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

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At the time of this trial, Carbamazepine (CBZ) was considered as first line therapy for focal epilepsy, though based on data comparing CBZ to valproate (VPA). However, several new anti-epileptic drugs (AEDs) had been licensed in the interim for focal epilepsy, and smaller trials had suggested that in addition to CBZ, gabapentin (GBP), lamotrigine (LTG), topiramate (TPM), and oxcarbazepine (OXC) were potentially effective as monotherapy for focal epilepsy as well. For several reasons, such trial data had not directly altered clinical practice. Therefore, Arm A of the SANAD trial was undertaken (concurrent with Arm B, see wk 24), to assess the efficacy, tolerability, and quality of life outcomes of the above 4 AEDs vs. CBZ for focal epilepsy.

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) via a central randomization center. Drug choice was randomized but doses, titration, and preparation were determined by the practicing physician. 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. 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 to 2yrs of seizure freedom, in addition adverse side effects (ASEs). Quality of life and cost effectiveness were also assessed. Statistically, time to event data was analyzed via log-rank tests and Cox proportional hazard models; time to remission data used cumulative incidence analyses. Non-inferiority analyses on select AEDs were conducted (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 both GBP and TPM performed most poorly (**Fig 2 and Table 3**). LTG and GBP had the lowest risk of treatment failure due to ASEs, while CBZ and TPM had the highest risk for ASEs. Treatment failure due to inadequate seizure control was highest with GBP and lowest with CBZ, but there were no differences between CBZ and LTG re: seizure control. Overall, LTG was found to be non-inferior to CBZ for treatment failure. For OXC, rates of treatment failure were similar to CBZ: OXC had fewer ASEs than CBZ but was associated with poorer seizure control. Overall, non-inferiority of OXC to CBZ was not met. Otherwise, in terms of time to 1yr of seizure

[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

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 (**Fig 3 and Table 4**). 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. Finally, CBZ performed better than all other AEDs for 2yr seizure freedom and for time to first seizure (GBP performed most poorly). ASEs were lowest with LTG and highest with TPM (**Table 5**), there were few QOL differences between drugs, and cost-effectiveness scores are 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 to CBZ (standard therapy) for focal epilepsy. The trial data here showed that LTG was generally better than CBZ for focal epilepsy, as LTG had fewer ASEs and similar rates of 1yr seizure freedom as compared to CBZ. OXC also performed better than/similar to CBZ, but data to support OXC over CBZ was not sufficient. The lack of blinding and placebo were limitations, but the trial was designed to be pragmatic and the use of intention-to-treat and per-protocol analyses helped to overcome these limitations. Ultimately, this study supported the potential use of LTG as a first choice AED for most cases of focal epilepsy.

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