Best Evidence Summaries of Topics in Mental Healthcare

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

Question

In patients with Alzheimer's dementia, how effective is memantine compared to either cholinesterase inhibitors or placebo in reducing anxiety and psychotic symptoms?

Clarification of question using PICO structure

Patients: adults with Alzheimer's dementia
Intervention: memantine
Comparator: cholinesterase inhibitors or placebo
Outcome: reduction in anxiety and psychotic symptoms

Clinical and research implications

There was some, very limited evidence that treatment with memantine (in addition to acetylcholinesterase inhibitors) may have a short term (6-12 weeks) beneficial effect on psychotic symptoms (delusions and hallucinations), in patients with moderate to severe Alzheimer's disease, compared to treatment with acetylcholinesterase inhibitors alone. However, it was not clear whether this effect was maintained in the longer term (results were inconsistent at 24 weeks). No study showed any significant effect of memantine on anxiety symptoms. No studies were identified which compared treatment with memantine alone to treatment with acetylcholinesterase inhibitors alone.

Larger, high quality RCTs are needed to fully assess the effects of memantine on anxiety and psychotic symptoms in patients with Alzheimer's disease.

What does the evidence say?

Number of included studies/reviews (number of participants)
We identified one article reporting a *post-hoc* meta-analysis of data from six randomised controlled trials (RCTs) assessing the effects of memantine on behavioural symptoms as measured by the Neuropsychiatric Inventory (NPI); it was not clear whether data from these RCTs were obtained as part of a systematic review.[1] Three of the included studies were conducted in participants with mild to moderate Alzheimer's disease (AD) and three were conducted in patients with moderate to severe AD. Overall, 1,826 of the included paricipants had a Mini-Mental State Examination (MMSE) score of <20. In two of the included studies, memantine or placebo was added to existing stable treatment with acetylcholinesterase inhibitors. No included study provided data comparing the effectiveness of memantine alone with acetylcholinesterase inhibitors alone.[1] All included studies

reported outcomes at 12 weeks and at the end of the study (24 or 28 weeks). Results were not reported separately for individual studies.
We identified two further RCTs, which were not included in the meta-analysis. The first compared memantine and donepezil with placebo and donepezil in patients with severe AD (MMSE score 5 to14).[2] This study used a variety of behavioural, cognitive, functional and global outcome measures, but data were only reported for NPI after 12 and 24 weeks of treatment.[2] The second study appeared to compare memantine with placebo in patients with severe AD (MMSE <20), who had been treated with an acetylcholinesterase inhibitor for ≥3 months; it was unclear whether acetylcholinesterase inhibitor treatment continued during the study.[3] This study reported a variety of behavioural, cognitive, functional and global outcome measures at six and 12 weeks.[3] The only outcome measure used, which included components for anxiety and psychotic symptom, was NPI.

Main Findings
The meta-analysis indicated that total NPI scores were significantly better in the memantine treated group at both 12 and 24 weeks, though it was not clear whether this result was consistant between studies of patients with mild to moderate AD and studies of patients with moderate to sever AD.[1] The two RCTs also showed better NPI scores for memantine-treated patients at 12 and 24 weeks,[2] and at six and 12 weeks.[3] Data from the meta-analysis and one RCT indicated that the difference between the memantine and placebo groups at 24 weeks was due to a decline in the placebo group rather than sustained improvement in the memantine group; NPI scores in the memantine groups were similar at baseline and 24 weeks.[1,2]

