NKR53_ Demens og adfærd_PICO9_SSRI

Review information

Authors

Sundhedsstyrelsen[1]

[1][Empty affiliation]

Citation example: S. NKR53_ Demens og adfærd_PICO9_SSRI. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Characteristics of studies

Characteristics of included studies

Banerjee 2011

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	For more information see: Orgeta, Vasiliki, et al. "Efficacy of Antidepressants for Depression in Alzheimer's Disease: Systematic Review and Meta-Analysis." *Journal of Alzheimer's Disease* 58.3 (2017): 725-733.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Finkel 2004

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	For more information see: Jones, Helen E., et al. "The effect of treatment with selective serotonin reuptake inhibitors in comparison to placebo in the progression of dementia: a systematic review and meta-analysis." *Age and ageing* 45.4 (2016): 448-456.

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Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Leonpacher 2016

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Age. Mean, SD*: 78 (9) ● *MMSE. Mean, SD*: 17.0 (6.2) Control ● *Age. Mean, SD*: 79 (8) ● *MMSE. Mean, SD*: 14.4 (6.9) **Included criteria:** To summarize, 186 study participants were diagnosedwith probable Alzheimer's disease as defined by the NationalInstitute of Neurological and Communicative Disorders andStroke–Alzheimer's Disease and Related Disorders Associ-ation criteria (26) and had Mini-Mental State Examination(27) scores ranging from 5 to 28. Additional inclusion cri-teria included"clinically significant agitation"for which aphysician determined that medication was appropriateand which was rated as occurring"very frequently"or"frequently"with"moderate"or"marked"severity, asassessed by the agitation/aggression item of the NPI. **Excluded criteria:** Exclusion criteria included a current major depressive episodeor psychosis requiring antipsychotic treatment. A readilyavailable caregiver was required, to provide information foroutcome measures and to supervise medication use. **Pretreatment:** The baseline characteristics were similar between thecitalopram and placebo groups, except that the placebogroup had a lower mean score on the Mini-Mental State Ex-amination

Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Citalopram 30mg/day ● *Length of treatment*: 9 weeks ● *Longest follow-up after end of treatment*: none Control ● *Description*: placebo ● *Length of treatment*: 9 weeks ● *Longest follow-up after end of treatment*: none
Outcomes	*BPSD (NPI, non-mood subscale)* ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** Supported by National Institute on Aging (NIA) and NIMH grantR01AG031348, and in part by NIH grant P50-AG05142 (to University ofSouthern California and Dr. Schneider). **Country:** USA **Setting:** Multicenter **Comments:** ClinicalTrials.gov identifier: NCT00898807 **Authors name:** Leonpacher **Institution:** Department of Psychiatry **Email:** anton_porsteinsson@urmc.rochester.edu
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: From Drye 2012: Participants are randomized in a 1:1 ratio to receive citalopram or matching placebo. Thetreatment assignment schedule was created by the coordinating center using a documented,auditable SAS program (SAS/STAT® software, Version 9.1 of the SAS System forWindows; Copyright © 2000–2004 SAS Institute Inc, Cary NC, USA) and was generated inblocks of permuted length and stratified by clinical center. Clinical centers request treatmentassignments using an online program

		accessible via the CitAD data system.
Allocation concealment (selection bias)	Low risk	Judgement Comment: From Drye 2012: The corresponding medication kits are packaged by the Johns Hopkins Bayview Medical Center Pharmacy to contain either citalopram or placebo according to the treatment assignment schedule and are labeled by medication kit ID only. Masking is accomplished by over-encapsulatingcitalopram tablets and creating matching placebos both backfilled with microcrystallinecellulose into opaque capsules.
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: Treatments are administeredin a double-masked fashion; participants, their caregivers and clinical center personnel areall masked to treatment assignment.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Nothing mentioned on outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Porsteinsson et al (ref 20) provide a flowchart including dropouts. Reasons for missing data are provided and balanced between groups
Selective reporting (reporting bias)	Low risk	Judgement Comment: Matches study protocol.
Other bias	Low risk	Judgement Comment: No other apparent sources of bias

Lyketsos 2003

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	For more information see: Orgeta, Vasiliki, et al. "Efficacy of Antidepressants for Depression in Alzheimer's Disease: Systematic Review and Meta-Analysis." *Journal of Alzheimer's Disease* 58.3 (2017): 725-733.

