NKR 53 demens og adfærdsforstyrrelser PICO 8 medicinske lægemidler

Review information

Authors

Sundhedsstyrelsen[1]

[1][Empty affiliation]

Citation example: S. NKR 53 demens og adfærdsforstyrrelser PICO 8 medicinske lægemidler. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Characteristics of studies

Characteristics of included studies

Ballard 2005

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Data obtained from: Seitz, D. P.; Gill, S. S.; Herrmann, N.; Brisbin, S.; Rapoport, M. J.; Rines, J.; Wilson, K.; Le Clair, K.; Conn, D. K. Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic reviewInternational psychogeriatrics 2013;25(2):185-203England 2013

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	reference: Seitz et al., 2013
Allocation concealment (selection bias)	Low risk	reference: Seitz et al., 2013
Blinding of participants and personnel (performance bias)	Low risk	reference: Seitz et al., 2013
Blinding of outcome assessment (detection bias)	Low risk	reference: Seitz et al., 2013
Incomplete outcome data (attrition bias)	Low risk	reference: Seitz et al., 2013
Selective reporting (reporting bias)	Low risk	reference: Seitz et al., 2013
Other bias	Low risk	reference: Seitz et al., 2013

Fox 2012

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Data obtained from: Wang, Jun; Yu, Jin-Tai; Wang, Hui-Fu; Meng, Xiang-Fei; Wang, Chong; Tan, Chen-Chen; Tan, Lan Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysisJournal of Neurology, Neurosurgery & Psychiatry 2015;86(1):101-109England 2015

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned with equal probability to twice daily memantine 10 mg (titrated in 5 mg increments over four weeks) or placebo. Randomisation used a secure internet based randomisation service independent of the study team."
Allocation concealment (selection bias)	Low risk	Quote: "participants, study personnel, clinicians and carers were blind to allocation,"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Blinding was achieved by using placebo and active drug identical in appearance and taste."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Since participants, study personnel, clinicians and carers were blind to allocation, no probabilistic element was introduced into the minimisation procedure. Blinding was achieved by using placebo and active drug identical in appearance and taste."
Incomplete outcome data (attrition bias)	Low risk	Quote: "The primary analysis was an intention to treat (ITT) analysis; participants were analysed as part of their allocated group irrespective of medication protocol adherence. Linear" Judgement Comment: Reasons for dropouts are provided and ITT analyses performed
Selective reporting (reporting bias)	Low risk	Quote: "ClinicalTrials.gov NCT00371059" Judgement Comment: Matches study protocol
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias

Herrmann 2013

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Data obtained from: Wang, Jun; Yu, Jin-Tai; Wang, Hui-Fu; Meng, Xiang-Fei; Wang, Chong; Tan, Chen-Chen; Tan, Lan Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysisJournal of Neurology, Neurosurgery & Psychiatry 2015;86(1):101-109England 2015

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: "Patients were randomly and equally allocated to one of the two treatment groups in accordance with randomization list generated by the sponsor following a standard routine"
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Allocation concealment is not described
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: All participants, care providers and raters were blinded
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: outcome assessors are blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Reasons for drop out are provided, and equally destributed between groups:Memantine: 31 out of 182 discontinuatedPlacebo: 32 out of 187 discontinuated. Further, efficacy analyses were performed on the FAS, using the last observation carried forward approach
Selective reporting (reporting bias)	Low risk	Judgement Comment: Clinicaltrials.gov: NCT00857649.Matches study protocol
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias

Holmes 2004

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Data obtained from: Wang, Jun; Yu, Jin-Tai; Wang, Hui-Fu; Meng, Xiang-Fei; Wang, Chong; Tan, Chen-Chen; Tan, Lan Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and

	meta-analysisJournal of Neurology, Neurosurgery & Psychiatry 2015;86(1):101-109England 2015

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: Patients were randomized using a computer-genrated randomization protocol to placebo or 10mg/day donepezil on a 3:2 ratio
Allocation concealment (selection bias)	Low risk	Judgement Comment: Randomization performed by an independent pharmacist who also provided numbered containers of identical tablets for each patient.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: All the patients where blinded, but it is unknown if the personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: The patients were outcome assessors and blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Reasons for drop out are provided and ITT analyses was performed
Selective reporting (reporting bias)	Low risk	Judgement Comment: reference to study protocol, but not available. The study appears to be free of selective outcome reporting
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias

