BIBLIOGRAPHIC REFERENCE TABLE FOR SODIUM VALPROATE IN CHILDHOOD EPILEPSY

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Marson AG et al. Carbamazepine versus valproate monotherapy for epilepsy (Review). The Cochrane Collaboration 2000	Systematic review of randomized controlled monotherapy studies; studies may be double, single or unblinded	1256	Children and adults	To compare the efficacy and tolerability of carbamazepine and valproate when used as monotherapy in people with partial onset seizures (simple partial, complex partial or secondarily generalizing tonic-clonic seizures) or generalized onset tonic-clonic seizures	Carbamazepine with valproate	12 months	Time to withdrawal of allocated treatment (due to lack of efficacy or intolerable adverse effects); time to 12 month remission; time to first seizure	Data were analysed using a stratified logrank analysis with results expressed as hazard ratios (HR) and 95% confidence intervals (CIs) where a HR >1 indicates an event is more likely on valproate. The main overall results (HR) were: time to treatment withdrawal 0.97 (95% CI 0.79-1.18); 12 month remission 0.87 (95% CI 0.74-1.02); first seizure 1.09 (95% CI 0.96-1.25)	External sources of support - Wellcome Trust UK; Medical Resarch Council UK	Results suggest no overall difference for the outcome measures described. The test for an interaction between seizure type was non-significant for time to treatment withdrawal and 12-month remission, but significant for time to first seizure.
De Silva M et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine or sodium valproate for newly diagnosed childhood epilepsy. Lancet, 1996; 347: 709-713	Randomised, prospective long-term clinical trial	167	Children aged 3-16 years	To compare the efficacy and toxicity of phenobarbitone, phenytoin, carbamazpeine and sodium valproate as monotherapy in children with newly diagnosed epilepsy	To compare the efficacy and toxicity of phenobarbitone, phenytoin, carbamazpeine and sodium valproate as monotherapy	44 months (range 3-88)	Time to first seizure; time to achieve a 1-year remission from all seizures	Significant difference between the groups in the proportion of children withdrawn from the randomized drugs because of unacceptable side-effects (X^2 = 35.1, P=0.001). Patients in phenobarbitone group were more likely to have the drug withdrawn than those in the other groups (X^2 = 33.9, p<0.001; odds ratio 24.7 95% CI 4.9-133). No significant difference in the proportion of	Ciba-Geigy, Parke-Davis and Sanofi	Overall outcome with all 4 drugs was good. Phenobarbitone showed an unacceptable incidence of side-effects that necessitated withdrawal of this treatment. all

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								patients withdrawn between the other 3 groups. Overall analysis for the 167 children showed that by 3 years of follow-up, 20% (95% CI 13-26) had remained seizure free and 73% had achieved a 1 year remission.		
Verity CM et al. A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. Dev Med Child Neurol 195; 37(2): 97-108	Randomised multicentre comparative trial	260	Children aged 5-16 years	To assess the long-term efficacy and side-effect profiles of sodium valproate and carbamazepine in children with primary generalized epilepsy (with or without secondary generalization)	Carbamazepine versus sodium valproate monotherapy	3 years	Efficacy (remission analyses at 6, 12 and 24 months) and tolerability of treatments	Remission analyses produced no statistically significant treatment difference between treatments at 6 months (RR 0.98; p=0.91; 95% CI 73 to 1.32); a marginal but non-significant advantage for sodium valproate in 12 month remission (RR 1.05; p=0.75; 95% CI 0.76 to 1.46) and a larger but still statistically insignificant advantage for sodium valproate in 24 month remission (RR 1.44; p=0.10; 95% CI 0.93-2.21) Both drugs achieved a high degree of seizure control with 75% of patients having at least 12 months and 45-55% at least 2 years of freedom from seizures.	Sanofi Winthrop	Little difference in overall efficacy between the drugs. Analysis of treatment failures showed there was little difference in failure rates between the drugs
Thilothammanl N et al. Comparison of	Randomised double blind trial	151	Children aged 4-12 years	Double-blind randomised, placebo	Comparison of phenobarbitone, phenytoin and	22-36 months (mean 29	Seizure recurrence and	127 children were followed up completely. During the study period,	Internation al Clinical Epidemiol	All 3 drugs were equally effective in controlling

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phenobarbitone, phenytoin with sodium valproate: randomised double-blind study. Indian Pediatr 1996; 33(7): 549-555				controlled study in patients with generalised toni-clonic seizures	sodium valproate	months)	assessment of side-effects	16 (95%CI 19-45) in phenobarbitone group, 14 (95% CI 16-41) and 10 (95% CI 10-34) in the sodium valproate group developed at least one attack of convulsion. Of these, 32/40 were because their serum AED levels were low or they were irregular in taking the drug. More than one side-effects was observed in 32% children on phenobarbitone, 40% on phenytoin and 19% on sodium valproate and this difference was statistically significant ($p<0.05$)	ogy Network; Boots Pharmaceuticals; Reckitt and Colman; Rhone-Poulenc	seizures. Side-effects were minimal with sodium valproate followed by phenobarbitone. Though side-effects were more frequent with phenytoin, most of them disappeared on adjusting drug dosage.
Callaghan N et al. A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. J Neurol Neurosurg Psychiatry 1985; 48: 639-644	Prospective, randomised study	180	Adults and children	Randomised trial of carbamazepine, phenytoin and sodium valproate in previously untreated and recently diagnosed patients with epilepsy	Carbamazepine, phenytoin and sodium valproate monotherapy	Upto 48 months (median 14-24 months)	Response to treatment	Generalised tonic clinic seizures (without focal features) – all 3 drugs improved seizure control. Poor response was similar for all 3 drugs. Ratio for excellent to good control varied – this difference is statistically significant when phenytoin is compared with carbamazepine for excellent control ($p<0.01$) Partial seizures with or without secondary generalised attacks – all 3 drugs less effective for partial seizures. No	Labaz Geigy, Warner-Lambert	All 3 drugs were highly effective in the control of generalised seizures but less effective for partial seizures. Excellent or good control was achieved with therapeutic levels of sodium valproate and carbamazepine but with subtherapeutic levels of phenytoin

