Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"In adults with Alzheimer's dementia, how long are cholinesterase inhibitors effective?"

Clarification of question using PICO structure

Patients: Adults with Alzheimer's dementia
Intervention: Continuation of Cholinesterase Inhibitors
Comparator: Discontinuation of Cholinesterase Inhibitors
Outcome: Improved patient outcomes and a reduction of symptoms.

Clinical and research implications

Evidence on the duration of effectiveness of cholinesterase inhibitors was very limited. There was good evidence, from two systematic reviews, that cholinesterase inhibitors can provide short term (six months) benefits in patients with mild to moderate Alzheimer's disease. Data from one randomised controlled trial (RCT) and one an observational study, which used follow-up data from participants in the galantamine arms of three RCTs, suggest that continued galantamine treatment beyond 12 months may be effective in slowing cognitive decline. However, it should be noted that the RCT found no statistically significant differences between the continued galantamine and discontinuation groups in either the number of participants withdrawn from the study due to a change in Assessment Scale Cognitive subscale (ADAS-cog) score ≥4, or the mean global assessment with carer input (CIBIC-plus) score. Further, no study included in this evidence summary reported data showing any statistically significant treatment effect for cholinesterase inhibitors (compared with placebo) beyond six months. Further research is required to establish the longer term effectiveness of cholinesterase inhibitors in the management of patients with Alzheimer's disease.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two systematic reviews,[1,2] one additional RCT,[4] and two observational studies,[3,5] which were considered potentially relevant to this evidence summary. Neither of the systematic reviews met the PICOS criteria for this summary; they did not include any studies which compared continued treatment with cholinesterase inhibitors to discontinuation. Both reviews included RCTs comparing cholinesterase inhibitors to placebo or another cholinesterase inhibitor in participants with Alzheimers disease and almost all data were for outcomes at six months.[1,2] The additional RCT compared continuation of galantamine treatment for 24 months, following an initial 12 month open-label phase, with discontinuation of galantamine at 12 months, in 139 participants with a diagnosis of probable Alzheimer's disease.[4] One study used observational follow-up data from the galantamine arms of three RCTs to estimate annual decline in Mini Mental State Examination (MMSE) scores in treated patients with Alzheimer's disease; modelling was used to compare these estimates with predicted decline in un-treated patients.[3] The final study was a three year, open-label, observational study, in which all patients were treated with cholinesterase inhibitors and changes in MMSE and measures of Activities of daily living were monitored; regression modelling was used to investigate factors associated with cognitive and functional decline.[5]

Main Findings

Both systematic reviews found evidence that treatment with cholinesterase inhibitors may be beneficial in the short term (six months) compared to placebo.[1,2] Statistically significant treatment effects were observed for measures of cognition, activities of daily living, behavioural disturbance and global assessment with carer input (CIBIC-plus).[1] However, almost all data were for treatment durations of six months. One study, included in the first systematic review, reported mean change from baseline in GBS-global assessment at 52 weeks and found no significant difference between the donepezil and placebo groups.[1] The RCT, which compared continuation of galantamine treatment beyond 12 months with discontinuation, found that participants in the placebo (discontinuation) group were more likely to leave the study early than those in the galantamine group, for any reason HR 1.76 (95% CI: 1.10 to 2.81) or due to lack of efficacy HR 1.80 (95% CI: 1.02 to 3.18).[4] However, there were no significant differences between the groups in either the number of participants withdrawn from the study due to a change in Assessment Scale Cognitive subscale (ADAS-cog) score ≥4, or the mean CIBIC-plus score.[4] The study using follow-up data from participants in the galantamine arms of three RCTs found that the mean estimated annual decline in MMSE score for participants receiving galantamine (2.4 (sd 6.0)) for participants receiving galantamine was lower than that for participants withdrawn from galantamine (2.6 (sd 5.5)). Modelling predicted that patients receiving long-term galantamine treatment would experience a lower rate of decline than those withdrawn from treatment; predicted decline was similar for patients withdrawn from treatment after one year and untreated patients.[3] The final observational study reported that performance on the Instrumental Activities of Daily Living (IADL) scale and Physical Self-Maintainance Scale (PSMS) was stable (no change or improvement) in 32% and 56% of the patients respectively after 1 year, 18% and 38% after 2 years and 14% and 32% after 3 years.[5] Regression modelling indicated that faster functional decline was associated with lower cognitive ability at baseline, older age, solitary living and higher education levels.[5] A higher mean dose of cholinesterase inhibitor was associated with slower decline.[5] No study included in this evidence summary reported data showing any statistically significant treatment effect for cholinesterase inhibitors (compared with placebo) beyond six months.

