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 a behavioural variant (particularly Progressive non fluent aphasia (PNFA), semantic dementia (SD), logopenic dementia) or frontotemporal dementia (FTDbv) how effective are cholinesterase inhibitors or memantine in achieving improved patient outcomes?"

Clarification of question using PICO structure

Patients:	Adults with a behavioural variant (particularly Progressive non fluent aphasia (PNFA), semantic dementia (SD), logopenic dementia) or frontotemporal dementia (FTDbv).
Intervention:	Cholinesterase inhibitors or memantine
Comparator:	Any other intervention
Outcome:	Any patient outcomes

Plain language summary

Evidence suggests that more substantial high quality research is needed into the effectiveness of cholinesterase inhibitors or memantine, in improving symptoms of behavioural variant and frontotemporal dementia.

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Clinical and research implications

No definite clinical implications may be made based on the evidence presented in this BEST summary. The authors of one well-conducted paper included in this summary suggested that memantine is not an effective treatment for frontotemporal lobar degeneration (FTD). There was general consensus among all study authors that there is a need to develop more effective therapeutics for FTD.

What does the evidence say?

Number of included studies/reviews (number of participants)

One systematic review (SR) (Nardell and Tampi, 2014) and one randomised controlled trial (RCT) (Boxer et al. 2013) met the inclusion criteria for this BEST summary.

Main Findings

The SR by Nardell and Tampi (2014) aimed to evaluate the effectiveness of various pharmacological treatments for frontotemporal dementias. Although this review included nine RCTs, only three reported treatments of interest to this BEST summary (i.e. cholinesterase inhibitors or memantine). One of the studies compared galantamine with placebo, and found that this treatment was not effective in treating patients with fvFTD. Similarly, two studies (including Boxer et al. 2013 below) compared memantine with placebo, and both found that treatment did not improve cognitive, functional or behavioural symptoms in patients with fvFTD.

The RCT by Boxer et al. (2013) evaluated a number of outcomes including changes in neuropsychiatric inventory (NPI) and clinical global impression of change (CGIC) scores as primary outcomes. The authors, however, found no benefit of 20 mg/day memantine treatment in frontotemporal lobar degeneration when compared with placebo.

Authors Conclusions

Nardell and Tampi (2014) concluded that 'none of the trials showed an improvement in cognition or function in patients with FTD', although some of the treatments (but not galantamine or memantine) improved behavioural symptoms.

Boxer et al. (2013) concluded that 'memantine treatment showed no benefit in patients with FTD. These data do not support memantine use in FTD.'

Reliability of conclusions/Strength of evidence

The SR by Nardell and Tampi (2014) was considered to have a high risk of bias. The RCT by Boxer et al. (2013) was well-conducted and was considered to have a low risk of bias.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Scottish Intercollegiate Guidelines Network (SIGN) guidelines comment upon the use cholinesterase inhibitors or memantine for behavioural variant (particularly Progressive non fluent aphasia (PNFA), semantic dementia (SD), logopenic dementia) or frontotemporal dementia.

Date question asked: 01/05/2015
Date searches conducted: 12/05/2015
Date answer completed: 27/06/2016

References

Systematic Reviews

Nardell, M., & Tampi, R. R. (2013). Pharmacological Treatments for Frontotemporal Dementias A Systematic Review of Randomized Controlled Trials. *American journal of Alzheimer's disease and other dementias*, 1533317513507375.

Randomised Controlled Trials

Boxer, A. L., Knopman, D. S., Kaufer, D. I., Grossman, M., Onyike, C., Graf-Radford, N., Koestler, M. (2013). Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. *The Lancet Neurology*, *12*(2), 149-156.

