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 older adults with dementia, are sodium valproate and other anticonvulsants more effective than antipsychotics in reducing agitation and excessive activity or 'drive'?"

Clarification of question using PICO structure

Patients:	Older adults with dementia
Intervention:	Sodium valproate and other anticonvulsants
Comparator:	Antipsychotics
Outcome:	Reducing agitation and excessive activity, or 'drive'

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Clinical and research implications

No definite clinical implications can be made from the available evidence. It does not appear that any studies have directly compared sodium valproate or other anticonvulsants with antipsychotics. Most of the studies evaluated have compared anticonvulsants with placebo.

There is a common theme in the literature - that there is limited evidence on the use of anticonvulsants, both in terms of number of studies, and in terms of the methodological quality of the available studies. In addition, many of the treatments were associated with problematic side effects, prompting some authors to suggest that they should be used with caution. There is also a lack of evidence specifically on valproate, and review authors have suggested that this treatment may not be recommended for the first-line treatment of demented patients with agitation.

All review authors suggested that more research is needed in this area, and most mentioned the need for the further development of safe and effective pharmacological and non-pharmacological interventions for patients with dementia.

What does the evidence say?

Number of included studies/reviews (number of participants)
Four systematic reviews (SRs) meet the inclusion criteria for this BEST summary (Dolder and Nealy 2012; Herrmann and Lanctôt 2007; Lonergan and Luxenberg 2010; Seitz et al. 2013).

Main Findings
One SR specifically aimed to evaluate valproate for the treatment of agitation of people with dementia (Lonergan and Luxenberg 2010). In total, 5 RCTS were included: three from an earlier review and two from an update in 2008. Overall, the authors found no significant difference between treatment and placebo for agitation or aggression. They did, however, observe an increase in adverse events (falls, infection, gastrointestinal disorders) among valproate treated patients.

Herrmann and Lanctôt (2007) aimed to review the pharmacotherapy of neuropsychiatric symptoms of Alzheimer's disease. Their review, conducted in March 2007, included the same five RCTS that were reported in Lonergan and Luxenberg (2010), plus an additional four that evaluated carbamazepine. The found little evidence for the effectiveness of antipsychotics (with the exception of carbamazepine), and reported concerns regarding their safety.

Dolder and Nealy (2012) evaluated the safety and efficacy of newer anticonvulsants including levetiracetam, oxcarbazepine, topiramate, and zonisamide, in patients with dementia. This review, with a search up to December 2011, included nine studies of various designs. Very few RCTs were included in this review, and the authors found no clear evidence for the efficacy (behavioural disturbances) and safety of any of these anticonvulsants.

The most recent SR evaluated the efficacy and safety of pharmacological treatments for neuropsychiatric symptoms (NPS) in long-term care settings (Seitz et al. 2014). Of 29 RCTs included in this review, 4 were trials of anticonvulsants: one evaluated carbamazepine, 2 examined divalproex

sodium and 1 study examined oxcarbazepine. All of these studies were also included in one or more of the other reviews. Only carbamazepine 300 mg/day was associated with a statistically significant reduction in NPS symptoms (BPRS total) ($p<0.05$) compared with placebo. The other RCTs showed no benefit for other anticonvulsants compared with placebo.

Authors Conclusions

Lonergan and Luxenberg (2010) concluded that valproate preparations are ineffective in treating agitation among demented patients, and that valproate therapy is associated with an unacceptable rate of adverse effects. More research on the use of valproate preparations for agitation of people with dementia is needed. On the basis of current evidence, valproate therapy cannot be recommended for management of agitation in dementia.

Herrmann and Lanctôt (2007) concluded that although there have been numerous well-designed studies of the pharmacotherapy of neuropsychiatric symptoms in AD, safer and more effective treatments are urgently needed.

Dolder and Nealy (2012) concluded that, due to the small number of methodologically limited studies included in the review, none of the four medications evaluated (levetiracetam, oxcarbazepine, topiramate, and zonisamide) can be recommended as behavioural treatment in patients with dementia. Of the four agents evaluated, the authors reported that only levetiracetam may have a role.

Seitz et al. (2013) concluded that there is limited evidence to support the use of some atypical antipsychotics and other medications for neuropsychiatric symptoms in patients in long-term care.

Reliability of conclusions/Strength of evidence

The SRs by Lonergan and Luxenberg (2010) and Seitz et al. (2013) were well-conducted (although the Lonergan and Luxeberg review was not always clearly reported), and the authors' cautious conclusions based on a limited evidence base appear appropriate.