Howard 2007

Methods	
Participants	
Interventions	
Outcomes	
Identification	

Notes	Data obtained from: Wang, Jun; Yu, Jin-Tai; Wang, Hui-Fu; Meng, Xiang-Fei; Wang, Chong; Tan, Chen-Chen; Tan, Lan Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysisJournal of Neurology, Neurosurgery & Psychiatry 2015;86(1):101-109England 2015

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Telephone randomization was performed centrally by the Medical Research Council (MRC) Clinical Trials Unit. Assignment of treatment to drug-pack numbers was performed with the use of a random sequence of numbers (fixed blocks of six).
Allocation concealment (selection bias)	Low risk	Quote: The data manager determined treatment as- signments using a fully blind minimization algo- rithm containing an embedded list of pack num- bers with corresponding treatment.
Blinding of participants and personnel (performance bias)	Low risk	Quote: Clinicians, those administering the trial medication, patients, caregivers, and outcome assessors were all un- aware of the treatment assignments.
Blinding of outcome assessment (detection bias)	Low risk	Quote: Clinicians, those administering the trial medication, patients, caregivers, and outcome assessors were all un- aware of the treatment assignments.
Incomplete outcome data (attrition bias)	High risk	Judgement comment: 1 dropout in risperidone. 19 in placebo group. Reason for dropouts not explained
Selective reporting (reporting bias)	Low risk	Quote: ClinicalTrials.gov number, NCT00142324 Judgement comment: Matches study protocol
Other bias	Low risk	Judgement comment: The study appears to be free of other sources of bias

Ikeda 2015

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Included criteria:** Eligible patientswere outpatients aged≥ 50 years with mild to moderate orsevere dementia (10 to 26 on the Mini-Mental StateExamination (MMSE) and Clinical Dementia Rating≥ 0.5)and behavioral and psychiatric symptoms (Neuropsychi-atric Inventory-plus (NPI-plus)≥ 8 and NPI (NPI-2)≥ 1).The NPI-plus consisted of 12 items: the original 10items, sleep [14,15] and cognitive fluctuation, which isreported as the Cognitive Fluctuation Inventory [16,17](see Additional file 1). The NPI-2 consisted of hallucina-tions and cognitive fluctuation [11]. The caregivers of theeligible patients had to routinely stay with them at least3 days per week and 4 hours per day, provide informationfor this study, assist with the compliance with treatmentand escort them to required visits. **Excluded criteria:** The exclusion criteria included Parkinson's diseasethat was diagnosed at least 1 year prior to the onset ofdementia; focal vascular lesions visualized on magnetic resonance imaging or computed tomographic scans thatmight cause cognitive impairment; other neurological orpsychiatric diseases; clinically significant systemic disease;complications or a history of severe gastrointestinal ulcer,severe asthma or obstructive pulmonary disease; systolichypotension (90 mmHg); bradycardia (50 m– 1); sicksinus syndrome; atrial or atrioventricular conductionblock; QT interval prolongation (≥ 450 ms); hypersen-sitivity to donepezil or piperidine derivatives; severeparkinsonism (Hoehn and Yahr stage IV or above) [18];and treatment with ChEIs or any investigational drugwithin 3 months prior to screening. ChEIs, antipsychoticsand antiparkinson drugs other than L-dopa or dopamineagonists were not allowed during the study
Interventions	**Intervention Characteristics** Donepezil 5mg ● *Length of treatment*: 12 weeks ● *Longest FU after end of treatment*: none Donepezil 10mg ● *Length of treatment*: 12 weeks ● *Longest FU after end of treatment*: none Placebo ● *Length of treatment*: 12 weeks ● *Longest FU after end of treatment*: none