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Other bias	Unclear risk	

Magai 2000

Methods	
Participants	
Interventions	
Outcomes	
Identification	
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Other bias	Unclear risk	

Petracca 2001

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	For more information see: Orgeta, Vasiliki, et al. "Efficacy of Antidepressants for Depression in Alzheimer's Disease: Systematic Review and Meta-Analysis." *Journal of Alzheimer's Disease* 58.3 (2017): 725-733.

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Other bias	Unclear risk	

Pollock 2002

Methods	
Participants	
Interventions	
Outcomes	
Identification	
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Other bias	Unclear risk	

Porsteinsson 2014

Methods	
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Interventions	
Outcomes	
Identification	
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Other bias	Unclear risk	

Rosenberg 2010

Methods	
Participants	
Interventions	
Outcomes	

Identification	
Notes	For more information see: Orgeta, Vasiliki, et al. "Efficacy of Antidepressants for Depression in Alzheimer's Disease: Systematic Review and Meta-Analysis." *Journal of Alzheimer's Disease* 58.3 (2017): 725-733.

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Weintraub 2010

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	For more information see: Jones, Helen E., et al. "The effect of treatment with selective serotonin reuptake inhibitors in comparison to placebo in the progression of dementia: a systematic review and meta-analysis." *Age and ageing* 45.4 (2016): 448-456.

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Other bias	Unclear risk	

Footnotes

Characteristics of excluded studies

An 2017

Reason for exclusion	Wrong intervention

Auer 1996

Reason for exclusion	Wrong outcomes

Banerjee 2013

Reason for exclusion	Wrong patient population

Callegari 2016

Reason for exclusion	Wrong intervention

Lyketsos 2016

Reason for exclusion	Abstract only

Mowla 2007

Reason for exclusion	Wrong patient population

Nyth 1992

Reason for exclusion	Wrong patient population

Olafsson 1992

Reason for exclusion	Wrong patient population

Schneider 2016

Reason for exclusion	Wrong study design

Viscogliosi 2017

Reason for exclusion	Wrong comparator

Footnotes

References to studies

Included studies

Banerjee 2011

Banerjee, S.; Hellier, J.; Dewey, M.; Romeo, R.; Ballard, C.; Baldwin, R.; Bentham, P.; Fox, C.; Holmes, C.; Katona, C.; Knapp, M.; Lawton, C.; Lindesay, J.; Livingston, G.; McCrae, N.; Moniz-Cook, E.; Murray, J.; Nurock, S.; Orrell, M.; O'Brien, J.; Poppe, M.; Thomas, A.; Walwyn, R.; Wilson, K.; Burns, A.. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. Lancet (London, England) 2011;378(9789):403-411. [DOI: 10.1016/S0140-6736(11)60830-1 [doi]]

Finkel 2004

Finkel, S. I.; Mintzer, J. E.; Dysken, M.; Krishnan, K. R.; Burt, T.; McRae, T.. A randomized, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. International journal of geriatric psychiatry 2004;19(1):9-18. [DOI: 10.1002/gps.998 [doi]]

Leonpacher 2016

Leonpacher, Anne K.; Peters, Matthew E.; Drye, Lea T.; Makino, Kelly M.; Newell, Jeffery A.; Devanand, D. P.; Frangakis, Constantine; Munro, Cynthia A.; Mintzer, Jacobo E.; Pollock, Bruce G.; Rosenberg, Paul B.; Schneider, Lon S.; Shade, David M.; Weintraub, Daniel; Yesavage, Jerome; Lyketsos, Constantine G.; Porsteinsson, Anton P.; CitAD, Research Group. Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia: Evidence From the CitAD Study. The American Journal of Psychiatry 2016;173(5):473-80. [DOI: https://dx.doi.org/10.1176/appi.ajp.2016.15020248]

