BEST in Mental Health

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Best Evidence Summaries of Topics in Mental Healthcare

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

Question

"In adults with dementia, what length of time should be left after stopping donepezil before initiating another cholinesterase inhibitor?"

Clarification of question

Patients:	Adults with dementia
Intervention:	Required period for switching from donepezil to another cholinesterase inhibitor
Outcome:	Side effects; cognition.

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Clinical and research implications

Information on the optimal washout period for donepezil, before initiating another cholinesterase inhibitor, was very limited. Two, poorly reported randomised controlled trials compared different methods of switching from donepezil to memantine and galantamine, respectively. There was no strong evidence from either trial to suggest that either the length of washout period or abrupt versus stepwise cessation of donepezil made a significant difference to the effectiveness or safety of treatment. One study reported that a shorter washout period (4 versus 7 days) was associated with fewer gastrointestinal adverse events during the final week of galantamine dose escalation, however, this finding was based on a small number of events and would require further investigation to confirm the apparent association.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two randomised controlled trials (RCTs) which reported data relevant to this evidence summary.[1,2] One trial compared abrupt discontinuation of donepezil (10 mg/d) to stepwise discontinuation (5 mg/d for two weeks); concomitant up-titration of memantine to 20 mg/d, over a four week period, was applied to both groups.[1] The second study compared washout periods of four and seven days for donepezil (dose not specified) prior to up-titration of galantamine to 24 mg/d over a four week period.[2] The first study was conducted in people with moderate to severe Alzheimer's disease,[1] and the second study was conducted in people with mild to moderate probable Alzheimer's disease.[2]

Main Findings

Both studies found no clinically or statistically significant differences in measures of efficacy (cognition or clinical impression) between the two groups.[1,2] Similarly, there were no apparent differences in overall treatment-emergent adverse event (TEAE) rates between groups, in either study.[1,2] The second study reported that the rate of gastrointestinal adverse events at week 4, when the galantamine dose was increased from 16 mg to 24 mg, appeared higher in the seven day washout group than in the four day washout group (9 versus 1); this difference was no longer apparent during the open label-phase.[2]

Authors Conclusions

Both studies concluded that the alternative cholinesterase inhibitor, being introduced to replace donepezil, was well tolerated. One study concluded that the AE profile was similar regardless of the method of transition and the other study concluded that, whilst efficacy was similar, use of a shorter washout period (4 days rather than 7) may result in fewer GI AEs.

Reliability of conclusions/Strength of evidence

Both of the studies included in this assessment were poorly reported with respect to study methods, making it impossible to fully assess risk of bias.[1,2] The only apparent difference in safety or efficacy observed between different methods of transition from donepezil to other cholinesterase inhibitors was limited to GI AEs in the final phase of galantamine dose escalation.[2] This finding was based on a small number of events and would require further investigation to confirm the apparent association with the length of donepezil washout period.

What do guidelines say?

Neither NICE nor SIGN guidelines look at the wash out period of donepezil before initiating on another cholinesterase inhibitor.

Date question received: 29/04/2014
Date searches conducted: 08/05/2014
Date answer completed: 02/06/2014

References

1. Waldemar, G., Hyvarinen, M., Josiassen, M.K., Korner, A., Lehto, H. and Wetterberg, P. (2008) Tolerability of switching from donepezil to memantine treatment in patients with moderate to severe Alzheimer's
2. Wilkinson, D.G. and Howe, I. (2005) Switching from donepezil to galantamine: a double-blind study of two wash-out periods. *International Journal of Geriatric Psychiatry 20* pp.489-491.