Outcomes	*Serious adverse events, %* ● **Outcome type**: DichotomousOutcome *BPSD (NPI), SE* ● **Outcome type**: ContinuousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally according to a dynamic allocation, adjusting for MMSE and NPI-2 scores at screening."
Allocation concealment (selection bias)	Low risk	Judgement Comment: A member of the research staff whowas in charge of randomization and who was independentof all the parties concerned with the study securelykept the randomization list with limited access only inan emergency. No other members of the research staff,including the physicians, nurses and study institutionstaff were aware of the treatment assignment, nor wereany of the participants
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: No other members of the research staff,including the physicians, nurses and study institutionstaff were aware of the treatment assignment, nor wereany of the participants.Patients received two study drug tablets, which werecomposed of a combination of 3 mg, 5 mg, or the matchedplacebo tablets with the same physical appearance, oncedaily in the morning
Blinding of outcome assessment (detection bias)	Low risk	Quote: "No other members of the research staff, including the physicians, nurses and study institution staff were aware of the treatment assignment," Judgement Comment: as the potcome assessors were not aware of the intervention this could not affect the outcome
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Describe incomplete data. Over sample study population.Detecting the significantdifference, predefined to be determined only with statisticalsignificance in both MMSE and NPI-2 results, withat least 80% statistical power between the placebo and5 mg groups required at least 126 patients (42 per group)(statistical power of 80.7%). The number was expected toprovide power of 85.4% to

		detect a significant differencebetween the placebo and 10 mg groups. Given that 10% ofthe patients were excluded from the full analysis set (FAS),the target number of patients in this study was set at 141
Selective reporting (reporting bias)	Low risk	Judgement Comment: ClinicalTrials.gov Identifier: NCT01278407 No apparent sources of bias
Other bias	Low risk	Judgement Comment: Trial registration: Trial registration: ClinicalTrials.gov Identifier: NCT01278407 (trial registration date: 14 January 2011). No apparent sources of bias

Tariot 2001

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Data obtained from: Seitz, D. P.; Gill, S. S.; Herrmann, N.; Brisbin, S.; Rapoport, M. J.; Rines, J.; Wilson, K.; Le Clair, K.; Conn, D. K. Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic reviewInternational psychogeriatrics 2013;25(2):185-203England 2013 and Wang, Jun; Yu, Jin-Tai; Wang, Hui-Fu; Meng, Xiang-Fei; Wang, Chong; Tan, Chen-Chen; Tan, Lan Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysisJournal of Neurology, Neurosurgery & Psychiatry 2015;86(1):101-109England 2015

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	reference: Seitz et al., 2013
Allocation concealment (selection bias)	Unclear risk	reference: Seitz et al., 2013
Blinding of participants and personnel (performance bias)	Low risk	reference: Seitz et al., 2013
Blinding of outcome assessment (detection bias)	Low risk	reference: Seitz et al., 2013

Incomplete outcome data (attrition bias)	Low risk	reference: Seitz et al., 2013
Selective reporting (reporting bias)	Low risk	reference: Seitz et al., 2013
Other bias	High risk	reference: Seitz et al., 2013

