The effect of treatment with Selective Serotonin Reuptake Inhibitors incomparison to placebo in the progression of dementia: a systematic review and meta-analysis

OXFORD UNIVERSITY PRESS | Age And Ageing

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Journal:	*Age and Ageing*
Manuscript ID	AA-15-0785.R1
Manuscript Category:	Systematic Review
Keywords:	SSRI, dementia, systematic review
Keypoints:	In patients with dementia there was no evidence of benefit or harm from SSRIs in terms of cognition, mood, agitation or ADLs., SSRIs were generally well tolerated with no increase in mortality but premature withdrawal from studies was high., Large, methodologically robust studies are required.

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Revision Sheet

Instructions for authors:

1. In the first column please briefly summarise each point raised by the referee or editor.
2. In the second column, briefly explain how you have responded to each point.
3. In the third column, give the location in the text of the modification – with page and paragraph number reference.
4. Please upload this form to Manuscript Central alongside your revised paper.

Manuscript title: **The effect of treatment with Selective Serotonin Reuptake Inhibitors in comparison to placebo in the progression of dementia: a systematic review and meta-analysis**

Please note that line number references linked to our responses correspond to the revised manuscript and not the manuscript with tracked changes.

Referee 1

Point raised by referee (please summarise)	Response by author (briefly explain)	Location in text: Page and paragraph reference
1. Is it possible to analyse the subtype of dementia such as Alzheimer Disease or other dementia?	Thank you. We agree that this is an important issue. We have clarified in the abstract and paper that we include all subtypes of dementia (see response to reviewer 2). As stated in the methods (lines 142-146). "Eight studies [15,16,20-22,24,26,28] restricted entry to only those with Alzheimer's dementia and three [23,25,27] recruited participants with vascular dementia and/or Alzheimer's. One study only recruited participants with frontotemporal dementia using internationally agreed criteria for diagnosis [19]." We did not prespecify any subgroup analyses when the systematic review protocol was registered, so did not conduct these. Details on the dementia subtype are included in Table 1. The studies included in the meta-analysis are all solely Alzheimer's disease (AD) (except Petracca 2011 which was mixed AD and vascular dementia (VaD), and only provided 6.7% weighting). We have added the description of the dementia diagnosis to the results section (lines 180, 185, 207, 210, 216). The studies where both AD and VaD were included did not provide data for dementia subtype separately, and only one study included fronto temporal dementia alone. We have added a sentence to the discussion (lines 335-340). "The majority of studies (n=8) included only patients with Alzheimer's disease (DSM III, DSM IV, or NINCDS-ADRDA criteria). Three included patients with either Alzheimer's or vascular dementia, and one just patients with fronto-temporal dementia. Data were insufficient to establish if dementia subtype affected response to SSRI."	Lines 142-146; page 11 lines 180,185; page 14 lines 207, 210; page 15 line 216; page 16 lines 335-340; page 23
2. Figure 2 is a low resolution image	Many thanks for highlighting this. The image has been reformatted. All images have now also been uploaded as separate files in addition to embedding them into the text.	Page 15
3. With reference to the paper Sepehry et al 2012 What is different from your study?	Thank you for pointing out this interesting paper. Sepehry et al review 12 studies (meta-analysis of six with 621 participants) of participants with Alzheimer's disease and comorbid depression. This included four studies (Petracca et al, 2001, Banerjee et al, 2011, DIADS-1 and DIADS-2) that were included in our review, but two that were not (Magai, Rozzini). This study found no difference in post-treatment MMSE or depression scores in patients treated with SSRI or placebo. Our review specifically included subjects without concurrent depression, and with all dementia subtypes eligible for inclusion, and limited it to randomised control trials only. We have included a section on this in the introduction (lines 60-65).	Lines 60-65;page 6

Referee 2

Point raised by referee (please summarise)	Response by author (briefly explain)	Location in text: Page and paragraph reference
1. Important subject	Thank you	
2. Why would one expect SSRIs to have any beneficial effect?	This has been added into the introduction section (lines 49-55).	Lines 49-55 page 6
3. All dementias or just Alzheimer disease?	Thank you. We have clarified this in abstract and in methods section. See comments to reviewer 1.	
4. need to spell out "ALOIS" first time used	"ALzheimer's and cOgnitive Improvement Studies" register added to abstract and methods	Line 10; page 4, line 76; page 7
5. Methods: what languages?	English only. This has been added into the methods section (line 77).	Line 77; page 7
6. Methods: what kind of responses, from how many?	Two authors kindly provided their continuous data on cognitive assessment. This information has been added (line 112-114).	Lines 112-114; page 9
7. Isn't this finding re a lack of response in depression outcomes a bit surprising given that SSRIs are antidepressants? Makes the reader wonder about internal validity of the analysis?	We agree, but it is consistent with an Health Technology Assessment funded randomised controlled trial of sertraline or mirtazapine in 326 patients (Banerjee et al, 2013, Health Technol Assess 2013;17:1–166) and the systematic review and meta-analysis of 621 patients Sepehry et al (2012) which shows no effect of SSRIs on patients with AD and concurrent depression, and suggests that they be used with caution and with an individualised approach. The lack of response could be a type II error, due to inadequate power in included studies, heterogeneity in included subjects, differences in outcome scales, short duration of follow-up, or may be a true negative: the effect of SSRIs on patients with dementia may be different than those without dementia. We have added a comment and this reference to the discussion (line 291).	Line 291; page 21
8. P19, line 8 suggest change wording : "…no increase in mortality with SSRI compared to placebo."	Wording changed as per your recommendations above – "compared to placebo" has been added in (line 261).	Line 261; page 20
9. P 20 lines 14-23.Why mention this? Isn't the purpose of a meta analysis to group and summarize data so we are not dependent on the results of only one study?	We agree with your comment and as it does not add anything to the review it has been deleted.	

Associate Editor

No action points required.

The effect of treatment with Selective Serotonin Reuptake Inhibitors in comparison to placebo in the progression of dementia: a systematic review and meta-analysis

TRACKED CHANGES

Abstract

Background: Selective serotonin reuptake inhibitors (SSRIs) may affect the neurodegenerative process of dementia, enhancing ~~memory and~~ cognition. This systematic review aims to determine whether SSRIs influence cognitive performance, mood and function in people with any type of dementia.

Method: Randomised placebo-controlled studies of SSRIs in people with dementia, which recorded cognitive outcomes, were identified in ALOIS (ALzheimer's and cOgnitive Improvement Studies register) in April 2013 and updated in January 2015. Data were extracted on cognition, agitation, mood, activities of daily living (ADLs) and adverse events. End of treatment statistics were calculated.

Results: Twelve studies met inclusion criteria (1174 participants), of which seven studies (710 participants) provided data for meta-analysis on cognition. There was no difference in MMSE score at end of treatment; mean difference (MD) was 0.28 (95%CI -0.83 to 1.39) (six studies,470 participants). For change in MMSE scores, there was a small improvement; MD was 0.53 (95%CI -0.07 to 1.14) (three studies,352 participants). The remaining studies showed no improvement in cognition. There was no statistically significant benefit of SSRIs on mood (four studies,317 participants); standard mean difference (SMD) -0.10 (95%CI -0.39 to 0.2), agitation (three studies,189 participants); SMD -0.01 (95%CI -0.86 to 0.83), or ADLs at end of treatment (four studies,336 participants); SMD -0.15 (95%CI -0.45 to 0.15). ~~SSRIs were generally well tolerated with~~ There was no difference ~~no increase~~

in mortality between the two groups. Study quality was mixed with concerns over incomplete data.

Conclusion: A small number of relatively low-powered studies showed no benefit or harm from SSRIs in terms of ~~Evidence from few studies shows neither benefit nor harm from SSRIs in terms of~~ cognition, mood, agitation or ADLs. Large, methodologically robust studies are needed.

Key words: SSRI, dementia, systematic review, placebo

Key findings:

In patients with dementia ~~The available evidence from few studies shows neither~~there was no evidence of benefit or harm from SSRIs in terms of cognition, mood, agitation or ADLs.

SSRIs were generally well tolerated with no increase in mortality but premature withdrawal from studies was high.

Large, methodologically robust studies are required.

Background

Selective Serotonin Reuptake Inhibitors (SSRIs) are effective in the treatment of depression [1], and other conditions such as obsessive–compulsive disorder, panic disorder, and bulimia [2], but whether they have a role in the treatment of dementia is unclear. SSRIs have been used to manage neuropsychiatric symptoms in dementia, for example, a recent Cochrane review ~~by Seitz *et al* found some evidence to~~ supported the use of certain antidepressants for agitation and psychosis[3], but they are not used clinically to stabilise or improve cognition.

~~n theory, SSRIs could impact on the neurodegenerative process of dementia and help to enhance memory and cognition by promoting neurogenesis in the hippocampus [4]. Indeed, in patients with Alzheimer's dementia, reduced levels of serotonin and precursors such as tryptophan have been demonstrated at post-mortem [5].~~ SSRIs are highly selective for the neurotransmitter 5-hydroxytryptamine (5HT, serotonin) receptor and act by increasing the extracellular levels of serotonin through reuptake inhibition into the presynaptic cell [4]. In Alzheimer's dementia, there are reduced levels of serotonin and its precursors such as tryptophan [5]. In theory, SSRIs could increase these, promote neurogenesis [6], encourage migration of new neurones to damaged brain areas [7] and decrease inflammation [8]. All of which in turn could affect neurodegeneration, and thus have an impact on cognition.

~~A review of SSRIs in Alzheimer's dementia suggested some indirect evidence to support SSRIs as cognitive enhancers, but Chow *et al* used both preclinical and human clinical trial evidence [6]. There was a suggestion of benefit from fluoxetine~~

Comment [1]: This paragraph has been expanded below to include more on the biological plausibility of SSRIs

Comment [2]: This paragraph has been rephrased and the review by Sepehry et al included

~~treatment in one trial of fluoxetine versus placebo in mild cognitive impairment; the only trial found in a systematic review on this topic, the sample size was small and further randomised clinical studies were recommended [7].~~ It is unclear whether SSRIs affect cognition in dementia. A review including preclinical and clinical trials found some evidence to support SSRIs as cognitive enhancers [~~6~~9]. A randomised control trial of fluoxetine versus placebo in mild cognitive impairment showed some improvement [10], whereas a meta-analysis of SSRIs in patients with Alzheimer's disease and comorbid depression (six studies, 621paticipants) [11] found no effect on cognition or depression.

There is therefore a need for an updated review of the evidence for use of SSRIs in patients not just with Alzheimer's disease, but all subtypes of dementia, without limiting to those with a diagnosis of depression. The primary purpose of this new review was to assess the effect of SSRI medications compared with placebo on cognitive performance in people with dementia. Secondary outcomes were agitation, mood, the patient's ability to perform activities of daily living (ADLs) and adverse events.

