The efficacy and safety of newer anticonvulsants in patients with dementia

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CRD summary
The review found that there was no good quality evidence that newer anticonvulsants were effective for treating behavioural or cognitive problems in individuals with dementia or seizure disorders. All were associated with problematic side effects. The authors took into account the almost complete lack of controlled evidence in interpreting their findings and their cautious overall conclusions appear reliable.

Authors' objectives
To evaluate the safety and efficacy of newer anticonvulsants with respect to cognitive and behavioural outcomes in individuals with dementia.

Searching
The reviewers searched MEDLINE, IPA, PsycINFO and ClinicalTrials.gov up to December 2011 for papers or trials in English. Search terms were reported. Reference lists of published articles were checked.

Study selection
Eligible studies reported a behavioural or cognitive outcome in patients with dementia who were taking anticonvulsants that had gained regulatory approval in the USA between 1996 and 2001 for treatment of seizure disorders. Studies of other drugs were excluded.

Participants in the review were nursing home residents, in-patients and outpatients with various types of dementia plus either behavioural disturbances or recent onset epilepsy. From 40% to 100% of the participants were women. Mini-Mental State Examination (MMSE) baseline scores ranged from 6 to 26 points. Anticonvulsants included in the review were levetiracetam, oxcarbazepine, topiramate and zonisamide in various doses. Controls (where relevant) received placebo, an anticonvulsant with an antipsychotic or an antipsychotic alone. Some participants received co-medications. The review reported adverse effects as an outcome. Study duration ranged from 17 days to 52 weeks (where stated).

The authors did not state how many reviewers performed study selection.

Assessment of study quality
Study quality was assessed using SORT (Strength of Recommendation Taxonomy) to rate studies as level one (good quality patient-orientated evidence), two (limited quality patient-orientated evidence) or three (other evidence).

The authors did not state how many reviewers performed the assessment.

Data extraction
Descriptive data were extracted for each study, with p values for significant outcomes.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Studies were combined in a narrative synthesis organised by intervention and outcome.

Results of the review
Nine studies (389 participants, range one to 103) were included in the review: two double-blind randomised controlled trials (RCTs), one case-control study, three uncontrolled open-label trials, one retrospective observational study, one case series study and one case report study. Two studies were rated for quality as level one evidence, one as level two and six as level three.

Levetiracetam (four studies): Two open-label trials (39 participants) measured behavioural disturbances using various tools and both reported significant improvements from baseline to discharge/follow-up (four weeks). All three studies
(one case-control and two open-label trials; 139 participants) that reported the effects of levetiracetam on cognition reported MMSE scores. The case-control study found that MMSE scores at 52 weeks follow-up were significantly better with levetiracetam than with phenobarbital or lamotrigine (p<0.05) but all three drugs were significantly inferior to placebo (p<0.05). One open-label trial reported significant improvements in MMSE scores with levetiracetam (p<0.01) at 12 weeks follow-up but a second found a significant deterioration (p<0.05). Adverse events occurred in 6% to 26% of participants across these studies. These studies reported mixed findings for other cognition assessment tools.

**Oxcarbazepine:** One RCT (103 participants) compared oxcarbazepine with placebo and found similar improvements in behavioural disturbances for both groups with no significant difference between them. Adverse events were significantly more frequent in the oxcarbazepine group (p<0.01).

**Topiramate:** One RCT and one retrospective observational study (56 participants) evaluated topiramate alone versus antipsychotics (with or without topiramate). Improvements in behavioural disturbances were reported with all of the drugs with no significant differences observed between them. In the RCT, drop-out rates for adverse events were four out of 21 in the topiramate group and three out of 20 in the antipsychotic group.

One case report study and one case series study evaluated zonisamide and reported behavioural improvements from baseline to follow-up in three of the four participants.

**Authors' conclusions**

There was no good quality evidence that any of the newer anticonvulsants were effective for treating behavioural or cognitive problems in individuals with dementia or seizure disorders. All were associated with problematic side effects.

**CRD commentary**

The objectives and inclusion criteria of the review were clear and relevant sources were searched for published and unpublished studies. The search was restricted by language so the review may have been subject to language bias. It was unclear whether review processes were undertaken with sufficient attempts to minimise reviewer error and bias. Although study design was assessed, the quality assessment did not appear to address study methods (participant selection methods, follow-up rates). Most of the studies were very poor quality and had tiny sample sizes and no controls. Major clinical and methodological differences were evident between the studies. One study cited in the results section was not listed as an included study and its characteristics were not reported.

The authors suggested that levetiracetam might be more useful than other anticonvulsants but this statement was based on very weak and limited evidence and may not be reliable. The authors took into account the almost complete lack of controlled evidence in interpreting their findings and their cautious overall conclusions appear reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that the medications reviewed (levetiracetam, oxcarbazepine, topiramate and zonisamide) could not be recommended for treating behavioural or cognitive problems in individuals with dementia. If used, these medications required caution due to their propensity to cause side effects in older people (such as somnolence, dizziness, hyponatraemia and weight loss).

**Research:** The authors stated that prospective trials of at least four to six weeks duration (with sufficient power) were needed to assess whether any of the newer anticonvulsants reviewed was at least as effective as the more commonly used antipsychotics when used for behavioural symptoms in older adults with dementia. Studies should assess what types of symptoms the newer antipsychotics may or may not be helpful for, assess any cognitive effects and investigate their safety.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.