Lamotrigine was more effective than carbamazepine, gabapentin, and topiramate for treatment failure in partial epilepsy

Marson AG, Al-Kharusi AM, Alwaidh M, et al. **The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial.** Lancet. 2007;369:1000-15.

Clinical impact ratings: Neurology ★★★★★★★

QUESTION

In patients diagnosed with partial-onset seizures, how do carbamazepine (CBZ), gabapentin (GPT), lamotrigine (LTG), oxcarbazepine (OXC), and topiramate (TPM) compare?

METHODS

Design: Randomized controlled trial (Standard and New Antiepileptic Drugs [SANAD] trial, Arm A)
Allocation: Concealed.*
Blinding: Unblinded.*
Follow-up period: Up to 6 years.
Setting: Hospital-based outpatient clinics in the United Kingdom.
Patients: 1721 patients (mean age 38 y, 55% men) who had ≥ 2 clinically definite, unprovoked epileptic seizures in the past year and were recommended to take CBZ over valproate 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: CBZ (n = 378), GPT (n = 377), LTG (n = 378), OXC (n = 210), or TPM (n = 378).
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: 96% (intention-to-treat analysis).

MAIN RESULTS

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

CONCLUSION

Lamotrigine was more effective than carbamazepine, gabapentin, and topiramate for treatment failure in partial-onset seizures.

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*See Glossary.

Comparisons of carbamazepine (CBZ), gabapentin (GPT), lamotrigine (LTG), oxcarbazepine (OXC), and topiramate (TPM) in partial epilepsy†

Outcomes at ≤ 6 y	Comparisons	Event rates	RRR (95% CI)	NNT (CI)
Treatment failure	LTG vs CBZ	41% vs 47%	17% (2.2 to 30)	13 (8 to 99)
	LTG vs GPT	41% vs 56%	26% (14 to 38)	7 (5 to 13)
	LTG vs TPM	41% vs 54%	28% (15 to 39)	7 (5 to 13)
	OXC vs GPT	44% vs 56%	18% (1.3 to 33)	11 (6 to 138)
First seizure	CBZ vs GPT	72% vs 80%	11% (5 to 15)	12 (9 to 25)
	CBZ vs LTG	72% vs 79%	7.9% (1.6 to 13)	16 (10 to 80)
			RBI (CI)	
1-y remission	CBZ vs GPT‡	70% vs 60%	17% (5.2 to 31)	10 (6 to 31)
	LTG vs GPT	67% vs 60%	12% (0.6 to 23)	15 (8 to 275)
	OXC vs GPT	64% vs 60%	19% (3.6 to 34)	9 (5 to 47)
2-y remission	CBZ vs GPT‡	46% vs 37%	21% (5.7 to 34)	11 (6 to 41)
	CBZ vs TPM‡	46% vs 39%	16% (0.2 to 29)	14 (7 to 1433)

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

COMMENTARY

After deciding to begin treatment for patients with epilepsy, physicians have a wide array of drugs from which to choose. Because some drugs are better at preventing specific types of seizures and some types of seizures may be exacerbated by specific drugs, physicians must first attempt to determine whether the seizures are of partial (focal) or generalized onset. The results of the SANAD trial by Marson and colleagues may then be used as a guide for the choice of medications.

Although the unblinded nature of the studies might have introduced some bias, the practical aspects of masking treatment allocation (e.g., developing identical dosage forms for different medications and the different titration schedules for each drug) in such large trials would have been complicated and expensive, if not impossible.

Because the study of partial epilepsy showed that the 5-year probability of remaining on the best drug (LTG) was < 60%, it can be inferred that none of the drug choices are particularly good. The study design considered treatment failure to be either lack of adequate control or intolerable side effects, which reflects the real-world use of anticonvulsants. This is often difficult to measure in studies because patients may consider some adverse effects (e.g., weight gain) to be tolerable if seizure control is complete but intolerable if seizures lead to lifestyle restrictions.

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