~~Some studies have trialled SSRIs as a treatment for cognitive decline in dementia, and other studies investigating the effect of SSRIs on other outcomes such as mood have used cognition as an outcome measure, but there has been no recent systematic review of this evidence.~~

Methods

Search Strategy

The strategy was registered with Prospero in 2013: CRD42013003539 [~~8~~12]. ALOIS (ALzheimer's and cOgnitive Improvement Studies register) was used to identify all randomised controlled studies using SSRIs in dementia in English. ALOIS is a specialised open-access register maintained by Cochrane Dementia and Cognitive Improvement Group, derived from regular searches of a variety of major healthcare databases including MEDLINE and EMBASE [~~9~~13]. The search was performed in April 2013 and then again in January 2015 to identify any new studies.

The search was composed of the following terms: Selective Serotonin Reuptake Inhibitors; SSRI; citalopram**;** escitalopram**;** fluoxetine**;** fluvoxamine; paroxetine; and sertraline; combined with dementia (including subtypes). (The full search strategy used is shown in Supplement 1 in *Age and Ageing* online).

Selection Criteria

Two authors (AJ and HJ) independently assessed all titles and abstracts, obtained full texts for potentially relevant studies and applied the following inclusion criteria:

1. **Study type:** Published randomised placebo-controlled studies. Ongoing studies, studies not available in English and unpublished studies were excluded.
2. **Study group:** Individuals with a diagnosis of any type of dementia according to standard criteria. There was no age restriction and any type and severity of dementia was accepted. Participants with an additional diagnosis of depression

were accepted. Studies including participants with mild cognitive impairment and/or delirium without a distinct dementia group were excluded.

3. **Study intervention:** Placebo-controlled studies of SSRIs. Studies that referred to other antidepressants or used comparisons with other alternative active treatment were accepted if they included SSRI and placebo.

4. **Study outcomes:** Cognitive performance assessed by a validated cognitive test. Only one cognitive test was chosen from each study based on our pre-determined ranking system (Supplement 2 available in *Age and Ageing* online)[~~10~~14].

Any discrepancy or uncertainty regarding the eligibility of a study was discussed with a third author (GM or SS) until consensus was reached. If more than one publication reported data from the same participants, the publication which provided the most detail on our primary aim was used. Data was included as stated in the published papers, original protocols were not retrieved. Data from eligible studies were extracted by two independent reviewers (AJ and HJ) using a paper extraction form. Investigators were contacted for any missing data related to our primary aim. Two authors kindly responded and provided their continuous data on cognitive assessment [15,16].

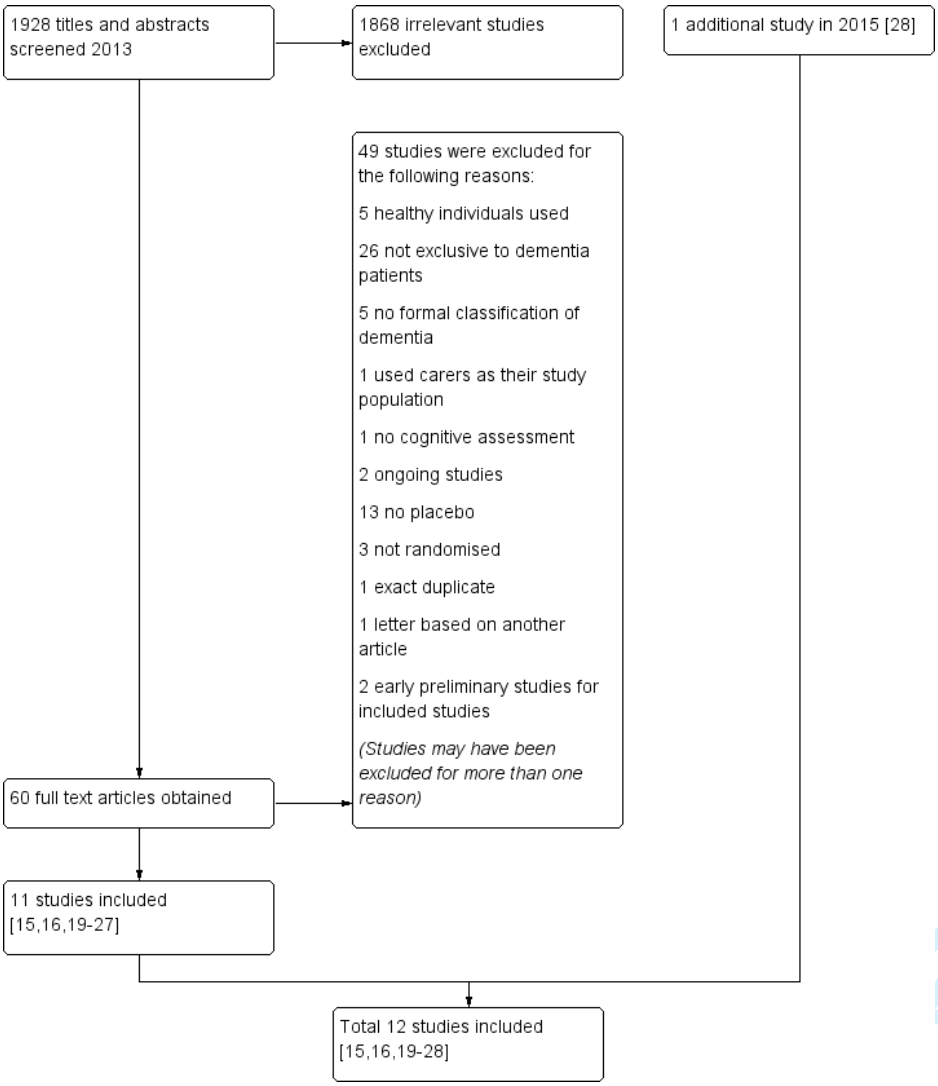
For studies with a placebo arm and two active arms, only data from the control arm and the SSRI arm were analysed. Methodological quality of included trials was assessed based on criteria listed in the Cochrane's Reviewers Handbook [~~11~~17]. Review Manager (RevMan5.1) software was used to calculate summary statistics at the end of intervention and follow-up using a random effects model [~~12~~18]. ~~Where~~

studies used the same scale to measure an outcome, mMean difference (MD) was used if studies used the same scales for outcomes, . If different scales were used, standard mean difference (SMD) was presentedif not [1117]. Statistical heterogeneity between studies and subgroups was assessed by I^2 statistic and interpreted according to the Cochrane Handbook. For dichotomous data, risk ratios (RRs) were reported.

Results

A total of 1928 study abstracts were assessed and 60 full texts were read (Figure 1). In total tTwelve studies met the inclusion criteria.

Figure 1. Flow diagram of selected studies



Patient characteristics

The 12 studies recruited ~~a total of~~ 1174 participants from nine countries~~.~~ (Table 1). Seven studies recruited from outpatient clinics, three studies [24-26] recruited inpatients and two studies [15,27] did not report the source of participants. The number of participants in each trial (SSRI and placebo participants only) ranged from

Comment [3]: all reference numbers have been altered due to the inclusion of new references earlier on

10 to 245, with five studies recruiting less than ~~a total of~~ 50 participants [15,19,22,23,25]. Nine studies [19-24,26-28] reported mean ages ~~which ranged~~ranging from 66.3 [19] to 80.9 years [24]. Eight studies [15,16,20-22,24,26,28] restricted entry to only those with Alzheimer's dementia and three [23,25,27] recruited participants with vascular dementia and/or Alzheimer's. One study only recruited participants with frontotemporal dementia using internationally agreed criteria for diagnosis [19]. Six [15,20,24-27] used DSM IV/DSM III (depending on the date of the study) ~~as part of their inclusion criteria~~to diagnose dementia and five ~~studies~~ [16,21-23,28] used NINCDS-ADRD.

~~One used internationally agreed criteria for frontotemporal dementia [13].~~

Study Characteristics

All 12 studies randomised participants to SSRI or placebo. Four used sertraline [15,20-22], three fluoxetine [15,23,26], three citalopram [24,27,28], one paroxetine [19] and one fluvoxamine [25]. Two studies had three arms: SSRI, placebo and a third treatment group [16,24]. The data from the third group have not been included in this review. In three studies [19,25,26], the primary aim was to assess efficacy of SSRI medications as a treatment for cognitive impairment in dementia. The remaining nine studies had this as a secondary aim.

The duration of treatment ranged from 17 days [24] to 39 weeks [16], ~~with a~~ mean of 14.3 weeks. ~~In addition, s~~Some studies incorporated other phases into the study such as a wash out or open label phase. In 11 studies, the dose of SSRI was gradually increased; some followed a set weekly regime, others allowed clinicians to

adjust doses based on response and tolerability [16,19-28]. Dose adjustment information was not available for one [15].

Table 1: Studies included in systematic review of SSRIs and placebo in the progression of dementia (ordered by reference number)

	AUTHOR	YEAR	COUNTRY	SAMPLE POPN	ENTRY NUMBER	DEMENTIA TYPE & CLASS	AGE years*	SEX (male)‡	SSRI USED	ADDITIONAL GROUP
[15]	Auer	1996	USA	-	17 Fluoxetine 13 Placebo	Alzheimer's Disease DSM IV	-	-	Fluoxetine	-
[16]	Banerjee	2011	UK	Outpatient	107 Sertraline 111 Placebo	Alzheimer's Disease NINCDS-ADRDA	-	SSRI 32% Placebo 36%	Sertraline	Mirtazapine
[19]	Deakin	2003	UK	Outpatient	10 total (cross over trial)	FTD internationally agreed criteria	Total 66.3(6.88)	70%	Paroxetine	-
[20]	Weintraub	2010	USA	Outpatient	67 Sertraline 64 Placebo	Alzheimer's Disease DSM IV	SSRI 76.5(8) Placebo 78.2(8)	54%	Sertraline	-
[21]	Finkel	2004	Finland	Outpatient	124 Sertraline 121 Placebo	Alzheimer's Disease NINCDS-ADRDA	Total 76.3(7.5) SSRI 75.7(7.7) Placebo 76.9(7.4)	43%	Sertraline	-
[22]	Lyketsos	2003	USA	Outpatient	24 Sertraline 20 Placebo	Alzheimer's Disease NINCDS-ADRDA	Total 77(8.4)	SSRI 18% Placebo 50%	Sertraline	-

[23]	Petracca	2001	Argentina	Outpatient	17 Fluoxetine 24 Placebo	Alzheimer's Disease and vascular dementia NINCDS-ADRDA	SSRI 70.2(6.3) Placebo 71.3 (6.9)	SSRI 53%, Placebo 29%	Fluoxetine	-
[24]	Pollock	2002	USA	Inpatient	31 Citalopram 21 Placebo	Alzheimer's Disease DSM IV	SSRI 80.9(6.9) Placebo 78.5 (8.5)	SSRI 79% Placebo 88%	Citalopram	Perphenazine
[25]	Olafsson	1992	Denmark	Inpatient	22 Fluvoxamine 24 Placebo	Alzheimer's Disease Vascular Dementia DSM III	SSRI 81[#] placebo 80[#]	SSRI 36% Placebo 46%	Fluvoxamine	-
[26]	Mowla	2007	Iran	Inpatient	41 Rivastigmine and Fluoxetine 41 Rivastigmine and Placebo	Alzheimer's Disease DSM IV	Total 69.2[†]	46.5%	Fluoxetine	-
[27]	Nyth	1990	Sweden, Norway and Denmark	-	44 Citalopram 45 Placebo	Alzheimer's Disease and vascular dementia DSM III	Total 77.6[†]	22%	Citalopram	-
[28]	Porsteinsson	2014	USA/Canada	Outpatient	94 Citalopram 92 Placebo	Alzheimer's Disease NINCDS-ADRDA	Total 78 (8) SSRI 78 (9) Placebo 79 (8)	15%	Citalopram	-

*mean (standard deviation) unless stated otherwise. # median † No standard deviation given. ‡ Overall % unless otherwise stated.
Abbreviations: FTD - Frontotemporal dementia. DSM III - Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition. DSM IV - Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. NINCDS-ADRDA - National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria.

