

APPENDIX O

1.1 Individual Patient Data (IPD) network meta-analysis in epilepsy monotherapy trials

During the literature review we identified a network meta-analysis of Individual Patient Data (IPD). The IPD network meta-analysed IPD evidence from randomized controlled trials of eight different AEDs (carbamazepine, sodium valproate, phenytoin, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin and topiramate) in monotherapy⁸⁷ obtained from eight IPD Cochrane reviews and the SANAD randomised controlled trial.

An individual patient data (IPD) approach is an alternative method to conduct meta-analysis in which the full original trial data sets are used and allows a more thorough interpretation of results¹. The IPD analyses were considered as supplementary evidence to the direct evidence for monotherapy for focal seizures and generalised tonic clonic seizures

The IPD meta-analysis for focal seizures in monotherapy included data from 20 randomised controlled trials (6418 participants), 17 for time to treatment failure (1552 generalised and 4265 focal participants), 14 randomised controlled trials for time to 12 month remission (1360 generalised and 3526 partial participants) and 19 for time to first seizure (1765 generalised and 2959 focal participants). The following tables show the results for the various outcomes, comparing each AED with the current standard AED, carbamazepine. The significant results are highlighted in bold.

IPD data for monotherapy for focal seizures

Time to treatment failure

Intervention	Comparator	Hazard ratio (95% CI)
Lamotrigine	Carbamazepine	0.70 (0.58 to 0.83)
Oxcarbazepine	Carbamazepine	0.88 (0.69 to 1.12)
Sodium valproate	Carbamazepine	1.00 (0.82 to 1.24)
Topiramate	Carbamazepine	1.13 (0.93 to 1.37)
Gabapentin	Carbamazepine	1.16 (0.96 to 1.41)
Phenytoin	Carbamazepine	1.24 (0.98 to 1.57)
Phenobarbital	Carbamazepine	1.60 (1.22 to 2.10)

(a) *HR*<1 CBZ worse; *HR* >1 CBZ better

When compared with all the AEDs in the IPD analysis lamotrigine was found to be significantly better compared to other AEDs except from oxcarbazepine for time to treatment failure.

Time to 12 month remission

Intervention	Comparator	Hazard ratio
Carbamazepine	Oxcarbazepine	1.00 (0.82 to 1.22)
Carbamazepine	Phenobarbital	1.01 (0.77 to 1.31)
Carbamazepine	Phenytoin	1.15 (0.94 to 1.41)
Carbamazepine	Lamotrigine	1.15 (0.96 to 1.37)
Carbamazepine	Topiramate	1.19 (0.99 to 1.43)
Carbamazepine	Sodium valproate	1.20 (1.01 to 1.42)
Carbamazepine	Gabapentin	1.38 (1.15 to 1.67)

(a) *HR*<1 CBZ worse; *HR* >1 CBZ better

Carbamazepine was found to be significantly better than sodium valproate and gabapentin for time to 12 month remission.

Time to first seizure

Intervention	Comparator	Hazard ratio
Phenobarbital	Carbamazepine	0.77 (0.61 to 0.96)
Oxcarbazepine	Carbamazepine	0.99 (0.83 to 1.19)
Topiramate	Carbamazepine	1.00 (0.85 to 1.18)
Phenytoin	Carbamazepine	1.04 (0.88 to 1.24)
Sodium valproate	Carbamazepine	1.23 (1.06 to 1.41)
Lamotrigine	Carbamazepine	1.29 (1.13 to 1.48)
Gabapentin	Carbamazepine	1.35 (1.15 to 1.59)

(a) *HR*<1 CBZ worse; *HR* >1 CBZ better

Carbamazepine was found to be significantly better than sodium valproate, lamotrigine and gabapentin for time to first seizure. Phenobarbital was significantly better than carbamazepine.

Table 1: Time to treatment failure

Carbamazepine							
0.70 (0.58 to 0.83)	Lamotrigine						
0.88 (0.69 to 1.12)	1.26 (0.97 to 1.63)	Oxcarbazepine					
1.00 (0.82 to 1.24)	1.44 (1.11 to 1.87)	1.15 (0.84 to 1.56)	Sodium valproate				
1.13 (0.93 to 1.37)	1.62 (1.31 to 1.99)	1.29 (0.99 to 1.67)	1.12 (0.85 to 1.48)	Topiramate			
1.16 (0.96 to 1.41)	1.66 (1.35 to 2.05)	1.32 (1.02 to 1.72)	1.16 (0.88 to 1.52)	1.03 (0.84 to 1.26)	Gabapentin		
1.60 (1.22 to 2.10)	2.29 (1.67 to 3.14)	1.82 (1.29 to 2.57)	1.59 (1.15 to 2.19)	1.42 (1.02 to 1.96)	1.38 (0.99 to 1.91)	Phenobarbitone	
1.24 (0.98 to 1.57)	1.77 (1.34 to 2.35)	1.41 (1.05 to 1.90)	1.23 (0.93 to 1.64)	1.10 (0.82 to 1.47)	1.07 (0.80 to 1.43)	0.78 (0.59 to 1.02)	Phenytoin

Numbers in bold highlight statistically significant results (P<0.05).