Lyketsos 2003

Lyketsos, C. G.; DelCampo, L.; Steinberg, M.; Miles, Q.; Steele, C. D.; Munro, C.; Baker, A. S.; Sheppard, J. M.; Frangakis, C.; Brandt, J.; Rabins, P. V.. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. Archives of General Psychiatry 2003;60(7):737-746. [DOI: 10.1001/archpsyc.60.7.737 [doi]]

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Pollock 2002

Pollock, B. G.; Mulsant, B. H.; Rosen, J.; Sweet, R. A.; Mazumdar, S.; Bharucha, A.; Marin, R.; Jacob, N. J.; Huber, K. A.; Kastango, K. B.; Chew, M. L.. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. The American Journal of Psychiatry 2002;159(3):460-465. [DOI: 10.1176/appi.ajp.159.3.460 [doi]]

Porsteinsson 2014

Porsteinsson, A. P.; Drye, L. T.; Pollock, B. G.; Devanand, D. P.; Frangakis, C.; Ismail, Z.; Marano, C.; Meinert, C. L.; Mintzer, J. E.; Munro, C. A.; Pelton, G.; Rabins, P. V.; Rosenberg, P. B.; Schneider, L. S.; Shade, D. M.; Weintraub, D.; Yesavage, J.; Lyketsos, C. G.; CitAD Research Group. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. Jama 2014;311(7):682-691. [DOI: 10.1001/jama.2014.93 [doi]]

Rosenberg 2010

Rosenberg, P. B.; Drye, L. T.; Martin, B. K.; Frangakis, C.; Mintzer, J. E.; Weintraub, D.; Porsteinsson, A. P.; Schneider, L. S.; Rabins, P. V.; Munro, C. A.; Meinert, C. L.; Lyketsos, C. G.; DIADS-2 Research Group. Sertraline for the treatment of depression in Alzheimer disease. The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry 2010;18(2):136-145. [DOI: 10.1097/JGP.0b013e3181c796eb [doi]]

Weintraub 2010

Weintraub, D.; Rosenberg, P. B.; Drye, L. T.; Martin, B. K.; Frangakis, C.; Mintzer, J. E.; Porsteinsson, A. P.; Schneider, L. S.; Rabins, P. V.; Munro, C. A.; Meinert, C. L.; Lyketsos, C. G.; DIADS-2 Research Group. Sertraline for the treatment of depression in Alzheimer disease: week-24 outcomes. The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry 2010;18(4):332-340. [DOI: 10.1097/JGP.0b013e3181cc0333 [doi]]

Excluded studies

An 2017

An, Hoyoung; Choi, Booyeol; Park, Kun-Woo; Kim, Do-Hoon; Yang, Dong-Won; Hong, Chang Hyung; Kim, Seong Yoon; Han, Seol-Heui. The Effect of Escitalopram on Mood and Cognition in Depressive Alzheimer's Disease Subjects. Journal of Alzheimer's disease : JAD 2017;55(2):727-735. [DOI:]

Auer 1996

Auer, SR; Monteiro, I.; Torossian, C.; Sinaiko, E.; Boksay, I.; Reisberg, B.. The treatment of behavioral symptoms in dementia: haloperidol, thioridazine, and fluoxetine: a double blind, placebo controlled eigth month study. In: Fifth International Conference on Alzheimer's Disease and Related Disorders, Osaka, Japan, July 24–29, 1996. 1996;(Report):S162. [DOI:]