Authors Conclusions

Both systematic reviews concluded that the evidence suggests that treatment with cholinesterase inhibitors may be beneficial for patients with Alzheimer's disease. One RCT, which compared continued galantamine treatment beyond 12 months with discontinuation, concluded that participants who responded to 12 months of galantamine treatment benefited from continuation for up to 36 months and that galantamine was effective in delaying time to cognitive deterioration in subjects with mild to moderate Alzheimer's disease. An observational study, using follow-up data from participants in the galantamine arms of three RCTs, also concluded that galantamine treatment slowed decline in cognitive function and further concluded that patients who stopped treatment after one year experienced subsequent decline at a rate similar to that predicted for untreated patients. The final observational study, included in this evidence summary, concluded that functional ability declined over a three year period of treatment with cholinesterase inhibitors and identified lower cognitive ability at baseline, older age, higher education levels, and solitary living as risk factors for faster decline.

Reliability of conclusions/Strength of evidence

There is good evidence, from two systematic reviews, that cholinesterase inhibitors can provide short term (six months) benefits in patients with mild to moderate Alzheimer's disease.[1,2] Evidence from one high quality RCT[4] and one observational and modelling study, using follow-up data from participants in the galantamine arms of three RCTs,[3] suggests that continued galantamine treatment beyond 12 months may be effective in slowing cognitive decline. However, it should be noted that the RCT found no statistically significant differences between the continued galantamine and discontinuation groups in either the number of participants withdrawn from the study due to a change in Assessment Scale Cognitive subscale (ADAS-cog) score ≥4, or the mean CIBIC-plus score.[4] Further, no study included in this evidence summary reported data showing any statistically significant treatment effect for cholinesterase inhibitors (compared with placebo) beyond six months. Data from one observational study indicated that lower cognitive ability at baseline, older age, higher education levels, and solitary living may be associated with faster decline.[5]

What do guidelines say?

NICE guidelines do not discuss the length of effect of cholinesterase inhibitors, however NICE Technology Assessment (2011, T217) makes the following statements;

<u>Donepezil vs. Placebo</u>

"The manufacturer of donepezil included prospective longitudinal and observational studies to support the view that cognitive benefits from donepezil are maintained for up to 3 years. The submission also included new data from a placebo-controlled trial of at least a 2-year duration and a sub analysis of a previous placebo-controlled study of 1 year duration. The manufacturer also presented evidence from randomised and non-randomised controlled trials to demonstrate that benefit was lost when treatment was stopped, the benefits of continuing treatment despite initial decline or stabilisation of MMSE, and the impact of improvement of neuropsychiatric symptoms on caregiver stress and burden." (pp.16)

"A representative from the manufacturer of donepezil informed the Committee that an analysis of a single open-label study found an average of 17.5 months delay in the time to institutionalisation with donepezil treatment." (pp.17)

Galantamine vs. Placebo

"The Assessment Group found three new randomised controlled trials measuring functional outcomes for galantamine. The Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) data from the new trials were pooled with those of the studies found in 2004, and the overall pooled estimates showed statistically significant functional benefit from galantamine compared with placebo at 21-26 weeks. Only one study included by the Assessment Group provided additional data for the effectiveness of galantamine in relieving behavioural symptoms, when compared with placebo. However, this did not show any statistically significant benefit. When the new data were pooled with previous data, at 13 weeks no significant benefit was found, but at 2126 weeks the overall pooled estimate favoured galantamine significantly. Two new studies found by the Assessment Group measured global outcomes for galantamine. One found a significant benefit from galantamine measured by the CIBIC-plus compared with placebo at 1316 weeks. When the new studies' data were pooled with existing evidence, the overall pooled estimates of the CIBIC-plus at 26 weeks showed a statistically significant benefit from galantamine compared with placebo." (pp.18-19)

