

## NOW WE KNOW THE DRUG OF FIRST CHOICE—OR DO WE?

**The SANAD Study of Effectiveness of Carbamazepine, Gabapentin, Lamotrigine, Oxcarbazepine, or Topiramate for Treatment of Partial Epilepsy: An Unblinded Randomised Controlled Trial.** Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaidis P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD Study group. *Lancet* 2007;369(9566):1000–1015. **BACKGROUND:** Carbamazepine is widely accepted as a drug of first choice for patients with partial onset seizures. Several newer drugs possess efficacy against these seizure types but previous randomised controlled trials have failed to inform a choice between these drugs. We aimed to assess efficacy with regards to longer-term outcomes, quality of life, and health economic outcomes. **METHODS:** SANAD was an unblinded randomised controlled trial in hospital-based outpatient clinics in the UK. Arm A recruited 1,721 patients for whom carbamazepine was deemed to be standard treatment, and they were randomly assigned to receive carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate. Primary outcomes were time to treatment failure, and time to 12-months remission, and assessment was by both intention to treat and per protocol. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN38354748. **FINDINGS:** For time to treatment failure, lamotrigine was significantly better than carbamazepine (hazard ratio [HR] 0.78 [95% CI 0.63–0.97]), gabapentin (0.65 [0.52–0.80]), and topiramate (0.64 [0.52–0.79]), and had a non-significant advantage compared with oxcarbazepine (1.15 [0.86–1.54]). For time to 12-month remission carbamazepine was significantly better than gabapentin (0.75 [0.63–0.90]), and estimates suggest a non-significant advantage for carbamazepine against lamotrigine (0.91 [0.77–1.09]), topiramate (0.86 [0.72–1.03]), and oxcarbazepine (0.92 [0.73–1.18]). In a per-protocol analysis, at 2 and 4 years the difference (95% CI) in the proportion achieving a 12-month remission (lamotrigine-carbamazepine) is 0 (–8 to 7) and 5 (–3 to 12), suggesting non-inferiority of lamotrigine compared with carbamazepine. **INTERPRETATION:** Lamotrigine is clinically better than carbamazepine, the standard drug treatment, for time to treatment failure outcomes and is therefore a cost-effective alternative for patients diagnosed with partial onset seizures.

**The SANAD Study of Effectiveness of Valproate, Lamotrigine, or Topiramate for Generalised and Unclassifiable Epilepsy: An Unblinded Randomised Controlled Trial.** Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaidis P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD Study group. *Lancet* 2007;369(9566):1016–1026. **BACKGROUND:** Valproate is widely accepted as a drug of first choice for patients with generalised onset seizures, and its broad spectrum of efficacy means it is recommended for patients with seizures that are difficult to classify. Lamotrigine and topiramate are also thought to possess broad spectrum activity. The SANAD study aimed to compare the longer-term effects of these drugs in patients with generalised onset seizures or seizures that are difficult to classify. **METHODS:** SANAD was an unblinded randomised controlled trial in hospital-based outpatient clinics in the UK. Arm B of the study recruited 716 patients for whom valproate was considered to be standard treatment. Patients were randomly assigned to valproate, lamotrigine, or topiramate between Jan 12, 1999, and Aug 31, 2004, and follow-up data were obtained up to Jan 13, 2006. Primary outcomes were time to treatment failure, and time to 1-year remission, and analysis was by both intention to treat and per protocol. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN38354748. **FINDINGS:** For time to treatment failure, valproate was significantly better than topiramate (hazard ratio 1.57 [95% CI 1.19–2.08]), but there was no significant difference between valproate and lamotrigine (1.25 [0.94–1.68]). For patients with an idiopathic generalised epilepsy, valproate was significantly better than both lamotrigine (1.55 [1.07–2.24]) and topiramate (1.89 [1.32–2.70]). For time to 12-month remission valproate was significantly better than lamotrigine overall (0.76 [0.62–0.94]), and for the subgroup with an idiopathic generalised epilepsy 0.68 (0.53–0.89). But there was no significant difference between valproate and topiramate in either the analysis overall or for the subgroup with an idiopathic generalised epilepsy. **INTERPRETATION:** Valproate is better tolerated than topiramate and more efficacious than lamotrigine, and should remain the drug of first choice for many patients with generalised and unclassified epilepsies. However, because of known potential adverse effects of valproate during pregnancy, the benefits for seizure control in women of childbearing years should be considered.