All studies reported duration of treatment and measured outcomes at the end of treatment. For all but one trial [20], the end of treatment was the termination point of the trial with no subsequent follow-up reported.

Cognition

Mean score after treatment: There was no difference in mean MMSE (Mini Mental State Examination) scores at the end of treatment between SSRI and placebo groups. ~~Duration of treatment for t~~Trials that used MMSE scoring ~~was~~ lasted between 6 [23] and 39 weeks [16] ~~with a~~ mean of 16.75 weeks. Eight studies (841 participants) [15,16,20-23,26,28] used MMSE to assess cognition before and end of treatment, with six (470 participants) [15,16,22,23,26,28] reporting the mean MMSE at end of treatment, allowing data to be combined in meta-analysis. The MD at the end of treatment was 0.28 MMSE points (95% CI -0.83 to 1.39) with moderate heterogeneity (I^2 =38%, P=0.15) (Table 2, Figure 2a). All of these studies except one small study [23] included solely patients with Alzheimer's disease.

~~However, one study within the meta-analysis [24] showed the SSRI group to have a statistically significantly better MMSE score at the end of treatment compared to placebo (MD=1.50, 95% CI 0.60 to 2.90) with no difference at baseline. This study was considered to be of good quality and low risk for all aspects of bias.~~

Change in score after treatment: In studies that reported cognitive change, there was less cognitive decline when treated with SSRI. Three of the eight studies (352 participants) [15,21,26], all in patients with Alzheimer's disease, reported the difference in MMSE scores ~~between pre and post~~following treatment; MD was 0.53 (95% CI -0.07 to1.14), I^2= 0% P=0.92, Figure 2b). ~~Unfortunately, i~~It was not possible

to include all studies in the change of score analysis due to lack of availability of primary data.

Figure 2a. Mean MMSE scores at end of treatment (ordered by weighting)

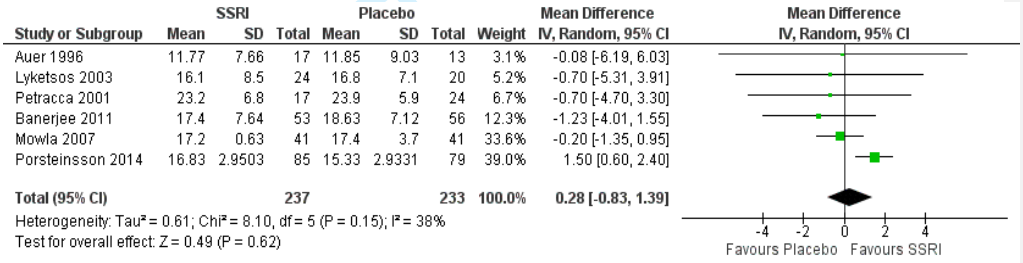
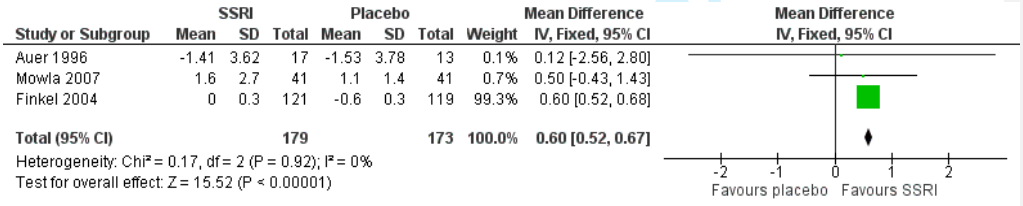


Figure 2b. Mean difference between MMSE scores before and after treatment (ordered weighting)



One study [20] only presented median scores and so the data could not be incorporated into either meta-analysis, but found no difference between groups. The median score (1st, 3rd quartiles) at the end of treatment was 21 (16.5, 24) and 20 (14.75, 24) in the control. Treatment effect was χ^2= 0.5 (degrees of freedom 1); p=0.50.

Four studies (196 participants) [19,24,25,27] including patients with Alzheimer's, vascular or fronto-temporal dementia ~~using other cognitive tools also~~ showed no

difference in cognition at the end of treatment with SSRI. One (10 participants) [19] found no significant differences on the Neuropsychiatric Inventory between paroxetine and placebo. For ~~another~~ one study in patients with Alzheimer's disease [24], the Neurobehavioural Factor cognition score from baseline to study termination was approximately 0.22 for citalopram and 0.06 for placebo (readings taken from graph). Within the citalopram group this was a statistically significant improvement from baseline, however, the difference in the change of score between the citalopram and placebo group was not statistically significant. ~~–~~Two studies ~~Another study [21]~~ in patients with Alzheimer's or vascular dementia found no difference in ~~examined~~ cognitive subscale scores on the GBS (Gottfries-Bråne-Steen) rating scale. At the end of treatment the median (range) was 38 (10-62) in the SSRI group and 42 (12-60) with placebo in one study [25], and in the other ~~. A further study~~ [27] ~~also showed no statistical difference between the groups on the GBS cognitive subscale~~there was no difference between the groups (T=32 (51), p=0.321) (Table 2). ~~The cognitive results of all the studies are detailed in Table 2.~~

The quality of the studies, as reported, was mixed, and the results should be interpreted with caution. ~~affecting our confidence in the results.~~ For many studies, the proportion of incomplete outcome data was a concern and at risk of introducing bias. Across the 12 studies, 338 of 1174 participants (29%) withdrew prior to the final assessment. At least 157 of these were from the SSRI group; one study [22] did not differentiate the groups from which the six participants withdrew. Six studies [16,21,23,25-27] had a significant drop out rate (~~defined as greater than~~> 5% [10]) and did not use intention-to-treat analysis. There was no statistically significant difference between the two groups in terms of premature trial withdrawal; (T-value=

0.44 and p=0.66). The main reasons for withdrawal were loss of efficacy, administrative reasons and adverse effects. Several studies also lacked sufficient information to determine risk of bias in relation to randomisation, allocation and blinding methods. The risk of bias for each trial is detailed in Supplement Table 1 (available in *Age and Ageing* online).

Table 2: Results of studies included in systematic review of SSRIs and placebo in the progression of dementia (ordered by reference number)

	AUTHOR	Highest Ranking Cognition Test [1]	SSRI Cognition Score		Placebo Cognition Score		Other outcomes
			Baseline	End of treatment	Baseline	End of treatment	
[15]	Auer	MMSE	12.94 (8.03)	11.77 (7.66)	13.30 (7.47)	11.85 (9.03)	-
[16]	Banerjee	MMSE	18.5 (6.7)	17.4 (7.64)	18.2 (7.4)	18.63 (7.12)	Mood, ADL impairment, Agitation, AE
[19]	Deakin	Neuropsychiatry Inventory	-	32.4 (7.2)*	-	28.8 (4.8)*	-
[20]	Weintraub	MMSE	21(17,35)#†	21(16.5,24)#†	19.5(15, 23.25)#†	20 (14.75,24)#†	Mood, ADL impairment, Agitation, AE
[21]	Finkel	MMSE	18.8 (0.5)*	[0 (0.3)*‡[	18.0 (0.5)*	[-0.6 (0.3)*‡]	Mood, Agitation
[22]	Lyketsos	MMSE	17.5 (6.5)	16.1 (8.5)	16.3 (6.8)	16.8 (7.1)	Mood, ADL impairment, Agitation, AE
[23]	Petracca	MMSE	23.2(4.5)	23.1 (6.8)	23.2 (5.3)	23.9 (5.9)	Mood, ADL impairment, AE

[24]	Pollock	Neurobehavioral subscale	-	[0.22‡]	-	[0.06‡]	Mood, Agitation, AE
[25]	Olafsson	GBS subscale	43 (3-62)#+	38 (10-62) #+	40 (15-62) #+	42(12-60) #+	AE
[26]	Mowla	MMSE	15.6 (0.73)	17.2 (0.63)	16.3 (4.1)	17.4 (3.7)	Mood, ADL impairment, AE
[27]	Nyth	GBS subscale	22.6	21.3	20.1	19.9	AE
[28]	Porsteinsson	MMSE	17.0 (6.2)	16.83 (2.95)	14.4 (6.9)	15.33 (2.93)	Agitation, ADL impairment, AE,

Data are mean cognition score (standard deviation) unless otherwise stated. *SE(standard error) #median † (1st and 3rd quartiles) + (ranges) ‡ mean change in score from baseline (end treatment value not available). Abbreviations: MMSE: Mini Mental State Examination, GBS: Gottfries-Bthne-Steen geriatric rating scale, ADL: Activities of Daily Living, AE: Adverse Events. [1] Supplementary data 2

Mood

There was no difference in ~~depression outcomes in people with dementia~~mood at the end of treatment between the SSRI and placebo group. Four studies (317 participants) [16,22,23,26] reported depression scores and demonstrated an SMD of -0.10 (95% CI, −0.39 to 0.2, I^2=37% P=0.19; Supplementary Figure 1 available in *Age and Ageing* online). The remaining eight studies either did not examine mood or did not report the results in a format compatible with the meta-analysis.

Agitation

There was no difference in mean agitation scores at the end of treatment. Three studies [19,24,28] reported agitation, of which two [19,28] could be included in ~~our~~ meta-analysis (189 participants); (SMD = -0.01, 95% CI -0.86 to 0.83, I^2=70%, P=0.07); Supplementary Figure 2 available in *Age and Ageing* online). The remaining trial [24] showed a significantly greater improvement in agitation/aggression (from baseline using the Neurobehavioural Factor Score) in the SSRI group (0.98) compared to placebo (0.38), (readings taken off graph; Kruskal-Wallis test X^2=6.7,df=2, p<0.04). Whilst this result is promising, methods used for concealment of allocation and randomisation were unclear, raising the possibility of selection bias. Nine studies did not examine agitation as an outcome.

Patient's ability to perform activities of daily living

There was no difference in a patient's ability to complete ADLs between the two groups. Four studies (336 participants) [22,23,26,28] reported participants' ability to perform ADLs at the end of treatment; (SMD = -0.15, 95%CI -0.45 to 0.15, I^2=41% P=0.17; Supplementary Figure 3 available in *Age and Ageing* online).