Rivastigmine vs. Placebo

"Three new studies for rivastigmine were identified by the Assessment Group that measured cognition using ADAS-cog and/or MMSE and showed significant benefit (patch and capsule were not differentiated). When the results of these were added to the randomised controlled trials in NICE technology appraisal guidance 111, it demonstrated a statistically significant improvement in cognition with rivastigmine compared with placebo at 2426 weeks." (pp.20)

The evidence contained in this summary is consistent with current guidelines.

Date question received: 27/09/2013
Date searches conducted: 01/10/2013
Date answer completed: 01/11/2013

References

SRs

1. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database of Systematic Reviews 2006, Issue 1. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005593/pdf

2. Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, et al. The clinical and costeffectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. Health Technol Assess 2006;10(1).

RCTs and observational studies

3. Kavanagh, S., Van, Baelen, B. and Schauble, B. (2012) Long-Term Effects of Galantamine on Cognitive Function in Alzheimer's Disease: A Large-Scale International Retrospective Study. Journal of Alzheimers Disease 27 (3) pp. 521-530.

4. Scarpini, E., Bruno, G., Zappala, G., Adami, M., Richarz, U., Gaudig, M., Jacobs, A. and Schauble, B. (2011) Cessation versus Continuation of Galantamine Treatment after 12

Months of Therapy in Patients with Alzheimer's Disease: A Randomized, Double Blind, Placebo Controlled Withdrawal Trial. Journal of Alzheimer's Disease 26 pp. 211-220.

5. Wattmo, C., Wallin, A.K., Londos, E. and Minthon, L. (2011) Long-term Outcome and Prediction Models of Acytivities of Daily Living in Alzheimer Disease With Cholinesterase Inhibitor Treatment. Alzheimer Disease and Associated Discord 25 (1) pp. 63-72.

Guidelines

6. National Institute for Health and Care Excellence (2011) Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease.TA217. London: National Institute for Health and Care Excellence. http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Birks (2012)	12/06/2005	*Participants* Adults with mild, moderate or severe dementia due to Alzheimer's disease, diagnosed using accepted criteria such as ICD-10, DSM and NINCDS-ADRDA. *Intervention*: Cholinesterase inhibitors at the usual recommended dose *Comparator* Placebo or another cholinesterase inhibitor *Outcomes* Primary outcomes were cognitive function, clinical global impression, changes in global disease severity, performance of activities of daily living, behavioural disturbance, quality of life, effect on carer, dependency, death, acceptability of treatment, and safety. *Study design* Unconfounded, randomised, double-blinded trials	10 studies (n = 8,299 participants)	The review aimed to assess the effects of donepezil, galantamine and rivastigmine in people with mild, moderate or severe dementia due to Alzheimer's disease. No study included in this review directly addressed the duration of effectiveness of cholinesterase inhibitors. None of the studies met the PICOS criteria for this evidence summary; there were no discontinuation studies comparing ongoing treatment with cholinesterase inhibitors with discontinuation of treatment. Meta-analyses indicated that cholinesterase inhibitors have a significant treatment effect, compared to placebo, at six months, for the following outcome measures: weighted mean difference (WMD) in mean change from baseline in Alzheimer's Diseae Assessment Scale Cognitive subscale (ADAS-Cog) score -2.37 (95% CI: -2.73 to -2.02), 10 studies, n=4,236; WMD in mean change from baseline in Mini Mental State	The review stated a clear objective and defined appropriate inclusion criteria. Literature searches were extensive and included sources of published and unpublished material. The review process appears to have been undertaken by one reviewer and no measures to minimise error and/or bias were reported. The methodological quality of included

