Which should be the first-line drug for newly diagnosed epilepsy? Commentary on the SANAD study

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This year saw the publication of the SANAD study, published as 2 papers in the *Lancet* by Marson et al. [1,2]. The SANAD study consisted of 2 arms. In arm A1, the effectiveness of carbamazepine, taken as the standard treatment for partial onset seizures, was compared to that of 4 other anti-epileptic drugs, gabapentin, lamotrigine, oxcarbazepine and topiramate. One thousand seven hundred and twenty-one patients were recruited and randomly assigned to one of the treatments. Primary outcome measures, the same for both arms of the study, were 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) and time to achieve a 12-month remission.

Lamotrigine had the lowest treatment failure rates and was statistically superior to all drugs in this regard except oxcarbazepine. The superiority of lamotrigine over carbamazepine was based on its apparant better tolerability but there was evidence that lamotrigine was not inferior to carbamazepine in measures of efficacy. Based on these findings, the authors recommend that lamotrigine is a cost-effeective alternative to carbamazepine and should replace it as standard treatment for patients with partial onset epilepsy. However, it should be noted that the differences in the drugs was slight – and a more striking conclusion is the similarity in outcome rather than the difference.

In the second arm of the study [2], the effectiveness of the accepted standard treatment for generalised onset or unclassified seizures sodium valproate, was compared with that of lamotrigine and topiramate. Seven hundred and sixteen patients were recruited and randomly assigned to one of the treatment arms. Primary outcome measures were as before. Valproate was significantly better tolerated than topiramate For time to treatment failure, valproate was superior to both topiramate and lamotirigine. Valproate was the least likely to be associated with treatment failure due ro inadequate seizure control and most likely to achieve a 12-month remission. Based on these results, the authors recommend that sodium valpraote remain the standard treatment of generalised onset and unclassified seizures.

We will examine the positive aspects and criticisms of the study.

Positive aspects SANAD

When it is decided to initiate medication in a patient newly diagnosed with epilepsy, the single most important therapaeutic decision is the correct choice of the first anti-epileptic drug (AED). This decision is influenced by a number of factors including age of the patient, gender and classification of epileptic syndrome. With the advent of evidence based medicine, randomised control trials (RCTs) have been established as the gold standard for the comparsion of one treatment modality to other. Prior to SANAD however, there were few RCTs in newly diagnosed epilepsy, the RCTs were short-term and very few were head to head comparisons of standard drugs. The recent ILAE guidelines [3] highlight the limitations with the existing AED RCT data and makes recommendations for future studies. Furthermore, the SANAD study has a number of outstanding design features which raise it above the level of most preceding studies:

1. It entered a large number of patients, and was thus adequately powered to detect clinically important differences in efficacy between drugs.
2. The study randomised a large number of patients (over 2400, had a long period of follow-up (nearly 8000 patient years, with 95% completeness.
3. It contained multiple ages and seizure types.
4. The design, conduct and analysis of the study was independent of industry.
5. In diagnosis, study entry criteria and flexibility of management, SANAD is a pragmatic study designed to reflect contemporary practice.

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Criticisms of SANAD

Perhaps because of its importance, SANAD has been heavily scrutinised with commentors critising various aspects of the design of the study as well as its conclusions [4-9]. A number of negative aspects have been pointed out:

1. The study was not blinded, and so it's conclusions can not be considered as class I evidence. Indeed Dr French in her commentary categorises the study as an open low, class III grade study [4].

2. The syndromic classification of epilepsy was completely ignored, which is a serious deficiency as certain syndromes have quite specific treatment.

3. The SANAD study took years to complete, and by the time of publication was partially outdated [7]. The first arm of the study contained the use of gabapentin which never received a monotherapy license in the UK. Moveover since the start of the study, we have seen the release of three new anti-epileptic drugs, Pregablin (2005), Zonisamide (2005) and Levetiracetam (2000); and this drug is rapidily attaining the status of potential first line therapy.

