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Newer drugs for epilepsy in adults: how good are the trials from a systematic review?

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Introduction

- Seven newer anti-epileptic drugs (AEDs) were selected for appraisal in accordance with their licensed indications (Table 1)[1] by the UK National Institute for Clinical Excellence (NICE).

Table 1 Newer AEDs and their licensed indications

Newer AED	Licensed indication			
	Epilepsy type		Seizure type	
	Refractory	Newly diagnosed	Partial onset	Generalised onset
Licensed for adjunctive therapy only				
Gabapentin	✔	✘	✔	✘
Levetiracetam	✔	✘	✔	✘
Tiagabine	✔	✘	✔	✘
Topiramate	✔	✘	✔	✔
Vigabatrin	✔	✘	✔	✘
Licensed for monotherapy and Adjunctive therapy				
Lamotrigine	✔	✔	✔	✔
Oxcarbazepine	✔	✔	✔	✘

- International League Against Epilepsy (ILAE) guidelines[2] recommend:
  - Trials should recruit at least 100 to 150 participants with clinically relevant characteristics
  - Trials should be six to 12 months long
  - Time to exit/withdrawal due to inadequate drug efficacy and/or poor tolerability is the most useful measure to inform clinical practice for monotherapy trials
  - Time to achieve six months, one year or two years remission has greater clinical significance (unless the population has infrequent seizures) than time to first seizure

Methods

- A systematic search of 20 electronic databases (inception to September 2002) and additional sources was undertaken.
- RCTs of newer AEDs (compared to placebo, older AEDs, or other newer AEDs) for adults with epilepsy were included.
- Two reviewers independently assessed articles for inclusion.
- Data extraction and quality assessment of included trials was conducted by one reviewer and checked by another. Disagreements were resolved through discussion.

Results

Characteristics of the included trials

- 21 monotherapy and 66 adjunctive therapy trials were included (Table 2).

Quality of the included trials

Reporting of information

- Around two thirds of trials failed to report on methods of randomisation and allocation concealment. 59% and 70%, respectively, did not report if those administering the intervention or outcome assessors were blinded.
- Almost a third of trials did not present baseline characteristics of treatment groups, and of those that did, many did not present all the relevant information.
- Less than half of the trials reported a sample size calculation sufficient to demonstrate a defined treatment effect.
- Only around a quarter of trials reported use of a valid intention-to-treat analysis.

ILAE recommendations

- Many trials failed to meet ILAE guidelines concerning:
  - Sample size: around 40% of trials included 150 participants or more
  - Clinically relevant patient groups: trials of AEDs licensed only for treatment of partial onset seizures often recruited mixed populations of partial onset and generalised onset seizure types. The proportion with each seizure type was rarely reported, and results were not reported separately according to seizure type
  - Length of follow-up: less than 10% of trials reported follow-up of at least 12 months
  - Outcome measures: less than half of the monotherapy trials provided data for time to exit/withdrawal due to inadequate drug efficacy and/or poor tolerability. None reported time to six months, one year, or two years remission.

Conclusions

- Much of the available literature is of poor quality and has limited applicability when it comes to informing clinical practice about the optimal use of newer AEDs. Many trials failed to meet ILAE recommendations.
- The true methodological quality of trials was difficult to assess due to poor reporting.
- Good quality well-reported RCTs adopting ILAE recommendations are needed.

Table 2 Summary details for each newer AED by type of therapy and type of comparator

