Valproate was more effective than lamotrigine and better tolerated than topiramate in generalized or unclassified epilepsy

Marson AG, Al-Kharusi AM, Alwaidh M, et al. **The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial.** Lancet. 2007;369:1016-26.

Clinical impact ratings: Emergency Med ★★★☆☆☆ Neurology ★★★★★☆

QUESTION

In patients with generalized onset or unclassified seizures, how do valproate (VAL), lamotrigine (LTG), and topiramate (TPM) compare?

METHODS

Design: Randomized controlled trial (Standard and New Antiepileptic Drugs [SANAD] trial, Arm B).
Allocation: Concealed.*
Blinding: Unblinded.*
Follow-up period: Up to 6 years.
Setting: Hospital-based outpatient clinics in the United Kingdom.
Patients: 716 patients (mean age 23 y, 60% men) who had ≥ 2 clinically definite, unprovoked epileptic seizures in the past year and were recommended to take VAL over carbamazepine by the recruiting clinician. Exclusion criteria were age ≤ 4 years, acute symptomatic seizures (including febrile seizures), history of progressive neurologic disease, and contraindications to treatment.
Intervention: VAL (n = 238), LTG (n = 239), or TPM (n = 239).
Outcomes: Treatment failure (i.e., stopping drug because of inadequate seizure control, intolerable side effects, or both or addition of other antiepileptic drugs) and 1-year remission. Secondary outcomes included 2-year remission and time to first seizure.
Patient follow-up: 97% (intention-to-treat analysis).

MAIN RESULTS

For treatment failure, VAL was more effective than TPM (Table) but did not differ from LTG. For 1- and 2-year remission, VAL was more effective than LTG (Table) but did not differ from TPM; LTG and TPM did not differ. The VAL group had fewer first seizures than did the LTG group (Table) but did not differ from the TPM group; the LTG and TPM groups did not differ.

CONCLUSION

Valproate was more effective than lamotrigine and was better tolerated than topiramate in generalized or unclassified epilepsy.

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*See Glossary.

Valproate (VAL) vs lamotrigine (LTG) and topiramate (TPM) in generalized or unclassified epilepsy†

Outcomes at ≤ 6 y	Comparisons	Event rates	RRR (95% CI)	NNT (CI)
Treatment failure	VAL vs TPM	36% vs 49%	27% (10 to 41)	8 (5 to 22)
First seizure	VAL vs LTG	66% vs 78%	16% (6.3 to 26)	8 (5 to 22)
			RBI (CI)	
1-y remission	VAL vs LTG‡	78% vs 73%	13% (2.7 to 22)	11 (6 to 48)
2-y remission	VAL vs LTG	53% vs 44%	21% (0.4 to 46)	11 (6 to 567)

†Abbreviations defined in Glossary. RRR, RBI, NNT, and CI calculated from data in article.
‡RBI, NNT, and CI calculated from hazard ratio and control event rate in article.

COMMENTARY *(continued from page 74)*

The findings suggest that patients can reasonably start treatment with either CBZ or LTG, but treatment with GPT or TPM is less likely to be successful at the doses compared. The lack of diplopia may indicate that the final dose of CBZ could have been higher, but the design and execution of the trial is otherwise admirable. The differences between CBZ and LTG were not important, suggesting that other factors, such as costs of the drugs and ancillary testing, may be reasons to choose 1 drug first. The study also underscores the likelihood that patients may have to switch drugs 1 or more times, a point that physicians should stress at each visit.

Although VAL is not a useful first-choice drug for partial epilepsy, its inclusion in the study would have provided useful data for making therapeutic decisions.

The cost–benefit analysis presented is dependent on the way that drugs are purchased and may not be applicable in countries other than the United Kingdom.

In the study of treatment of generalized epilepsy, the newer drugs (LTG and TPM) were not better at controlling seizures than the older, established VAL. However, individual patients will require different approaches to treatment, especially when pregnancy is involved and LTG is the better choice (1).

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Reference

1. **Cunnington M and Tennis P.** Lamotrigine and the risk of malformations in pregnancy. Neurology. 2005;64:955-60.