Two of the systematic reviews (Dolder and Nealy 2012; Herrmann and Lanctôt 2007) did not report full SR review methodology, so that the reliability of their results and conclusions is uncertain.

What do guidelines say?

SIGN guidelines for the management of people with dementia (CG86, 2006) make the following recommendations regarding the use of anticonvulsants to treat behavioural symptoms in individuals with dementia:

"No robust evidence was identified to suggest that valproate is effective in reducing associated symptoms in people with dementia.
Valproate is not recommended for the treatment of behavioural symptoms associated with dementia.
One small RCT suggested carbamazepine reduced behavioural problems associated with severe dementia.
An open label study of gabapentin showed no statistical significance in outcome measures on completion of the study.

Anticonvulsants may be considered for the symptomatic treatment of seizures or myoclonus associated with dementia but are not recommended for other symptoms of dementia."

NICE guidelines do not provide guidance regarding the use of anticonvulsants to treat behavioural symptoms in individuals with dementia.

Date question received: 30/06/2014
Date searches conducted: 03/07/2014
Date answer completed: 21/07/2014

References

Systematic reviews

1. Dolder, C. R., & Nealy, K. L. (2012). The Efficacy and Safety of Newer Anticonvulsants in Patients with Dementia. *Drugs & Aging, 29*(8): 627.637. DOI:117a-229X/12/W08-0627/S49.9S/0
2. Herrmann, N., & Lanctot, K. (2007). Pharmacologic management of neuropsychiatric symptoms of Alzheimer disease. *Canadian Journal of Psychiatry, 52*(10), 630-646. DOI:0706-7437;1497-0015
3. Lonergan, E., & Luxenberg, J. (2009). Valproate preparations for agitation in dementia. *Cochrane Database of Systematic Reviews,* 3. Art. No.: CD003945. DOI:10.1002/14651858.CD003945.pub3.
4. Seitz, D. P., Gill, S. S., Herrmann, N., Brisbin,S., Rapoport, M. J., Rines, J., Wilson, K., & Le Clair, K., & Conn, D. K. (2013). Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic review. *International Psychogeriatrics*, *25*(2), 185–203. DOI:10.1017/S1041610212001627

Guidelines

5. Scottish Intercollegiate Guidelines Network (2006) Management of patients with dementia. A national clinical guideline. CG86. Edinburgh. Scottish Intercollegiate Guidelines Network. http://www.sign.ac.uk/pdf/sign86.pdf

Results

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Dolder & Nealy (2012)	12/2011	*Population:* Patients with dementia. *Intervention:* The following anticonvulsants were searched for: lacosamide, tiagabine, pregabalin, vigabatrin, zonisamide, levetiracetam, topiramate, oxcarbazepine. *Comparator:* Any comparator. *Outcomes:* Any behavioural or cognitive outcome. *Study designs:* All types of studies were included.	9 studies (3 prospective controlled trials, 3 uncontrolled open-lable studies and 3 case reports, or case series using a retrospective design)	**Levietiracetam**: Two of four studies reported on behavioural disturbances in dementia, but both were uncontrolled, open-label studies with small sample sizes. The authors stated that the results were positive, but no recommendations can be made. In studies of elderly patients with dementia or mild cognitive impairment, common adverse events included somnolence, lethargy and fatigue. **Oxcarbazepine**: One RCT reported on behavioural disturbances in dementia. No significant differences were observed compared with placebo for outcomes measured using the Neuropsychiatric Inventory – Nursing Home version. Adverse events in the treatment group included sedation, fainting, and ataxia. **Topiramate**: Two studies (1 RCT and 1 retrospective study) reported on behavioural disturbances in dementia. No differences	High

				were observed in comparison with the antipsychotic control groups. Fatigue and weight loss were the most problematic adverse events in the elderly. **Zonisamide**: Two case studies were included that reported the use of zonisamide in patients with dementia with Lewy bodies. Behavioural improvements were noted compared to baseline in 3 of 4 patients. Adverse events included dizziness and drowsiness.	
Herrmann & Lanctot (2007)	03/2007	*Population:* Patients with dementia. *Intervention:* Any anticonvulsant. *Comparator:* Placebo. *Outcomes:* Neuropsychiatric symptoms of Alzheimer disease. *Study designs*: Randomised controlled trials, open-label case series and observational studies.	9 RCTs that evaluate anticonvulsants (a number of other studies were included that evaluated other classes of medicati	Carbamazepine appears to have significant benefits for agitation and aggression, based on 4 RCTs. The authors stated that this treatment is infrequently used because of concerns regarding its tolerability in elderly patients, and because of the potential for significant drug-drug interactions. Five RCTs that evaluated valproate did also not show any significant improvement over placebo, and was associated with poor tolerability; one trial was terminated early due to high rates of adverse events. The authors noted that other anticonvulsants, such as gabapentin, topiramate, and lamotrigine, have been	High

