APPENDIX O

Network meta-analysis of pharmacological interventions in the treatment of epilepsy

1.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in appendix N) make it difficult to determine which intervention is most effective in the treatment of epilepsy. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among all the different AEDs, and in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial (for example, adjunctive phenytoin versus placebo for an adult population with refractory focal seizures).

- There are frequently multiple overlapping comparisons (for example, adjunctive lamotrigine versus placebo, gabapentin versus placebo and gabapentin versus lamotrigine for an adult population with focal seizures), that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different interventions to facilitate simultaneous inference regarding all treatments. In this case, in order of efficacy, defined as:

- the proportion of people achieving seizure freedom in newly diagnosed focal seizures and
- the proportion of people achieving at least 50% reduction in seizure frequency in refractory focal seizures

and tolerability, defined as

- the proportion of people who withdraw due to adverse events.

The analysis also provided estimates of effect (with 95% credible intervals[1]) for each intervention compared to one another and compared to a single baseline risk. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates were used to parameterise treatment effectiveness of first line interventions in the de novo cost-effectiveness modelling presented in appendix P.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that the relative effects of intervention A compared ot intervention B are expected to be transferable across different trials comparing A versus C and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same relative effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term "network" better describes the data structure, whereas "***mixed*** treatments" could easily be misinterpreted as referring to combinations of treatments.

1.2 Limitations of the network meta-analysis

In the monotherapy networks, we included studies presenting with mixed age (adults and children), something that may have biased the estimate of effects. Studies aimed to test efficacy and/or tolerability of AEDs' monotherapies in newly diagnosed focal seizures only in children were not included. However, recent EMA[2] decisions regarding licensing of AEDS for use in children indicate that for 'focal epilepsies especially cryptogenic and symptomatic,

[1] Credible intervals are the Bayesian equivalent of confidence intervals and are based on the percentiles of the posterior distribution of the parameter of interest.

[2] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070043.pdf

and idiopathic generalised epilepsies, with absences, myoclonic and/or generalised convulsive seizures, (…) the efficacy of AEDs seems to be comparable in childhood and adulthood. Focal epilepsies in children older than 4 years old have a similar clinical expression to focal epilepsies in adolescents and adults. *In refractory focal epilepsies, the results of efficacy trials performed in adults could to some extent be extrapolated to children provided the dose is established*.' As a result of this and with the agreement of the GDG, we have included adults' and childrens' studies in the NMA by combining data for adults and children in refractory focal seizures.

Furthermore, the approach of transforming time to event data from SANAD trial to our predefined categorical outcomes (seizure freedom, withdrawal due to adverse events) had limitations (censoring of events, loss of statistical power) which may have also affected the NMA results.

In order to check the consistency of the adjunctive networks in our NMA (3rd and 4th networks), we checked whether there was a change in placebo response due to variation in characterisitics of participants in placebo groups across studies over time. We did not find any significant heterogeneity in participants in placebo groups in terms of age and gender distribution over time. In addition, the magnitude of the placebo effect did not significantly differ over time.

1.3 Methods

1.3.1 Study selection and data collection

To estimate the odds ratios and relative risks, we performed a NMA that simultaneously used all the relevant randomised controlled trial evidence from the clinical evidence review [2]. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

From the outset, we sought to minimise any clinical or methodological heterogeneity by focusing the analysis on specific patient subgroups, identifying similar outcomes

and including only RCTs that followed patients for a minimum and comparable length of time, and which included anti-epileptic drugs (AEDs) whose dosages were within the therapeutic range as indicated by the BNF and SPC. Based on this principle, we chose to perform a NMA for newly diagnosed and refractory focal seizures. The main justification was that the evidence on focal seizures included multiple comparisons and a NMA would allow us to synthesize the evidence in a more comprehensive way. We did not perform an NMA on children for the monotherapy of focal seizures as the direct evidence included three comparisons of AEDs that did not form a joint network (please see details on Appendix N. The evidence on adjunctive treatment for refractory focal seizures was amalgamated for adults and children. As such, four networks of evidence were identified, defined by their type of treatment: either monotherapy or adjunctive treatment, and outcome measure:

- Proportion of people achieving seizure freedom (henceforth referred to as seizure freedom);
- Proportion of people achieving at least 50% reduction in seizure frequency (henceforth referred to as 50% reduction in seizure frequency);
- Proportion of people withdrawing due to adverse events (henceforth referred to as withdrawal due to adverse events).