Footnotes

Characteristics of excluded studies

Alva 2015

Reason for exclusion	Wrong comparator

Araki 2014

Reason for exclusion	Wrong patient population

Bago 2015

Reason for exclusion	Abstract only

Bakchine 2008

Reason for exclusion	Wrong patient population

Ballard 2015

Reason for exclusion	Wrong comparator

Black 2007

Reason for exclusion	Wrong patient population

Bogaisky 2014

Reason for exclusion	Abstract only

Brodaty 2005

Reason for exclusion	Wrong patient population

Carrasco 2011

Reason for exclusion	Wrong patient population

Courtney 2004

Reason for exclusion	Wrong patient population

Cumbo 2014

Reason for exclusion	Wrong patient population

Cummings 2006

Reason for exclusion	Wrong intervention

Farlow 2013

Reason for exclusion	Abstract only

Feldman 2001

Reason for exclusion	Wrong patient population

Fox 2011

Reason for exclusion	Abstract only

Fox 2012a

Reason for exclusion	Duplicate

Freund Levi 2014

Reason for exclusion	Wrong comparator

Freund Levi 2014a

Reason for exclusion	Wrong comparator

Gauthier 2008

Reason for exclusion	Wrong patient population

Graham 2013

Reason for exclusion	Wrong comparator

Grossberg 2013

Reason for exclusion	Wrong patient population

Herrmann 2005

Reason for exclusion	Wrong study design

Herrmann 2011

Reason for exclusion	Wrong study design

Holmes 2007

Reason for exclusion	Wrong comparator

Howard 2012

Reason for exclusion	Wrong patient population

Johannsen 2006

Reason for exclusion	Wrong patient population

Kaufer 1998

Reason for exclusion	Wrong patient population

Kitamura 2011

Reason for exclusion	Wrong study design

Lyketsos 2004

Reason for exclusion	Wrong patient population

Morris 1998

Reason for exclusion	Wrong patient population

Nakamura 2011

Reason for exclusion	Wrong study design

Nakamura 2016

Reason for exclusion	Wrong study design

Oh 2015

Reason for exclusion	Wrong patient population

Peskind 2006

Reason for exclusion	Wrong patient population

Petrovska 2017

Reason for exclusion	Abstract only

Porsteinsson 2008

Reason for exclusion	Wrong patient population

Raskind 1999

Reason for exclusion	Wrong patient population

Reisberg 2003

Reason for exclusion	Wrong patient population

Rockwood 2001

Reason for exclusion	Wrong patient population

Tariot 2000

Reason for exclusion	Wrong patient population

Tariot 2004

Reason for exclusion	Wrong patient population

vanDyck 2007

Reason for exclusion	Wrong patient population

Waldemar 2011

Reason for exclusion	Wrong patient population

Winblad 2006

Reason for exclusion	Wrong patient population

Yoon 2011

Reason for exclusion	Wrong intervention

Yoon 2017

Reason for exclusion	Wrong patient population

Zhang 2015

Reason for exclusion	Wrong patient population

Footnotes

References to studies

Included studies

Ballard 2005

Ballard, C.; Margallo-Lana, M.; Juszczak, E.; Douglas, S.; Swann, A.; Thomas, A.; O'Brien, J.; Everratt, A.; Sadler, S.; Maddison, C.; Lee, L.; Bannister, C.; Elvish, R.; Jacoby, R.. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ (Clinical research ed.) 2005;330(7496):874. [DOI: bmj.38369.459988.8F [pii]]

Fox 2012

Fox, C.; Crugel, M.; Maidment, I.; Auestad, B. H.; Coulton, S.; Treloar, A.; Ballard, C.; Boustani, M.; Katona, C.; Livingston, G.. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. PloS one 2012;7(5):e35185. [DOI: 10.1371/journal.pone.0035185 [doi]]

Herrmann 2013

Herrmann, N.; Gauthier, S.; Boneva, N.; Lemming, O. M.; 10158 Investigators. 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(6):919-927. [DOI: 10.1017/S1041610213000239 [doi]]

Holmes 2004

Holmes, C.; Wilkinson, D.; Dean, C.; Vethanayagam, S.; Olivieri, S.; Langley, A.; Pandita-Gunawardena, N. D.; Hogg, F.; Clare, C.; Damms, J.. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. Neurology 2004;63(2):214-219. [DOI: 63/2/214 [pii]]

Howard 2007

Howard, R. J.; Juszczak, E.; Ballard, C. G.; Bentham, P.; Brown, R. G.; Bullock, R.; Burns, A. S.; Holmes, C.; Jacoby, R.; Johnson, T.; Knapp, M.; Lindesay, J.; O'Brien, J. T.; Wilcock, G.; Katona, C.; Jones, R. W.; DeCesare, J.; Rodger, M.; CALM-AD Trial Group. Donepezil for the treatment of agitation in Alzheimer's disease. The New England journal of medicine 2007;357(14):1382-1392. [DOI: 357/14/1382 [pii]]

Ikeda 2015

Ikeda, Manabu; Mori, Etsuro; Matsuo, Kazutaka; Nakagawa, Masaki; Kosaka, Kenji. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial.. Alzheimer's Research & Therapy 2015;7(1):4. [DOI:]

Tariot 2001

Tariot, P. N.; Cummings, J. L.; Katz, I. R.; Mintzer, J.; Perdomo, C. A.; Schwam, E. M.; Whalen, E.. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. Journal of the American Geriatrics Society 2001;49(12):1590-1599. [DOI: 49266 [pii]]

Excluded studies

Alva 2015

Alva G.; Ellison N.; Hendrix S.; Pejovic V.; Otcheretko V.. Adding memantine to stable cholinesterase inhibitor therapy in patients with moderate to severe alzheimer's disease is associated with improvement in various neuropsychiatric symptoms: A pooled analysis. Neurology 2015;84(Journal Article). [DOI:]