Comparison	*No. of trials	No. of patients	Mean (SD) no. of patients	Median (range) no. of patients	Mean (SD) length of follow-up (weeks)	Median (range) length of follow-up (weeks)	No. of trials reporting each outcome measure					
							% seizure free	% responders	Time to first seizure	Time to exit	Cognitive function	Quality of life
Monotherapy	**21**	**5797**	**276.0 (220.2)**	**249 (37-877)**	**31.5 (14.5)**	**30 (1.4-50)**	**18**	**5**	**7**	**10**	**2**	**9**
v placebo	*2*	*169*	*84.5 (24.7)*	*84.5 (67-102)*	*7.1 (8.1)*	*7.1 (1.4-12.9)*	*2*	*0*	*1*	*1*	*0*	*0*
Oxcarbazepine	2	169	84.5 (24.7)	84.5 (67-102)	7.1 (8.1)	7.1 (1.4-12.9)	2	0	1	1	0	0
v old	*18*	*5319*	*295.5 (228.5)*	*254.5 (37-877)*	*34.3 (12.9)*	*32 (12-50)*	*15*	*5*	*5*	*8*	*2*	*9*
Lamotrigine	11	3625	329.5 (249.7)	260 (115-877)	28.4 (11.3	26 (12-48)	10	3	4	5	1	6
Oxcarbazepine	6	1073	178.8 (112.0)	221.5 (37-287)	47 (3.5)	48 (40-50)	5	2	0	2	1	3
Topiramate	1	621	-	-	24	-	0	0	1	1	0	0
v new	*1*	*309*	*-*	*-*	*30*	*-*	*1*	*0*	*1*	*1*	*0*	*0*
Gabapentin v LTG	1	309	-	-	30	-	1	0	1	1	0	0
Adjunctive therapy	**66**	**7957**	**120.6 (125.8)**	**64 (10-694)**	**18.3 (11.4)**	**16 (1-72)**	**31**	**56**	**0**	**0**	**15**	**38**
v placebo	*55*	*6526*	*118.7 (125.5)*	*60 (10-694)*	*16.6 (9.3)*	*14 (1-46)*	*25*	*49*	*0*	*0*	*12*	*31*
Gabapentin	5	775	155 (128.6)	127 (27-306)	12.4 (0.9)	12 (12-14)	1	5	0	0	1	3
Levetiracetam	3	737	245.7 (110.7)	294 (119-324)	12.7 (1.2)	12 (12-14)	3	3	0	0	0	1
Lamotrigine	17	1154	67.9 (84.0)	34 (10-334)	20.8 (12.5)	18 (1-46)	4	14	0	0	2	9
Oxcarbazepine	1	694	-	-	28	-	1	1	0	0	0	0
Tiagabine	5	859	171.8 (131.8)	154 (44-318)	12.6 (6.6)	12 (6-22)	2	5	0	0	3	2
Topiramate	12	1517	126.4 (748)	104 (46-263)	16.75 (4.8)	17 (11-28)	10	11	0	0	0	9
Vigabatrin	12	790	65.8 (58.8)	36.5 (23-182)	10.7 (3.9)	11 (4-18)	4	10	0	0	6	7
v old	*7*	*794*	*113.4 (122.9)*	*59 (22-349)*	*22.3 (10.0)*	*24 (12-40)*	*2*	*3*	*0*	*0*	*3*	*4*
Gabapentin	2	47	23.5 (2.1)	23.5 (22-25)	40 (11.3)	40 (12-28)	1	1	0	0	0	1
†Oxcarbazepine	1	48	-	-	40	-	0	0	0	0	0	0
Tiagabine	1	349	-	-	16	-	0	1	0	0	1	1
Topiramate	2	135	67.5 (12.0)	67.5 (59-76)	24 (0)	24 (24-24)	0	0	0	0	1	2
Vigabatrin	1	215	-	-	12	-	1	1	0	0	0	0
v new	*4*	*637*	*159.3 (164.7)*	*92.5 (48-404)*	*35 (24.7)*	*24 (20-72)*	*4*	*4*	*0*	*0*	*0*	*3*
Gabapentin v Lamotrigine	2	356	178 (134.4)	178 (83-273)	48 (33.9)	48 (24-72)	2	2	0	0	0	1
Gabapentin v Vigabatrin	2	384	192 (127.3)	192 (102-282)	48 (33.9)	48 (24-72)	2	2	0	0	0	1
Lamotrigine v Tiagabine	1	48	-	-	20	-	1	1	0	0	0	1
Lamotrigine v Vigabatrin	1	253	-	-	72	-	1	1	0	0	0	0
All trials	**87**	**13754**	**158.1 (166.5)**	**98 (10-877)**	**21.5 (13.4)**	**18 (1-72)**	**49**	**61**	**7**	**10**	**17**	**47**

*One trial (adjunctive therapy, v new) had three comparisons; †One trial reported adverse event data only

References

1. British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary.* 44th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2002.
2. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389-99.