Network 1: Seizure freedom in monotherapy for newly diagnosed focal seizures

- Evidence for seizure freedom in newly diagnosed focal seizures in an adult population receiving monotherapy

Network 2: Withdrawal due to adverse events in monotherapy for newly diagnosed focal seizures

- Evidence for withdrawal due to adverse events in newly diagnosed focal seizures in an adult population receiving monotherapy

Network 3: 50% reduction in seizure frequency in adjunctive therapy for refractory focal seizures

- Evidence for 50% reduction in seizure frequency in refractory focal seizures in an adult population receiving adjunctive treatment.

Network 4: Withdrawal due to adverse events in adjunctive therapy for refractory focal seizures

- Evidence for withdrawal due to adverse events in refractory focal seizures in an adult population receiving adjunctive treatment.

1.3.2 Outcome measures

The NMA evidence reviews for interventions considered two clinical efficacy outcomes identified from the review of clinical evidence; seizure freedom and 50% reduction in seizure frequency and a tolerability outcome, defined by withdrawal due to adverse events.

For the primary outcome measures of studies reviewing efficacy of medication in the treatment of epilepsy, the GDG chose seizure freedom as the most important outcome measure, and thereafter, for adjunctive therapy, those with more than 50% reduction of seizures from baseline. The aim of all antiepileptic treatment is for the individual to achieve seizure freedom with minimal if any side effects; when initial drugs have failed and adjunctive treatment is used, seizure reduction is likely to be the aim. Seizure freedom was defined as participant's seizure free on an ITT analysis over defined period during maintenance. More than 50% reduction in seizure frequency was defined as those experiencing a >50% reduction in seizures over a defined end of maintenance period compared to baseline, on an intention to treat analysis. The GDG recognised that many of the studies were performed over a relatively short period of time, and that the majority used these measures as the primary outcome variables. The most ideal measure of effect would appear to be time to exit from study, whether due to lack of efficacy or adverse events as a measure of retention on the medication. Limited studies appear to have reported this data; where available this was reported. However, for the NMA seizure freedom

and >50% reduction in seizures were used in order to maximise the availability of data available.

Although withdrawal due to lack of efficacy was included as an outcome in the direct evidence, it was not included in the list of outcome measures for the NMA purposes as it was less reported across the studies compared to the other efficacy outcomes (seizure freedom, at least 50% reduction in seizure frequency). More specifically, withdrawal due to lack of efficacy was reported in four AED comparisons whereas seizure freedom was reported in 17 monotherapy trials for newly diagnosed populations. Similarly, in adjunctive treatment of refractory focal seizures, withdrawal due to lack of efficacy was reported in 14 AEDs comparisons and more than 50% reduction of seizure frequency was reported in 20 comparisons. Nevertheless, results on withdrawal due to lack of efficacy from direct evidence still informed GDG decision making during the development of recommendations.