4. Far too few children were entered to allow its conclusions to be extended to children.

5. The conclusion from arm A [1] is that lamotrigine should replace carbamazepine as the standard treatment of partial onset epilepsy has been heavily debated and critised for several reasons:

1) one commentator considered that the dosing used seemed biased against carbamazepine. Most adults with newly diagnosed epilpesy who achieve seizure freedom do so on an average dose of 400 mg/24h [10]. Titration to higher doses (600 mg/24h over 4 weeks) might have lead to higher rates of intolerability and dropout rates. The fact that the trend in effiacacy favoured carbamazepine but that lamotrigine was better tolerated might be influenced by this [5]
2) about 10% of the arm A patients had generalised or unclassified seizures which are more likely to respond to lamotrigine, thus prejudicing the results against carbamazepine [5-7]
3) use of immediate-release carbamazepine in a number of patients as opposed to sustained release carbamazepine could have lead to a higher rate of treatment failure as the sustained release carbamazepine is better tolerated then the immediate-release carbamazepine, with similar retention rates as lamotrigine [5,11,12]
4) the median age was 38 ±18 years, in addition to the fact that 87.6% had symptomatic or crytogenic epilepsy as opposed to only 1.4% with idiopathic focal epilepsy. This suggests a predomaintly adult population and therefore limits its applicability to the paediatric population [8]
5) in the analysis of the results, there was no subgroup analysis done which may inadvertately lead to the erroneous conclusion that focal onset epilepsies are a homogenous grouping where one drug fits all, as opposed to a diverse collection of different epileptic syndromes [8]
6) in fact, the superiority of lamotrigine is based only on the tolerability of the two drugs in the very early period of therapy. If anything, carbamazepine in terms of efficacy performed rather better than lamotrigine
7) a surprisingly high number of patients developed a rash on carbamazepine, a figure higher than would be expected from previous studies
8) lamotrigine is significantly more costly then carbamazepine [13], and the small differences in tolerability shown in this study do not justify its widespread first-line use.

6. The conclusion from arm B [2] is that valproate should remain the first line treatment has also been criticised on the following bases:

1) as in arm A, the population was pooled with a combination of idopathic generalised epilpesy and unclassified seizures (26.7%). Subgroup analysis of the IGE group was not included in the paper. This would include patients with absence seizures against which topiramate has not been shown to be effective. Morover if patients with myoclonic epilepsy, which lamotrigine is known to exacerbate [14], were excluded from the analysis it is possible that lamotrigine would have performed better in comparsion to valproate
2) diagnosis may have been suboptimal as this was based on clinical assessment as EEG and brain imaging were optimal. Many generalised seizures may be initially classified as focal onset seizures without the use of EEG [15]
3) while the authors state that the study was not designed or powered to examine pregnancy outcomes, no mention is made of the recent concerns about lamotrigine in pregnancy [16] or problems with toxicity [9,17]. No mention is made of the limited available data on topiramate in pregnancy [16].

In conclusion, SANAD is an outstanding study and a remarkable acheivement. It has clearly moved the debate on about optimal treatment of epilepsy, and is the result of a huge amount of work and commitment. However, based on its findings and the commentaries which have followed, we would not recommend that lamotrigine replace carbamazepine as standard treatment of focal onset epilepsy in Poland and we do not consider that the case for prefering lamotrigine is made in this study. Sodium valproate should still be considered the standard treatment of those with generalised seizures provided that accurate epileptic syndromic classification has been established.

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From the Editor

Synopsis: Marson AG, Al-Kharusi AM, Alwaidh M. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet. 2007; 369: 1000-1015.

In this randomized controlled trial the authors sought to investigate whether in patients with partial epilepsy new anticonvulsants (lamotrigine, gabapentin, oxcarbazepine, topiramate) are noninferior to carbamazepine. In the analysis including 1,721 patients after 6 years of study (a mean of 3.1 years of follow-up) in the lamotrigine group as compared to the cabamazepine group treatment failure for any reason was less frequent (HR 0.78), mainly because of lower risk of treatment failure due to unacceptable side-effects (HR 0.62; in the lamotrigine group around 10% patients less than in carbamazepine group). The authors of the study concluded that lamotrigine is an alternative to carbamazepine – a drug of first choice so far – and could be the drug of first choice and there are no reasons to prefer gabapentin or topiramate as drugs of first choice, except where there might be individual mitigating factors. The noninferiority of oxcarbazepine in comparison with carbamazepine was not excluded with certainty.

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From the Editor

Synopsis: Marson AG, Al-Kharusi AM, Alwaidh M. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet. 2007; 369: 1016-1026.

In this randomized controlled trial the long-term effects of monotherapy with lamotrigine, topiramate or valproate in patients with generalised and unclassified epilepsy were compared. In the analysis including 716 patients after 6 years of study (mean, 3.3 years of follow-up of individual patients) treatment failure was more frequent in the topiramate group in comparison with the valproate group (HR 1.57, NNT 7 in favour of valproate) and 12-month remission was less frequent after lamotrigine treatment in comparison with Valproate (HR 0.76, NNT 11 in favour of valproate). Autors concluded that valproate should remain the drug of first choice in the treatment of patients with generalised and unclassified epilepsy.

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