Specific data on anxiety and psychotic symptoms were very sparse. The meta-analysis indicated that patients treated with memantine scored significantly better (NPI) for delusions and hallucinations at 12 weeks, however, this difference was not sustained at 24/28 weeks.[1] When the analysis was restricted to patients who had the symptom at baseline, memantine-treated patients had significantly better scores for delusions than those in the placebo group at 24/28 weeks.[1] There were no significant differences in anxiety between the two groups.[1] Data from one RCT indicated that, among patients without the specific symptom at baseline, significantly fewer patients in the memantine-treated group showed emergence of delusions (94% versus 85% remained asymptomatic) at 12 weeks, however, this effect was not maintained at 24 weeks.[2] This trial showed no significant differences in anxiety or psychotic symptoms (NPI), for all patients treated, and no significant difference for improvement in symptoms (restriction of the analyses to patients who had the symptom at baseline).[2] The second RCT reported results a *post-hoc* analysis for the NPI symptom cluster (agitation/aggression, delusions and hallucinations) which favoured memantine-treated patients compared to the placebo group, mean difference -2.1 (95% CI:-4.0 to -0.2) p=0.03 at six weeks. However, this difference was not maintained at 24 weeks.[3]

The majority of the available evidence appears to have been derived from studies comparing treatment with memantine in addition to acetylcholinesterase inhibitors to treatment with acetylcholinesterase inhibitors alone, in patients with moderate to severe AD. No studies were identified which compared treatment with memantine alone to treatment with acetylcholinesterase inhibitors alone.

Authors Conclusions
The authors of the meta-analysis concluded that memantine is effective in treating and preventing the behavioural symptoms of moderate to severe AD, with specific persistent benefits observed on the symptoms of delusions and agitation/aggression.[1] However, they note that their analysis was *post-hoc* and advice caution in interpreting their findings.[1] The first RCT concluded that treatment with memantine reduced agitation/aggression, irritability and appetite/eating disturbances; no conclusions were drawn with respect to anxiety or psychotic symptoms.[2] The second RCT concluded that treatment with memantine did not improve significant agitation in patients with moderate to severe AD; again, no conclusions were drawn with respect to anxiety or psychotic symptoms.[3]

Reliability of conclusions/Strength of evidence
The evidence included in this summary was derived from one *post-hoc* met-analysis of six RCTs (the methodological quality of these RCTs was uncertain, it was not clear whether they were identified as part of a systematic review, and data from clinically heterogeneous studies were combined) and two additional good quality RCTs. Combining information from all of these sources, there was some, very limited evidence that treatment with memantine (in addition to acetylcholinesterase inhibitors) may have a short term (6-12 weeks) beneficial effect on psychotic symptoms (delusions and hallucinations), in patients with moderate to severe AD, compared to treatment with acetylcholinesterase inhibitors alone. However, it was not clear whether this effect was maintained in the longer term (results were inconsistent at 24 weeks). No study showed any significant effect of memantine on anxiety symptoms. No studies were identified which compared treatment with memantine alone to treatment with acetylcholinesterase inhibitors alone.

Data were extremely sparse for the specific outcomes and comparisons of interest. Larger, high quality RCTs are needed to fully assess the effects of memantine on anxiety and psychotic symptoms in patients with AD.

What do guidelines say?
No relevant clinical guidelines were identified.

Date question received: 22/05/2012
Date searches conducted: 24/05/2012
Date answer completed: 18/06/2012

References

SRs

1. Gauthier S, Loft H, Cummings J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *International Journal of Geriatric Psychiatry*, 2008; 23: 537–545.

RCTs

2. Cummings J L, Schneider E, Tariot P N, Graham S M. Behavioural effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology*, 2006 July 11; 67(1):57-63.

3. Fox C, Crugel M, Maidment I, Auestad B H, Coulton S, Treloar A, Ballard C, Boustani M, Katona C, Livingston G. (2012). Efficacy of Memantine for Agitation in Alzheimer's Dementia: A Randomised Double-Blind Placebo Controlled Trial. *PLoS ONE* 7(5): e35185. doi:10.1371/journal.pone.0035185.

