Best Evidence Summaries of Topics in Mental Healthcare

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

Question

"In adults with psychosis already taking anti-psychotic medication, how effective are cholinesterase inhibitors, compared to treatment as usual, in improving cognitive function?" Additionally, "Are the risks of cardiac side effects found to outweigh the benefits of CEIs due to parasympathetic activity and risk of exacerbating heart block, or is this not documented as a problem?"

Clarification of question using PICO structure

Patients: Adults with psychosis already taking anti-psychotic medication.
Intervention: Cholinesterase inhibitors.
Comparator: Treatment as usual.
Outcome: Improving cognitive function.

Clinical and research implications

No definite clinical implications can be made from the available evidence. Data from one well-conducted systematic review included 17 studies, but the authors stated the majority of these studies were of short-term duration (i.e. up to 12 weeks) and were of poor methodological quality. Due to the lack of good quality studies, the authors stated that the evidence was not good enough for recommending acetylcholinesterase inhibitors routinely as an add-on intervention along with antipsychotics. They did suggest, however, that the combined treatment could be tried when all other interventions have failed, but withdrawn when no clinical benefit is observed. The authors also stated that more high-quality, long-term studies are needed.

What does the evidence say?

Number of included studies/reviews (number of participants)
One systematic review (SR) (Singh et al. 2012) met the inclusion criteria for this BEST summary.

Main Findings
This systematic review evaluated several cognitive outcomes, but only some showed a significant effect in favour of acetylcholinesterase inhibitor plus antipsychotic compared with antipsychotic and placebo. These were: attention, (1 RCT, n = 73, MD 1.20 95% CI 0.14 to 2.26), visual memory (2 RCTs, n = 48, MD 1.90 95% CI 0.52 to 3.28), verbal memory and language (3 RCTs, n = 42, MD 3.46 95% CI 0.67 to 6.26) and executive functioning (1 RCT, n = 24, MD 17.10 95% CI 0.70 to 33.50). In contrast, placebo showed superiority on attention aspect as measured by digit span forward (2 RCTs, n = 36, MD -0.89 95% CI -1.68 to -0.10) and backward tests (2 RCTs, n = 36, MD -0.69 95% CI -1.35 to -0.02).

Only one of the studies included in the SR evaluated cardiovascular events. This study reported no significant differences between groups (1 RCT, n = 245, RR 0.51, 95% CI 0.23 to 1.15).

Authors Conclusions
The authors concluded that the results seem to favour the use of acetylcholinesterase inhibitors in combination with antipsychotics on a few domains of mental state and cognition, but because of the various limitations in the studies, the evidence is weak.

Reliability of conclusions/Strength of evidence
This was a well-conducted SR that included a large number of methodologically weak studies. Thus, the authors' cautious conclusions reflect the evidence and are likely to be reliable.

What do guidelines say?

Neither NICE nor SIGN guidelines discuss the use of cholinesterase inhibitors for addressing cognitive impairments in those with psychosis.

Date question received: 13/11/2013
Date searches conducted: 13/11/2013
Date answer completed: 22/11/2013

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Singh et al. (2012)	02/2009	P: People with schizophrenia or other type of schizophrenia-like psychosis (e.g. schizophreniform and schizoaffective disorders) irrespective of the diagnostic criteria used, age, ethnicity or sex. Excluded children, people with a dementing illness, depression or primary problems associated with substance misuse. I: Acetylcholinesterase inhibitors alone or in combination with other drugs. C: Any comparator (e.g. other intervention, no intervention, placebo). O: Clinical global response, global state, mental state, general functioning, quality of life/satisfaction with treatment, cognitive functioning, service use, adverse effect, economic outcomes, behaviour, engagement with services. S: Randomised controlled trials.	17 (in 41 publications)	The acetylcholinesterase inhibitor plus antipsychotic showed benefit over antipsychotic and placebo in the following outcomes: **Cognitive domains**: attention, (1 RCT, n = 73, MD 1.20 95% CI 0.14 to 2.26), visual memory (2 RCTs, n = 48, MD 1.90 95% CI 0.52 to 3.28), verbal memory and language (3 RCTs, n = 42, MD 3.46 95% CI 0.67 to 6.26) and executive functioning (1 RCT, n = 24, MD 17.10 95% CI 0.70 to 33.50). Several other cognitive functioning outcomes measures using various scales/subscales were assessed, but no significant differences between treatment groups were observed. **Mental state**: PANSS negative symptoms average end point score (2 RCTs, n = 31, MD -1.69 95% CI -2.80 to -0.57), PANSS General Psychopathology average end point score (2 RCTs, n = 31, MD -3.86 95% CI -5.40 to -2.32), and improvement in depressive	Low