Araki 2014

Araki, T.; Wake, R.; Miyaoka, T.; Kawakami, K.; Nagahama, M.; Furuya, M.; Limoa, E.; Liaury, K.; Hashioka, S.; Murotani, K.; Horiguchi, J.. The effects of combine treatment of memantine and donepezil on Alzheimer's disease patients and its relationship with cerebral blood flow in the prefrontal area. International journal of geriatric psychiatry 2014;29(9):881-889. [DOI: 10.1002/gps.4074 [doi]]

Bago 2015

Bago, Rozankovic P.; Badzak J.. Impact of donepezil and memantine on behavioral and psychological symptoms in patients with Alzheimer's disease. European Journal of Neurology 2015;22(Journal Article):579. [DOI: http://dx.doi.org/10.1111/ene.12808]

Bakchine 2008

Bakchine, S.; Loft, H.. Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. Journal of Alzheimer's disease : JAD 2008;13(1):97-107. [DOI:]

Ballard 2015

Ballard, Clive; Thomas, Alan; Gerry, Stephen; Yu, Ly-Mee; Aarsland, Dag; Merritt, Claire; Corbett, Anne; Davison, Christopher; Sharma, Narenda; Khan, Zunera; Creese, Byron; Loughlin, Paul; Bannister, Carol; Burns, Alistair; Win, Soe Nyunt; Walker, Zuzana; MAIN-AD investigators. 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):316-322. [DOI:]

Black 2007

Black, S. E.; Doody, R.; Li, H.; McRae, T.; Jambor, K. M.; Xu, Y.; Sun, Y.; Perdomo, C. A.; Richardson, S.. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. Neurology 2007;69(5):459-469. [DOI: 69/5/459 [pii]]

Bogaisky 2014

Bogaisky, Michael. Galantamine versus risperidone treatment of neuropsychiatric symptoms in patients with probable dementia: An open randomized trial. The American Journal of Geriatric Psychiatry 2014;22(9):951. [DOI: http://dx.doi.org/10.1016/j.jagp.2014.04.010; http://dx.doi.org/10.1016/j.jagp.2014.04.010]

Brodaty 2005

Brodaty, H.; Corey-Bloom, J.; Potocnik, F. C.; Truyen, L.; Gold, M.; Damaraju, C. R.. Galantamine prolonged-release formulation in the treatment of mild to moderate Alzheimer's disease. Dementia and geriatric cognitive disorders 2005;20(2-3):120-132. [DOI: 86613 [pii]]

Carrasco 2011

Carrasco, Manuel Martin; Aguera, Luis; Gil, Pedro; Morinigo, Angel; Leon, Teresa. Safety and effectiveness of donepezil on behavioral symptoms in patients with Alzheimer disease.. Alzheimer Disease & Associated Disorders 2011;25(4):333-340. [DOI:]

Courtney 2004

Courtney, C.; Farrell, D.; Gray, R.; Hills, R.; Lynch, L.; Sellwood, E.; Edwards, S.; Hardyman, W.; Raftery, J.; Crome, P.; Lendon, C.; Shaw, H.; Bentham, P.; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet (London, England) 2004;363(9427):2105-2115. [DOI: 10.1016/S0140-6736(04)16499-4 [doi]]

Cumbo 2014

Cumbo, Eduardo; Ligori, Leonarda Domenica. 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):477-485. [DOI:]

Cummings 2006

Cummings, J. L.; Schneider, E.; Tariot, P. N.; Graham, S. M.; Memantine MEM-MD-02 Study Group. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. Neurology 2006;67(1):57-63. [DOI: 67/1/57 [pii]]

Farlow 2013

Farlow M.R.; Ferris S.; Somogyi M.; Meng X.. Efficacy of 13.3 mg/24 h rivastigmine patch on global functioning and behavior in severe alzheimer's disease. Annals of Neurology 2013;74(Journal Article):S91. [DOI: http://dx.doi.org/10.1002/ana.24068]

Feldman 2001

Feldman, H.; Gauthier, S.; Hecker, J.; Vellas, B.; Subbiah, P.; Whalen, E.; Donepezil MSAD Study Investigators Group. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001;57(4):613-620. [DOI:]