				Examination (MMSE) score 1.37 (95% CI: 1.13 to1.61), 9 studies, n=3,118; WMD in mean change from baseline in activities of daily living (DAD) 4.39 (95% CI: 1.96 to 6.81), 2 studies, n=669; WMD in mean change from baseline in activities of daily living (PDS score) 2.46 (95% CI: 1.55 to 3.37), 5 studies, n=2,188; behavioural disturbance WMD in mean change from baseline in NPI score -2.44 (95% CI: -4.12 to -0,76), 3 studies, n=1,005; Global assessment with carer input (CIBIC-plus) numbers improved or unchanged 1.84 (95% CI: 1.47 to 2.30), 3 studies, n=1,306. Only two studies provided data for participants with sever Alzheimer's disease. One study (n=282) reported mean change from baseline in GBS-global assessment at 52 weeks and found no significant difference between the donepezil and placebo groups. No other data were reported for longer treatment durations.	studies was assessed according to Cochrane Collaboration criteria. Meta-analysis methods were broadly appropriate, though subgroup analyses to investigate potential differences in the effectiveness of different cholinesterase inhibitors may have been useful.
Loveman et al. (2006)	07/2004	*Participants* Adults diagnosed with Alzheimer's disease who met the criteria for treatment with cholinesterase inhibitors or memantine. *Intervention* Cholinesterase inhibitors; donepezil,	Donepezil: 13 published RCTs and 1 unpublished RCT	The review was an up-date review, which aimed to assess the clinical effectiveness and cost-effectiveness of donepezil, rivastigmine, and galantamine for mild to moderately severe Alzheimer's disease.	The review stated a clear objective and defined appropriate inclusion criteria.

		rivastigmine, galantamine or memantine. *Comparator* Placebo, another intervention drug, or non-drug comparators. *Outcomes* Measures of global functioning, cognition, function, behaviour and mood and health-related quality of life. *Study design* Randomised controlled trials.	Rivastigmine: 4 published RCTs and 2 unpublished RCTs Galantamine: 6 published RCTs and 1 unpublished RCT	No study included in this review directly addressed the duration of effectiveness of cholinesterase inhibitors. None of the studies met the PICOS criteria for this evidence summary; there were no discontinuation studies comparing ongoing treatment with cholinesterase inhibitors with discontinuation of treatment. Donepezil: Outcome measures varied and results were reported as a narrative summary, with some forest plots; no meta-analyses were presented for donepezil (10 mg/day versus placebo). The review reported that data suggest that donepezil is beneficial on global and cognitive outcome measures, with mixed results on measures of function behaviour and mood. All data were for durations up to six months. Rivastigmine: Outcome measures varied and results were reported as a narrative summary; no meta-analyses were presented. The review reported that data suggest that rivastigmine is beneficial on global and cognitive outcome measures, with mixed results on measures of function; there were no significant treatment effects on measures of behaviour	Literature searches included bibliographic database and sources of unpublished material, however, non-English language studies were excluded. This raises the possibility of language bias and potential omission of relevant data. The review process included appropriate measures to minimise error and/or bias. The methodological quality of included studies was assessed using modified criteria recommended by the Centre for

				and mood. All data were for durations up to six months. Galantamine: Outcome measures varied. A pooled estimate of WMD in mean change from baseline in ADAS-Cog indicated a significant benefit for treatment with 24 mg/day galantamine versus placebo, at six months, -3.30 (95% CI: -3.94 to -2.67), 3 studies, n=1,352. Meta-analysis of the number of CIBIC responders at six months (2 studies, n=791) showed no significant difference between galantamine and placebo. Remaining results were presented as a narrative summary The review reported that data suggest that galantamine is beneficial on global and cognitive outcome measures, with mixed results on measures of function behaviour and mood. All data were for durations up to six months.	Reviews and Dissemination (CRD). Analysis methods were broadly appropriate, few pooled estimates were presented and data were analysed separately for each individual cholinesterase inhibitor.