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Nardell and Tampi (2014)	July 30, 2013	*Inclusion criteria were not described in detail. The studies included in the review were as follows:* *Participants*: Patients diagnosed with (i) frontotemporal dementia (3 studies); (ii) behavioral-variant frontemporal dementia (bvFTD) (1 study); (iii) frontal-variant frontemporal dementia (fvFTD) (6 studies); (iv) semantic dementia (1 study); (v) primary progressive aphasia (PPA) (1 study). *Interventions*: (i) Paroxetine (SSRI; 2 studies); (ii) Trazodone (1 study); (iii) Methylphenidate (1 study); (iv) Dextrophetamine (1 study); (v) Galantamine (acetylcholinesterase inhibitor; 1 study); (vi) Memantine (2 studies); (vii) Oxytocin (1 study). *Comparator*: Placebo, other than one study comparing Paroxetine to Piracetam, and one study comparing Dextrophetamine to Quetiapine. *Outcome*: Behavioural symptoms (measured primarily by Neuropsychiatric Inventory (NI and cognition (using various outcome measures). *Study design*: Randomised, double-blinded,	9 RCTs	This review reported on one study that evaluated an acetylcholinesterase inhibitor (galantamine), and two that evaluated memantine. Other results have not been extracted as they are not relevant to this BEST summary. One trial (n=36) found no significant differences between galantamine vs. placebo in language or behaviour in patients with fvFTD and primary progressive aphasia. No data or statistical results were reported. One trial that evaluated memantine (n=49) found no significant differences between treatment and placebo for the primary outcome of Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) scores after 52 weeks in patients with fvFTD (p=0.45). In addition, no significant differences between groups were observed in the secondary outcomes of	High

		controlled trials.		MMSE, MDRS, NPI, ZBI, or DAD, although the FBI score was lower in the memantine group (p=0.04). The other trial included in this review is described in detail below (Boxer et al. 2013).	

Randomised controlled trials

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Boxer et al (2013)	*Participants*: Adults aged 40-80 years in America, with a MMSE score of 15 or higher; all patients had to have a CT or MRI scan of the brain within 24 months before randomisation consistent with a diagnosis of bvFTD or semantic dementia. *Intervention*: 20 mg memantine taken orally daily. *Comparator*: Matched placebo tablets *Outcome*: Change in neuropsychiatric inventory (NPI) score and clinical global impression of change (CGIC) score. A number of secondary outcomes were also assessed: clinical dementia rating sum of boxes (CDR-SB-FTD); functional activities questionnaire (FAQ); Texas functional living scale (TFLS); MMSE; the executive interview (EXIT25); letter fluency; category fluency; digit symbol; digits backwards; Boston naming test; modified unified Parkinson's disease rating scale (UPDRS). *Duration:* 26 weeks.	N=81 (memantine arm n=39, placebo arm n=42)	No statistically significant differences between the treatment groups were observed for: **Primary outcomes**: NPI: mean difference 2.2 (95% CI: –3.9 to 8.3), p=0.47; CGIC: 0.0 (95% CI:–0.4 to 0.4), p=0.90 **Secondary outcomes:** CDR-SB-FTD: mean difference 0.0 (95% CI: –0.9 to 0.9), p=0.99; FAQ: –1.5 (95% CI: –4.0 to 1.0), p=0.23; TFLS: 0.9 (95% CI: –1.7 to 3.5), p=0.49; Cognitive MMSE: 0.1 (95% CI:–1.3 to 1.5), p=0.69; EXIT25: –1.2 (95% CI:–3.8 to 1.4), p=0.34; Letter fluency: –0.2 (95% CI: –1.5 to 1.1), p=0.75; Category fluency: 0.4 (95% CI: –1.7 to 2.4), p=0.72; Digits backwards: –0.3 (95% CI: –0.8 to 0.2), p=0.28; UPDRS: mean difference –0.3 (95% CI: –3.0 to 2.4), p=0.83 Significant differences in favour of placebo were observed for two secondary outcome measures: Digit symbol: 8·1 (95% CI: 1.1 to 15.1), p=0.024; Boston naming test 2.2 (95% CI: 0.7 to 3.6), p=0·004 There were numerically more cognitive adverse events (confusion, memory loss, language disorders) in the memantine group compared with the placebo group (6 vs. 1, p=0.6), but there were less psychiatric adverse events in the memantine group (8 vs. 16, p=0.03).	Low

Risk of Bias:

SRs

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Nardell et al. (2014)	☹	☺	?	☺	☹

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Boxer et al (2013)	☺	☺	☺	☺	☺	?