Table 2: Time to 12 month remission

Carbamazepine							
1.00 (0.82 to 1.22)	Oxcarbazepine						
1.01 (0.77 to 1.31)	1.01 (0.74 to 1.38)	Phenobarbitone					
1.15 (0.96 to 1.37)	1.15 (0.92 to 1.43)	1.14 (0.84 to 1.55)	Lamotrigine				
1.15 (0.94 to 1.41)	1.15 (0.90 to 1.47)	1.14 (0.87 to 1.50)	1.00 (0.78 to 1.29)	Phenytoin			
1.19 (0.99 to 1.43)	1.19 (0.95 to 1.50)	1.19 (0.87 to 1.62)	1.04 (0.86 to 1.26)	1.04 (0.80 to 1.35)	Topiramate		
1.20 (1.01 to 1.42)	1.20 (0.93 to 1.54)	1.19 (0.89 to 1.59)	1.04 (0.83 to 1.32)	1.04 (0.83 to 1.31)	1.00 (0.79 to 1.28)	Sodium valproate	
1.38 (1.15 to 1.67)	1.38 (1.10 to 1.74)	1.37 (1.00 to 1.88)	1.21 (0.99 to 1.46)	1.20 (0.93 to 1.57)	1.16 (0.95 to 1.41)	1.15 (0.90 to 1.47)	Gabapentin

Numbers in bold highlight statistically significant results (P<0.05).

Table 3: Time to first seizure

Phenobarbital							
1.30 (0.99 to 1.70)	Oxcarbazepine						
1.30 (1.04 to 1.63)	1.01 (0.84 to 1.21)	Carbamazepine					
1.31 (1.00 to 1.71)	1.01 (0.82 to 1.24)	1.00 (0.85 to 1.18)	Topiramate				
1.36 (1.08 to 1.71)	1.05 (0.86 to 1.29)	1.04 (0.88 to 1.24)	1.04 (0.84 to 1.30)	Phenytoin			
1.60 (1.25 to 2.05)	1.23 (0.99 to 1.53)	1.23 (1.06 to 1.41)	1.22 (1.00 to 1.50)	1.18 (0.97 to 1.42)	Sodium valproate		
1.68 (1.30 to 2.17)	1.30 (1.07 to 1.57)	1.29 (1.13 to 1.48)	1.29 (1.09 to 1.52)	1.24 (1.01 to 1.51)	1.05 (0.88 to 1.26)	Lamotrigine	
1.77 (1.35 to 2.31)	1.36 (1.11 to 1.67)	1.35 (1.15 to 1.59)	1.35 (1.14 to 1.61)	1.30 (1.04 to 1.61)	1.10 (0.90 to 1.36)	1.05 (0.89 to 1.23)	Gabapentin

Numbers in bold highlight statistically significant results (P<0.05).

IPD data for monotherapy for Generalised tonic-clonic seizures

The outcomes included in the IPD analysis for generalised tonic-clonic seizures were time to treatment failure due to inadequate seizure control, intolerable adverse effects or a combination of both; time to 12 month remission from seizures (days from randomisation and end of a period of

12 months without seizures); and time to first seizure after randomisation. It included data from 1552 generalised tonic-clonic participants for time to treatment withdrawal, 1360 generalised tonic-clonic participants for time to 12 month remission and 1765 generalised tonic-clonic participants for time to first seizure. The following tables show the results for the various outcomes, comparing each AED with the current standard AED, sodium valproate. The significant results are highlighted in bold.

Time to treatment failure

Intervention	Comparator	Hazard ratio
Phenytoin	Sodium valproate	1.03 (0.71 to 1.51)
Lamotrigine	Sodium valproate	1.30 (0.97 to 1.75)
Oxcarbazepine	Sodium valproate	1.50 (0.84 to 2.68)
Gabapentin	Sodium valproate	1.59 (0.22 to 11.50)
Carbamazepine	Sodium valproate	1.45 (1.07 to 1.96)
Topiramate	Sodium valproate	1.74 (1.28 to 2.36)
Phenobarbital	Sodium valproate	1.83 (1.07 to 3.13)

(a) $HR < 1$ VPA worse; $HR > 1$ VPA better

Sodium valproate was found to be significantly better than carbamazepine, topiramate and phenobarbital for time to treatment failure.

Time to 12 month remission

Intervention	Comparator	Hazard ratio
Gabapentin	Sodium valproate	0.26 (0.04 to 1.86)
Phenytoin	Sodium valproate	0.92 (0.72 to 1.18)
Carbamazepine	Sodium valproate	1.00 (0.81 to 1.22)
Topiramate	Sodium valproate	1.09 (0.86 to 1.37)
Oxcarbazepine	Sodium valproate	1.10 (0.73 to 1.67)
Phenobarbital	Sodium valproate	1.28 (0.89 to 1.84)
Lamotrigine	Sodium valproate	1.41 (1.10 to 1.80)

(a) $HR < 1$ VPA worse; $HR > 1$ VPA better

Sodium valproate was found to be significantly better than lamotrigine for time to 12 month remission.