			on)	examined for behavioural and psychological symptoms of dementia, although none have been studied in RCTs.	
Lonergan & Luxenberg (2009)	10/2008	*Population:* Any gender/age; inpatients or outpatients; identified as having dementia, with agitation. *Intervention:* Valproate therapy. *Comparator:* Placebo. *Outcomes:* Overall effect of treatment on agitation; effect of treatment on one or more specific aspects of agitation; adverse effects of treatment; and withdrawal from treatment. *Study designs*: Randomised controlled trials.	5 RCTs (3 from an earlier review plus 2 in this update)	**Agitation** (as measured using the Cohen-Mansfield Agitation Index): Meta-analysis of 3 trials demonstrated no difference between patients who received 6 weeks' treatment compared with those who received placebo (MD -2.20 [95% CI: -6.38, 1.99]. **Aggression:** No study demonstrated overall improvement of aggression in treated compared with placebo patients (P > 0.05). The authors reported an increase in adverse events (falls, infection, gastrointestinal disorders) among valproate treated patients.	Low
Seitz et al. (2013)	10/2011	*Population:* Individuals with dementia, in long-term care settings. *Intervention:* Any pharmacological intervention. *Comparator:* Any comparator. *Outcomes:* Neuropsychiatric symptoms (e.g., agitation, psychosis, or aggression). *Study designs*: RCTs	29 RCTs (4 that evaluated anticonvulsants)	Of the four placebo-controlled studies involving anticonvulsants**,** one evaluated carbamazepine, 2 examined divalproex sodium and 1 study examined oxcarbazepine. Only carbamazepine 300 mg/day was associated with a statistically significant reduction in NPS symptoms (BPRS total) ($p<0.05$) compared with placebo. The other RCTs showed no benefit for other anticonvulsants compared with placebo.	Low

Risk of Bias

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Dolder & Nealy (2012)	☺	☺	?	☺	☹
Herrmann & Lanctot (2007)	☺	☹	?	?	☹
Lonergan & Luxenberg (2009)	☺	☺	☺	☺	☺
Seitz et al. (2013)	☺	☺	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Dementia anticonvulsant	8	1
DARE	(anticonvulsant* OR anti-convulsant*) IN DARE 226 Delete 2 (antiepileptic* OR anti-epileptic*) IN DARE 155 Delete 3 (valproate) IN DARE 92 Delete 4 (epilim OR episenta OR epival OR depakote) IN DARE 1 Delete 5 MeSH DESCRIPTOR Anticonvulsants EXPLODE ALL TREES 252 Delete 6 MeSH DESCRIPTOR Valproic Acid EXPLODE ALL TREES 53 Delete 7 (valproate OR valproic*) IN DARE 117 Delete 8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 479 Delete 9 (dement* OR alzheimer*) IN DARE 676 Delete 10 MeSH DESCRIPTOR Alzheimer Disease EXPLODE ALL TREES 291 Delete 11 MeSH DESCRIPTOR Dementia EXPLODE ALL TREES 575 Delete 12 MeSH DESCRIPTOR Dementia, Vascular EXPLODE ALL TREES 21 Delete 13 MeSH DESCRIPTOR Frontotemporal Dementia EXPLODE ALL TREES 3 Delete 14 MeSH DESCRIPTOR Lewy Body Disease EXPLODE ALL TREES 4 Delete 15 #9 OR #10 OR #11 OR #12 OR #13 OR #14 908 Delete 16 #8 AND #15	13	3
Primary studies			
CENTRAL	#1 MeSH descriptor: [Dementia] explode all trees 3788 #2 MeSH descriptor: [Alzheimer Disease] explode all trees 2185	2	0