Results

Randomised controlled trials

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Waldemar (2008)	**Population:** Outpatients with moderate to severe Alzheimer's disease (DSM-IV TR criteria) an MMSE score of ≤ 18 & receiving donepezil for ≥ 6 months preceding screening. People were eligible for the trial if their clinician judged that the donepezil was failing (also confirmed through change in MMSE score, worsening of behaviour and/or ADL function). **Intervention:** Abrupt discontinuation of donepezil 10 mg per day (placebo provided for two weeks) and concomitant up-titration of memantine, starting at 5mg/day and increasing by this dose each week to 20mg/day at week four. **Comparison:** Stepwise discontinuation (5mg per day for two weeks) and concomitant up-titration of memantine, following the same dosage as the intervention group. **Outcomes:** Cognition (MMSE and the CGI-	n=46 (23 in each switching group)	This study aimed to assess the tolerability, safety and efficacy of abrupt versus stepwise switching from donepezil to memantine treatment in patients with moderate-to-severe Alzheimer's disease. There were no apparent differences between the two switching groups in age and gender distribution, or baseline Mini Mental State Examination (MMSE) and Clinical Global Impression – Severity (CGI-S) scores. Withdrawal rates were similar between groups; 2 participants withdrew from the abrupt discontinuation groups dues to an AE and 1 withdrew from the stepwise group due to lack of efficacy. There were no clinically or statistically significant differences between the two groups, wither in measures of efficacy or in occurrence of TEAEs. Overall, the majority of participants either improved or stabilised according to the Clinical Global Impression – Change (CGI-C) (32/43 (74%)) or MMSE (23/43 (53%)).	The study was reported as a research letter, with limited details of methods. No details of the randomisation procedure or allocation concealment were reported. All study personnel and participants were blind to the switching group for the duration of

	C) and treatment emergent adverse events (TEAE).			the study. All randomised participants, who took at least one dose of memantine and had at least one valid post-baseline CGI-C assessment, were included in the efficacy analyses. Results were reported for all specified outcome measures.

Wilkinson (2005)	**Participants:** People with mild to moderate probable Alzheimer's Disease, who had been taking donepezil for ≤12 weeks and who were considered to be in need of alternative anti-dementia medication. All participants had an MMSE score of 10-25 and an Alzheimer's Disease Assessment scale (ADAS-cog/11) total score of ≤12. **Intervention:** Two week run-in period (continued donepezil). Four-week double-blind washout/dose escalation period; washout period of four days, followed by commencement of galantamine 4mg twice daily, increasing by 8 mg/week 24 mg/day by the end of week 4. Open-label phase for the next 48 weeks. **Comparison:** As for intervention, but with a washout period of seven days. **Outcomes:** Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog/11), discontinuations, adverse events (AEs)	n=105 (53 in the four day washout group and 52 in the seven day washout group)	This study aimed to assess the optimum length of the washout period in patients switching from donepezil to galantamine. Demographic characteristics and baseline MMSE and ADAS-cog/11 scores were similar in the two groups. There were 8 discontinuations during the double blind phase; 3 in the four day washout group and 5 in the seven day washout group. During the open-label phase there were 12 further discontinuations in the four day washout group and 14 in the seven day washout group; these were mainly due to AEs. During the double blind phase, there was no apparent difference in overall safety profile between the two groups; 22 participants in the four day washout group and 24 in the seven day washout group had at least one treatment-emergent adverse event or worsening of an ongoing pre-treatment event. The rate of gastrointestinal (GI) AEs at week 4, when the galantamine dose was increased from 16 mg to 24 mg, appeared higher in the seven day washout group than in the four day washout group (9 versus 1); rates of GI AEs were similar between groups during the open-lable phase. Adverse event rates were low during the open label phase; 5 in the four day washout group versus 2 in the seven day washout group. Changes in ADAS-cog/11 from screening baseline and to the	No details of the randomisation procedure or allocation concealment were reported. The washout/dose escalation period of the study was described as 'double blind', but it was not clear whether outcome assessors were blinded to group allocation. It was not clear whether all participants were included

			end of the double blind phase were <1 point. There was no significant difference between the groups in mean change in ADAS-cog/11 from baseline to the end of the study (week 52); 4.9 ± 6.69 in the four-day group and 4.6 ± 6.45 in the seven-day group.	in the analyses. Results were reported for all specified outcome measures.