Results

Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Gauthier et al. (2008)	None	The dataset used in this article was originally created for the regulatory submission to the European Authorities in the expansion of memantine's indication to include moderate AD. The article reports a *post hoc* analysis of this data set, to investigate the effects of memantine treatment on behavioural symptoms of AD. The included studies were multicentre, randomised, placebo-controlled, parallel-group, double blind studies of memantine 20mg daily. Participants were outpatients with mild/moderate or moderate/severe AD, aged 50 and over at baseline. Five of the included studies took place over 24 weeks, one of the studies took place over 28 weeks. Dosing began at 5mg/day and were titrated up in weekly increments of 5mg to 20mg/day in all included studies. In two studies, memantine or placebo was added to existing stable treatment with acetylcholinesterase inhibitor; patients on concomitant acetylcholinesterase inhibitor treatment had to be treated for at least six months before	6 (n=2,311)	This article reported the results of a *post hoc* analysis of six placebo-controlled RCTs, conducted to assess the effects of memantine treatment on behavioural symptoms of AD. Three studies (n=1,306) were conducted in patients with mild to moderate AD, and three (n=1,005) were conducted in patients with moderate to severe AD. Overall, 1,826 patients had a Mini-Mental State Examination (MMSE) score of <20. In two studies, memantine or placebo was added to existing stable treatment. No assessment of the methodological quality of the included trials was reported. However, the authors stated that 'randomisation was preserved' and that baseline demographic and clinical characteristics were well matched between the memantine and placebo groups. The outcome measure used was the Neuropsychiatric Inventory (NPI), a 12-item scale that assesses a range of different behavioural symptoms including anxiety and	The article reported a *post hoc* meta-analysis and it was not clear whether data were derived from a systematic review; no systematic review methods were reported. It was unclear how the six studies were identified and selected and how data were extracted for the analysis. Pooled estimates of effect included both data from patients with mild to moderate AD and patients with

		starting the study, and to be on stable dosing for at least three months prior to, and throughout, the study. Concomitant psychotropic medications were allowed in all except one study.		some psychotic symptoms. The pooled analysis assessed change from baseline in NPI score using a modified intention-to-treat approach, which included all patients from each study who received at least one dose of memantine/placebo and had at least one post-baseline efficacy assessment. The effect of treatment, relative to the presence or absence of symptoms (single items on the NPI scale) at baseline was also assessed. Subgroup analyses were conducted, on single items, to assess improvement in symptoms in patients who had the symptom at baseline and emergence of new symptoms in patients who did not have the symptom at baseline. Total NPI score: Pooled data indicted that patients treated with memantine had significantly better NPI scores at week 12 and at the end of the studies than those treated with placebo. No numerical values for the NPI scores in each group, at different time points, were reported. However, graphical presentation appeared to indicate a decline in NPI score in the placebo group, whilst the NPI score in the memantine group appeared to be similar at the end of the study following a transient improvement at 12 weeks.	moderate to severe AD. In addition, it appeared that four studies reported comparisons of mematnine versus placebo and two reported comparisons of memantine+ acetylcholinesterase inhibitor versus placebo+ acetylcholinesterase inhibitor. Pooling data from these apparently heterogeneous study populations is of questionable validity.

				Single NPI items: Patients treated with memantine had significantly better single item scores for delusions, hallucinations and agitation/aggression at 12 weeks, and for agitation/aggression and irritability/lability at the end of the studies. There were no significant differences between treatment and placebo for any other item, including anxiety. Symptom improvement: When analyses were restricted to patients who had individual symptoms at baseline, patients treated with memantine had significantly better NPI scores for delusions, agitation/aggression and disinhibition, at the end of the studies, than those in the placebo group. Symptom emergence: When analyses were restricted to patients who were asymptomatic for individual symptoms at baseline, significantly more memantine-treated patients than placebo-treated patients remained asymptomatic for agitation/aggression, irritability/lability and night time behaviour at the end of the studies.	