Banerjee 2013

Banerjee, S.; Hellier, J.; Romeo, R.; Dewey, M.; Knapp, M.; Ballard, C.; Baldwin, R.; Bentham, P.; Fox, C.; Holmes, C.; Katona, C.; Lawton, C.; Lindesay, J.; Livingston, G.; McCrae, N.; Moniz-Cook, E.; Murray, J.; Nurock, S.; Orrell, M.; O'Brien, J.; Poppe, M.; Thomas, A.; Walwyn, R.; Wilson, K.; Burns, A.. 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 (Winchester, England) 2013;17(7):1-166. [DOI: 10.3310/hta17070 [doi]]

Callegari 2016

Callegari, Ilaria; Mattei, Chiara; Benassi, Francesca; Krueger, Frank; Grafman, Jordan; Yaldizli, Ozgur; Sassos, Davide; Massucco, Davide; Scialo, Carlo; Nobili, Flavio; Serrati, Carlo; Amore, Mario; Cocito, Leonardo; Emberti Gialloreti, Leonardo; Pardini, Matteo. Agomelatine Improves Apathy in Frontotemporal Dementia. Neuro-degenerative diseases 2016;16(5-6):352-6. [DOI: https://dx.doi.org/10.1159/000445873]

Lyketsos 2016

Lyketsos C.G.; Pollock B.G.; Schneider L.; Porsteinsson A.P.. Citalopram for agitation in ad (CitAD): Pharmacokinetic studies, subgroup analyses, and effect on other neuropsychiatric symptoms. American Journal of Geriatric Psychiatry 2016;24(3):S36-S37. [DOI:]

Mowla 2007

Mowla, A.; Mosavinasab, M.; Haghshenas, H.; Borhani Haghighi, A.. Does serotonin augmentation have any effect on cognition and activities of daily living in Alzheimer's dementia? A double-blind, placebo-controlled clinical trial. Journal of clinical psychopharmacology 2007;27(5):484-487. [DOI: 10.1097/jcp.0b013e31814b98c1 [doi]]

Nyth 1992

Nyth, A. L.; Gottfries, C. G.; Lyby, K.; Smedegaard-Andersen, L.; Gylding-Sabroe, J.; Kristensen, M.; Refsum, H. -E; Öfsti, E.; Eriksson, S.; Syversen, S.. A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. Acta Psychiatrica Scandinavica 1992;86(2):138-145. [DOI: 10.1111/j.1600-0447.1992.tb03242.x]

Olafsson 1992

Olafsson, K.; Jorgensen, S.; Jensen, H. V.; Bille, A.; Arup, P.; Andersen, J.. Fluvoxamine in the treatment of demented elderly patients: a double-blind, placebo-controlled study. Acta Psychiatrica Scandinavica 1992;85(6):453-456. [DOI:]

Schneider 2016

Schneider, Lon S.; Frangakis, Constantine; Drye, Lea T.; Devanand, D. P.; Marano, Christopher M.; Mintzer, Jacob; Mulsant, Benoit H.; Munro, Cynthia A.; Newell, Jeffery A.; Pawluczyk, Sonia; Pelton, Gregory; Pollock, Bruce G.; Porsteinsson, Anton P.; Rabins, Peter V.; Rein, Lisa; Rosenberg, Paul B.; Shade, David; Weintraub, Daniel; Yesavage, Jerome; Lyketsos, Constantine G.; CitAD, Research Group. Heterogeneity of Treatment Response to Citalopram for Patients With Alzheimer's Disease With Aggression or Agitation: The CitAD Randomized Clinical Trial. The American Journal of Psychiatry 2016;173(5):465-72. [DOI: https://dx.doi.org/10.1176/appi.ajp.2015.15050648]

Viscogliosi 2017

Viscogliosi G.; Chiriac I.M.; Ettorre E.. Efficacy and Safety of Citalopram Compared to Atypical Antipsychotics on Agitation in Nursing Home Residents With Alzheimer Dementia. Journal of the American Medical Directors Association 2017;18(9):799-802. [DOI: http://dx.doi.org/10.1016/j.jamda.2017.06.010]