Risk of Bias

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Waldemar 2008	?	?	☺	☺	☺	☺
Wilkinson 2005	?	?	☺	?	?	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	donepezil	15	0
DARE	(donepezil) (cholinesterase*) MeSH DESCRIPTOR Acetylcholinesterase EXPLODE ALL TREES MeSH DESCRIPTOR Cholinesterase Inhibitors EXPLODE ALL TREES (taper OR chang* OR switch* OR (wash adj out)) #1 OR #2 OR #3 OR #4 #5 AND #6 (alzheimer*):TI (dement*):TI MeSH DESCRIPTOR Alzheimer Disease EXPLODE ALL TREES MeSH DESCRIPTOR Dementia EXPLODE ALL TREES #8 OR #9 OR #10 OR #11 #7 AND #12	49	0
Primary studies			
CENTRAL	#1 MeSH descriptor: [Cholinesterase Inhibitors] explode all trees 845 #2 donepezil 889 #3 "time frame" or "time period" 4333 #4 "drug withdrawal" 2949 #5 "wash out" 2787 #6 taper 1955 #7 switch 6097 #8 "switching strategies" 17	25	

	#9 "length of time" 1416 #10 "drug holiday" 22 #11 discontinu* 16400 #12 #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 31862 #13 #1 and #2 and #12 42 Central only 25		
PsycINFO	1. PsycINFO; exp CHOLINESTERASE INHIBITORS/; 2225 results. 2. PsycINFO; donepezil.ti,ab; 1126 results. 3. PsycINFO; INTERRESPONSE TIME/; 368 results. 4. PsycINFO; "time frame".ti,ab; 1758 results. 5. PsycINFO; DRUG WITHDRAWAL/; 5114 results. 6. PsycINFO; "wash out".ti,ab; 278 results. 7. PsycINFO; taper.ti,ab; 426 results. 8. PsycINFO; "length of time".ti,ab; 3513 results. 9. PsycINFO; "time period".ti,ab; 4677 results. 10. PsycINFO; "drug holiday".ti,ab; 35 results. 11. PsycINFO; switch*.ti,ab; 15958 results. 12. PsycINFO; "switching strategies".ti,ab; 82 results. 13. PsycINFO; discontin*.ti,ab; 15620 results. 14. PsycINFO; (fail* adj3 benefit).ti,ab; 168 results. 15. PsycINFO; (cessation adj3 medication).ti,ab; 116 results. 16. PsycINFO; (cessation adj3 "drug therapy").ti,ab; 11 results. 17. PsycINFO; (stop* adj3 medication).ti,ab; 272 results. 18. PsycINFO; (stop* adj3 "drug therapy").ti,ab; 6 results. 19. PsycINFO; (stop* adj3 donepezil).ti,ab; 7 results. 20. PsycINFO; 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19; 46478 results. 21. PsycINFO; "time period".ti,ab; 4677 results. 22. PsycINFO; 20 OR 21; 46478 results.	34	

	23. PsycINFO; 1 AND 2 AND 22; 76 results. 24. PsycINFO; CLINICAL TRIALS/; 7531 results. 25. PsycINFO; random*.ti,ab; 129036 results. 26. PsycINFO; groups.ti,ab; 365146 results. 27. PsycINFO; (double adj3 blind).ti,ab; 17791 results. 28. PsycINFO; (single adj3 blind).ti,ab; 1399 results. 29. PsycINFO; EXPERIMENTAL DESIGN/; 9071 results. 30. PsycINFO; controlled.ti,ab; 80247 results. 31. PsycINFO; (clinical adj3 study).ti,ab; 7891 results. 32. PsycINFO; trial.ti,ab; 67940 results. 33. PsycINFO; "treatment outcome clinical trial".md; 26815 results. 34. PsycINFO; 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33; 565120 results. 35. PsycINFO; 23 AND 34; 34 results.		
Embase	22. EMBASE; donepezil.ti,ab; 3161 results. 23. EMBASE; INTERRESPONSE TIME/; 1 results. 24. EMBASE; "time frame".ti,ab; 8914 results. 25. EMBASE; DRUG WITHDRAWAL/; 110609 results. 26. EMBASE; "wash out".ti,ab; 6134 results. 27. EMBASE; taper.ti,ab; 3632 results. 28. EMBASE; "length of time".ti,ab; 10084 results. 29. EMBASE; "time period".ti,ab; 33533 results. 30. EMBASE; "drug holiday".ti,ab; 261 results. 31. EMBASE; switch*.ti,ab; 112686 results. 32. EMBASE; "switching strategies".ti,ab; 126 results. 33. EMBASE; discontin*.ti,ab; 112887 results. 34. EMBASE; (fail* adj3 benefit).ti,ab; 1159 results. 35. EMBASE; (cessation adj3 medication).ti,ab; 555 results. 36. EMBASE; (cessation adj3 "drug therapy").ti,ab; 86 results.	166	

