Oxcarbazepine for refractory epilepsy: systematic review of the literature
Saconato H, do Prado GF, dos Santos Puga ME, Atallah AN

CRD summary
The review found that oxcarbazepine was effective as an alternative treatment for refractory partial or generalised epilepsy in children and adults. Given the limited evidence base, limitations in the review process and methodological flaws in the included studies, the authors' conclusion should be treated with caution.

Authors' objectives
To evaluate the effectiveness of oxcarbazepine for refractory partial or generalised epilepsy.

Searching
PubMed (1966 to July 2008), EMBASE, LILACS and Cochrane Central Register of Controlled Trials (CENTRAL) (2008) were searched for relevant studies in any language; search terms were reported. Reference lists from retrieved studies and relevant reviews were searched for additional studies and websites of clinical trial registers were searched for ongoing studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) or quasi randomised trials of patients with any type of refractory partial or generalised epilepsy taking oxcarbazepine versus placebo, oxcarbazepine versus other antiepileptic drugs and oxcarbazepine as adjuvant treatment for another antiepileptic drug versus other antiepileptic drugs. Eligible outcomes were reduction in seizure frequency of at least 50%, absence of convulsive crises during the follow-up period, treatment dropout rate (from lack of efficacy or adverse events) and adverse events.

Participants were either exclusively children, exclusively adults or a combination of children and adults with simple or complex crises of partial or generalised epilepsy not adequately controlled or with undesirable effects from treatment. Doses of oxcarbazepine ranged from 30mg to 46mg (in children) to 2,400mg; these were compared with placebo or carbamazepine 300mg, increasing to 1,200mg.

The authors did not state how study selection was performed.

Assessment of study quality
Studies were assessed for quality by criteria of Schulz 1995 and criteria suggested by Cochrane Handbook for Systematic Reviews of Interventions. These criteria included randomisation method, allocation concealment, blinding, freedom from selective reporting and freedom from other bias.

The authors did not state how the quality assessment was performed.

Data extraction
Dichotomous outcome data were extracted to calculate relative risks (RRs) and risk differences (RDs) with 95% confidence intervals (CIs); continuous outcome data were extracted to calculate weighted mean differences (WMDs) and 95% CIs.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Studies were combined in meta-analysis, if appropriate; relative risks, risk differences and weighted mean differences with 95% CIs were combined using a fixed-effects model. If meta-analysis could not be performed, relative risks and weighted mean differences with 95% CIs for each individual study were displayed on forest plots. Numbers needed to treat (NNT) and numbers needed to harm (NNH) were calculated.
Heterogeneity was assessed by the $X^2$ test and $I^2$ value. When $p<0.1$, a random-effects model was used to calculate summary effect measures.

**Results of the review**

Four RCTs ($n=1,095$) were included. Three studies compared oxcarbazepine to placebo. One study compared oxcarbazepine to carbamazepine. Studies were considered to be of poor to moderate quality. Three studies had adequate blinding and two studies had adequately described randomisation method, adequate allocation concealment or were free of selective reporting of outcomes. One study was free of other likely bias. Follow-up ranged from 10 to 112 days. There were some discrepancies in the relative risks reported in the text and forest plots (figures presented here were from the forest plots).

In adult patients, oxcarbazepine was associated with a greater chance of a 50% or greater reduction in seizure frequency at all doses: 600mg (RR 2.1, 95% CI 1.3 to 3.4, NNT=7; one trial), 1,200mg (RR 3.2, 95% CI 2.1 to 5.0, NNT=4; one trial) and 2,400mg (RR 3.9, 95% CI 2.6 to 6.0, NNT=3; one trial). The same applied to children who took doses of 30mg to 46mg per day (RR reported in the forest plots 1.9, 95% CI 1.3 to 2.8, NNT=5; one trial).

In adults, oxcarbazepine was associated with a greater chance of no seizures during follow-up at higher doses: 1,200mg (RR 17.6, 95% CI 2.4 to 130.4, NNT not reported; one trial) and 2,400mg (RR 25.4, 95% CI 6.3 to 103.1, NNT=5; two trials). There was no evidence of a difference in absence of seizures when the dose of 600mg of oxcarbazepine was compared to placebo in children on doses of 30mg to 46mg per day.

In adult patients, higher doses of oxcarbazepine were associated with significantly more adverse events than placebo: 1,200mg (RR 1.2, 95% CI 1.1 to 1.3, NNH=7; one trial) and 2,400mg (RR 1.3, 95% CI 1.2 to 1.4, NNH=5; two trials). There was no evidence of significant differences at the lower dose of 600mg of oxcarbazepine in adults or among children who took 30mg to 46mg per day.

Dropout rates from adverse events were significantly higher with higher doses of oxcarbazepine: 1,200mg (RR 4.2, 95% CI 2.5 to 7.0; one trial) and 2,400mg (RR 7.7, 95% CI 4.7 to 12.6; one trial). Dropout rates were also significantly higher in children at a dose of 30mg to 46mg per day (RR 3.3, 95% CI 1.1 to 9.7; one trial). There was no evidence of a difference in dropout rates from adverse events with the lower dose (600mg) of oxcarbazepine in adults.

One trial found no evidence of significant differences in outcomes when oxcarbazepine was compared with carbamazepine.

There was no evidence of significant heterogeneity in the one subgroup analysis where two trials were combined.

**Authors' conclusions**

There was moderate evidence that oxcarbazepine was effective as an alternative treatment for partial or generalised epilepsy in children and adults who were refractory to previous treatment.

**CRD commentary**

The review question was clearly stated and inclusion criteria appeared appropriate. Four electronic databases and reference lists of retrieved studies were searched for relevant studies. There were no language restrictions. Attempts were made to find unpublished studies by searching trial registers. The authors did not describe the methods used for study selection, validity assessment and data extraction, so reviewer error and bias could not be ruled out. The tool used for quality assessment was appropriate, but the included studies were mostly poor to moderate quality. The studies varied in their assessment of therapeutic response. Follow-up was short in most of the studies. Results of individual studies were displayed in forest plots in separate subgroups according to population (adults or children) and dose of oxcarbazepine; synthesis was possible for only two studies of oxcarbazepine 2,400mg that assessed adverse events and freedom from seizures.

Given the limited evidence base, lack of documentation of the review process and methodological flaws in the included studies, the authors’ conclusion should be treated with caution.
Implications of the review for practice and research

Practice: The authors stated that oxcarbazepine was effective for treating refractory partial or generalised epilepsy among children or adults, but there was insufficient evidence to determine its safety. There was no evidence to determine the effect of oxcarbazepine on cognition and insufficient evidence to determine whether oxcarbazepine was equal or superior to carbamazepine.

Research: The authors stated that further RCTs to assess the efficacy and safety of oxcarbazepine in adults and children with refractory epilepsy were needed with adequate randomisation methods, sufficient samples and follow-up periods of at least six months. A systematic review of observational studies was needed to evaluate the safety and cognitive effects of oxcarbazepine.

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