

A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial

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Executive summary

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Executive summary

Background

Epilepsy is a common disorder (prevalence 0.5–1%) that is associated with varied prognosis but with considerable consequences for quality of life (QoL) and costs for society. The primary form of treatment is pharmacological. Current National Institute for Health and Clinical Excellence (NICE) guidelines for the treatment of epilepsy identify carbamazepine and valproate as being first-choice treatments.

Objectives

The aims of the study were to compare clinicians' choice of one of the standard drug treatments (carbamazepine or valproate) versus appropriate comparator new drugs in patients who are managed with single drug treatment and to examine outcomes of treatment with regard to seizure recurrence, QoL impairments, chronic epilepsy and the cost-effectiveness of medical management strategies.

Design

The study was a pragmatic, randomised, unmasked, parallel group clinical trial comprising two arms, one comparing new drugs with carbamazepine and the other comparing new drugs with valproate.

Setting

This was a multicentre study recruiting patients with epilepsy from hospital outpatient clinics. At least 90% of new treatments of epilepsy would be expected to be initiated in this setting.

Participants

Patients with an adequately documented history of two or more clinically definite unprovoked epileptic seizures within the last year for whom treatment with a single antiepileptic drug represented the optimal therapeutic option were

recruited. The study did not recruit children under the age of 5 years, those with acute symptomatic seizures or those who had a history of progressive neurological or medical disease.

Interventions

Arm A was carbamazepine (CBZ) versus gabapentin (GBP) versus lamotrigine (LTG) versus oxcarbazepine (OXC) versus topiramate (TPM) and Arm B valproate (VPS) versus LTG versus TPM. When clinicians felt that CBZ was the optimal standard drug, patients were allocated to Arm A, and when VPS was the optimal drug they were allocated to Arm B. In both arms, guidelines were given as to initial dosing, but choice of dose and variation in dose with seizure response and adverse events were at the discretion of the clinician.

Main outcome measures

Primary outcome measures

1. Time to treatment failure (withdrawal of the randomised drug for reasons of unacceptable adverse events or inadequate seizure control or a combination of the two).
2. Time to achieve a 12-month remission of seizures.

Secondary outcome measures

1. Clinical outcomes: time from randomisation to first seizure, 24-month remission of seizures, incidence of clinically important adverse events.
2. QoL outcomes.
3. Health economic outcomes.

Results

A total of 1721 patients were recruited to Arm A and 716 to Arm B. Arm A recruited 88% of patients with symptomatic or cryptogenic partial epilepsy and 10% with unclassified epilepsy. Arm B recruited 63% of patients with idiopathic generalised epilepsy and 25% with unclassified epilepsy.

Arm A

LTG had the lowest incidence of treatment failure and was statistically superior to all drugs for this outcome with the exception of OXC. Some 12% and 8% fewer patients experienced treatment failure on LTG than CBZ, the standard drug, at 1 and 2 years after randomisation, respectively. The superiority of LTG over CBZ was due to its better tolerability but there is satisfactory evidence indicating that LTG is not clinically inferior to CBZ for measures of its efficacy (treatment failure due to inadequate seizure control and time to achieving a 12-month remission). No consistent differences in QoL outcomes were found between treatment groups, although patients achieving a 12-month remission by 2 years after randomisation had superior QoL outcomes to those who had not, and patients who had experienced a treatment failure outcome exhibited poorer QoL than those who remained on their randomised treatment. Health economic analysis supported LTG being preferred to CBZ for both cost per seizure avoided and cost per quality-adjusted life-year gained.

Arm B

For time to treatment failure, VPS, the standard drug, was preferred to both TPM and LTG. VPS was the drug least likely to be associated with treatment failure for inadequate seizure control and was the preferred drug for time to achieving a 12-month remission. QoL assessments did not show any between-treatment differences, though patients achieving a 12-month remission by 2 years after randomisation had superior QoL outcomes to those who had not and patients who had experienced a treatment failure outcome exhibited poorer QoL. The health economic assessment supported the conclusion that VPS should remain the drug of first choice for idiopathic generalised or unclassified epilepsy,

although there is a suggestion that TPM is a cost-effective alternative to VPS.

Conclusions

Implications for healthcare

The study provides evidence that LTG may be a clinical and cost-effective alternative to the existing standard drug treatment, CBZ. Some 88% of patients in Arm A were diagnosed as having partial seizures, so conclusions are applicable to patients with these epilepsy syndromes. For patients in Arm B with idiopathic generalised epilepsy or difficult to classify epilepsy, VPS remains the clinically most effective drug, although TPM may be a cost-effective alternative for some patients.

It should be noted that the SANAD trial was not designed to address the issue of safety during pregnancy, an important factor for choice of antiepileptic drugs in women during their childbearing years.

Recommendations for research

Since the design and start of the trial, three new antiepileptic drugs have been licensed in the UK for the treatment of epilepsy (levetiracetam, zonisamide and pregabalin). It will be important that these drugs are compared in a similarly designed trial with LTG and OXC and also with VPS.

Publication

Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al.* A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial. *Health Technol Assess* 2007;11(37).

NIHR Health Technology Assessment Programme

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The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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