Adverse events and mortality

There was no increase in mortality with SSRI compared to placebo. Four studies [16,20,27,28] (624 participants) reported a combined total of 13 deaths. The risk ratio (RR) for death in the SSRI group was 0.91 (95% CI 0.33 to 2.50). Adverse events were reported in all but two studies [15,19] and were collected either systematically or volunteered by the patient. The RR for the number of participants experiencing at least one adverse event was 1.25 (95%CI 0.67, to 2.31, I^2=87% p<0.001) favouring placebo [16,20,27,28]. In studies reporting Other studies [15,18] reported the number of adverse events rather than the number of patients experiencing an event [21,23]. In these studies, there were 143 adverse events with sertraline, compared to 119 with placebo. One study [24] found no significant change in total UK Side Effect Rating Scale score in any of the groups (F=1.49, df=2, 81, p=0.23)., whilst 3 Three studies [22,25,26] just reported the most common side effects in both groups. Across the studies, these were typicallySide effects were gastrointestinal, neurological and autonomic disturbances.

Discussion

Summary of key findings

Twelve completed studies comparing SSRIs with placebo were indentified, of which seven provided data that could be used in a meta-analysis on cognition [15,16,21-23,26,28]. Sertraline was the most commonly used SSRI. All participants had a formal diagnosis of dementia, mostly Alzheimer's disease or vascular dementia, but none of the studies stipulated how long this had to have been present. Some, but not

all, studies required participants to have depression at the point of entry. The duration of treatment varied from days to months with a mean of 14.3 weeks. Only one study [19] followed up participants after treatment.

Overall, there were no beneficial effects of SSRIs on cognition, with the meta-analysis of MMSE scores at end of treatment demonstrating no statistically significant difference between SSRI and placebo. ~~However, one study [24] within the meta-analysis showed the SSRI group to have a significantly better MMSE score at the end of treatment compared to placebo. The change in MMSE scores, although a much smaller analysis, showed a slight small improvement in favour of SSRIs. However, this finding has to be interpreted with caution given the unclear quality of the included studies and concern over incomplete outcome data.~~ There was no statistical benefit of SSRI on mood, agitation or ADLs, though the number of studies is small and there was methodological bias in these studies. SSRIs may not be effective in treating depression in patients with dementia [11,16]. ~~The~~ Number of deaths was low with no ~~significant statistical~~ difference between the groups. There was no statistically significant difference in side effects between the two groups.~~, but a suggestion that there were more side-effects in those taking SSRIs.~~ .

Limitations of included studies

It is possible that variations in the quality of the evidence may have influenced the results of this review. The studies were generally small, the largest recruiting 245 participants [21], and were of mixed quality, with many displaying multiple different sources of bias. Some lacked important methodological detail, for example on sequence generation and allocation concealment, making it difficult to determine the

risk of bias. The funding source was declared in the majority of the trials, with occasional links to the pharmaceutical industry (e.g. funding [21], provision of drugs [16]).

All participants were generally recruited from tertiary centres, which often have more complex patients with more challenging symptoms. It is therefore unclear whether the findings can be extrapolated to the overall dementia population. The severity of dementia of participants included in the meta-analysis also varied, with mean scores ranging from 11 to 24 in the meta-analysis. It is therefore also feasible that there may be differences in effect depending on the stage of disease. Most studies did not exclude participants who also had concurrent depression and this could have acted as a confounding factor in influencing any changes to a patient's cognition [29]. Cognition scores may have also been affected for other reasons, including hearing impairment or non-English speaking participants.

The lack of long-term treatment and follow-up after treatment is a major limitation. From studies in participants with depression, it is known that SSRIs take time to show benefit and the dosage required can vary [2]. Some studies only lasted six weeks and had strict titration schedules. If cognitive tests are repeated there is the likelihood of practice effects, and this may mask a decline in cognition, though the effects would be similar in both groups. It is unlikely that cognitive change in a general, 30 point, cognitive test like the MMSE would be detectable over a period of several weeks. Although there was no significance difference in the withdrawal rate between the SSRI and placebo groups, there was an overall high premature drop out

of 29% with lack of efficacy and side effects being the main reasons. Ten studies reported side effects, but not all explained how these were collected.

Limitations of the review

The search criteria were deliberately broad to reduce the likelihood of any relevant published studies being missed when searching ALOIS. The main weakness of the search strategy was that any grey literature or unpublished studies would have been missed. Reported data was not checked against original published protocols and so this review is reliant on the reporting of the primary investigators.

The majority of studies (n=8) included only patients with Alzheimer's disease (DSM III, DSM IV, or NINCDS-ADRDA criteria) [15,16,20-22,24,26,28] . Three included patients with either Alzheimer's or vascular dementia [23,25,27], and one just patients with fronto-temporal dementia [19]. The majority of patients in the meta-analysis had Alzheimer's disease. Data were insufficient to establish if dementia subtype affected response to SSRI.

Conclusion

~~This review shows that a~~A small number of relatively low-powered studies show no benefit or harm from SSRIs in terms of cognitive outcomes in people with dementia~~, with one study suggestive of a small, statistically significant benefit.~~ .There is insufficient data to say whether SSRIs are beneficial for cognition, and there is some suggestion of increased side effects. Future studies require adequate numbers of different dementia subtypes to allow subgroup analyses, a longer duration of follow-

up, systematic reporting of adverse events, and clearer reporting of factors which may bias the results.

Conflicts of interest

None declared

Acknowledgements

Cochrane Dementia and Cognitive Improvement Group for providing the search database and Maureen Harding for sourcing full texts. The authors also wish to express their gratitude to Dr Banerjee and Dr Auer for providing additional primary data.

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The effect of treatment with Selective Serotonin Reuptake Inhibitors in comparison to placebo in the progression of dementia: a systematic review and meta-analysis

Abstract

Background: Selective serotonin reuptake inhibitors (SSRIs) may affect the neurodegenerative process of dementia, enhancing cognition. This systematic review aims to determine whether SSRIs influence cognitive performance, mood and function in people with any type of dementia.

Method: Randomised placebo-controlled studies of SSRIs in people with dementia, which recorded cognitive outcomes, were identified in ALOIS (ALzheimer's and cOgnitive Improvement Studies register) in April 2013 and updated in January 2015. Data were extracted on cognition, agitation, mood, activities of daily living (ADLs) and adverse events. End of treatment statistics were calculated.

Results: Twelve studies met inclusion criteria (1174 participants), of which seven studies (710 participants) provided data for meta-analysis on cognition. There was no difference in MMSE score at end of treatment; mean difference (MD) was 0.28(95%CI -0.83 to 1.39) (six studies,470 participants). For change in MMSE scores, there was a small improvement; MD was 0.53(95%CI -0.07 to 1.14) (three studies,352 participants). The remaining studies showed no improvement in cognition. There was no statistically significant benefit of SSRIs on mood (four studies,317 participants); standard mean difference (SMD) -0.10(95%CI -0.39 to 0.2), agitation (three studies,189 participants); SMD -0.01(95%CI -0.86 to 0.83), or ADLs at end of treatment (four studies,336 participants); SMD -0.15(95%CI -0.45 to 0.15). There was no difference in mortality between the two groups. Study quality was mixed with concerns over incomplete data.

Conclusion: A small number of relatively low-powered studies showed no benefit or harm from SSRIs in terms of cognition, mood, agitation or ADLs. Large, methodologically robust studies are needed.

Key words: SSRI, dementia, systematic review, placebo

Key findings:

In patients with dementia there was no evidence of benefit or harm from SSRIs in terms of cognition, mood, agitation or ADLs.

SSRIs were generally well tolerated with no increase in mortality but premature withdrawal from studies was high.

Large, methodologically robust studies are required.

Background

Selective Serotonin Reuptake Inhibitors (SSRIs) are effective in the treatment of depression [1], and other conditions such as obsessive–compulsive disorder, panic disorder, and bulimia [2], but whether they have a role in the treatment of dementia is unclear. SSRIs have been used to manage neuropsychiatric symptoms in dementia, for example, a recent Cochrane review supported the use of certain antidepressants for agitation and psychosis[3], but they are not used clinically to stabilise or improve cognition.

SSRIs are highly selective for the neurotransmitter 5-hydroxytryptamine (5HT, serotonin) receptor and act by increasing the extracellular levels of serotonin through reuptake inhibition into the presynaptic cell [4]. In Alzheimer's dementia, there are reduced levels of serotonin and its precursors such as tryptophan [5]. In theory, SSRIs could increase these, promote neurogenesis [6], encourage migration of new neurones to damaged brain areas [7] and decrease inflammation [8]. All of which in turn could affect neurodegeneration and thus have an impact on cognition.

It is unclear whether SSRIs affect cognition in dementia. A review including preclinical and clinical trials found some evidence to support SSRIs as cognitive enhancers [9]. A randomised control trial of fluoxetine versus placebo in mild cognitive impairment showed some improvement [10], whereas a meta-analysis of SSRIs in patients with Alzheimer's disease and comorbid depression (six studies, 621paticipants) [11] found no effect on cognition or depression.

There is therefore a need for an updated review of the evidence for use of SSRIs in patients not just with Alzheimer's disease, but all subtypes of dementia, without limiting to those with a diagnosis of depression. The primary purpose of this new review was to assess the effect of SSRI medications compared with placebo on cognitive performance in people with dementia. Secondary outcomes were agitation, mood, the patient's ability to perform activities of daily living (ADLs) and adverse events.

Methods

Search Strategy

The strategy was registered with Prospero in 2013: CRD42013003539 [12]. ALOIS (ALzheimer's and cOgnitive Improvement Studies register) was used to identify all randomised controlled studies using SSRIs in dementia in English. ALOIS is a specialised open-access register maintained by Cochrane Dementia and Cognitive Improvement Group, derived from regular searches of a variety of major healthcare databases including MEDLINE and EMBASE [13]. The search was performed in April 2013 and then again in January 2015 to identify any new studies.

The search was composed of the following terms: Selective Serotonin Reuptake Inhibitors; SSRI; citalopram**;** escitalopram**;** fluoxetine**;** fluvoxamine; paroxetine; and sertraline; combined with dementia (including subtypes). (The full search strategy used is shown in Supplement 1 in *Age and Ageing* online).

Selection Criteria

Two authors (AJ and HJ) independently assessed all titles and abstracts, obtained full texts for potentially relevant studies and applied the following inclusion criteria:

1. **Study type:** Published randomised placebo-controlled studies. Ongoing studies, studies not available in English and unpublished studies were excluded.
2. **Study group:** Individuals with a diagnosis of any type of dementia according to standard criteria. There was no age restriction and any type and severity of dementia was accepted. Participants with an additional diagnosis of depression were accepted. Studies including participants with mild cognitive impairment and/or delirium without a distinct dementia group were excluded.
3. **Study intervention:** Placebo-controlled studies of SSRIs. Studies that referred to other antidepressants or used comparisons with other alternative active treatment were accepted if they included SSRI and placebo.
4. **Study outcomes:** Cognitive performance assessed by a validated cognitive test. Only one cognitive test was chosen from each study based on our pre-determined ranking system (Supplement 2 available in *Age and Ageing* online)[14].