RCTs/DTAs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Cummings et al. (2006)	*Patients:* Participants had a diagnosis of possible AD, had a MMSE score of 5 to 14 at both screening and baseline, were at least 50 years of age, had MRI or a CT scan within the previous 12 months consistent with a diagnosis of AD, were receiving ongoing therapy with donepezil for at least 6 months and had been on a stable dose for at least 3 months, had a knowledgeable caregiver who could provide health-related information, were residents in the community, were ambulatory or ambulatory assisted and were stable medically. Patients were excluded if they had vitamin B_{12} or folate deficiency, active systemic illness, or a history of psychiatric or central nervous system disorder other than ADE. *Intervention:* Memantine treatment (memantine and donepezil). Memantine treatment was titrated at 5mg/week to 20 mg/day at the beginning of week four, from a starting dose of 5-20 mg/day. *Comparator:* Placebo which was	n=404 randomised n=403 started trial (one patient in the memantine group withdrew consent before receiving treatment) n=395 analysed n=379 NPI analyses	This, double blind RCT compared treatment with memantine and an acetylcholinesterase inhibitor (donepezil) with treatment with donepezil alone. Demographic and clinical characteristics appeared to be similar, at baseline, between the two treatment groups. The study duration was 24 weeks and all participants had MMSE score of <20. Change from baseline in Severe Impairment Battery (SIB) and the AD co-operative Study Activities of Daily Living Inventory (ADCS-ADL) were listed as the primary outcome measures. However, reporting of results focussed on a secondary outcome measure (NPI). NPI was measured at baseline, 12 weeks and 24 weeks. Subgroup analyses were conducted, on single NPI items, to assess improvement in symptoms in patients who had the symptom at baseline and emergence of new symptoms in patients who were asymptomatic at baseline. Analyses were based on a modified intention-to-treat population, which included randomised patients who completed at least one post-baseline assessment of a primary efficacy measure (n=395, memantine+donezepil n=198, placebo+donezepil n=197). For the NPI analyses n=379 (memantine+donezepil n=193, placebo+donezepil n=186). Total NPI score: Total NPI scores were significantly better, at both 12 and 24	The authors reported use of a randomised, double-blind design and provided details of the randomisation process. The use of a placebo, which was visually identical to memantine tablets means that blinding was likely to have been adequate. The authors reported use of a modified intention-to-treat approach for primary

	visually identical to memantine tablets (donepezil only) *Outcomes:* Behavioural, cognitive, functional (activities of daily living) and global outcome measures. Secondary outcomes included the NPI, the Clinician's Interview-Based Impression of Change with Caregiver Input (CIBIC-Plus; ADCS version), and the Behavioral Rating Scale for Geriatric Patients (BGP).		weeks, in the memantine+donepezil group than in the placebo+donepezil group. Depending upon the statistical method used, the mean difference at 12 weeks was 4.2 or 4.4 points and the mean difference at 24 weeks was 3.8 or 3.4 points. The mean total NPI score in the placebo+donezepil group showed a significant worsening throughout the study, whilst the mementine+donezepil group showed a significant improvement at week 12 followed by a return to baseline at week 24. Single NPI items: There were significant differences in favour of the memantine+donezepil group on agitation, irritability and appetite/eating changes at both weeks 12 and 24. Symptom improvement: For patients who had specific symptoms at baseline, agitation was improved in the memantine+donezepil group relative to the placebo+donezepil group at 12 weeks -1.2 (95% CI: -2.2 to -0.2), *p*=0.018 and at 24 weeks -1.3 995% CI: -2.3 to -0.2), *p*=0.021. Appetite changes were also improved at 12 weeks. Symptom emergence: Among patients with no behavioural symptoms for specific domains at baseline, fewer patients in the memantine+donezepil group showed emergence of delusions (94% versus 85% remained asymptomatic) and agitation (89% versus 79% remained asymptomatic) at 12 weeks. At 24 weeks, fewer patients in the memantine+donezepil group showed emergence of agitation (85% versus 73% remained	outcome measures, but it was not clear whether a similar approach was used for the secondary outcome that they actually reported. The authors reported data for a secondary outcome measure only (NPI) and no data were reported for the non-significant items of this measure.