Data and analyses

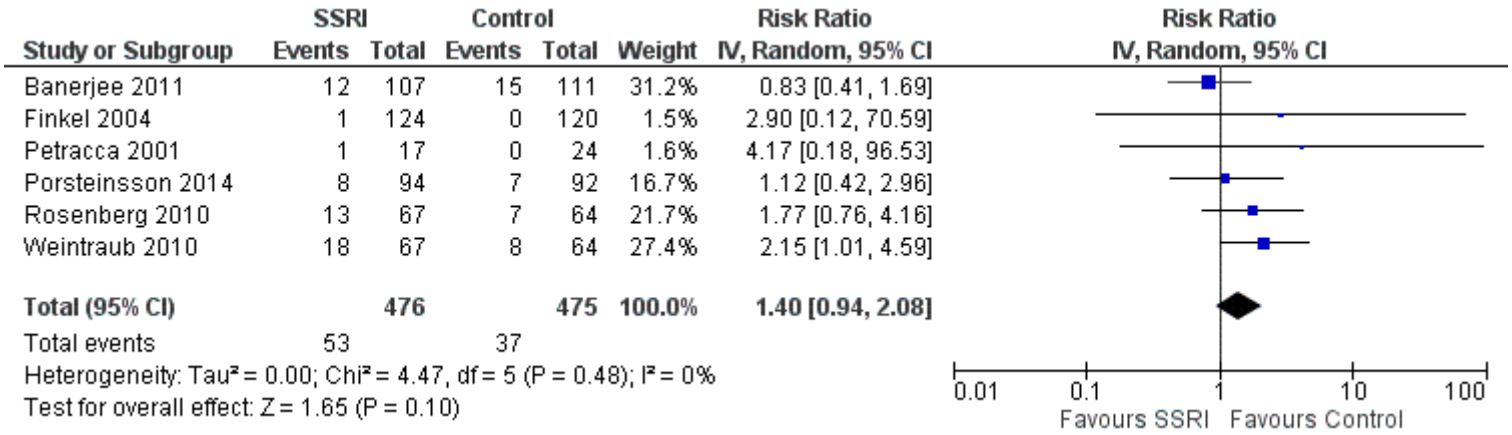
2 SSRI vs Control

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Serious adverse events	6	951	Risk Ratio (IV, Random, 95% CI)	1.40 [0.94, 2.08]
2.2 Usage of antipsychotics	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.3 Mortality	3	535	Risk Ratio (IV, Random, 95% CI)	0.80 [0.27, 2.32]
2.4 BPSD (NPI+Neurobehavioural rating scale+nonmood.) End of treatment	7		Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.48, 0.10]
2.11 BPSD (NPI) Longest follow-up	1		Mean Difference (IV, Fixed, 95% CI)	2.02 [-2.94, 6.98]
2.13 Kogntition	7	786	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.39, 0.20]

2.14 ADL (ADCS-ADL + PGDRS+ functional impairment+ BADL)	5		Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.20, 0.24]