				symptoms showed at least by one short-term study (out of two studied evaluated) as measured by CDSS scale (data skewed). **Tolerability**: EPSE: AIMS, (1 RCT, n = 35, MD 1.50 95% CI 1.04 to 1.96). No difference was noted between the two arms for other outcomes. The overall rate of participants leaving studies early was low (13.6 %) and showed no clear difference between the two groups. Only one short-term study (Keefe 2008a) reported data on cardiovascular events. This study found no significant differences between groups (1 RCT, n = 245, RR 0.51 95% CI 0.23 to 1.15). There was no significant difference between groups for the following outcomes: global effect; any PANSS measures in short-term studies; medium term studies: PANSS total; PANSS positive symptoms; average end point score on HAM-D - short-term; average end point score on SANS - short- term; GAF: average end point score; Quality of life; average end point score on K- MMSE.	

Risk of Bias: SRs

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

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Cholinesterase Inhibitors AND psychosis	11	0
DARE	(psycho*) IN DARE 3817 Delete 2 (schizo*) IN DARE 591 Delete 3 MeSH DESCRIPTOR Psychotic Disorders EXPLODE ALL TREES 138 Delete 4 MeSH DESCRIPTOR Schizophrenia EXPLODE ALL TREES 457 Delete 5 #1 OR #2 OR #3 OR #4 4284 Delete 6 (cholinesteras* OR anti-cholinesteras* OR acetylcholinesteras* OR antidement* OR anti-dement*) IN DARE 108 Delete 7 (galanthamin* OR galantamin* Or reminyl OR acumor OR galsya OR reminyl) IN DARE 40 Delete 8 (donepezil* Or aricept) IN DARE 59 Delete 9 (rivastigmin* OR exelon) IN DARE 39 Delete 10 MeSH DESCRIPTOR Cholinesterase Inhibitors EXPLODE ALL TREES 88 Delete 11 MeSH DESCRIPTOR Acetylcholinesterase EXPLODE ALL TREES 1 Delete 12 MeSH DESCRIPTOR Galantamine EXPLODE ALL TREES 25 Delete 13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 167 Delete 14 #5 AND #13	42	1
Primary studies			
CENTRAL	#1 MeSH descriptor: [Cholinesterase Inhibitors] 802 #2 "cholinesterase inhibit*""cholinesterase inhibit*" 1070 #3 donepezil or rivastigmine or galantaminedonepezil or rivastigmine or galantamine 1332 #4 acetylcholinesterase 434 #5 #1 or #2 or #3#1 or #2 or #3 or #4 2061 #6 "cognitive impair*""cognitive impair*" 2213 #7 cognitive and (deficit or dysfunction)cognitive and (deficit or dysfunction) 2965 #8 #5 or #6#6 or #7 4599	21	0