☺Low risk ☹High risk ? Unclear risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
NICE	progressive non fluent aphasia or semantic dementia or logopenic dementia or primary progressive aphasia or language based frontotemporal dementia	15	0
DARE	1 MeSH descriptor: [Frontotemporal Lobar Degeneration] explode all trees 14 #2 "cholinesterase inhibitors" or memantine 1502 #3 logopenic or "semantic dementia" 23 #4 #1 or #3 35 #5 #2 and #4 4 Filter 2014 DARE only 0	1	0
CDSR	1 MeSH descriptor: [Frontotemporal Lobar Degeneration] explode all trees 14 #2 "cholinesterase inhibitors" or memantine 1502 #3 logopenic or "semantic dementia" 23 #4 #1 or #3 35 #5 #2 and #4 4 Filter 2014 Cochrane only 1	1	0
MEDLINE	28. MEDLINE; exp FRONTOTEMPORAL LOBAR DEGENERATION/; 2157 results. 29. MEDLINE; SEMANTIC DEMENTIA/; 1077 results. 30. MEDLINE; "logopenic dementia".ti,ab; 0 results. 31. MEDLINE; 28 OR 29; 2157 results. 32. MEDLINE; CHOLINESTERASE INHIBITOR/ OR DONEPEZIL/ OR GALANTAMINE/ OR RIVASTIGMINE/; 1278 results. 33. MEDLINE; MEMANTINE/; 1651 results. 34. MEDLINE; 32 OR 33; 2827 results. 35. MEDLINE; 31 AND 34; 16 results. 36. MEDLINE; 35 [Limit to: Publication Year 2014-2015]; 2 results.	2	1

EMBASE	1. EMBASE; exp FRONTOTEMPORAL LOBAR DEGENERATION/; 9137 results. 2. EMBASE; SEMANTIC DEMENTIA/; 847 results. 3. EMBASE; "logopenic dementia".ti,ab; 0 results. 4. EMBASE; 1 OR 2; 9137 results. 5. EMBASE; CHOLINESTERASE INHIBITOR/ OR DONEPEZIL/ OR GALANTAMINE/ OR RIVASTIGMINE/; 25511 results. 6. EMBASE; MEMANTINE/; 7285 results. 7. EMBASE; 5 OR 6; 29536 results. 8. EMBASE; 4 AND 7; 471 results. 9. EMBASE; 8 [Limit to: Publication Year 2014-2015]; 44 results.	44	1
PsychINFO	10. PsycINFO; exp FRONTOTEMPORAL LOBAR DEGENERATION/; 0 results. 11. PsycINFO; SEMANTIC DEMENTIA/; 1041 results. 12. PsycINFO; "logopenic dementia".ti,ab; 0 results. 13. PsycINFO; 10 OR 11; 1041 results. 14. PsycINFO; CHOLINESTERASE INHIBITOR/ OR DONEPEZIL/ OR GALANTAMINE/ OR RIVASTIGMINE/; 1663 results. 15. PsycINFO; MEMANTINE/; 0 results. 16. PsycINFO; 14 OR 15; 1663 results. 17. PsycINFO; 13 AND 16; 2 results. 18. PsycINFO; 17 [Limit to: Publication Year 2014-2015]; 0 results. 19. PsycINFO; SEMANTIC DEMENTIA/; 1041 results. 20. PsycINFO; "frontotemporal dementia".ti,ab; 2245 results. 21. PsycINFO; "language based frontotemporal dementia".ti,ab; 1 results. 22. PsycINFO; "primary progressive aphasia".ti,ab; 481 results. 23. PsycINFO; 19 OR 20 OR 22; 3048 results. 24. PsycINFO; memantine.ti,ab; 1002 results. 25. PsycINFO; 14 OR 24; 2569 results. 26. PsycINFO; 23 AND 25; 30 results. 27. PsycINFO; 26 [Limit to: Publication Year 2014-2015]; 3 results.	3	0

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