Any discrepancy or uncertainty regarding the eligibility of a study was discussed with a third author (GM or SS) until consensus was reached. If more than one publication reported data from the same participants, the publication which provided the most detail on our primary aim was used. Data was included as stated in the published papers, original protocols were not retrieved. Data from eligible studies were extracted by two independent reviewers (AJ and HJ) using a paper extraction form.

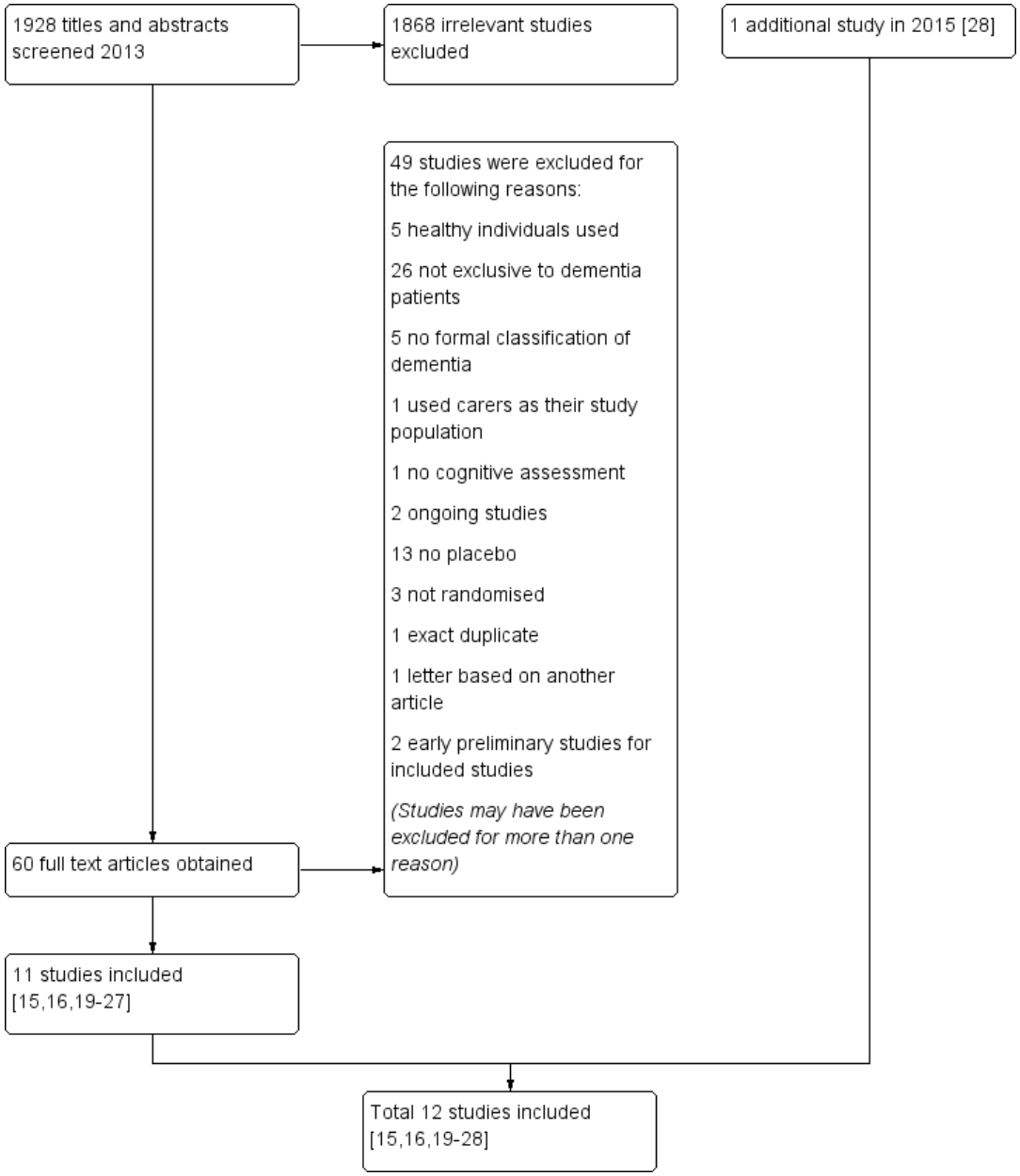
Investigators were contacted for any missing data related to the primary aim. Two authors kindly responded and provided their continuous data on cognitive assessment [15,16].

For studies with a placebo arm and two active arms, only data from the control arm and the SSRI arm were analysed. Methodological quality of included trials was assessed based on criteria listed in the Cochrane's Reviewers Handbook [17]. Review Manager (RevMan5.1) software was used to calculate summary statistics at the end of intervention and follow-up using a random effects model [18]. Mean difference (MD) was used if studies used the same scales for outcomes, standard mean difference (SMD) if not [17]. Statistical heterogeneity between studies and subgroups was assessed by I^2 statistic and interpreted according to the Cochrane Handbook. For dichotomous data, risk ratios (RRs) were reported.

Results

1928 study abstracts were assessed and 60 full texts were read (Figure 1). Twelve studies met the inclusion criteria.

Figure 1. Flow diagram of selected studies



Patient characteristics

The 12 studies recruited 1174 participants from nine countries (Table 1). Seven studies recruited from outpatient clinics, three studies [24-26] recruited inpatients and two studies [15,27] did not report the source of participants. The number of

participants in each trial (SSRI and placebo participants only) ranged from 10 to 245, with five studies recruiting less than 50 participants [15,19,22,23,25]. Nine studies [19-24,26-28] reported mean ages ranging from 66.3 [19] to 80.9 years [24]. Eight studies [15,16,20-22,24,26,28] restricted entry to only those with Alzheimer's dementia and three [23,25,27] recruited participants with vascular dementia and/or Alzheimer's. One study only recruited participants with frontotemporal dementia using internationally agreed criteria for diagnosis [19]. Six [15,20,24-27] used DSM IV/DSM III (depending on the date of the study) to diagnose dementia and five [16,21-23,28] used NINCDS-ADRD.

Study Characteristics

All 12 studies randomised participants to SSRI or placebo. Four used sertraline [16,20-22], three fluoxetine [15,23,26], three citalopram [24,27,28], one paroxetine [19] and one fluvoxamine [25]. Two studies had three arms: SSRI, placebo and a third treatment group [16,24]. The data from the third group have not been included in this review. In three studies [19,25,26], the primary aim was to assess efficacy of SSRI medications as a treatment for cognitive impairment in dementia. The remaining nine studies had this as a secondary aim.

The duration of treatment ranged from 17 days [24] to 39 weeks [16], mean of 14.3 weeks. Some studies incorporated other phases into the study such as a wash out or open label phase. In 11 studies, the dose of SSRI was gradually increased; some followed a set weekly regime, others allowed clinicians to adjust doses based on response and tolerability [16,19-28]. Dose adjustment information was not available for one study [15].

Table 1: Studies included in systematic review of SSRIs and placebo in the progression of dementia (ordered by reference number)

	AUTHOR	YEAR	COUNTRY	SAMPLE POPN	ENTRY NUMBER	DEMENTIA TYPE & CLASS	AGE years*	SEX (male)‡	SSRI USED	ADDITIONAL GROUP
[15]	Auer	1996	USA	-	17 Fluoxetine 13 Placebo	Alzheimer's Disease DSM IV	-	-	Fluoxetine	-
[16]	Banerjee	2011	UK	Outpatient	107 Sertraline 111 Placebo	Alzheimer's Disease NINCDS-ADRDA	-	SSRI 32% Placebo 36%	Sertraline	Mirtazapine
[19]	Deakin	2003	UK	Outpatient	10 total (cross over trial)	FTD internationally agreed criteria	Total 66.3(6.88)	70%	Paroxetine	-
[20]	Weintraub	2010	USA	Outpatient	67 Sertraline 64 Placebo	Alzheimer's Disease DSM IV	SSRI 76.5(8) Placebo 78.2(8)	54%	Sertraline	-
[21]	Finkel	2004	Finland	Outpatient	124 Sertraline 121 Placebo	Alzheimer's Disease NINCDS-ADRDA	Total 76.3(7.5) SSRI 75.7(7.7) Placebo 76.9(7.4)	43%	Sertraline	-
[22]	Lyketsos	2003	USA	Outpatient	24 Sertraline 20 Placebo	Alzheimer's Disease NINCDS-ADRDA	Total 77(8.4)	SSRI 18% Placebo 50%	Sertraline	-

[23]	Petracca	2001	Argentina	Outpatient	17 Fluoxetine 24 Placebo	Alzheimer's Disease and vascular dementia NINCDS-ADRDA	SSRI 70.2(6.3) Placebo 71.3 (6.9)	SSRI 53%, Placebo 29%	Fluoxetine	-
[24]	Pollock	2002	USA	Inpatient	31 Citalopram 21 Placebo	Alzheimer's Disease DSM IV	SSRI 80.9(6.9) Placebo 78.5 (8.5)	SSRI 79% Placebo 88%	Citalopram	Perphenazine
[25]	Olafsson	1992	Denmark	Inpatient	22 Fluvoxamine 24 Placebo	Alzheimer's Disease Vascular Dementia DSM III	SSRI 81[#] placebo 80[#]	SSRI 36% Placebo 46%	Fluvoxamine	-
[26]	Mowla	2007	Iran	Inpatient	41 Rivastigmine and Fluoxetine 41 Rivastigmine and Placebo	Alzheimer's Disease DSM IV	Total 69.2[†]	46.5%	Fluoxetine	-
[27]	Nyth	1990	Sweden, Norway and Denmark	-	44 Citalopram 45 Placebo	Alzheimer's Disease and vascular dementia DSM III	Total 77.6[†]	22%	Citalopram	-
[28]	Porsteinsson	2014	USA/Canada	Outpatient	94 Citalopram 92 Placebo	Alzheimer's Disease NINCDS-ADRDA	Total 78 (8) SSRI 78 (9) Placebo 79 (8)	15%	Citalopram	-

*mean (standard deviation) unless stated otherwise. # median † No standard deviation given. ‡ Overall % unless otherwise stated.
Abbreviations: FTD - Frontotemporal dementia. DSM III - Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition. DSM IV - Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. NINCDS-ADRDA - National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria.

All studies reported duration of treatment and measured outcomes at the end of treatment. For all but one trial [20], the end of treatment was the termination point of the trial with no subsequent follow-up reported.

Cognition

Mean score after treatment: There was no difference in mean MMSE (Mini Mental State Examination) scores at the end of treatment between SSRI and placebo groups. Trials that used MMSE scoring lasted between 6 [23] and 39 weeks [16] mean of 16.75 weeks. Eight studies (841 participants) [15,16,20-23,26,28] used MMSE to assess cognition before and end of treatment, with six (470 participants) [15,16,22,23,26,28] reporting the mean MMSE at end of treatment, allowing data to be combined in meta-analysis. The MD at the end of treatment was 0.28 MMSE points (95% CI -0.83 to 1.39) with moderate heterogeneity (I^2 =38%, P=0.15) (Table 2, Figure 2a). All of these studies except one small study [23] included solely patients with Alzheimer's disease.

