Neuropsychological outcomes in randomized controlled trials of antiepileptic drugs: a systematic review of methodology and reporting standards

Authors' objectives
To evaluate the neuropsychological outcomes of anti-epileptic drugs (AEDs) in randomised controlled trials or controlled trials of patients with epilepsy or febrile convulsions.

Searching
The authors compiled a database of trials by searching the electronic database of MEDLINE (1966 to 1996) and by handsearching journals. Trials were excluded if they were not published in English.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) investigating the cognitive effects of AEDs using neuropsychological tests or behaviour assessments. Trials were excluded if they were AED-discontinuation studies.

Specific interventions included in the review
Anti-epileptic drugs in various dosages and combinations (carbamazepine (CBZ), phenytoin (PHT), phenobarbitone (PB), vigabatrin (VGB), valproate (VPA), zonisamide (ZNS), oxcarbazepine (OCBZ), ethosuximide (ESM), lamotrigine (LTG)). Comparator interventions included placebo, folic acid, piracetam, flunarizine, methylphenidate, oxiracetam, chlorazepate, sulthiame and tiagabine.

Participants included in the review
Included participants were child and adult patients who had seizures. Patients ages ranged from 4 to 88 years of age. Trials were excluded if they used only healthy volunteers. Patients after head injuries were excluded.

Outcomes assessed in the review
Changes in cognitive function using neuropsychological tests such as the Stroop Test, Finger Tapping Test, Digit Span, Weschler Adult Intelligence Test, Trail Making Test, Digit Symbol Modalities, LaFayette/Perdue Peg Board, Raven's Standard Progressive Matrices, Seashore Rhythm Test, Rey Complex Figure, Continuous Performance Reaction Task, Choice Reaction Time and Letter Cancellation Test. There were 70 other tests used less frequently in the included trials.

How were decisions on the relevance of primary studies made?
Two authors applied the inclusion and exclusion criteria when selecting the articles for the review.

Assessment of study quality
There was no formal assessment of the quality of the included studies. However the authors have listed whether there was randomisation, blinding, and whether intention-to-treat was stated.

Data extraction
One author developed and used a proforma to extract methodologic, treatment, patient and neuropsychological test data.

Methods of synthesis
How were the studies combined?
The trials were not statistically combined because of the large differences in study design and study populations. The
authors carried out a narrative review of the data.

How were differences between studies investigated?
There were no formal tests for homogeneity.

Results of the review
Forty-three reports, representing 40 RCTs (20 actively-controlled and 18 placebo-controlled), were included in the review with a total of 2,681 participants.

Two studies were excluded as they recruited patients after head injuries.

Of the 22 actively controlled studies, 20 were monotherapy and two were add-on studies. Of these, only four described the method of randomisation, and only 3 stated that an intention-to-treat analysis had been undertaken.

In studies with placebo-controlled designs, the majority were add-on studies, and VGB was studied most frequently. Only three studies stated the method of randomisation, and only one study reported the use of an intention-to-treat analysis.

Of the 87 neuropsychological tests used, 20 were found to show statistically significant cognitive effects.

Studies comparing the cognitive effects of PHT and CBZ appeared to produce the most frequent statistically significant cognitive effects, with CBZ favoured for the majority of the tests used. Other AEDs were only represented by one or two small trials.

One study comparing PHT and CBZ in adults with partial and generalised seizures found the results of the Stroop Colour Word Test, the Trail Making Test, and the Hapstead-Wepman Aphasia Test all significantly favoured CBZ, although the remainder of the 12 tests used found no significant differences.

Authors’ conclusions
The authors state that much of the literature can only at best give an approximate extent of the side effects of studied AEDs due to methodologic errors in design and an obvious lack of consistency in neuropsychological assessments. Such a lack of consistency in assessment coupled with practice effects and other artifacts could result in attributing to AEDs adverse or beneficial changes that probably should be related to other factors. To better understand the neuropsychological effects of AEDs, a more rational approach is needed, for which recommendations are:

1. The establishment of a commission to make recommendations for which neuropsychological tests to use in which trials.

2. Uniformity in the selection of neuropsychological tests which include a minimum of measures to assess motor speed, attention and concentration, learning, memory and higher executive functioning.

3. The development of epilepsy-specific neuropsychological instruments.

4. The standardisation of reporting the outcome of neuropsychological tests in randomised controlled trials.

CRD commentary
The authors have stated their research question and have listed inclusion and exclusion criteria for the review. The literature search used only one database which may have missed studies published outside the United States and non-English publications and unpublished data were also excluded so there may be publication bias in this review.

The authors report who, and how many individuals, selected the articles and extracted the data however the authors have not reported how the quality of studies was assessed. The data from each study are presented in several tables.
Statistical pooling was not appropriate and the authors have instead conducted a narrative summary of the data because of the many differences in assessment tests, treatment regimes and study populations in the included trials. It was not possible to make any clinical recommendations from the results presented in this review. The main benefit of the review is the identification of a lack of synthesis in this area and the authors have provided several recommendations for the conduct of future evaluation research on this topic.

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

**Practice:** The authors state that a battery of tests that has been proven reliable and valid, and has been designed and standardised to assess people with epilepsy, should be used to detect cognitive changes due to AEDs in people with epilepsy.

**Research:** The authors state that there should be better reporting of methods.

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