Best Evidence Summaries of Topics in Mental Healthcare

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

Question

"In adults with dementia, what is the association between cholinesterase inhibitor use and falls?"

Clarification of question using *PRO* structure

Patients:	Adults with dementia
Risk Factor:	Cholinesterase inhibitors
Outcome:	Falls

Clinical and research implications

No definite clinical implications can be made from the available evidence. The current evidence from one well-conducted systematic review (SR) does suggest that the risk of falls and fall-related adverse events is similar between patients who receive cholinesterase inhibitors (ChEIs) compared with patients who receive placebo. The authors cautioned, however, that due to small numbers and possible underreporting of events, the possibility of small benefits or harms cannot be excluded. Two other studies reported low rates of falls in patients taking cholinesterase inhibitors for Alzheimer's disease. As stated by the authors of the SR, it is clear that more high-quality observational research is needed to evaluate the effect of ChEIs (and other agents) on fall-related adverse events in people with dementia.

What does the evidence say?

Number of included studies/reviews (number of participants)
One SR (Kim et al. 2011), one randomised controlled trial (RCT) (Farlow et al. 2011), and one prospective, longitudinal and observational cohort survey (Froelich et al. 2009) met the inclusion criteria for this BEST summary.

Main Findings
The systematic review evaluated the effects of ChEIs (donepezil, galantamine, rivastigmine, and tacrine), and also memantine, on the risk of falls and fall-related adverse events (syncope, fracture, and accidental injury) in older adults with mild cognitive impairment and dementia. Based on data from 40 randomised controlled trials, no significant difference was found between ChEIs and placebo for falls, fracture, or accidental injury, but significantly more syncope was observed with ChEIs: OR 1.53 (95% CI 1.02, 2.30; P=0.04).

The RCT evaluated the safety and tolerability of increasing donepezil to 23 mg/d compared with continuing 10 mg/d in patients with moderate to severe Alzheimer's disease (Farlow et al. 2011). In terms of falls, they found very little difference between the groups: 4.0% in the 23 mg/d group and 3.8% in the 10 mg/d group (n= 963 and n=471, respectively). Moreover, they reported that the majority of falls (74.4% in one group and 72.2% in the other groups) were not considered to be related to the study medication.

The prospective, longitudinal and observational cohort survey evaluated several outcomes (including MMSE, Disability Assessment for Dementia (DAD), Neuropsychiatric Inventory (NPI), and Clinical Global Impression (CGI) – and adverse events) for people with mild-to-moderate Alzheimer's disease living in the community (Froelich et al. 2009). In this study, there was no intervention *per se*, and patients included those managed with or without acetylcholinesterase inhibitors, although 75.2% were taking ChEIs during the survey. The authors reported that 2.4% of the patients experienced a fall during the 2-year survey.

Authors Conclusions
The authors of the SR concluded that ChEIs may increase the risk of syncope, with no effects on falls, fracture, or accidental injury in cognitively impaired older adults.

Farlow et al. (2011) concluded that the rate of serious AEs was low in patients treated with donepezil 23 mg/d, and that it was similar to that seen with donepezil 10 mg/d.

Froelich et al. (2009) did not make any conclusions regarding falls specifically, but stated that relatively low rates of AEs were apparent during the survey. They also concluded that community patients with AD experience progressive and interconnected decline in cognition, behaviour and functioning over time, placing increased burden on caregivers.

Reliability of conclusions/Strength of evidence

The SR had a low risk of bias, and the results are likely reliable. The methods used to conduct the RCT were not well-reported in the publication by Farlow et al. (2011), which presented safety and tolerability results only. Thus, the reliability of the results of this study are uncertain. Due to the inherent biases of prospective, longitudinal surveys, the reliability of the results of the Froelich et al. (2009) study are also uncertain.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Scottish Intercollegiate Guidelines Network (SIGN) guidelines discuss the association between cholinesterase inhibitor use and falls.

Date question received: 15/11/2013
Date searches conducted: 21/11/2013
Date answer completed: 05/12/2013

References

Systematic reviews

Kim, D.H., Brown, R.T., Ding, E.L., Kiel, D.P. and Berry, S.D. (2011) Dementia Medications and Risk of Falls, Syncope, and Related Adverse Events: Meta-Analysis of Randomized Controlled Trials. *The American Geriatrics Society 59* (**6**) pp. 1019-1031.

Primary studies

Farlow, M., Veloso, F., Moline, M., Yardley, J., Brand-Schieber, E., Bibbiani, F., Zou, H., Hsu, T. and Satlin, A. (2011) Safety and tolerability of donepezil 23 mg in moderate to severe Alzheimer's disease. *Biomed Central 11* (**57**).