			asymptomatic), irritability (88% vesus 78% remained asymptomatic) and night time behavious (89% versus 80% remained asymptomatic.	
Fox et al. (2012)	*Patients:* The inclusion criteria for this trial were a diagnosis of probable AD, with a Standardised Mini-mental State (SMMSE) score of <20, Hachinski score of <5, aged >44, and a history of at least two weeks of clinically significant agitation that required treatment. Participants were excluded if they had: used memantine in the four weeks before study commencement; used a cholinesterase inhibitor for <3 months; Altered dose of any anti-psychotic, antidepressant, benzodiazepine, hypnotic or lithium in the two weeks before the study; used anti-parkinsonian medication; hypersensitivity to memantine; severe renal impairment; epilepsy, or history of convulsions or seizure; concomitant usage of NMDA antagonists; recent myocardial infarction, uncompensated congestive heart failure, uncontrolled hypertension; severe, unstable or poorly controlled medical illness; any disability interfering with the participant completing the study as	n=153 randomised n= 149 (72 memantine, 77 placebo) started trial	This double-blind, placebo-controlled RCT assessed the effectiveness of memantine treatment on a number of outcome measures CMAI, CGI-C, SMMSE, SIB and NPI; only NPI includes items for anxiety and some psychotic symptoms. All included participants had a baseline SMMSE score of <20 and the exclusion criteria appear to indicate that memantine or placebo were added to existing treatment (≥3 months) with acetylcholinesterase inhibitor, though this was not clearly reported. Demographic and clinical characteristics appeared to be similar, at baseline, between the two treatment groups. The study duration was 12 weeks and there was no significant difference in withdrawals between the two groups. NPI was assessed at baseline, six weeks and 12 weeks. Analyses used an intention-to-treat approach, with participants analysed in their allocated group regardless of medication protocol adherence. A *post-hoc* analysis of NPI scores for the symptom cluster (agitation/aggression, delusions and hallucinations) was also reported. Total NPI score: The total NPI score was significantly better in the memantine-treated group than the placebo group at six weeks, mean difference -6.9 (95% CI: -12.2 to -1.6), p=0.012, and at 12 weeks, mean difference -9.6 (95% CI: -15.0 to -4.3), p=0.0005.	The authors reported use of a randomised, double-blind design and provided details of the randomisation and allocation concealment methods. The use of a placebo, which was visually identical to memantine tablets means that blinding was likely to have been adequate. Results appear to have been reported for all specified

	judged by the recruiting physician. *Intervention & Comparator*: Participants were randomised to either 10mg twice daily memantine (titrated in 5mg increments over 4 weeks) or placebo. *Outcomes:* Outcomes were measured with the Cohen-Mansfield Agitation Inventory (CMAI), the neuropsychiatric inventory (NPI), the Standardised Mini-Mental State Examination (SMMSE), the Clinical Global Impression Change (CGI-C) and the Severe Impairment Battery (SIB).		NPI symptom cluster (agitation/aggression, delusions and hallucinations): Assessment of this symptom cluster at six weeks favoured memantine, mean difference -2.1 (95% CI:-4.0 to -0.2), *p*=0.03. However, at 24 weeks, the difference was not significant. Other outcomes with a significant difference in favour of memantine were SMMSE and SIB, at 12 weeks only. There were no outcomes with a significant difference in favour of placebo.	outcome measures.