Fox 2011

Fox C.; Boustani M.; Crugel M.; Maidment I.; Ballard C.; Katona C.; Livingston G.; Adrian T.; Coulton S.; Mcshane R.. Magd trial-memantine for agitation in alzheimer's dementia. Journal of the American Geriatrics Society 2011;59(Journal Article):S65-S66. [DOI: http://dx.doi.org/10.1111/j.1532-5415.2011.03416.x]

Fox 2012a

Fox, Chris; Crugel, Monica; Maidment, Ian; Auestad, Bjorn Henrik; Coulton, Simon; Treloar, Adrian; Ballard, Clive; Boustani, Malaz; Katona, Cornelius; Livingston, Gill. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial.. PLoS ONE [Electronic Resource] 2012;7(5):e35185. [DOI:]

Freund Levi 2014

Freund-Levi, Yvonne; Jedenius, Erik; Tysen-Backstrom, Ann Christine; Larksater, Marie; Wahlund, Lars-Olof; Eriksdotter, Maria. Galantamine versus risperidone treatment of neuropsychiatric symptoms in patients with probable dementia: an open randomized trial.. American Journal of Geriatric Psychiatry 2014;22(4):341-348. [DOI:]

Freund Levi 2014a

Freund-Levi, Yvonne; Bloniecki, Victor; Auestad, Bjorn; Tysen Backstrom, Ann Christine; Larksater, Marie; Aarsland, Dag. Galantamine versus risperidone for agitation in people with dementia: a randomized, twelve-week, single-center study.. Dementia & Geriatric Cognitive Disorders 2014;38(3-4):234-244. [DOI:]

Gauthier 2008

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Graham 2013

Graham S.M.; Hendrix S.; Miller M.L.; Pejovic V.; Tocco M.. Extended-release memantine (28 mg, once daily) provides behavioral benefits across a wide range of disease severity in patients with moderate to severe alzheimer's disease: Post hoc analysis from a randomized trial. American Journal of Geriatric Psychiatry 2013;21(3):S139. [DOI:]

Grossberg 2013

Grossberg, G. T.; Manes, F.; Allegri, R. F.; Gutierrez-Robledo, L. M.; Gloger, S.; Xie, L.; Jia, X. D.; Pejovic, V.; Miller, M. L.; Perhach, J. L.; Graham, S. M.. 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):469-478. [DOI: 10.1007/s40263-013-0077-7 [doi]]

Herrmann 2005

Herrmann, N.; Rabheru, K.; Wang, J.; Binder, C.. Galantamine treatment of problematic behavior in Alzheimer disease: post-hoc analysis of pooled data from three large trials. The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry 2005;13(6):527-534. [DOI: S1064-7481(12)61444-4 [pii]]

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Howard 2012

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Johannsen 2006

Johannsen, P.; Salmon, E.; Hampel, H.; Xu, Y.; Richardson, S.; Qvitzau, S.; Schindler, R.; AWARE Study Group. Assessing therapeutic efficacy in a progressive disease: a study of donepezil in Alzheimer's disease. CNS drugs 2006;20(4):311-325. [DOI: 2045 [pii]]

Kaufer 1998

Kaufer, D.. Beyond the cholinergic hypothesis: the effect of metrifonate and other cholinesterase inhibitors on neuropsychiatric symptoms in Alzheimer's disease. Dementia and geriatric cognitive disorders 1998;9 Suppl 2(Journal Article):8-14. [DOI: dem9b008 [pii]]

Kitamura 2011

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Lyketsos 2004

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Other references

Additional references

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Classification pending references