Froelich, L., Andreasen, N., Tsolaki, M., Foucher, A., Kavanagh, S., Van Baelen, B. and Schwalen, S. (2009) Long-term treatment of patients with Alzheimer's disease in primary and secondary care: results from an international survey. *Current Medical Research and Opinion 25* (**12**) pp.3059-3068.

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Kim et al. (2011)	July 2009	Population: Males and females recruited from community and nursing homes, aged 69-86 years. Mean MMSE scores of 6-27. Risk Factor: Cholinesterase inhibitors and/or memantine. Outcome: Falls, syncope, fracture and accidental injury. Study designs: Randomised controlled trials (RCTs).	54	Forty of the included studies evaluated cholinesterase inhibitors, 22 of which reported on falls (9,882 participants and 589 events), 15 reported on syncope (8,227 participants and 131 events), 8 reported on fracture (3,554 participants and 50 events for fracture), and 25 studies reported on accidental injury (13,001 participants and 828 events). The pooled ORs comparing ChEIs with placebo were 0.88 (95% CI 0.74, 1.04; P=0.14 [with no heterogeneity]) for falls, 1.53 (95% CI 1.02, 2.30; P=0.04 with no heterogeneity]) for syncope, 1.39 (95% CI 0.75, 2.56; P=0.29 with no heterogeneity]) for fracture, and 1.13 (95% CI 0.87, 1.45; P=0.37, I squared=55%) for accidental injury. When studies that reported on falls were analysed in subgroups (i.e. by type - and severity of cognitive impairment, residential	

				status [community and nursing home], and length of follow-up), no significant results were found.	

Primary Studies

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Farlow et al (2011)	Population: Adults with moderate to severe Alzheimer's disease, mean age 73 years, mean MMSE score 13. Intervention/comparator: Donepezil 23mg vs. donepezil 10mg/d. Outcome: Any adverse events and premature discontinuation from the study. Study design: Randomised, double-blind, parallel group study.	N=1467	The safety population comprised 1434 patients i.e. all randomised patients who took at least 1 dose of study drug and had at least 1 post baseline safety assessment): donepezil 23 mg/d (n = 963); donepezil 10 mg/d (n = 471). AEs were generally more common in the 23 mg/d group, occurring in 73.7% of patients, compared with 63.7% of patients in the donepezil 10 mg/d group. Falls were reported in 4% of patients who received the higher dose of donepezil, and 3.8% of patients who received the lower dose. Twenty-nine of 39 cases (74.4%) in the 23 mg/d group and 13 of 18 cases (72.2%) in the 10 mg/d group were not considered related to study medication. Generally, the most common AEs were nausea, vomiting, and diarrhoea (donepezil 23 mg/d: 11.8%, 9.2%, 8.3%; donepezil 10 mg/d: 3.4%, 2.5%, 5.3%, respectively). AEs that contributed most to early discontinuations were vomiting (2.9% of patients in the 23 mg/d group and 0.4% in the 10 mg/d group), nausea (1.9% and 0.4%), diarrhoea (1.7% and 0.4%), and dizziness (1.1% and 0.0%). Serious AEs were	Unclear

			uncommon (23 mg/d, 8.3%; 10 mg/d, 9.6%).	
Froelich et al (2009)	Population: Adults with mild to moderate Alzheimer's disease with MMSE scores of 10-26 living in an ordinary household. Risk Factor: Cholinesterase inhibitors and/or memantine. Outcome: Adverse events, time to institutionalisation (Kaplan-Meiser analysis), clinical presentation (MMSE, DAD, NPI and CGI). Study design: 2-year, international, prospective, longitudinal and observational cohort survey.	N=2288	The majority of the patients in the survey (75.2%) were being treated with AChEI therapy that was not given in combination with memantine. During the survey, AChEI treatment was stopped in 576 patients after a mean duration of 484.8 days. 1382 (60.4%) patients completed the survey. MMSE, DAD, NPI and CGI scores all showed that patients experienced deterioration of AD symptoms during the survey. Mean caregivers' feeling of strain and caregiver distress increased during the survey. At least one AE was experienced by 927 patients (41%), of whom 271 (11.8%) had an AE considered to be possibly, probably or likely to be drug-related. AEs occurring in more than 2% of patients were nausea (3.0%), injury (2.6%), fall (2.4%), depression (2.2%) and urinary tract infection (2.2%). SAEs occurred in 405 patients (17.7%); the only SAE that occurred in more than 1% of patients was injury (1.2%).	High

Risk of Bias

Systematic review

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Kim et al (2011)	☺	☺	☺	☺	☺

Primary Studies

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Farlow et al (2011)	?	?	☺	☺	☺	?
Froelich et al (2009)	☹	☹	☹	☹	☺	?