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Gauthier et al. (2008)	?	?	?	?	☹

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Cummings et al. (2006)	☺	☺	☺	☺	☹	☹
Fox et al. (2012)	☺	☺	☺	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	memantine AND (psychosis OR anxiety) [restricted by guidelines > produced by NICE or SIGN]	9	0
DARE	1 MeSH DESCRIPTOR Alzheimer Disease EXPLODE ALL TREES 215 2 MeSH DESCRIPTOR Dementia EXPLODE ALL TREES 380 3 MeSH DESCRIPTOR Delirium, Dementia, Amnestic, Cognitive Disorders EXPLODE ALL TREES 516 4 MeSH DESCRIPTOR Dementia, Vascular EXPLODE ALL TREES 14 5 MeSH DESCRIPTOR Lewy Body Disease EXPLODE ALL TREES 1 6 (dement*) IN DARE 388 7 (alzheimer* OR ADD OR AD) IN DARE 667 8 (parkinson*) IN DARE 202 9 MeSH DESCRIPTOR Cholinesterase Inhibitors EXPLODE ALL TREES 77 10 MeSH DESCRIPTOR Galantamine EXPLODE ALL TREES 23 11 MeSH DESCRIPTOR Memantine EXPLODE ALL TREES 29 12 cholinesterase adj inhibitor* 112 13 acetylcholinesterase adj inhibitor* 31 14 donepezil* 93 15 galantamin* 59 16 memantin* 45	157	1

	17 rivastigmin* 61 18 tacrin* 23 19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 1333 20 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 181 21 #19 AND #20 157		
Primary studies			
CENTRAL	#1 MeSH descriptor Memantine, this term only 149 edit delete #2 memantin* 373 edit delete #3 axura 4 edit delete #4 namenda 5 edit delete #5 ebixa 10 edit delete #6 d124 0 edit delete #7 "d-145" 4 edit delete #8 akatinol 12 edit delete #9 ebix 1 edit delete #10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9) 379 edit delete #11 MeSH descriptor Alzheimer Disease, this term only 1894 edit delete #12 MeSH descriptor Dementia, this term only 1090 edit delete #13 dementia 8759 edit delete #14 alzheimer* 4547 edit delete #15 (#11 OR #12 OR #13 OR #14) 9872 edit delete #16 (#10 AND #15) 274 edit delete #17 (#16), from 2011 to 2012 28 edit delete Central only 11	11	2
PsycINFO	1. PsycINFO; CLINICAL TRIALS/; 6058 results. 2. PsycINFO; random*.ti,ab; 109173 results.	193	

	11. PsycINFO; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10; 497909 results. 3. PsycINFO; groups.ti,ab; 324368 results. 4. PsycINFO; (double adj3 blind).ti,ab; 15973 results. 5. PsycINFO; (single adj3 blind).ti,ab; 1187 results. 7. PsycINFO; controlled.ti,ab; 68235 results. 6. PsycINFO; EXPERIMENTAL DESIGN/; 8224 results. 8. PsycINFO; (clinical adj3 study).ti,ab; 6803 results. 10. PsycINFO; "treatment outcome clinical trial".md; 21891 results. 9. PsycINFO; trial.ti,ab; 57469 results. 12. PsycINFO; memantine.ti,ab,tw; 748 results. 13. PsycINFO; axura.ti,ab; 0 results. 14. PsycINFO; namenda.ti,ab; 4 results. 15. PsycINFO; ebixa.ti,ab; 0 results. 16. PsycINFO; d145.ti,ab; 2 results. 17. PsycINFO; d-145.ti,ab; 2 results. 18. PsycINFO; ALZHEIMER DISEASE/; 26816 results. 19. PsycINFO; alzheimer*.ti,ab,ti; 33156 results. 20. PsycINFO; alzheimer*.ab; 32169 results. 21. PsycINFO; DEMENTIA/; 20921 results. 22. PsycINFO; dementia.ti; 17367 results. 23. PsycINFO; dementia.ab; 34887 results. 24. PsycINFO; 22 OR 23; 36746 results. 25. PsycINFO; PRESENILE DEMENTIA/; 271 results. 26. PsycINFO; 12 OR 13 OR 14 OR 15 OR 16 OR 17; 752 results. 27. PsycINFO; 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 25; 56649 results. 28. PsycINFO; 26 AND 27; 458 results. 29. PsycINFO; 11 AND 28; 193 results. _____		
MEDLINE	Search History:	753	