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								significant difference between them		
Tudur Smith C et al. Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures (Review) The Cochrane Collaboration 2001	Systematic review of randomised, controlled trials in adults and children with partial epeilspy	669	Children and adults	To review the best evidence comparing phenytoin and valproate when used as monotherapy in people with partial onset seizures or generalised onset tonic-clonic seizures with or without other generalised seizure types	Comparison of phenytoin monotherapy with valproate monotherapy	12 months	Time to withdrawal of treatment; time to 12 month remission; time to 6 month remission; time to first seizure post randomisation	Data were analysed using stratified logrank analysis with results expressed as HR and 95% CI; HR>1 indicates an event is more likely on phenytoin. Results only apply to generalised tonic-clonic seizures. Time to withdrawal of allocated treatment 1.10 (95% CI 0.79 to 1.54); time to 12 month remission 1.04 (95% CI 0.78 to 1.38); time to 6 month remission 0.89 (95% CI 0.71 to 1.11); time to first seizure 0.92 (95% CI 0.74 to 1.14)	External sources of support – Medical Research Council UK; NHS R+D UK	No overall difference between the two drugs
Steinhoff BJ et al. The LAM-SAFE Study: Lamotrigine versus carbamazepine or valproic acid in newly diagnosed focal and generalised epilepsies in adolescents and adults. Seizure 2005; 14(8): 597-605	Open label randomised comparative multicentre trial	239	Adults and adolescents of 12 years and over	Patients with newly diagnosed focal epilepsy and idiopathic generalised epilepsies	Those with generalised epilepsies (n=63) were randomised to receive either lamotrigine or valproic acid	24 weeks	Primary outcome measure was the number of seizure-free patients during study weeks 17 and 24	In the generalised epilepsy group, 83.3% of the valproate patients (25/30) became seizure free compared to 60.6% of lamotrigine patients (20/33). During study weeks 17 and 24 (not statistically significant)	Glaxo Smith Kline	No particular difference between the 3 tested antiepileptic drugs and suggest that the 3 agents are equal in their effectiveness
Coppola G et al. Lamotrigine versus valproic acid as first-line	Randomised, open-label parallel group design	38	Children aged 3 to 13 years	Patients with newly diagnosed typical absence seizures	Lamotrigine with valproic acid	Up to 12 months	Primary outcome measure – seizure	After 1 month of treatment, 10 (52.6%) patients taking VA and 1 (5.3%) patients taking	None	Both valproic acid and lamotrigine can be efficacious in

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monotherapy in newly diagnosed typical absence seizures: an open-label, randomised, parallel group study. Epilepsia, 2004; 45(9): 1049-1053				randomised to receive lamotrigine or valproic acid			freedom	LTG were seizure free (p=0.004). At 3 months, seizure freedom was seen in 12 (63.1%) patients taking VA and in 7 (36.8%) patients on LTG (difference failing to reach statistical significance p=0.19). At 12 months 68.4% VA and 52.6% LTG were seizure free (p=0.51)		absence seizures although valproic acid shows a much faster onset of action
Posner EB et al. Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents (Review) The Cochrane Collaboration 2005	Systematic review of randomised parallel group monotherapy or add-on trials in children and adolescents								No sources of support supplied	5 small trials found of which 4 were of poor methodological quality. Insufficient number of patients. No results
Wheless JW et al. Topiramate, carbamazepine and valproate monotherapy: double-blind comparison on newly diagnosed epilepsy. J Child Neurol 2004; 19(2): 135-141	Randomised, double-blind multicentre trial	613 (of whom 119 were children or adolescents)	Adults and children (6-16 years)	To compare the efficacy of topiramate monotherapy with carbamazepine and valproate as first line therapy in patients with newly diagnosed epilepsy	Topiramate with carbamazepine and valproate	Variable since treatment was continued until the patients exited or until 6 months after the last patient was enrolled	Efficacy and tolerability/safety	For the paediatric subsection – efficacy analyses showed no statistically significant differences between topiramate and carbamazepine or valproate. Fewer patients in the carbamazepine and topiramate groups discontinued treatment due to adverse effects compared to valproate	Johnson and Johnson Pharmaceutical Research and Development	For the paediatric subsection – efficacy analyses showed no statistically significant differences between topiramate and carbamazepine or valproate.