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Cholinesterase inhibitors AND falls	10	0
DARE	(fall* OR faller*) IN DARE 454 Delete 2 MeSH DESCRIPTOR Accidental Falls EXPLODE ALL TREES 182 Delete 3 #1 OR #2 513 Delete 4 (donepezil OR E2020 OR aricept) IN DARE 59 Delete 5 (galantamin* OR galanthamin*) IN DARE 40 Delete 6 (reminyl) IN DARE 4 Delete 7 (rivastigmine) IN DARE 39 Delete 8 (exelon) IN DARE 4 Delete 9 ((ENA adj2 713) OR ENA-713) IN DARE 3 Delete 10 MeSH DESCRIPTOR Cholinesterase Inhibitors EXPLODE ALL TREES 88 Delete 11 MeSH DESCRIPTOR Galantamine EXPLODE ALL TREES 25 Delete 12 (cholinesterase*) IN DARE 92 Delete 13 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 156 Delete 14 #3 AND #13	6	1
Primary studies			
CENTRAL	#1 "cholinesterase inhibitors":ti,ab,kw (Word variations have been searched) 994 #2 "cholinesterase inhibitor""cholinesterase inhibitor" 311 #3 donepezil or galantamine or rivastigminedonepezil or galantamine or rivastigmine 1332 #4 acetylcholinesterase inhibitor*acetylcholinesterase inhibitor* 369 #5 MeSH descriptor: [Cholinesterase Inhibitors] explode all trees 802 #6 #1 or #2 or #3 or #4 or #5#1 or #2 or #3 or #4 or #5 1966 #7 dementia or alzheimer*dementia or alzheimer* 11022 #8 MeSH descriptor: [Dementia] explode all trees 3477	3	

	#9 #7 or #8#7 or #8 11129 #10 falls or fracturesfalls or fractures 24536 #11 "broken bones""broken bones" 14 #12 accidental or accidentsaccidental or accidents 4765 #13 balance or gaitbalance or gait 17664 #14 MeSH descriptor: [Accidental Falls] explode all trees 843 #15 MeSH descriptor: [Fractures, Bone] explode all trees 3730 #16 #10 or #11 or #13 or #14 or #1539739 #17 #6 and #9 and #16 = 101 = 3 with date limit		
PsycINFO	1. PsycINFO; CHOLINESTERASE INHIBITORS/; 1423 results. 2. PsycINFO; (cholinesterase adj3 inhibit*).ti,ab; 1509 results. 3. PsycINFO; (acetylcholinesterase adj3 inhibit*).ti,ab; 969 results. 4. PsycINFO; AChEI.ti,ab; 89 results. 5. PsycINFO; AChEIs.ti,ab; 77 results. 6. PsycINFO; ChEI.ti,ab; 107 results. 7. PsycINFO; ChEIs.ti,ab; 129 results. 8. PsycINFO; donepezil.ti,ab; 1103 results. 9. PsycINFO; rivastigmine.ti,ab; 514 results. 10. PsycINFO; galantamine.ti,ab; 469 results. 11. PsycINFO; galanthamine.ti,ab; 57 results. 12. PsycINFO; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11; 3467 results. 13. PsycINFO; (dementia OR alzheimer*).ti,ab; 62571 results. 14. PsycINFO; exp DEMENTIA/; 50065 results. 15. PsycINFO; ALZHEIMER'S DISEASE/; 30268 results. 16. PsycINFO; 13 OR 14 OR 15; 64780 results. 17. PsycINFO; (falls OR fractures).ti,ab; 7954 results. 18. PsycINFO; "broken bones".ti,ab; 30 results. 20. PsycINFO; (accidental OR accidents).ti,ab; 10508 results. 21. PsycINFO; balance.ti,ab; 26904 results. 22. PsycINFO; gait.ti,ab; 4389 results. 23. PsycINFO; FALLS/ OR exp ACCIDENTS/; 9371 results.	13	