Time to first seizure

Intervention	Comparator	Hazard ratio
Phenytoin	Sodium valproate	0.97 (0.77 to 1.23)
Gabapentin	Sodium valproate	1.11 (0.16 to 7.90)
Topiramate	Sodium valproate	1.19 (0.94 to 1.51)
Carbamazepine	Sodium valproate	1.21 (0.99 to 1.47)
Phenobarbital	Sodium valproate	1.28 (0.92 to 1.77)
Oxcarbazepine	Sodium valproate	1.32 (0.90 to 1.94)
Lamotrigine	Sodium valproate	1.47 (1.20 to 1.80)

(a) $HR < 1$ VPA worse; $HR > 1$ VPA better

Sodium valproate was found to be significantly better than lamotrigine for time to first seizure.

Table 1: Time to treatment failure

Sodium valproate							
1.03 (0.71 to 1.51)	Phenytoin						
1.30 (0.97 to 1.75)	1.26 (0.82 to 1.94)	Lamotrigine					
1.45 (1.07 to 1.96)	1.40 (0.93 to 2.11)	1.11 (0.79 to 1.57)	Carbamazepine				
1.50 (0.84 to 2.68)	1.45 (0.79 to 2.67)	1.15 (0.63 to 2.10)	1.04 (0.58 to 1.86)	Oxcarbazepine			
1.59 (0.22 to 11.50)	1.54 (0.21 to 11.33)	1.22 (0.17 to 8.87)	1.10 (0.15 to 7.95)	1.06 (0.14 to 8.12)	Gabapentin		
1.74 (1.28 to 2.36)	1.68 (1.07 to 2.64)	1.34 (0.98 to 1.82)	1.20 (0.83 to 1.74)	1.16 (0.63 to 2.15)	1.09 (0.15 to 7.99)	Topiramate	
1.83 (1.07 to 3.13)	1.77 (0.99 to 3.17)	1.41 (0.80 to 2.47)	1.26 (0.74 to 2.15)	1.22 (0.59 to 2.52)	1.15 (0.15 to 8.76)	1.05 (0.59 to 1.88)	Phenobarbital

Numbers in bold highlight statistically significant results (P<0.05).

Table 2: Time to 12 month remission

Gabapentin							
3.56 (0.49 to 25.71)	Phenytoin						
3.85 (0.54 to 27.68)	1.08 (0.83 to 1.41)	Carbamazepine					
3.87 (0.54 to 27.75)	1.09 (0.85 to 1.39)	1.00 (0.82 to 1.23)	Sodium valproate				
4.21 (0.58 to 30.47)	1.18 (0.85 to 1.63)	1.09 (0.81 to 1.47)	1.09 (0.86 to 1.37)	Topiramate			
4.27 (0.58 to 31.57)	1.20 (0.79 to 1.82)	1.11 (0.72 to 1.70)	1.10 (0.73 to 1.67)	1.01 (0.64 to 1.61)	Oxcarbazepine		
4.95 (0.67 to 36.34)	1.39 (0.95 to 2.03)	1.29 (0.89 to 1.85)	1.28 (0.89 to 1.84)	1.18 (0.77 to 1.79)	1.16 (0.70 to 1.93)	Phenobarbital	
5.45 (0.75 to 39.51)	1.53 (1.10 to 2.13)	1.41 (1.05 to 1.92)	1.41 (1.10 to 1.80)	1.29 (1.01 to 1.67)	1.28 (0.80 to 2.04)	1.10 (0.72 to 1.68)	Lamotrigine

Numbers in bold highlight statistically significant results (P<0.05).

Table 3: Time to first seizure

Phenytoin							
1.03 (0.81 to 1.30)	Sodium valproate						
1.14 (0.16 to 8.17)	1.11 (0.16 to 7.90)	Gabapentin					
1.23 (0.90 to 1.66)	1.19 (0.94 to 1.51)	1.07 (0.15 to 7.68)	Topiramate				
1.24 (0.96 to 1.59)	1.21 (0.99 to 1.47)	1.08 (0.15 to 7.72)	1.01 (0.77 to 1.33)	Carbamazepine			
1.31 (0.93 to 1.86)	1.28 (0.92 to 1.77)	1.15 (0.16 to 8.33)	1.07 (0.73 to 1.57)	1.06 (0.76 to 1.47)	Phenobarbital		
1.35 (0.91 to 2.02)	1.32 (0.90 to 1.94)	1.19 (0.16 to 8.67)	1.11 (0.72 to 1.69)	1.09 (0.74 to 1.62)	1.03 (0.65 to 1.65)	Oxcarbazepine	
1.51 (1.15 to 1.98)	1.47 (1.20 to 1.80)	1.32 (0.19 to 9.41)	1.23 (0.97 to 1.56)	1.22 (0.97 to 1.53)	1.15 (0.81 to 1.64)	1.11 (0.74 to 1.67)	Lamotrigine

Numbers in bold highlight statistically significant results (P<0.05).