	#9 MeSH descriptor: [Schizophrenia] 4585 #10 MeSH descriptor: [Psychotic Disorders] 1414 #11 psychosis or psychotic or schizo*psychosis or psychotic or schizo* 11987 #12 #9 or #10 or #11 11987 #13 #5 and #8 and #12 #5 and #8 and #12 85 #14 MeSH descriptor: [Antipsychotic Agents] 3487 #15 antipsychotic*5297 #16 #14 or #15 5297 #17 #13 and #16 = 21		
PsycINFO	1. PsycINFO; CHOLINESTERASE INHIBITORS/; 1423 results. 2. PsycINFO; donepezil.ti,ab; 1102 results. 3. PsycINFO; rivastigmine.ti,ab; 514 results. 4. PsycINFO; galantamine.ti,ab; 469 results. 5. PsycINFO; (Acetylcholinesterase AND inhibit*).ti,ab; 1136 results. 6. PsycINFO; (cholinesterase AND inhibit*).ti,ab; 1574 results. 7. PsycINFO; (AChE OR AChEI).ti,ab; 966 results. 8. PsycINFO; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7; 4110 results. 9. PsycINFO; COGNITIVE IMPAIRMENT/; 20951 results. 10. PsycINFO; "cognitive* impair*".ti,ab; 20626 results. 11. PsycINFO; 9 OR 10; 31144 results. 12. PsycINFO; exp PSYCHOSIS/; 88890 results. 13. PsycINFO; (psychosis OR psychotic).ti,ab; 48680 results. 14. PsycINFO; schizo*.ti,ab; 97601 results. 15. PsycINFO; exp SCHIZOPHRENIA/; 70005 results. 16. PsycINFO; 12 OR 13 OR 14 OR 15; 133046 results. 17. PsycINFO; exp NEUROLEPTIC DRUGS/; 24534 results. 18. PsycINFO; (antipsychotic* OR neuroleptic*).ti,ab; 29569 results. 19. PsycINFO; 17 OR 18; 36389 results. 20. PsycINFO; 8 AND 11 AND 16 AND 19; 38 results. 21. PsycINFO; CLINICAL TRIALS/; 7121 results. 22. PsycINFO; random*.ti,ab; 124078 results. 23. PsycINFO; groups*.ti,ab; 354801 results. 24. PsycINFO; (doubl* adj3 blind*).ti,ab; 17795 results.	26	0

	25. PsycINFO; (singl* adj3 blind*).ti,ab; 1554 results. 26. PsycINFO; EXPERIMENTAL DESIGN/; 8846 results. 27. PsycINFO; controlled.ti,ab; 77265 results. 28. PsycINFO; (clinical adj3 study).ti,ab; 7605 results. 29. PsycINFO; trial.ti,ab; 65318 results. 30. PsycINFO; "treatment outcome clinical trial".md; 25260 results. 31. PsycINFO; 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30; 548180 results. 32. PsycINFO; 20 AND 31; 26 results.		
EMBASE	33. EMBASE; CHOLINESTERASE INHIBITOR/; 17183 results. 34. EMBASE; donepezil.ti,ab; 3128 results. 35. EMBASE; rivastigmine.ti,ab; 1667 results. 36. EMBASE; galantamine.ti,ab; 1433 results. 37. EMBASE; (Acetylcholinesterase AND inhibit*).ti,ab; 11012 results. 38. EMBASE; (cholinesterase AND inhibit*).ti,ab; 8416 results. 39. EMBASE; DONEPEZIL/; 8375 results. 40. EMBASE; RIVASTIGMINE/; 5095 results. 41. EMBASE; GALANTAMINE/; 5199 results. 42. EMBASE; 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41; 33840 results. 43. EMBASE; COGNITIVE IMPAIRMENT/; 92267 results. 44. EMBASE; "cognitive* impair*".ti,ab; 43563 results. 45. EMBASE; (cognitive adj3 deficit).ti,ab; 2697 results. 46. EMBASE; (cognitive adj3 dysfunction).ti,ab; 10305 results. 47. EMBASE; 43 OR 44 OR 45 OR 46; 110392 results. 48. EMBASE; exp PSYCHOSIS/; 205504 results. 49. EMBASE; exp SCHIZOPHRENIA/; 134228 results. 50. EMBASE; (psychosis OR psychotic OR schizo*).ti,ab; 161633 results. 51. EMBASE; 48 OR 49 OR 50; 239780 results. 52. EMBASE; exp ATYPICAL ANTIPSYCHOTIC AGENT/; 70457 results. 53. EMBASE; exp NEUROLEPTIC AGENT/; 202296 results. 54. EMBASE; antipsychotic*.ti,ab; 37464 results. 55. EMBASE; neuroleptic*.ti,ab; 22637 results. 56. EMBASE; 52 OR 53 OR 54 OR 55; 211917 results. 57. EMBASE; 42 AND 47 AND 51 AND 56; 682 results.	116	0