	37. EMBASE; (stop* adj3 medication).ti,ab; 1490 results. 38. EMBASE; (stop* adj3 "drug therapy").ti,ab; 65 results. 39. EMBASE; (stop* adj3 donepezil).ti,ab; 11 results. 40. EMBASE; 23 OR 24 OR 25 OR 26 OR 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; 375883 results. 41. EMBASE; random*.ti,ab; 863047 results. 42. EMBASE; factorial*.ti,ab; 22507 results. 43. EMBASE; (crossover* OR cross-over*).ti,ab; 67695 results. 44. EMBASE; placebo*.ti,ab; 194986 results. 45. EMBASE; (doubl* ADJ blind*).ti,ab; 139045 results. 46. EMBASE; (singl* ADJ blind*).ti,ab; 14074 results. 47. EMBASE; assign*.ti,ab; 233500 results. 48. EMBASE; allocat*.ti,ab; 81589 results. 49. EMBASE; volunteer*.ti,ab; 172804 results. 50. EMBASE; CROSSOVER PROCEDURE/; 38658 results. 51. EMBASE; DOUBLE BLIND PROCEDURE/; 112848 results. 52. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 340479 results. 53. EMBASE; SINGLE BLIND PROCEDURE/; 18159 results. 54. EMBASE; 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53; 1380418 results. 55. EMBASE; 21 AND 22 AND 40; 399 results. 56. EMBASE; 54 AND 55; 166 results.		
Medline	21. MEDLINE; exp CHOLINESTERASE INHIBITORS/; 41640 results. 22. MEDLINE; donepezil.ti,ab; 2208 results. 23. MEDLINE; INTERRESPONSE TIME/; 0 results. 24. MEDLINE; "time frame".ti,ab; 6826 results. 25. MEDLINE; DRUG WITHDRAWAL/; 0 results. 26. MEDLINE; "wash out".ti,ab; 4787 results. 27. MEDLINE; taper.ti,ab; 3092 results. 28. MEDLINE; "length of time".ti,ab; 8894 results.	120	

	29. MEDLINE; "time period".ti,ab; 25248 results. 30. MEDLINE; "drug holiday".ti,ab; 173 results. 31. MEDLINE; switch*.ti,ab; 101010 results. 32. MEDLINE; "switching strategies".ti,ab; 96 results. 33. MEDLINE; discontin*.ti,ab; 88076 results. 34. MEDLINE; (fail* adj3 benefit).ti,ab; 861 results. 35. MEDLINE; (cessation adj3 medication).ti,ab; 424 results. 36. MEDLINE; (cessation adj3 "drug therapy").ti,ab; 77 results. 37. MEDLINE; (stop* adj3 medication).ti,ab; 987 results. 38. MEDLINE; (stop* adj3 "drug therapy").ti,ab; 57 results. 39. MEDLINE; (stop* adj3 donepezil).ti,ab; 5 results. 40. MEDLINE; 23 OR 24 OR 25 OR 26 OR 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; 236519 results. 41. MEDLINE; "DRUG WITHDRAWAL".ti,ab; 2684 results. 42. MEDLINE; 40 OR 41; 238861 results. 43. MEDLINE; 21 AND 22 AND 42; 126 results. 44. MEDLINE; "randomized controlled trial".pt; 372783 results. 45. MEDLINE; "controlled clinical trial".pt; 88303 results. 46. MEDLINE; randomized.ab; 292550 results. 47. MEDLINE; placebo.ab; 153577 results. 48. MEDLINE; "drug therapy".fs; 1694666 results. 49. MEDLINE; randomly.ab; 211913 results. 50. MEDLINE; trial.ab; 303781 results. 51. MEDLINE; groups.ab; 1349786 results. 52. MEDLINE; 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51; 3327582 results. 53. MEDLINE; 43 AND 52; 120 results.		
Summary	**NA**	**NA**	

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