	24. PsycINFO; 17 OR 18 OR 20 OR 21 OR 22 OR 23; 52198 results. 25. PsycINFO; 12 AND 16 AND 24; 33 results. 26. PsycINFO; 25 [Limit to: Publication Year 2009-Current]; 13 results.		
Embase	27. EMBASE; CHOLINESTERASE INHIBITORS/; 17217 results. 28. EMBASE; (cholinesterase adj3 inhibit*).ti,ab; 6862 results. 29. EMBASE; (acetylcholinesterase adj3 inhibit*).ti,ab; 7159 results. 30. EMBASE; AChEI.ti,ab; 280 results. 31. EMBASE; AChEIs.ti,ab; 235 results. 32. EMBASE; ChEI.ti,ab; 305 results. 33. EMBASE; ChEIs.ti,ab; 275 results. 34. EMBASE; donepezil.ti,ab; 3146 results. 35. EMBASE; rivastigmine.ti,ab; 1672 results. 36. EMBASE; galantamine.ti,ab; 1439 results. 37. EMBASE; galanthamine.ti,ab; 579 results. 38. EMBASE; DONEPEZIL/; 8423 results. 39. EMBASE; RIVASTIGMINE/; 5117 results. 40. EMBASE; GALANTAMINE/; 5225 results. 41. EMBASE; (dementia OR alzheimer*).ti,ab; 167158 results. 42. EMBASE; exp DEMENTIA/; 219357 results. 43. EMBASE; (falls OR fractures).ti,ab; 149261 results. 44. EMBASE; "broken bones".ti,ab; 171 results. 45. EMBASE; (accidental OR accidents).ti,ab; 61088 results. 46. EMBASE; balance.ti,ab; 161116 results. 47. EMBASE; gait.ti,ab; 34292 results. 49. EMBASE; FALLS/; 22 results. 50. EMBASE; FALLING/; 24437 results. 51. EMBASE; falling.ti,ab; 22183 results. 52. EMBASE; 43 OR 44 OR 45 OR 46 OR 47 OR 49 OR 50 OR 51; 417482 results. 53. EMBASE; 41 OR 42; 246195 results. 54. EMBASE; 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40;	69	

	30395 results. 55. EMBASE; 52 AND 53 AND 54; 550 results. 56. EMBASE; 55 [Limit to: Publication Year 2009-Current]; 253 results. 57. EMBASE; random*.tw; 859632 results. 58. EMBASE; factorial*.tw; 22048 results. 59. EMBASE; placebo*.tw; 197640 results. 60. EMBASE; (crossover* OR cross-over*).tw; 68630 results. 61. EMBASE; (doubl* adj3 blind*).tw; 142096 results. 62. EMBASE; (singl* adj3 blind*).tw; 16368 results. 63. EMBASE; assign*.tw; 234806 results. 64. EMBASE; allocat*.tw; 80854 results. 65. EMBASE; volunteer*.tw; 175065 results. 66. EMBASE; CROSSOVER PROCEDURE/; 39035 results. 67. EMBASE; DOUBLE-BLIND PROCEDURE/; 118796 results. 68. EMBASE; SINGLE-BLIND PROCEDURE/; 18539 results. 69. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 360573 results. 70. EMBASE; 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69; 1389240 results. 71. EMBASE; 56 AND 70 [Limit to: Publication Year 2009-Current]; 69 results.		
Medline	72. MEDLINE; CHOLINESTERASE INHIBITORS/; 16882 results. 73. MEDLINE; (cholinesterase adj3 inhibit*).ti,ab; 5769 results. 74. MEDLINE; (acetylcholinesterase adj3 inhibit*).ti,ab; 6194 results. 75. MEDLINE; AChEI.ti,ab; 215 results. 76. MEDLINE; AChEIs.ti,ab; 173 results. 77. MEDLINE; ChEI.ti,ab; 203 results. 78. MEDLINE; ChEIs.ti,ab; 197 results. 79. MEDLINE; donepezil.ti,ab; 2251 results. 80. MEDLINE; rivastigmine.ti,ab; 1139 results. 81. MEDLINE; galantamine.ti,ab; 1035 results. 82. MEDLINE; galanthamine.ti,ab; 465 results. 83. MEDLINE; DONEPEZIL/; 0 results.	43	

	84. MEDLINE; RIVASTIGMINE/; 0 results. 85. MEDLINE; GALANTAMINE/; 1309 results. 86. MEDLINE; 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85; 22851 results. 87. MEDLINE; (dementia OR alzheimer*).ti,ab; 135174 results. 88. MEDLINE; exp DEMENTIA/; 122386 results. 89. MEDLINE; 87 OR 88; 168767 results. 90. MEDLINE; (falls OR fractures).ti,ab; 129691 results. 91. MEDLINE; "broken bones".ti,ab; 156 results. 92. MEDLINE; (accidental OR accidents).ti,ab; 50766 results. 93. MEDLINE; balance.ti,ab; 142047 results. 94. MEDLINE; gait.ti,ab; 27588 results. 95. MEDLINE; ACCIDENTAL FALLS/; 15519 results. 96. MEDLINE; FRACTURES, BONE/; 47077 results. 97. MEDLINE; falling.ti,ab; 18937 results. 98. MEDLINE; 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97; 380333 results. 99. MEDLINE; 86 AND 89 AND 98; 113 results. 100. MEDLINE; 99 [Limit to: Publication Year 2009-Current]; 43 results.		
Summary	**NA**	**NA**	

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