	58. EMBASE; random*.tw; 856008 results. 59. EMBASE; factorial*.tw; 21978 results. 60. EMBASE; placebo*.tw; 196949 results. 61. EMBASE; (crossover* OR cross-over*).tw; 68421 results. 62. EMBASE; (doubl* adj3 blind*).tw; 141721 results. 63. EMBASE; (singl* adj3 blind*).tw; 16306 results. 64. EMBASE; assign*.tw; 234042 results. 65. EMBASE; allocat*.tw; 80532 results. 66. EMBASE; volunteer*.tw; 174605 results. 67. EMBASE; CROSSOVER PROCEDURE/; 38906 results. 68. EMBASE; DOUBLE-BLIND PROCEDURE/; 118541 results. 69. EMBASE; SINGLE-BLIND PROCEDURE/; 18485 results. 70. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 359603 results. 71. EMBASE; 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70; 1384238 results. 72. EMBASE; 57 AND 71; 116 results.		
MEDLINE	73. MEDLINE; CHOLINESTERASE INHIBITORS/; 16862 results. 74. MEDLINE; donepezil.ti,ab; 2249 results. 75. MEDLINE; rivastigmine.ti,ab; 1138 results. 76. MEDLINE; galantamine.ti,ab; 1031 results. 77. MEDLINE; (Acetylcholinesterase AND inhibit*).ti,ab; 9851 results. 78. MEDLINE; (cholinesterase AND inhibit*).ti,ab; 7269 results. 79. MEDLINE; DONEPEZIL/; 0 results. 80. MEDLINE; RIVASTIGMINE/; 0 results. 81. MEDLINE; GALANTAMINE/; 1308 results. 82. MEDLINE; 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81; 17663 results. 83. MEDLINE; COGNITIVE IMPAIRMENT/; 0 results. 84. MEDLINE; "cognitive* impair*".ti,ab; 33329 results. 85. MEDLINE; (cognitive adj3 deficit).ti,ab; 1999 results. 86. MEDLINE; (cognitive adj3 dysfunction).ti,ab; 7835 results. 87. MEDLINE; 83 OR 84 OR 85 OR 86; 40833 results.	60	0

	88. MEDLINE; exp PSYCHOSIS/; 38557 results. 89. MEDLINE; exp SCHIZOPHRENIA/; 86805 results. 90. MEDLINE; (psychosis OR psychotic OR schizo*).ti,ab; 133611 results. 91. MEDLINE; 88 OR 89 OR 90; 167047 results. 92. MEDLINE; exp ATYPICAL ANTIPSYCHOTIC AGENT/; 0 results. 93. MEDLINE; exp NEUROLEPTIC AGENT/; 122842 results. 94. MEDLINE; antipsychotic*.ti,ab; 27463 results. 95. MEDLINE; neuroleptic*.ti,ab; 18402 results. 96. MEDLINE; 92 OR 93 OR 94 OR 95; 135949 results. 97. MEDLINE; 82 AND 87 AND 91 AND 96; 64 results. 98. MEDLINE; "randomized controlled trial".pt; 390284 results. 99. MEDLINE; "controlled clinical trial".pt; 89931 results. 100. MEDLINE; randomi?ed.ab; 371731 results. 101. MEDLINE; placebo.ab; 163878 results. 102. MEDLINE; "drug therapy".fs; 1767235 results. 103. MEDLINE; randomly.ab; 216333 results. 104. MEDLINE; trial.ab; 321773 results. 105. MEDLINE; groups.ab; 1374185 results. 106. MEDLINE; 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105; 3437672 results. 107. MEDLINE; 97 AND 106; 57 results.		
Summary	**NA**	**NA**	

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