Change in score after treatment: In studies that reported cognitive change, there was less cognitive decline when treated with SSRI. Three of the eight studies (352 participants) [15,21,26], all in patients with Alzheimer's disease, reported the difference in MMSE scores following treatment; MD was 0.53 (95% CI -0.07 to1.14), I^2= 0% P=0.92, Figure 2b). It was not possible to include all studies in the change of score analysis due to lack of availability of primary data.

Figure 2a. Mean MMSE scores at end of treatment (ordered by weighting)

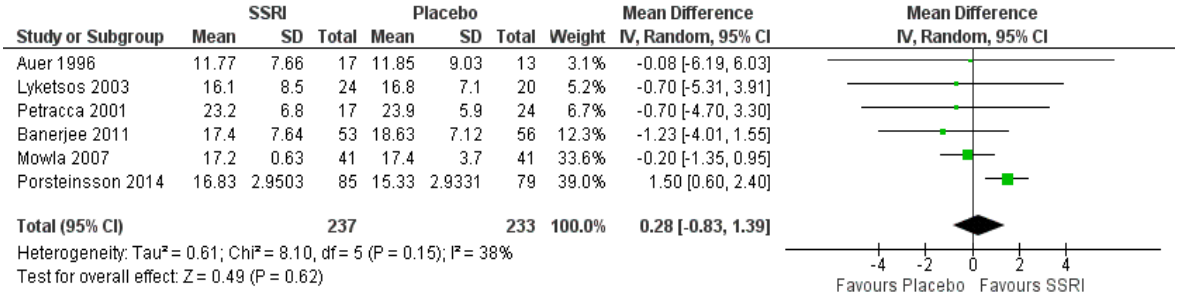
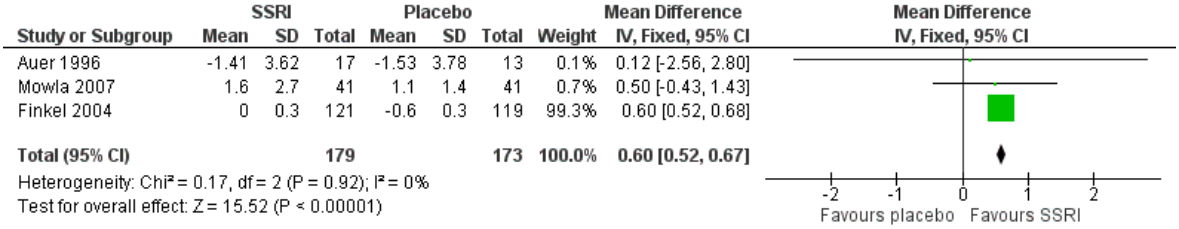


Figure 2b. Mean difference between MMSE scores before and after treatment (ordered by weighting)



One study [20] only presented median scores and so the data could not be incorporated into either meta-analysis, but found no difference between groups. The median score (1st, 3rd quartiles) at the end of treatment was 21 (16.5, 24) and 20 (14.75, 24) in the control. Treatment effect was χ^2= 0.5 (degrees of freedom 1); p=0.50.

Four studies (196 participants) [19,24,25,27] including patients with Alzheimer's, vascular or fronto-temporal dementia showed no difference in cognition at the end of treatment with SSRI. One (10 participants) [19] found no significant differences on the Neuropsychiatric Inventory between paroxetine and placebo. For one study in patients with Alzheimer's disease [24], the Neurobehavioural Factor cognition score from baseline to study termination was approximately 0.22 for citalopram and 0.06 for placebo (readings taken from graph). Within the citalopram group this was a

statistically significant improvement from baseline, however, the difference in the change of score between the citalopram and placebo group was not statistically significant. Two studies [25,27] in patients with Alzheimer's or vascular dementia found no difference in cognitive subscale scores on the GBS (Gottfries-Bråne-Steen) rating scale. At the end of treatment the median (range) was 38 (10-62) in the SSRI group and 42 (12-60) with placebo in one study [25], and in the other [27] there was no difference between the groups (T=32 (51), p=0.321) (Table 2).

The quality of the studies, as reported, was mixed, and the results should be interpreted with caution. For many studies, the proportion of incomplete outcome data was a concern and at risk of introducing bias. Across the 12 studies, 338 of 1174 participants (29%) withdrew prior to the final assessment. At least 157 of these were from the SSRI group; one study [22] did not differentiate the groups from which the six participants withdrew. Six studies [16,21,23,25-27] had a significant drop out rate (>5% [10]) and did not use intention-to-treat analysis. There was no statistically significant difference between the two groups in terms of premature trial withdrawal; (T-value= 0.44 and p=0.66). The main reasons for withdrawal were loss of efficacy, administrative reasons and adverse effects. Several studies also lacked sufficient information to determine risk of bias in relation to randomisation, allocation and blinding methods. The risk of bias for each trial is detailed in Supplement Table 1 (available in *Age and Ageing* online).

Table 2: Results of studies included in systematic review of SSRIs and placebo in the progression of dementia (ordered by reference number)

	AUTHOR	Highest Ranking Cognition Test [1]	SSRI Cognition Score		Placebo Cognition Score		Other outcomes
			Baseline	End of treatment	Baseline	End of treatment	
[15]	Auer	MMSE	12.94 (8.03)	11.77 (7.66)	13.30 (7.47)	11.85 (9.03)	-
[16]	Banerjee	MMSE	18.5 (6.7)	17.4 (7.64)	18.2 (7.4)	18.63 (7.12)	Mood, ADL impairment, Agitation, AE
[19]	Deakin	Neuropsychiatry Inventory	-	32.4 (7.2)*	-	28.8 (4.8)*	-
[20]	Weintraub	MMSE	21(17,35)#†	21(16.5,24)#†	19.5(15, 23.25)#†	20 (14.75,24)#†	Mood, ADL impairment, Agitation, AE
[21]	Finkel	MMSE	18.8 (0.5)*	[0 (0.3)*‡[	18.0 (0.5)*	[-0.6 (0.3)*‡]	Mood, Agitation
[22]	Lyketsos	MMSE	17.5 (6.5)	16.1 (8.5)	16.3 (6.8)	16.8 (7.1)	Mood, ADL impairment, Agitation, AE
[23]	Petracca	MMSE	23.2(4.5)	23.1 (6.8)	23.2 (5.3)	23.9 (5.9)	Mood, ADL impairment, AE

[24]	Pollock	Neurobehavioral subscale	-	[0.22‡]	-	[0.06‡]	Mood, Agitation, AE
[25]	Olafsson	GBS subscale	43 (3-62)#+	38 (10-62)#+	40 (15-62)#+	42(12-60)#+	AE
[26]	Mowla	MMSE	15.6 (0.73)	17.2 (0.63)	16.3 (4.1)	17.4 (3.7)	Mood, ADL impairment, AE
[27]	Nyth	GBS subscale	22.6	21.3	20.1	19.9	AE
[28]	Porsteinsson	MMSE	17.0 (6.2)	16.83 (2.95)	14.4 (6.9)	15.33 (2.93)	Agitation, ADL impairment, AE,

Data are mean cognition score (standard deviation) unless otherwise stated. *SE(standard error) #median † (1st and 3rd quartiles) + (ranges) ‡ mean change in score from baseline (end treatment value not available). Abbreviations: MMSE: Mini Mental State Examination, GBS: Gottfries-Bthne-Steen geriatric rating scale, ADL: Activities of Daily Living, AE: Adverse Events. [1] Supplementary data 2

Mood

There was no difference in mood at the end of treatment between the SSRI and placebo group. Four studies (317 participants) [16,22,23,26] reported depression scores and demonstrated an SMD of -0.10 (95% CI, −0.39 to 0.2, I^2=37% P=0.19; Supplementary Figure 1 available in *Age and Ageing* online). The remaining eight studies either did not examine mood or did not report the results in a format compatible with the meta-analysis.

Agitation

There was no difference in mean agitation scores at the end of treatment. Three studies [19,24,28] reported agitation, of which two [19,28] could be included in meta-analysis (189 participants); (SMD = -0.01, 95% CI -0.86 to 0.83, I^2=70%, P=0.07); Supplementary Figure 2 available in *Age and Ageing* online). The remaining trial [24] showed a significantly greater improvement in agitation/aggression (from baseline using the Neurobehavioural Factor Score) in the SSRI group (0.98) compared to placebo (0.38), (readings taken off graph; Kruskal-Wallis test X^2=6.7,df=2, p<0.04). Whilst this result is promising, methods used for concealment of allocation and randomisation were unclear, raising the possibility of selection bias. Nine studies did not examine agitation as an outcome.

Patient's ability to perform activities of daily living

There was no difference in a patient's ability to complete ADLs between the two groups. Four studies (336 participants) [22,23,26,28] reported participants' ability to perform ADLs at the end of treatment; (SMD = -0.15, 95%CI -0.45 to 0.15, I^2=41% P=0.17; Supplementary Figure 3 available in *Age and Ageing* online).

Adverse events and mortality

There was no increase in mortality with SSRI compared to placebo. Four studies [16,20,27,28] (624 participants) reported a total of 13 deaths. The risk ratio (RR) for death in the SSRI group was 0.91 (95% CI 0.33 to 2.50). Adverse events were reported in all but two studies [15,19] and were collected either systematically or volunteered by the patient. RR for the number of participants experiencing at least one adverse event was 1.25 (95%CI 0.67, to 2.31, I^2=87% p<0.001) favouring placebo [16,20,27,28]. In studies reporting the number of adverse events rather than the number of patients experiencing an event [21,23] there were 143 adverse events with sertraline, 119 with placebo. One study [24] found no significant change in total UK Side Effect Rating Scale score in any of the groups (F=1.49, df=2, 81, p=0.23).Three studies [22,25,26] reported the most common side effects in both groups. Side effects were gastrointestinal, neurological and autonomic disturbances.

Discussion

Summary of key findings

Twelve completed studies comparing SSRIs with placebo were indentified, of which seven provided data that could be used in a meta-analysis on cognition [15,16,21-23,26,28]. Sertraline was the most commonly used SSRI. All participants had a formal diagnosis of dementia, mostly Alzheimer's disease or vascular dementia, but none of the studies stipulated how long this had to have been present. Some, but not all, studies required participants to have depression at the point of entry. The

duration of treatment varied from days to months with a mean of 14.3 weeks. Only one study [19] followed up participants after treatment.

Overall, there were no beneficial effects of SSRIs on cognition, with the meta-analysis of MMSE scores at end of treatment demonstrating no statistically significant difference between SSRI and placebo. There was no statistical benefit of SSRI on mood, agitation or ADLs, though the number of studies is small and there was methodological bias in these studies. SSRIs may not be effective in treating depression in patients with dementia [11,16]. Number of deaths was low with no difference between the groups. There was no statistically significant difference in side effects between the two groups.