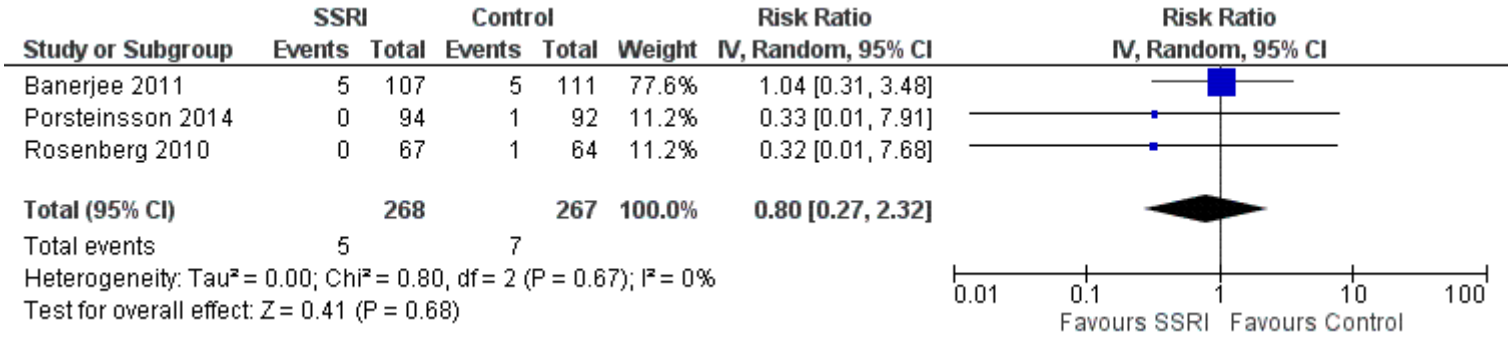
Figures

Figure 1 (Analysis 2.1)



Forest plot of comparison: 2 SSRI vs Control, outcome: 2.1 Serious adverse events.

Figure 2 (Analysis 2.3)

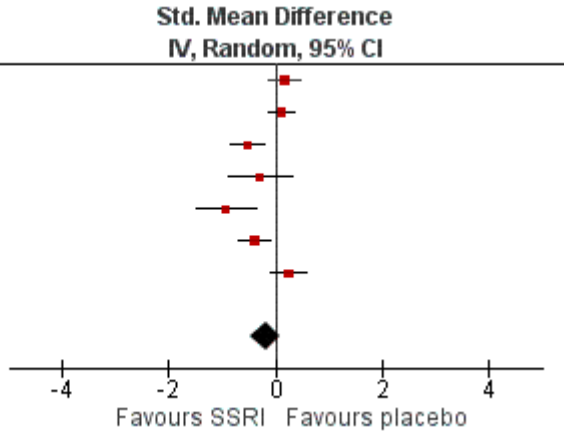


Forest plot of comparison: 2 SSRI vs Control, outcome: 2.3 Mortality.

Figure 3 (Analysis 2.4)

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Banerjee 2011	0.1715	0.1531	15.8%	0.17 [-0.13, 0.47]
Finkel 2004	0.12	0.1276	16.6%	0.12 [-0.13, 0.37]
Leonpacher 2016	-0.52	0.1582	15.6%	-0.52 [-0.83, -0.21]
Lyketsos 2003	-0.29	0.3061	10.4%	-0.29 [-0.89, 0.31]
Pollock 2002	-0.92	0.2959	10.8%	-0.92 [-1.50, -0.34]
Porsteinsson 2014	-0.39	0.1531	15.8%	-0.39 [-0.69, -0.09]
Weintraub 2010	0.25	0.1735	15.0%	0.25 [-0.09, 0.59]
Total (95% CI)			**100.0%**	**-0.19 [-0.48, 0.10]**

Heterogeneity: Tau² = 0.11; Chi² = 28.83, df = 6 (P < 0.0001); I² = 79%
Test for overall effect: Z = 1.27 (P = 0.20)

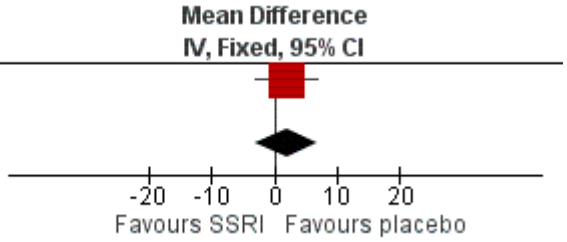


Forest plot of comparison: 2 SSRI vs Control, outcome: 2.4 BPSD (NPI+Neurobehavioural rating scale+nonmood.) End of treatment.