RCTs and observational studies

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Kavanagh et al. (2011)	*Participants* Patients were re-contacted following previous RCTs, in which data was collected from Canada, Finland, France, Norway, Sweden and UK. No details of the inclusion criteria for the individual trials were reported. *Intervention* Galantamine *Comparator* Placebo or no comparator *Outcomes* Cognitive decline according to MMSE scores	n=258.	The study aimed to evaluate the long-term effects (up to seven years) of galantamine on cognitive function in Alzheimer's disease. This re-contact study involved retrospective review of the notes of participants in two randomised, placebo-controlled trials of galantamine in participants with mild to moderate Alzheimer's Disease, as well as the galantamine arm of a study comparing galantatmine with donepezil in participants with moderate Alzheimer's disease. Data on disease progression (MMSE) were reported, for galantamine treated participants, up to five years. Long term outcome data were only available for treated participants; the rate of cognitive decline without treatment was estimated using an existing epidemiological model. Participants included in this study had a diagnosis of probable Alzheimer's Disease according to NINCDS-ADRA, mean baseline MMSE scores of between 9 and 24, and a mean age of 72.4 years. The mean estimated annual decline in MMSE scores was 2.4 (sd 6.0) for participants receiving galantamine, 4.5 (sd 6.4) for participants withdrawn from galantamine, and 2.6 (sd 5.5) for participants switching to another cholinesterase inhibitor. Modelling predicted that patients receiving long-term galantamine treatment would experience a lower rate of	This is a re-contact study, which includes patients from several randomised controlled trials, but which is not itself an RCT; risk of bias in this study cannot be assessed using the RCT risk of bias tool.

			decline than those withdrawn from treatment; predicted decline was similar for patients withdrawn from treatment after one year and untreated patients.	
Scarpini et al. (2011)	*Participants* Adults in Italy, ≥50 years of age with a probable diagnosis of Alzheimer's disease according to NINCDS-ADRDA, with mild to moderate cognitive impairment according to MMSE (score of 11-24). Exclusion criteria were: presence of a neurodegenerative disorder other than Alzheimer's Disease; any serious and clinically significant illness; history of previous cerebral infarction; use of cholinesterase inhibitors in previous 3 months. Anti-depressants, mood stabilizers, and cholinomimetics were not allowed during the trial. *Intervention* Continuing galantamine (16 mg daily) after 12 months of previous galantamine treatment (open-label phase). *Comparator* Placebo (twice daily) after 12 months of galantamine treatment (open-label phase). *Outcomes* Cognitive function (ADAS-cog/11), adverse events, changes in presentation (Clinical Interview Based Impression of Changes-Plus Caregiver Input (CIBIC-plus)).	n = 139 (Intervention n=76, control n=63).	The study aimed to investigate long-term outcomes of galantamine treatment by comparing continued galantamine treatment (after an initial 12 month open-label phase) with discontinuation. The mean age of study participants was 74.2 years. The mean baseline MMSE score was 18.9±3.6 and the mean baseline ADAS-Cog/11 score was 24.7±9.3. One hundred and seventy six participants completed the open label phase. Cognitive function (ADAS-Cog/11 score) improved significantly at seven months, relative to baseline, difference –1.2 (95% CI –2.3 to –0.1). There was no significant difference between the mean ADAS-Cog/11 score at the end of the open-label phase (12 months) and baseline. At the end of the open label phase (12 months), CIBIC-plus score improved in 34.3% of subjects, was unchanged in 30.9%, and worsened in 34.9%, compared with baseline. One hundred and thirty nine participants were randomised in the double-blind phase. Withdrawal criteria were change in ADAS-cog score ≥4 points compared with the score at the end of the open label phase, confirmed after one month. Thirty six participants (47.4%) in the galantamine group and 19 participants (30.2%) in the placebo group completed the double blind phase without meeting the withdrawal criteria.	Randomisation was by computer generated code, from an independent centre. Trial medication and placebo were provided in identical boxes. The discontinuation phase of the trial was double blinded. Efficacy analyses were conducted on an intention-to-treat (ITT) basis. The ITT population was