Limitations of included studies

It is possible that variations in the quality of the evidence may have influenced the results of this review. The studies were generally small, the largest recruiting 245 participants [21], and were of mixed quality, with many displaying multiple different sources of bias. Some lacked important methodological detail, for example on sequence generation and allocation concealment, making it difficult to determine the risk of bias. The funding source was declared in the majority of the trials, with occasional links to the pharmaceutical industry (e.g. funding [21], provision of drugs [16]).

All participants were generally recruited from tertiary centres, which often have more complex patients with more challenging symptoms. It is therefore unclear whether the findings can be extrapolated to the overall dementia population. The severity of

dementia of participants included in the meta-analysis also varied, with mean scores ranging from 11 to 24 in the meta-analysis. It is therefore also feasible that there may be differences in effect depending on the stage of disease. Most studies did not exclude participants who also had concurrent depression and this could have acted as a confounding factor in influencing any changes to a patient's cognition [29]. Cognition scores may have also been affected for other reasons, including hearing impairment or non-English speaking participants.

The lack of long-term treatment and follow-up after treatment is a major limitation. From studies in participants with depression, it is known that SSRIs take time to show benefit and the dosage required can vary [2]. Some studies only lasted six weeks and had strict titration schedules. If cognitive tests are repeated there is the likelihood of practice effects, and this may mask a decline in cognition, though the effects would be similar in both groups. It is unlikely that cognitive change in a general, 30 point, cognitive test like the MMSE would be detectable over a period of several weeks. Although there was no significance difference in the withdrawal rate between the SSRI and placebo groups, there was an overall high premature drop out of 29% with lack of efficacy and side effects being the main reasons. Ten studies reported side effects, but not all explained how these were collected.

Limitations of the review

The search criteria were deliberately broad to reduce the likelihood of any relevant published studies being missed when searching ALOIS. The main weakness of the search strategy was that any grey literature or unpublished studies would have been

missed. Reported data was not checked against original published protocols and so this review is reliant on the reporting of the primary investigators.

The majority of studies (n=8) included only patients with Alzheimer's disease (DSM III, DSM IV, or NINCDS-ADRDA criteria) [15,16,20-22,24,26,28] . Three included patients with either Alzheimer's or vascular dementia [23,25,27], and one just patients with fronto-temporal dementia [19]. The majority of patients in the meta-analysis had Alzheimer's disease. Data were insufficient to establish if dementia subtype affected response to SSRI.

Conclusion

A small number of relatively low-powered studies show no benefit or harm from SSRIs in terms of cognitive outcomes in people with dementia. There is insufficient data to say whether SSRIs are beneficial for cognition, and there is some suggestion of increased side effects. Future studies require adequate numbers of different dementia subtypes to allow subgroup analyses, a longer duration of follow-up, systematic reporting of adverse events, and clearer reporting of factors which may bias the results.

Conflicts of interest

None declared

Acknowledgements

Cochrane Dementia and Cognitive Improvement Group for providing the search database and Maureen Harding for sourcing full texts. The authors also wish to express their gratitude to Dr Banerjee and Dr Auer for providing additional primary data.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	21
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	supplement
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	table 1,2 and figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-20
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	20-21
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	n/a

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplements

Supplement 1: Search strategy used in ALOIS April 2013 and again January 2015

1. Dementia OR Alzheimer Disease OR AD OR Alzheimer OR Alzheimers OR Alzheimer's OR Lewy Body Disease OR Lewy Body OR Lewy OR Vascular dementia

   AND

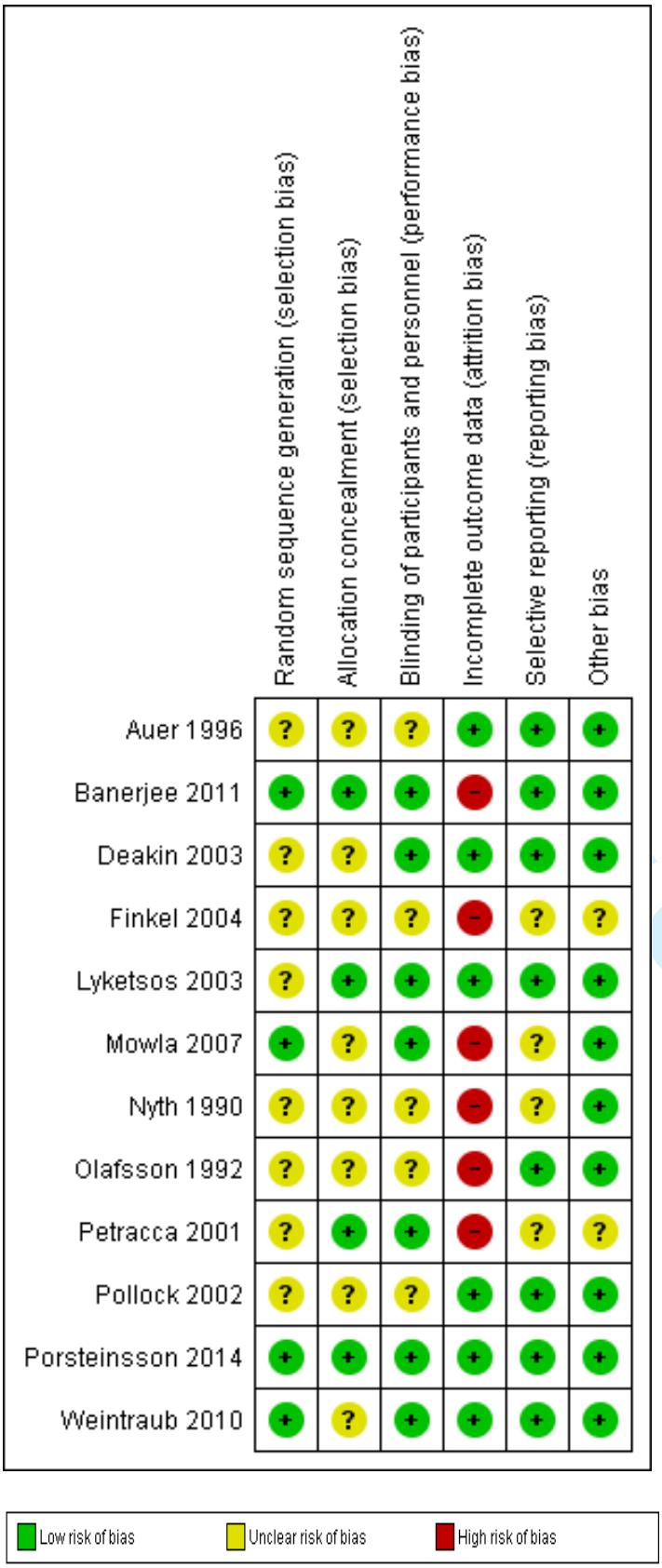
2. SSRI OR SSRIs OR Selective Serotonin Reuptake Inhibitors OR Citalopram Escitalopram OR Fluoxetine OR Sertraline OR Fluvoxamine OR Paroxetine

Supplement 2: Predetermined ranking system for inclusion of cognitive tests[1]

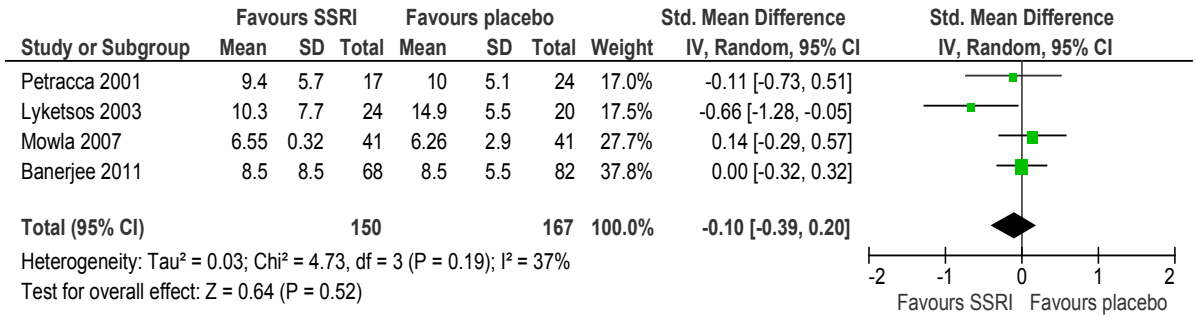
1. Mini Mental State Examination (MMSE)
2. Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS –Cog)
3. Addenbrooke's Cognitive Examination (Revised) (ACE-R)
4. The General Practitioner assessment of Cognition (GPCOG)
5. Montreal Cognitive Assessment (MoCA) – clinical diagnosis only
6. The 6 Item Cognitive Impairment Test (6-CIT) – clinical diagnosis only
7. Neurobehavioural Rating Scale - cognition component
8. Gottfries-Bthne-Steen geriatric rating scale - cognition component
9. Neuropsychiatric Inventory – cognition component

[1]Sheehan B. Assessment scales in dementia. *Therapeutic Advances in Neurological Disorders*. 2012;5(6):349-358.

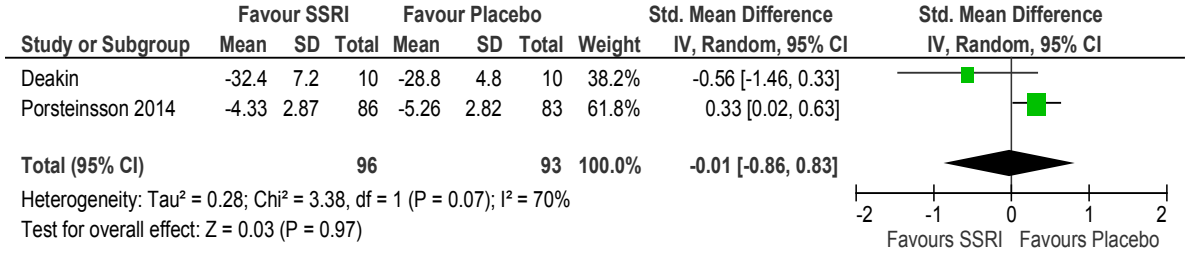
Supplementary Table 1: Risk of Bias (alphabetical order)



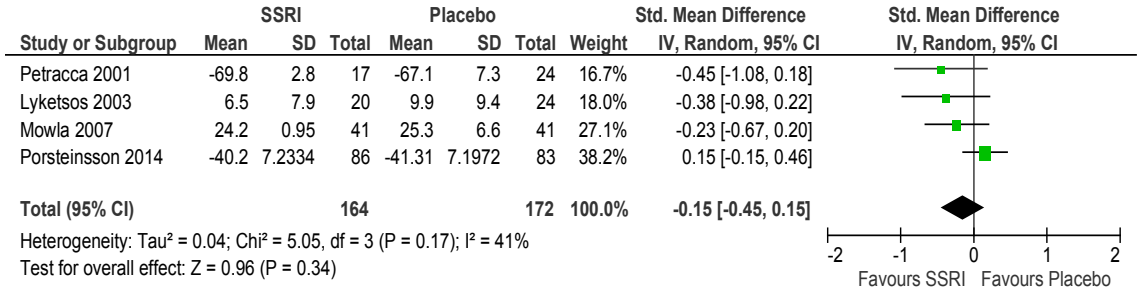
Supplement Figure 1. Mean mood scores at the end of treatment (ordered by weighting)



