The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for the treatment of partial epilepsy: an unblinded randomized controlled trial

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At the time of this trial, Carbamazepine (CBZ) was recommended as first line therapy for patients with focal-onset seizures, though based on results from prior randomized-controlled trials comparing carbamazepine to valproate. However, several new anti-epileptic drugs (AEDs) had been licensed at the time of this trial, though mostly via add-on, randomized-controlled trials for refractory focal epilepsy. Nonetheless, some of this trial data had suggested that gabapentin (GBP), lamotrigine (LTG), topiramate (TPM), and oxcarbazepine (OXC) might be effective as monotherapy for focal epilepsy; for several reasons, such trial data had not directly altered clinical practice. Therefore, this trial, SANAD Arm A, was undertaken in concurrence with SANAD Arm B (generalized-onset seizures, see week 25), to assess the efficacy, tolerability, and quality of life outcomes of the above 4 AEDs vs. CBZ for focal-onset seizures.

Experimental design and statistics: This was an unblinded, randomized controlled trial conducted across hospital-based clinics in the UK, and included patients with $\geq$2 clinically unprovoked epileptic seizures, ideally focal in onset, and in whom CBZ would have been the optimal AED choice. Exclusion criteria is noted below.[1] After being identified by their practicing physician, participants were randomly allocated to 1 of the 5 AED choices (CBZ, GBP, LTG, TPM, or OXC; no placebo pills) via a central randomization center. Drug choice was randomized but doses, titration and preparation were determined by the practicing physician with standardized guidelines. The goal was seizure control via minimum effective dosing[2]. Patient neurological history and seizure/epilepsy classification were recorded at the time of study entry, and follow ups occurred at 3, 6, and 12 months post-randomization, then yearly thereafter. With this data, two primary outcomes were assessed: 1) time from randomization to treatment failure[3] and 2) time from randomization to a 1yr period of seizure remission. Major secondary outcomes included time from randomization to a first seizure, and time to a 2yr period of seizure remission, in addition to the incidence of adverse events. Quality of life and cost effectiveness were also assessed. Statistically, analyses of time to event data used log-rank tests and Cox proportional hazard models, while time to remission data used cumulative incidence analyses. Non-inferiority analyses on select AEDs were conducted on the above outcomes relative to CBZ as well. Of note, analyses that included OXC were conducted separately, as OXC was added only after the trial had been running for some time.

Results: A total of 1721 patients were randomized, with baseline characteristics noted in **Table 1**; most patients were classified as having focal epilepsy. In terms of time to treatment failure, LTG was better than all other AEDs and GBP + TPM performed most poorly (**Figure 2 and Table 3**, log-rank test statistics of 22.15 and 11.26). LTG and GBP had the lowest risk of treatment failure due to adverse side effects (ASEs), while CBZ and TPM had the highest risk for this effect, and treatment failure due to inadequate seizure control was highest with GBP and lowest with CBZ; there were no

[1] Exclusion criteria: history of only symptomatic seizures, age <4yrs old, treatment was felt to be contraindicated, h/o progressive neurologic disease

[2] This strategy allowed for dosing adjustments in the setting of inadequate seizure control.

[3] Treatment failure: stopping a medication due to ASEs, inadequate control or both OR addition of a 2nd AED

differences between CBZ and LTG regarding inadequate seizure control. Overall, LTG was non-inferior to CBZ for treatment failure. For OXC, rates of treatment failure on OXC were similar to CBZ; OXC had fewer ASEs than CBZ, though it was associated with poorer seizure control than CBZ. Overall, non-inferiority of OXC to CBZ was not met. Otherwise, in terms of time to 1yr of seizure remission, GBP and TPM performed most poorly while CBZ performed the best, and there were only small differences when comparing CBZ to LTG and to OXC (**Figure 3 and Table 4**, log-rank statistics of 9.394 and 10.57). As with treatment failure data, LTG was non-inferior to CBZ regarding time to 1yr seizure remission, though non-inferiority of OXC to CBZ was not met. For both of these primary outcomes, results did not differ when restricting analyses to only those patients with focal-onset seizures. Otherwise, in terms of the main secondary outcomes, CBZ performed better than all other AEDs for 2yr seizure freedom (small differences with OXC or LTG) and for time to first seizure (with GBP performing most poorly). Finally, adverse event rates were lowest with LTG and highest with TPM (see Table 5[4]), there were few QOL differences between drugs, and cost-effectiveness scores are outlined in Tables 6-8.

Conclusions: Overall, this trial was among the first comparative AED study of its size and duration to assess the efficacy and tolerability of several new AEDs vs. CBZ (standard therapy) for focal-onset seizures. Ultimately, this study found that LTG was generally better than CBZ for focal-onset seizures: LTG was better than CBZ regarding time to treatment failure due to a better ASE profile, and LTG was non-inferior to CBZ regarding 12-month seizure remission. OXC tended to perform similarly to (and sometimes better than) CBZ, but data to support the use of OXC over CBZ was not sufficient. Of note, the lack of blinding and placebo was a limitation to this study, but the trial was designed to be pragmatic and easily applicable, and the addition of both intention-to-treat and per-protocol analyses helped to overcome these limitations. Regardless, the data presented here, including QALY and cost-effectiveness data, supported the use of LTG as a first choice option for most patients with focal-onset seizures.

Summary created by Elaine Sinclair, D.O.

[4] The most common ASE associated with treatment failure was a rash, seen most often with CBZ, OXC, and LTG.