The SANAD (Standard and New Anti-Epileptic Drugs Project) study of effectiveness of valproate, lamotrigine, or topiramate for generalized and unclassifiable epilepsy

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Up to 40% of patients with epilepsy have seizures that are generalized at their onset, and at the time of this trial, guidelines had recommended the use of valproate (VPA) as first line therapy for these patients and for patients with unclassified seizures. However, evidence to support this first line use of VPA was primarily based on observational studies, and in the ~10yrs prior to this trial, newer anti-epileptic drugs, namely lamotrigine (LTG) and topiramate (TPM), had been studied as monotherapy for generalized-onset seizures in smaller trails. However, neither medication had been directly compared to VPA as monotherapy for generalized-onset seizures; this was particularly important in the setting of the safety of LTG for use in pregnancy, among other considerations. As such, the goal of this study was to compare the efficacy and tolerability of VPA to LTG and TPM, in patients for whom VPA would have been considered as first line treatment (i.e., generalized onset seizures).

Experimental design and statistics: This trail was designed as an unblinded, pragmatic trial. Patients were included into the trial if they had a history of ≥2 unprovoked epileptic seizures in the prior year, and if the treating clinician felt that VPA would have been the optimal medication choice[1]. Exclusion criteria are noted below.[2] At the time of study entry, neurological history, seizure history, EEG data, and imaging data were obtained, and treating clinicians identified seizure type and epilepsy syndromes by ILAE criteria. Enrolled patients were then randomized in a 1:1:1 fashion to receive either VPA, LTG, or TPM. Formulation, dosing, and titration schedules could be dictated by the treating clinicians as appropriate. Primary outcomes included time from randomization to stopping a medication due to treatment failure[3], and to 1yr of seizure freedom. Secondary outcomes included time from randomization to first seizure and to 2yrs of seizure freedom, and adverse side effects (ASEs) of the treatment medications. Quality of life and cost effectiveness were also assessed. Statistically, primary outcomes were assessed via Cox proportional hazard ratios (HRs) and follow up cumulative incidence analyses when indicated. Intention-to-treat and per-protocol analyses were both conducted.

Results: Over the course of the study period, a total of 716 patients were randomized to receive either VPA (238), LTG (239), or TPM (239). Most patients carried a diagnosis of idiopathic generalized epilepsy (63%) or unclassified epilepsy (27%), and baseline demographic data was similar (Table 1). Medication dosages used by individual clinicians are outlined in Table 2. Regarding the primary outcome, there were significant differences between the three medication groups in terms of time to treatment failure, with statistical models favoring VPA (HR for TPM: VPA = 1.57 and HR for LTG: VPA = 1.25; Table 3 and Figure 2). Follow up cumulative incidence analyses suggested that treatment failure due to ASEs was highest with TPM (see Table 5). Treatment failure due to inadequate seizure control was highest in LTG (HR of 1.95 for LTG: VPA) and was also higher in TPM vs. VPA (HR of 1.45 for TPM: VPA). In addition, VPA was also better than LTG (HR of 0.76) and TPM (HR of 0.93) in terms of time from randomization to 1yr of seizure freedom[4]. Regarding secondary outcomes, VPA was also better than both LTG and TPM in terms of time to first seizure and to 2yrs of seizure freedom. Notably, in subgroup analyses assessing the primary and secondary outcomes in those with idiopathic generalized epilepsy vs. unclassified

[1] Including those with new-onset seizures, those who had failed previous monotherapy, and those with prior remission then seizure recurrence
[2] Exclusion criteria: only acute symptomatic seizures, contraindication to study drugs, age <4yrs old, h/o progressive neurological disease
[3] Treatment failure: medication cessation due to inadequate control, ASEs, or both OR the need for an additional medication
[4] Results for time to 12-month seizure remission were similar in both intention-to-treat and per-protocol analyses

seizures, results in support of VPA were stronger in the idiopathic generalized epilepsy subgroup. Finally, cost-effectiveness data is presented in Tables 6-8.

Conclusions: Overall, this study supported the first line use of VPA for patients with generalized onset seizures, at least as compared to LTG and TPM, with the largest effects seen in patients with idiopathic generalized epilepsy (vs. unclassified seizures). As compared to VPA, LTG appears to be less efficacious in terms of adequate seizure control, and TPM has less tolerability. Of note, at the time of this trial, LTG had been regarded as a broad-spectrum medication, even though its efficacy in generalized epilepsies was not supported by this trial data. However, LTG (vs. several others) was found to be the preferred option for focal epilepsy in a separate arm of this trial, so the study authors noted that the combined data supported LTG for focal rather than generalized epilepsies. Otherwise, a limitation to the study was the higher proportion of men vs. women in the VPA group here, due to a risk of randomizing women of child-bearing age to VPA, though the study authors suggested that their data likely extended adequately to women as well.

Additional Reading, if interested:

1) Marson, A., et al., **The SANAD II study of the effectiveness and cost-effectiveness of valproate vs. levetiracetam for newly diagnosed generalized and unclassified epilepsy**. Lancet (2021); 397: 1375 - 1386