Supplement Figure 2: Mean agitation scores at end of treatment (ordered by weighting)



Supplement Figure 3: Mean activities of daily living (ADL) scores at end of treatment (ordered by weighting)



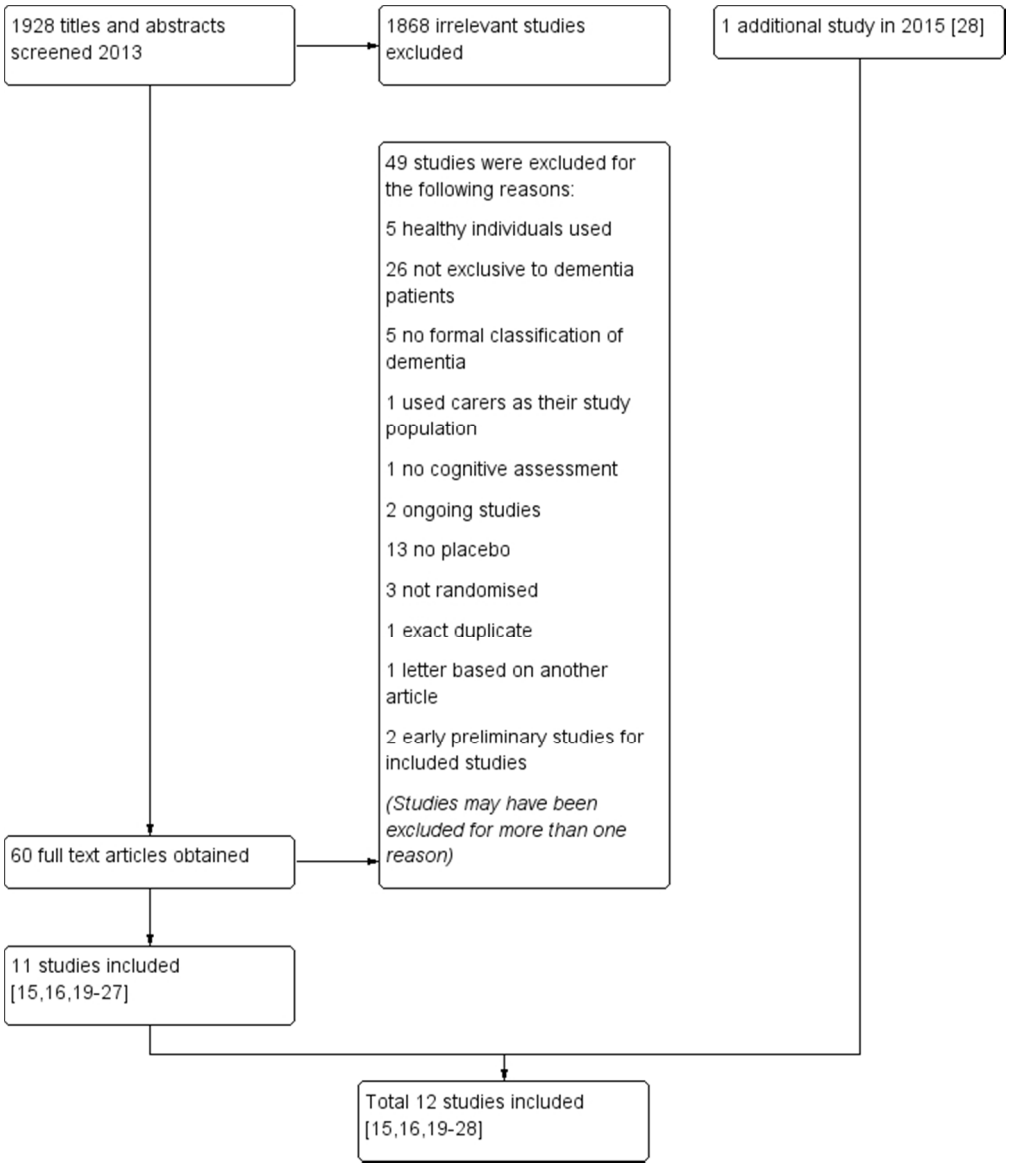


Figure 1. Flow diagram of selected studies
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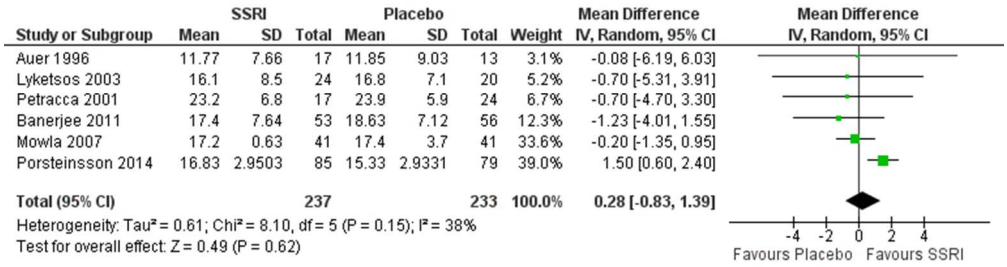


Figure 2a. Mean MMSE scores at end of treatment (ordered by weighting)
270x73mm (72 x 72 DPI)

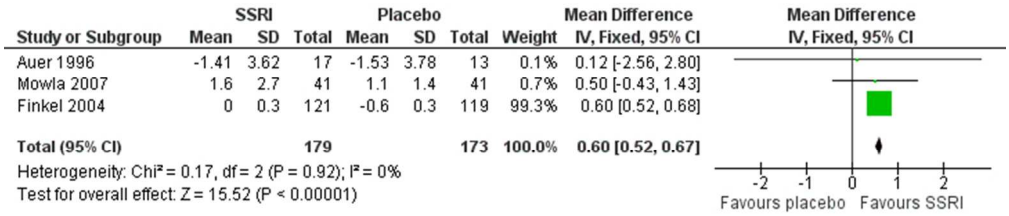
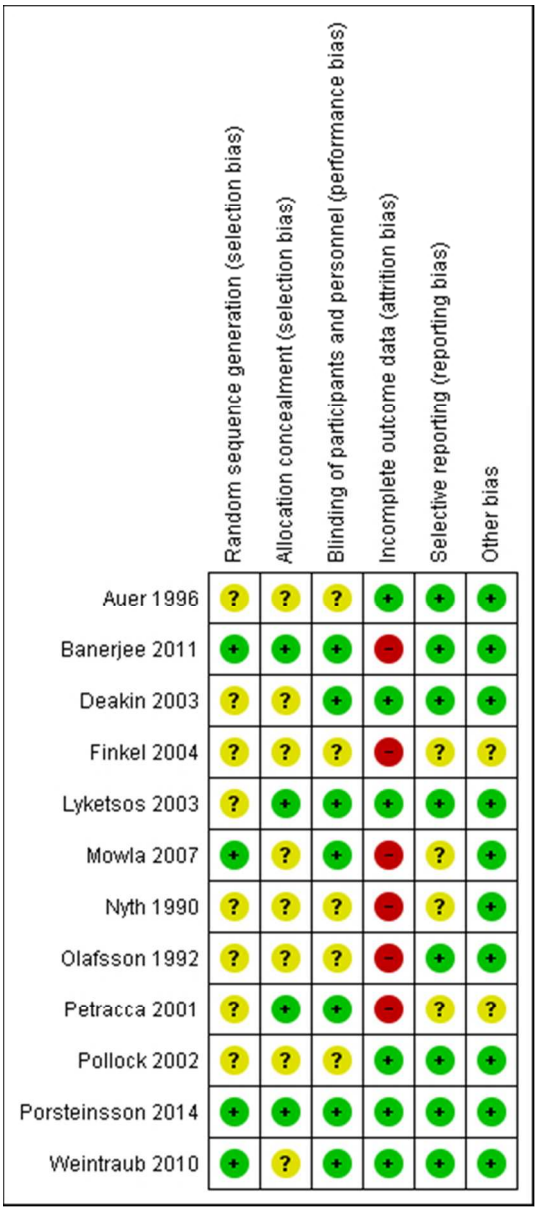


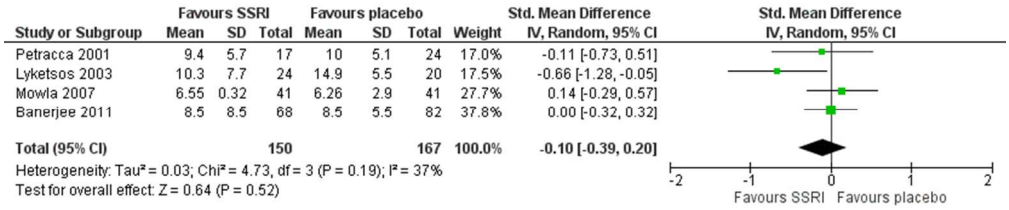
Figure 2b. Mean difference between MMSE scores before and after treatment (ordered by weighting)

255x56mm (72 x 72 DPI)

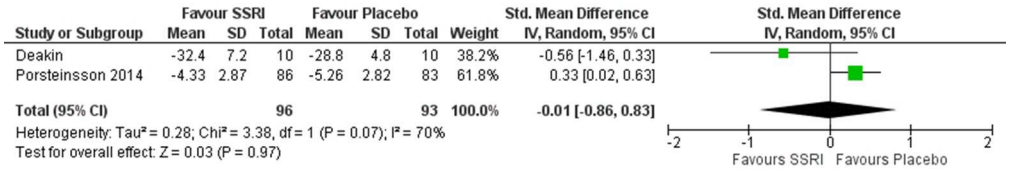


Supplementary Table 1: Risk of Bias (alphabetical order)

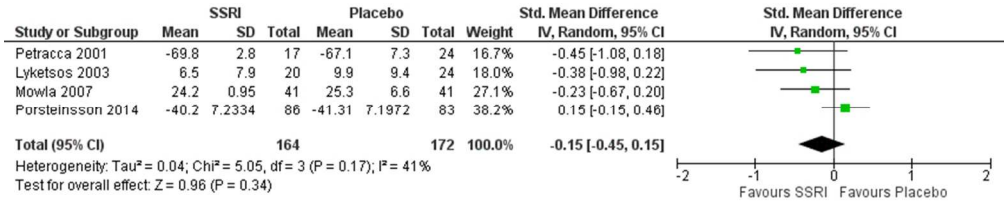
+ low risk of bias, ? unclear risk of bias, - high risk of bias
109x247mm (72 x 72 DPI)



Supplement Figure 1. Mean mood scores at the end of treatment (ordered by weighting)
291x62mm (72 x 72 DPI)



Supplement Figure 2: Mean agitation scores at end of treatment (ordered by weighting)
289x50mm (72 x 72 DPI)



Supplement Figure 3: Mean activities of daily living (ADL) scores at end of treatment (ordered by weighting)
299x62mm (72 x 72 DPI)