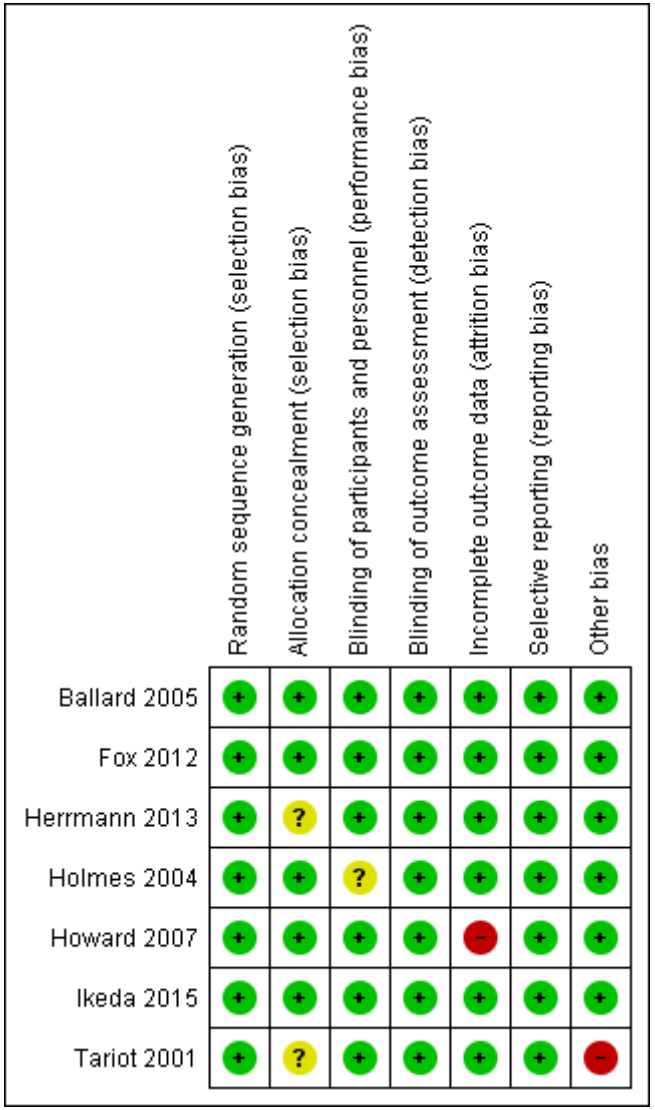
Data and analyses

1 Dementia medication vs Placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.2 BPSD, longest FU, max 12 mo	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 Quality of Life, end of treatment	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.4 Serious adverse events, end of treatment	5	1127	Risk Ratio (IV, Random, 95% CI)	0.81 [0.46, 1.42]
1.5 BPSD (NPI), end of treatment	7	1204	Mean Difference (IV, Random, 95% CI)	-1.60 [-4.28, 1.08]