	#3 Enter terms for search #1 or #2#1 or #2 3788 #4 Enter terms for search valproate or valproic or divalproexvalproate or valproic or divalproex 1661 #5 MeSH descriptor: [Anticonvulsants] explode all trees 2072 #6Enter terms for searc#4 or #53302 #7Enter terms for searc#3 and #6 29 (2 from 2011 in CENTRAL)		
PsycINFO	1. PsycINFO; VALPROIC ACID/; 1403 results. 2. PsycINFO; sodium-valproate.ti,ab; 516 results. 3. PsycINFO; exp ANTICONVULSIVE DRUGS/; 9417 results. 4. PsycINFO; 1 OR 2 OR 3; 9626 results. 5. PsycINFO; ALZHEIMER'S DISEASE/ OR DEMENTIA/; 49135 results. 7. PsycINFO; (alzheimer* OR dementia).ti,ab; 65531 results. 8. PsycINFO; 5 OR 7; 67000 results. 9. PsycINFO; (agitat* OR aggress* OR restless*).ti,ab; 70801 results. 10. PsycINFO; AGITATION/; 1091 results. 11. PsycINFO; AGGRESSIVE BEHAVIOR/ OR AGGRESSIVENESS/; 23678 results. 12. PsycINFO; 9 OR 10 OR 11; 73277 results. 13. PsycINFO; 4 AND 8 AND 12; 78 results. 14. PsycINFO; 13 [Limit to: Publication Year 2011-2014]; 10 results.	10	0
Embase	15. EMBASE; VALPROIC ACID/; 46462 results. 16. EMBASE; sodium-valproate.ti,ab; 3207 results. 17. EMBASE; divalproex.ti,ab; 998 results. 18. EMBASE; exp ANTICONVULSIVE DRUG/; 267572 results. 19. EMBASE; 15 OR 16 OR 17 OR 18; 267688 results. 20. EMBASE; (alzheimer* OR dementia).ti,ab; 170409 results. 21. EMBASE; DEMENTIA/ OR ALZHEIMER DISEASE/; 176847 results. 22. EMBASE; 20 OR 21; 210116 results. 23. EMBASE; (agitat* OR aggress* OR restless*).ti,ab; 198432 results. 24. EMBASE; AGITATION/; 17024 results. 25. EMBASE; AGGRESSION/; 39040 results.	28	0

	26. EMBASE; 23 OR 24 OR 25; 221542 results. 27. EMBASE; 19 AND 22 AND 26; 877 results. 28. EMBASE; 27 [Limit to: Publication Year 2011-2014]; 176 results. 29. EMBASE; random*.tw; 878911 results. 30. EMBASE; factorial*.tw; 22841 results. 31. EMBASE; placebo*.tw; 198073 results. 32. EMBASE; (crossover* OR cross-over*).tw; 68584 results. 33. EMBASE; (doubl* adj3 blind*).tw; 141161 results. 34. EMBASE; (singl* adj3 blind*).tw; 16687 results. 35. EMBASE; assign*.tw; 237149 results. 36. EMBASE; allocat*.tw; 83056 results. 37. EMBASE; volunteer*.tw; 174959 results. 38. EMBASE; CROSSOVER PROCEDURE/; 39286 results. 39. EMBASE; DOUBLE-BLIND PROCEDURE/; 113934 results. 40. EMBASE; SINGLE-BLIND PROCEDURE/; 18431 results. 41. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 344458 results. 42. EMBASE; 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41; 1403044 results. 43. EMBASE; 28 AND 42 [Limit to: Publication Year 2011-2014]; 28 results.		
Medline	44. MEDLINE; VALPROIC ACID/; 10288 results. 45. MEDLINE; sodium-valproate.ti,ab; 2509 results. 46. MEDLINE; divalproex.ti,ab; 751 results. 47. MEDLINE; exp ANTICONVULSIVE DRUG/; 118495 results. 48. MEDLINE; 44 OR 45 OR 46 OR 47; 119113 results. 49. MEDLINE; (alzheimer* OR dementia).ti,ab; 134308 results. 50. MEDLINE; DEMENTIA/; 37054 results. 51. MEDLINE; ALZHEIMER DISEASE/; 67769 results. 52. MEDLINE; 49 OR 50 OR 51; 150672 results. 53. MEDLINE; (agitat* OR aggress* OR restless*).ti,ab; 153537 results. 54. MEDLINE; PSYCHOMOTOR AGITATION/; 3533 results.	9	0

	55. MEDLINE; AGGRESSION/; 26653 results. 56. MEDLINE; 53 OR 54 OR 55; 165512 results. 57. MEDLINE; 48 AND 52 AND 56; 144 results. 58. MEDLINE; 57 [Limit to: Publication Year 2011-2014]; 9 results.		
Summary	**NA**	**NA**	

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