Figure 4 (Analysis 2.11)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Banerjee 2011	2.02	2.5307	100.0%	2.02 [-2.94, 6.98]
Total (95% CI)			**100.0%**	**2.02 [-2.94, 6.98]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)

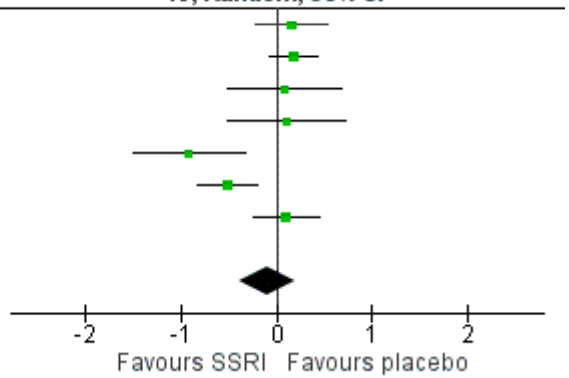


Forest plot of comparison: 2 SSRI vs Control, outcome: 2.11 BPSD (NPI) Longest follow-up.

Figure 5 (Analysis 2.13)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Banerjee 2011	-17.4	7.64	53	-18.63	7.12	56	15.5%	0.17 [-0.21, 0.54]
Finkel 2004	0	3.3407	124	-0.6	3.3	121	18.1%	0.18 [-0.07, 0.43]
Lyketsos 2003	-16.1	8.5	24	-16.8	7.1	20	11.2%	0.09 [-0.51, 0.68]
Petracca 2001	-23.2	6.8	17	-23.9	5.9	24	10.7%	0.11 [-0.51, 0.73]
Pollock 2002	43.5	12.1	31	56	15.2	21	11.4%	-0.92 [-1.50, -0.33]
Porsteinsson 2014	-16.83	2.95	85	-15.33	2.93	79	16.9%	-0.51 [-0.82, -0.20]
Weintraub 2010	21	11.7	67	20	6.85	64	16.2%	0.10 [-0.24, 0.45]
Total (95% CI)			**401**			**385**	**100.0%**	**-0.09 [-0.39, 0.20]**

Heterogeneity: Tau² = 0.11; Chi² = 22.50, df = 6 (P = 0.0010); I² = 73%
Test for overall effect: Z = 0.63 (P = 0.53)

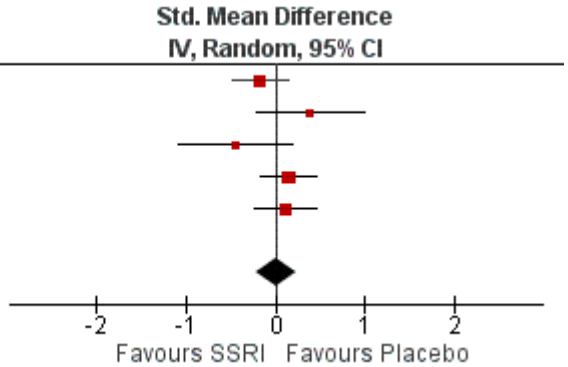


Forest plot of comparison: 2 SSRI vs Control, outcome: 2.13 Kogntition.

Figure 6 (Analysis 2.14)

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Banerjee 2011	-0.1756	0.1592	27.3%	-0.18 [-0.49, 0.14]
Lyketsos 2003	0.39	0.3061	11.1%	0.39 [-0.21, 0.99]
Petracca 2001	-0.45	0.3214	10.2%	-0.45 [-1.08, 0.18]
Porsteinsson 2014	0.15	0.1582	27.5%	0.15 [-0.16, 0.46]
Weintraub 2010	0.12	0.1786	23.9%	0.12 [-0.23, 0.47]
Total (95% CI)			**100.0%**	**0.02 [-0.20, 0.24]**

Heterogeneity: Tau² = 0.02; Chi² = 6.10, df = 4 (P = 0.19); I² = 34%
Test for overall effect: Z = 0.17 (P = 0.87)



Forest plot of comparison: 2 SSRI vs Control, outcome: 2.14 ADL (ADCS-ADL + PGDRS+ functional impairment+ BADL).