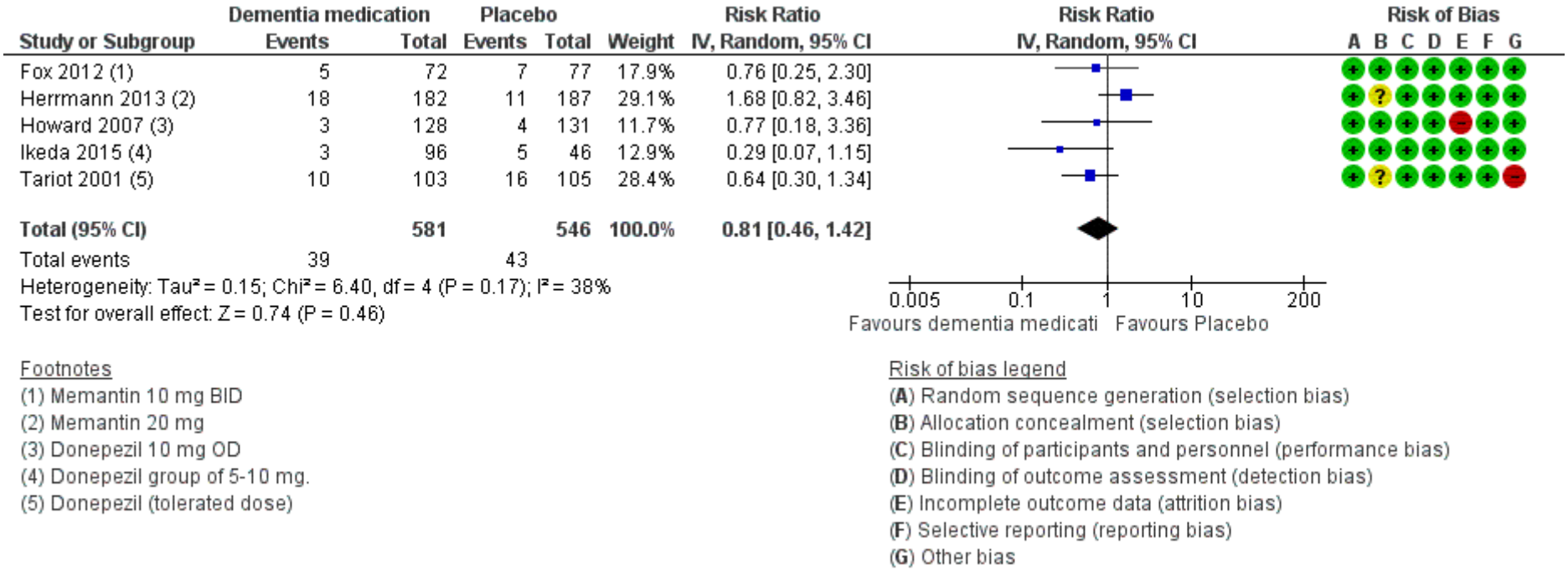
Figures

Figure 1



Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2 (Analysis 1.4)

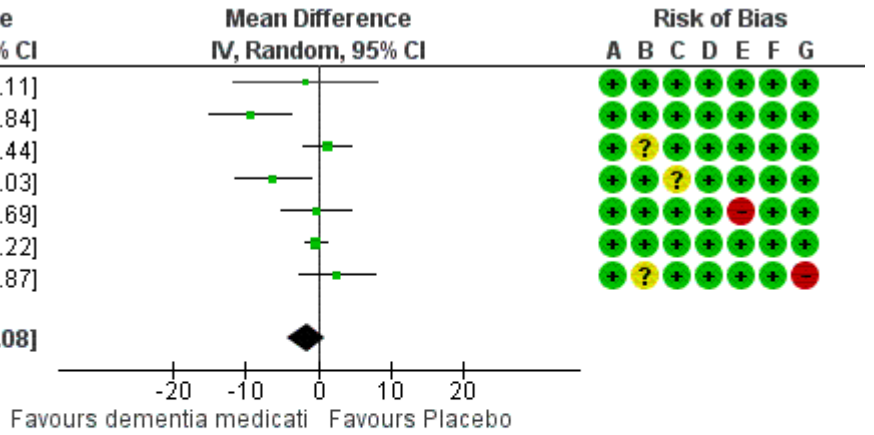


Forest plot of comparison: 1 Dementia medication vs Placebo, outcome: 1.4 Serious adverse events, end of treatment.

Figure 3 (Analysis 1.5)

Study or Subgroup	Dementia medication Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ballard 2005 (1)	-10.8	19.9	24	-9	16.5	30	5.7%	-1.80 [-11.71, 8.11]
Fox 2012 (2)	18.4	14.1438	73	27.8	18.5643	65	12.2%	-9.40 [-14.96, -3.84]
Herrmann 2013 (3)	-3.9	15.64	182	-5.13	15.8	187	18.7%	1.23 [-1.98, 4.44]
Holmes 2004 (4)	-2.9	10.24	41	3.3	15.57	55	13.1%	-6.20 [-11.37, -1.03]
Howard 2007 (5)	3.56	17.73	104	3.78	17.75	97	13.8%	-0.22 [-5.13, 4.69]
Ikeda 2015 (6)	-2.3255	4.5291	94	-2	4.2	44	23.6%	-0.33 [-1.87, 1.22]
Tariot 2001 (7)	-2.3	19.28	103	-4.9	19.5	105	12.9%	2.60 [-2.67, 7.87]
Total (95% CI)			**621**			**583**	**100.0%**	**-1.60 [-4.28, 1.08]**

Heterogeneity: Tau² = 7.30; Chi² = 16.96, df = 6 (P = 0.009); I² = 65%
Test for overall effect: Z = 1.17 (P = 0.24)



Footnotes
(1) Rivastigmine 6-12 mg/day
(2) Memantin 10 mg BID
(3) Memantin 20 mg
(4) Donepezil 10 mg OD
(5) Donepezil 10 mg OD
(6) NPI. Donepezil groups of 5 mg and 10 mg have been pooled.
(7) Donepezil (tolerated dose)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Forest plot of comparison: 1 Dementia medication vs Placebo, outcome: 1.5 BPSD (NPI), end of treatment.

Feedback