			Participants in the placebo group were more likely to discontinue the study prematurely than those in the galantamine group, for any reason HR 1.76 (95% CI: 1.10 to 2.81) or due to lack of efficacy HR 1.80 (95% CI: 1.02 to 3.18). There was no statistically significant difference between the groups in the likelihood of premature study discontinuation due to a change in ADAS-cog ≥4. There was no statistically significant difference in mean CIBIC-plus scores between the groups.	defined as all randomised participants known to have taken at least one dose of blinded study medication and who completed at least one ADAS-cog/11 score. Data were reported for all specified outcome measures.
Wattmo et al. (2011)	*Participants* Community-dwelling adults, aged ≥40 years, with a DSM-IV diagnosis of dementia and a diagnosis of probable Alzheimer's Disease according to NINCDS-ADRDA criteria. Participants were required to have baseline MMSE scores between 10 and 26. Participants were recruited from 14 memory clinics across Sweden. Most patients were in the mild-to-moderate stage.	n=790	The study aimed to investigate the long-term efficacy of cholinesterase inhibitors (donepezil, rivastigmine, galantamine) in patients with Alzheimer's disease in a routine clinical setting. This was a three year, open-label, observational study in which all participants received treatment with cholinesterase inhibitors. Choice of drug and dosage was at the discretion of physicians. Participants were divided into 4 groups, depending upon the length of their participation in the study: 3-year completers (group 3, n=337), 2-year completers	This was an observational study in which all participants received treatment with cholinesterase inhibitors; risk of bias in this study cannot be assessed

	Intervention Treatment with cholinesterase inhibitors; donepezil, rivastigmine or galantamine. *Comparator* Not applicable, this was an observational study in which all participants received treatment with cholinesterase inhibitors. *Outcomes* Activities of daily living (Instrumental Activities of Daily Living Scale (IADL)), ability to care for self (Physical Self-Maintenance Scale (PSMS))		(group 2, n=179), 1-year completers (group 1, n=191), and 6-month completers (group 0.5, n=83). The four groups were similar at baseline with respect to gender, APOE ε4 allele carrier status, solitary living, medication use, age at onset, duration of illness, and years of education. Participants in group 3 had significantly higher MMSE and IADL scores at baseline than those in other groups. Mean baseline PSMS score was similar for groups 2 and 3, but significantly better for participants in these two groups than for participants in groups 1 and 0.5. Performance on the IADL and PSMS scales was stable (no change or improvement) in 32% and 56% of the patients respectively after 1 year, 18% and 38% after 2 years and 14% and 32% after 3 years. Regression modelling indicated that faster functional decline was associated with lower cognitive ability at baseline, older age, and the interaction of higher education and longer time in the study. Participants living with a spouse or relative showed slower deterioration in IADL score. A higher mean dose of cholinesterase inhibitor was also associated with slower IADL decline.	using the RCT risk of bias tool.

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Birks (2012)	☺	☺	☹	☺	☺
Loveman et al. (2006)	☺	☹	☺	☺	☺

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Kavanagh et al. (2012)	Not applicable (not an RCT)					
Scarpini et al. (2011)	☺	☺	☺	☺	☺	☺
Wattmo et al. (2011)	Not applicable (not an RCT)					

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Alzheimer's disease	27	1
DARE	(donepezil) IN DARE 57 Delete 2 (E2020) IN DARE 4 Delete 3 (Aricept) IN DARE 6 Delete 4 (galantamin* OR galanthamin*) IN DARE 38 Delete 5 (reminyl) IN DARE 4 Delete 6 (rivastigmine) IN DARE 37 Delete 7 (exelon) IN DARE 4 Delete 8 (ENA adj2 713) IN DARE 3 Delete 9 ((ENA adj2 713) OR(ENA-713)) IN DARE 3 Delete 10 MeSH DESCRIPTOR Cholinesterase Inhibitors EXPLODE ALL TREES 87 Delete 11 MeSH DESCRIPTOR Galantamine EXPLODE ALL TREES 25 Delete 12 (alzheimer*) IN DARE 309 Delete 13 MeSH DESCRIPTOR Alzheimer Disease EXPLODE ALL TREES 270 Delete 14 (cholinesterase*) IN DARE 90 Delete 15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #14 154 Delete 16 #12 OR #13 427 Delete 17 #15 AND #16	98	2
Primary studies			
CENTRAL	#1 MeSH descriptor: [Cholinesterase Inhibitors] explode	16	

