission (Vienna, Austria : 1996). 2013;120(5):813-9.
135. Sekiguchi H, Iritani S, Fujita K. Bright light therapy for sleep disturbance in dementia is most effective for mild to moderate Alzheimer's type dementia: A case series. Psychogeriatrics. 2017;17(5):275-81.
136. Sloane PD, Figueiro M, Garg S, Cohen LW, Reed D, Williams CS, et al. Effect of home-based light treatment on persons with dementia and their caregivers. Lighting research & technology. 2015;47(2):161-76.
137. Suemoto CK, Apolinario D, Nakamura-Palacios EM, Lopes L, Leite RE, Sales MC, et al. Effects of a non-focal plasticity protocol on apathy in moderate Alzheimer's disease: a randomized, double-blind, sham-controlled trial. Brain Stimulation. 2014;7(2):308-13.
138. Ujkaj M, Davidoff DA, Seiner SJ, Ellison JM, Harper DG, Forester BP. Safety and efficacy of electroconvulsive therapy for the treatment of agitation and aggression in patients with dementia. American Journal of Geriatric Psychiatry. 2012;20(1):61-72.
139. Wahnschaffe A, Nowozin C, Haedel S, Rath A, Appelhoff S, Munch M, et al. Implementation of dynamic lighting in a nursing home: Impact on agitation but not on rest-activity patterns. Current Alzheimer Research. 2017;14(10):1076-83.
140. Wu Y, Xu W, Liu X, Xu Q, Tang L, Wu S. Adjunctive treatment with high frequency repetitive transcranial magnetic stimulation for the behavioral and psychological symptoms of patients with Alzheimer's disease: a randomized, double-blind, sham-controlled study. Shanghai archives of psychiatry. 2015;27(5):280-8.

Abbreviations

ABS: Abe's BPSD score
AD: Alzheimer's disease
AES: Apathy Evaluation Scale; AES-C: AES clinician version
AIS: Athens Insomnia Scale
AS: Apathy Scale
BARS: Brief Agitation Rating Scale
BAI: Beck Anxiety Inventory
BEHAVE-AD: Behavioural Pathology in Alzheimer's Disease
BPSD: behaviours and psychological symptoms associated with dementia
CERAD: Consortium to Establish a Registry for Alzheimer's Disease
ChEI: Cholinesterase inhibitor
CMAI: Cohen-Mansfield Agitation Inventory
CMAI-SF: Cohen-Mansfield Agitation Inventory - Short Form
CSDD: Cornell Scale for Depression in Dementia
CGBRS: Crichton Geriatric Behavioural Rating Scale
DLB: dementia with Lewy bodies; LBD: Lewy body dementia/disease
DMAS-17: Dementia Mood Assessment Scale 17 Item
DSAOA: Depressive Symptom Assessment in Older Adults
ES: effect size
ESS: Epworth Sleepiness Scale
FBI: Frontal Behavioral Inventory
FrSBe: Frontal System Behaviour Scale
FTD: frontotemporal dementia; bvFTD: behavioural variant FTD
f/u: follow-up
GDS: Geriatric Depression Scale; GDS-SF: GDS Short Form
HAM-D: Hamilton Rating Scale for Depression
IA: Apathy Inventory
n/a: not applicable
MWT: Maintenance of Wakefulness Test
NBRS: Neurobehavioral Rating Scale
NOSGER: Nurses' Observation Scale for Geriatric Patients
NPI: Neuropsychiatric Inventory; NPI-NH: NPI Nursing Home Version
NPI-Q: NPI Brief Questionnaire Form
PAS: Psychogeriatric Assessment Scale
PDD: Parkinson's disease dementia
PSQI: Pittsburgh Sleep Quality Index
RACS: residential aged care service
RCT: randomised controlled trial
rTMS: repetitive transcranial magnetic stimulation
SSRI: Selective serotonin reuptake inhibitor
tDCS: transcranial direct current stimulation
VaD: vascular dementia
VAS: Visual Analogue Scale