### COMMENTARY

The two studies reviewed here—one done with patients with newly diagnosed epilepsy for whom carbamazepine

would have been considered standard treatment (SANAD A, mostly partial) and the other with patients for whom valproate would have been considered standard treatment (SANAD B, mostly generalized or unclassified epilepsy)—are clearly landmark. It could be argued that no study since the Veterans Administration cooperative studies in the 1970s and 1980s has been designed with such intent to perform clinically meaningful (and therefore clinically useful) randomized, controlled trials to assess best treatment options for these patient populations (1,2). It is important to appreciate that the stated purpose of the studies was (i) to determine the “effectiveness” of each of the drugs tested and (ii) to assess which agent was the best option for the treatment of newly diagnosed epilepsy.

Recently, a great deal of discussion has centered on the ability of a trial to determine effectiveness rather than efficacy. “Efficacy” is defined as the ability of a treatment to obtain a prespecified outcome (e.g., seizure reduction) over the course of a prespecified (usually short) time frame. A drug can be highly efficacious yet not very clinically useful, that is, not clinically effective. For example, a drug could produce a 50% reduction in seizures but cause vomiting in all patients; could require four times a day dosing, which is likely to reduce compliance; or could be useful only in the narrow spectrum of patients eligible for the trial but not the larger population who would receive it, once approved. Effectiveness, in contrast to efficacy, is meant to be a more pragmatic measure that addresses the utility of a drug as it is actually employed in practice. To measure effectiveness, it is necessary to mirror a real-world environment as much as possible. Thus, the SANAD trials were performed primarily by general neurologists and not in highly specialized epilepsy centers. Physicians were offered guidance on titration schemes and maximal doses but were then permitted to treat patients according to their own assessment. They could discontinue treatment when they wished. To prevent an artificial environment and simplify the trial, the study was performed without blinding; these trial design aspects clearly add to the ability of the study to provide clinically useful data. Thus, the trial results likely adequately address the question of the effectiveness of each AED, as assessed in the hands (and minds) of neurologists in practice in the United Kingdom.

Let us now turn to the other question the authors claim to have addressed, namely, “Which drug should be first-line treatment?” This one is more difficult to definitively answer. Why? One reason is that almost by their nature, effectiveness trials sacrifice rigor. For example, since physicians were permitted to treat without strict guidance, it is not clear whether all of them used long-acting formulations (which would impact the effectiveness of carbamazepine). The clinicians might not have reached maximum dose in all cases, and titration schedules might have been too fast or too slow. They also very well might have been influenced by knowing which drug the patient

was receiving during the trial. Thus, the drug that was favored by a physician before the trial began might have a substantial advantage over a drug that he or she felt had problems with either efficacy or safety, thus producing a self-fulfilling prophecy. Preconceived notions and habits of use might have enough impact, in fact, that the “winner” could have been different if the same study were performed in the United States or elsewhere in Europe, rather than in the United Kingdom.

Other pertinent issues include the fact that the outcome was determined for “all comers.” For instance, in the SANAD B trial, all generalized syndromes were lumped together, as were all seizure types. Thus, if one drug, such as lamotrigine, was very effective for generalized tonic-clonic seizures, but less effective or even aggravating for myoclonic seizures, as some believe, this distinction would be lost in the analysis (3,4). Perhaps most important, one must consider whether a drug of first choice can be selected based only on the variables—namely, time to drug failure, time to 1-year remission, health economic assessment, and quality of life—that were tested (and testable) in these trials. In truth, this designation often rests on other issues as well. For example, felbamate is a very well-tolerated and effective drug that might have fared well if included in either arm of this study; however, it is considered a drug of last resort, based on idiosyncratic reactions (aplastic anemia and hepatic failure) that occur at a frequency of 1/3,000 (5). The number of patients included in SANAD was large yet not large enough to evaluate serious idiosyncratic events. Valproate can cause pancreatitis at a rate of 1/300 patients as well as hepatic failure, which has a high frequency rate in some subgroups (polytherapy under age 10 and any use under age 2) (6), yet it was chosen as drug of first choice. And, what of other variables not measured? How can one determine their “relative value” in selection of a drug of first choice? In a study performed in the 1970s, which is similar to the present one except that blinded, newly diagnosed patients were randomized to one of the four drugs commonly prescribed at the time, no differences were found between carbamazepine and phenytoin with respect to either safety or tolerability (1). So, why is phenytoin currently considered an inferior choice when compared with carbamazepine? Indeed, a number of other characteristics ultimately stood out, including bone health, long-term side effects (e.g., gum hyperplasia and neuropathy), as well as the difficulty of using a drug that respects zero-order kinetics at higher dosages. The phenytoin example highlights important issues that color drug choice, such as long-term side effects, safety, pharmacokinetics, and potential for teratogenicity, that cannot be easily evaluated, even in the best-designed randomized trial.

In conclusion, the epilepsy community should welcome the data provided by this trial. Picking a drug of first choice, however, may not yet be within our grasp.

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## References

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