	all trees 800 #2 Enter terms for search CHOLINESTERASE INHIBITORSCHOLINESTERASE INHIBITORS 1073 #3 Enter terms for search donepezil or galantamine or rivastigmine or tacrine or memantinedonepezil or galantamine or rivastigmine or tacrine or memantine 1861 #4 Enter terms for search #1 or #2 or #3#1 or #2 or #3 2351 #5 MeSH descriptor: [Dementia] explode all trees 3452 #6 Enter terms for search dementia or Alzheimer'sdementia or Alzheimer's 10640 #7 Enter terms for search #5 or #6#5 or #6 10868 #8 Enter terms for search "treatment duration" 3401 #9Enter terms for searc"long term"44651 #10Enter terms for searcduration56702 #11Enter terms for searc"one year" or "two year" or "three year"16612		

	#12Enter terms for searc"52 weeks"1763 #13Enter terms for searc#8 or #9 or #10 or #11 or #12102962 #14Enter terms for searc#4 and #7 and #13 392 Central only 201 2010 - 16		
PsycINFO	1. PsycINFO; exp CHOLINESTERASE INHIBITORS/; 2200 results. 2. PsycINFO; TREATMENT DURATION/ OR MAINTENANCE THERAPY/; 3969 results. 3. PsycINFO; "long term".ti,ab; 84590 results. 4. PsycINFO; duration.ti,ab; 64671 results. 5. PsycINFO; "1 year".ti,ab; 11037 results. 6. PsycINFO; "cholinesterase inhibitors".ti,ab; 917 results. 7. PsycINFO; (donepezil OR galantamine OR rivastigmine OR tacrine OR memantine).ti,ab; 2653 results. 37. PsycINFO; ("one year" OR "two year" OR "three year").ti,ab; 15580 results. 38. PsycINFO; "52 weeks".ti,ab; 288 results.	45	

	39. PsycINFO; ALZHEIMER'S DISEASE/ OR exp DEMENTIA/; 49649 results. 40. PsycINFO; dementia.ti,ab; 40600 results. 41. PsycINFO; 39 OR 40; 59809 results. 42. PsycINFO; 1 OR 6 OR 7; 4124 results. 43. PsycINFO; 41 AND 42; 2276 results. 44. PsycINFO; 2 OR 3 OR 4 OR 5 OR 37 OR 38; 170894 results. 45. PsycINFO; 43 AND 44; 396 results. 46. PsycINFO; 45 [Limit to: Publication Year 2010-Current]; 90 results. 47. PsycINFO; CLINICAL TRIALS/; 7055 results. 48. PsycINFO; random*.ti,ab; 123106 results. 49. PsycINFO; groups.ti,ab; 352912 results. 50. PsycINFO; (double adj3 blind).ti,ab; 17314 results. 51. PsycINFO; (single adj3 blind).ti,ab; 1326 results. 52. PsycINFO; EXPERIMENTAL DESIGN/; 8795 results. 53. PsycINFO; controlled.ti,ab; 76713 results.		

	54. PsycINFO; (clinical adj3 study).ti,ab; 7571 results. 55. PsycINFO; trial.ti,ab; 64836 results. 56. PsycINFO; "treatment outcome clinical trial".md; 25026 results. 57. PsycINFO; 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56; 545020 results. 58. PsycINFO; 46 AND 57 [Limit to: Publication Year 2010-Current]; 45 results.		
Embase	46. EMBASE; exp CHOLINESTERASE INHIBITORS/; 65015 results. 47. EMBASE; TREATMENT DURATION/ OR MAINTENANCE THERAPY/; 114796 results. 48. EMBASE; "long term".ti,ab; 638371 results. 49. EMBASE; duration.ti,ab; 493362 results. 50. EMBASE; "1 year".ti,ab; 157932 results. 51. EMBASE; "cholinesterase inhibitors".ti,ab; 3039 results. 52. EMBASE; (donepezil OR galantamine OR rivastigmine OR tacrine OR memantine).ti,ab; 8681 results. 53. EMBASE; ("one year" OR "two year" OR "three	21	