	1. MEDLINE; MEMANTINE/; 1316 results. 2. MEDLINE; memantin*.tw; 1712 results. 3. MEDLINE; axura.tw; 7 results. 4. MEDLINE; namenda.tw; 21 results. 5. MEDLINE; ebixa.tw; 17 results. 6. MEDLINE; d145.tw; 18 results. 7. MEDLINE; d-145.tw; 82 results. 8. MEDLINE; akatinol.tw; 17 results. 9. MEDLINE; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8; 2018 results. 10. MEDLINE; ALZHEIMER DISEASE/; 58428 results. 11. MEDLINE; alzheimer*.ti,ab; 76349 results. 12. MEDLINE; (alzheimer* adj2 disease).ti,ab; 67531 results. 13. MEDLINE; DEMENTIA/; 33018 results. 14. MEDLINE; dementia.ti,ab; 56032 results. 15. MEDLINE; 10 OR 11 OR 12 OR 13 OR 14; 126316 results. 16. MEDLINE; 9 AND 15; 1002 results. 17. MEDLINE; "randomized controlled trial".pt; 328205 results. 18. MEDLINE; "controlled clinical trial".pt; 84150 results. 20. MEDLINE; placebo.ab; 136265 results. 21. MEDLINE; "drug therapy".fs; 1533944 results. 19. MEDLINE; randomized.ab; 243606 results. 22. MEDLINE; randomly.ab; 178821 results. 23. MEDLINE; trial.ab; 252421 results. 24. MEDLINE; groups.ab; 1167318 results. 25. MEDLINE; 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24; 2938633 results. 26. MEDLINE; 16 AND 25; 753 results.		
EMBASE	2. EMBASE; memantin*.tw; 2450 results.	582	

	3. EMBASE; axura.tw; 104 results. 4. EMBASE; namenda.tw; 254 results. 5. EMBASE; d145.tw; 17 results. 6. EMBASE; d-145.tw; 105 results. 7. EMBASE; akatinol.tw; 115 results. 8. EMBASE; ebixa.tw; 218 results. 9. EMBASE; ebix.tw; 2 results. 10. EMBASE; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9; 5759 results. 11. EMBASE; ALZHEIMER DISEASE/; 103848 results. 12. EMBASE; alzheimer*.ti,ab; 96698 results. 13. EMBASE; (alzheimer* adj2 disease).ti,ab; 85300 results. 14. EMBASE; DEMENTIA/; 63851 results. 15. EMBASE; dementia.ti,ab; 73607 results. 16. EMBASE; PRESENILE DEMENTIA/; 493 results. 17. EMBASE; 11 OR 12 OR 13 OR 14 OR 15 OR 16; 177773 results. 18. EMBASE; 10 AND 17; 3356 results. 19. EMBASE; random*.ti,ab; 725523 results. 26. EMBASE; allocat*.ti,ab; 67829 results. 20. EMBASE; factorial*.ti,ab; 18785 results. 27. EMBASE; volunteer*.ti,ab; 155758 results. 21. EMBASE; (crossover* OR cross-over*).ti,ab; 60876 results. 29. EMBASE; DOUBLE BLIND PROCEDURE/; 108903 results. 30. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 322091 results. 28. EMBASE; CROSSOVER PROCEDURE/; 33877 results.		

	32. EMBASE; 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31; 1197617 results. 22. EMBASE; placebo*.ti,ab; 174214 results. 31. EMBASE; SINGLE BLIND PROCEDURE/; 15895 results. 23. EMBASE; (doubl* ADJ blind*).ti,ab; 127542 results. 25. EMBASE; assign*.ti,ab; 202369 results. 24. EMBASE; (singl* ADJ blind*).ti,ab; 12137 results. 33. EMBASE; 18 AND 32; 582 results.		
Summary	**NA**	**NA**	

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