	year").ti,ab; 136185 results. 54. EMBASE; "52 weeks".ti,ab; 5016 results. 55. EMBASE; ALZHEIMER'S DISEASE/ OR exp DEMENTIA/; 216660 results. 56. EMBASE; dementia.ti,ab; 84707 results. 57. EMBASE; 55 OR 56; 228472 results. 58. EMBASE; 46 OR 51 OR 52; 67414 results. 59. EMBASE; 57 AND 58; 14388 results. 60. EMBASE; 47 OR 48 OR 49 OR 50 OR 53 OR 54; 1401417 results. 61. EMBASE; 59 AND 60; 1910 results. 62. EMBASE; 61 [Limit to: Exclude MEDLINE Journals and Publication Year 2010-Current]; 90 results. 63. EMBASE; random*.ti,ab; 848139 results. 64. EMBASE; factorial*.ti,ab; 21796 results. 65. EMBASE; (crossover* OR cross-over*).ti,ab; 67987 results. 66. EMBASE; placebo*.ti,ab; 195646 results. 67. EMBASE; (doubl* ADJ blind*).ti,ab; 140706 results.		

	68. EMBASE; (singl* ADJ blind*).ti,ab; 13948 results. 69. EMBASE; assign*.ti,ab; 232177 results. 70. EMBASE; allocat*.ti,ab; 79803 results. 71. EMBASE; volunteer*.ti,ab; 173309 results. 72. EMBASE; CROSSOVER PROCEDURE/; 38578 results. 73. EMBASE; DOUBLE BLIND PROCEDURE/; 118011 results. 74. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 357438 results. 75. EMBASE; SINGLE BLIND PROCEDURE/; 18318 results. 76. EMBASE; 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75; 1372577 results. 77. EMBASE; 62 AND 76 [Limit to: Exclude MEDLINE Journals and Publication Year 2010-Current]; 21 results.		
Medline	46. MEDLINE; exp CHOLINESTERASE INHIBITORS/; 41894 results. 47. MEDLINE; TREATMENT DURATION/ OR MAINTENANCE THERAPY/; 0 results. 48. MEDLINE; "long term".ti,ab; 532596 results. 49. MEDLINE; duration.ti,ab; 407803 results. 50. MEDLINE; "1 year".ti,ab; 129363 results.	160	

	51. MEDLINE; "cholinesterase inhibitors".ti,ab; 2368 results. 52. MEDLINE; (donepezil OR galantamine OR rivastigmine OR tacrine OR memantine).ti,ab; 6474 results. 53. MEDLINE; ("one year" OR "two year" OR "three year").ti,ab; 100836 results. 54. MEDLINE; "52 weeks".ti,ab; 4074 results. 55. MEDLINE; ALZHEIMER'S DISEASE/ OR exp DEMENTIA/; 121542 results. 56. MEDLINE; dementia.ti,ab; 66208 results. 57. MEDLINE; 55 OR 56; 141558 results. 58. MEDLINE; 46 OR 51 OR 52; 45507 results. 59. MEDLINE; 57 AND 58; 5608 results. 60. MEDLINE; 47 OR 48 OR 49 OR 50 OR 53 OR 54; 1093859 results. 61. MEDLINE; 59 AND 60; 837 results. 62. MEDLINE; 61 [Limit to: Publication Year 2010-Current]; 179 results. 63. MEDLINE; "randomized controlled trial".pt; 388158 results. 64. MEDLINE; "controlled clinical trial".pt; 89760 results. 65. MEDLINE; randomized.ab; 303172 results. 66. MEDLINE; placebo.ab; 163015 results. 67. MEDLINE; "drug therapy".fs; 1760436 results. 68. MEDLINE; randomly.ab; 214577 results. 69. MEDLINE; trial.ab; 319152 results. 70. MEDLINE; groups.ab; 1364480 results. 71. MEDLINE; 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70; 3409448 results. 72. MEDLINE; 61 AND 71; 751 results. 73. MEDLINE; 62 AND 71 [Limit to: Publication Year		

	2010-Current]; 160 results.		
Summary	**NA**	**NA**	

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