1.3.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials included in the clinical evidence review already presented in chapter 10 of the full guideline and in appendix N. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The AEDs included in the first two networks on monotherapy for newly diagnosed focal seizures were:

- carbamazepine (CBZ)
- lamotrigine (LTG)
- oxcarbazepine (OXC)
- gabapentin (GBP)
- topiramate (TPM)
- vigabatrin (VGB)
- sodium valproate (VPA)

- phenytoin (PHT)

The following AEDs were included only in the second network (withdrawal due to adverse events) on monotherapy for newly diagnosed focal seizures:

- clonazepam (CLN)
- primidone (PRM)
- phenobarbitone (PHB)

The pharmacological interventions included in both the third and fourth networks on adjunctive treatment for refractory focal seizures were:

- lamotrigine (LTG)
- vigabatrin (VGB)
- gabapentin (GBP)
- levetiracetam (LEV)
- topiramate (TPM)
- oxcarbazepine (OXC)
- pregabalin (PGB)
- lacosamide (LCS)
- eslicarbazepine acetate (ESL)
- zonisamide (ZNM)
- sodium valproate (VPA)
- levetiracetam extended release (LEV-XR)
- lamotrigine extended release (LTG-XR)
- tiagabine (TGB)
- primidone (PRM)
- carbamazepine (CBZ) and phenytoin (PHT) only in the third network (50% reduction in seizure frequency in adjunctive therapy for a refractory adult population)
- and clobazam (CLB) and felbamate (FBM) only in the fourth network (withdrawal due to adverse events in adjunctive therapy for a refractory adult population)

The details of these interventions can be found in the clinical evidence review in chapter 10 of the full guideline and appendix N.

1.3.4 Baseline risk

The baseline risk is defined here as the adult or young person's risk of achieving the outcome of interest (seizure freedom, 50% reduction in seizure frequency, withdrawal due to adverse events) in the "control" group. This figure is useful because it allows us to convert the results of the NMA from odds ratios to relative risks.

Deriving the figures from our randomised controlled trials involved two different routes:

- Monotherapy for newly diagnosed focal seizures: by aggregating the number of people achieving seizure freedom or withdrawing due to adverse events across the carbamazepine arms of the studies included in the monotherapy networks and dividing by the aggregate sample size from the same arms. Thus, carbamazepine was assigned the position of baseline drug (control group), as carbamazepine is the standard AED for monotherapy in newly diagnosed focal seizures.

- Adjunctive treatment in refractory focal seizures: by aggregating the number of people achieving at least 50% reduction in seizure frequency and withdrawing due to adverse events across the placebo arms included in the adjunctive treatment networks and dividing by the aggregate sample size from the same arms.

This method produced a baseline probability of 46.6% for seizure freedom and 23.2% for withdrawal due to adverse events for monotherapy in newly diagnosed population and 15.8% for 50% reduction in seizure frequency and 4% for withdrawal due to adverse events for adjunctive therapy in refractory population.

1.3.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS [3]. We adapted a multi-arm random effects model template for the monotherapy networks and a three-arm random effects model template for the adjunctive treatment networks, both from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between arms in trials with any number of trial arms.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each population and outcome subgroup, a diagram of the evidence network was produced in figures 1a-1b and presented in section 1.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of 0 and standard deviation of 10,000.

For all analyses, a series of 100,000 burn-in simulations were run to allow convergence and then a further 20,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Appendix N). In preparation for the NMA, these conventional meta-analyses were re-run to produce odds ratios and these are presented as part of the NMA results section.

The outputs of the NMA were odds ratios. Odds ratios and their 95% credible intervals were generated for every possible pair of comparisons by combining direct and indirect evidence in the network. To be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation, relative risks were computed from the outputs of the NMA. Relative risks were derived from the odds ratios for each intervention compared back to a "control" group, using the baseline risk as described above and the following formula:

$$RR = \frac{OR}{(1 - P_0) + (P_0 \times OR)}$$

where P_o is the baseline risk.

We estimated the RR for each of the 20,000 simulations, treating P_o as a constant. The point estimate of the RR was taken to be the median of the 20,000 simulations and the 95% confidence intervals for the RR were taken to be the 2.5th and 97.5th centiles from the distribution of the RR.

We also assessed the probability that each intervention was the best treatment by calculating the relative risk of each intervention compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk. Using this same method, we also calculated the overall ranking of interventions according to their relative risk compared to control group.

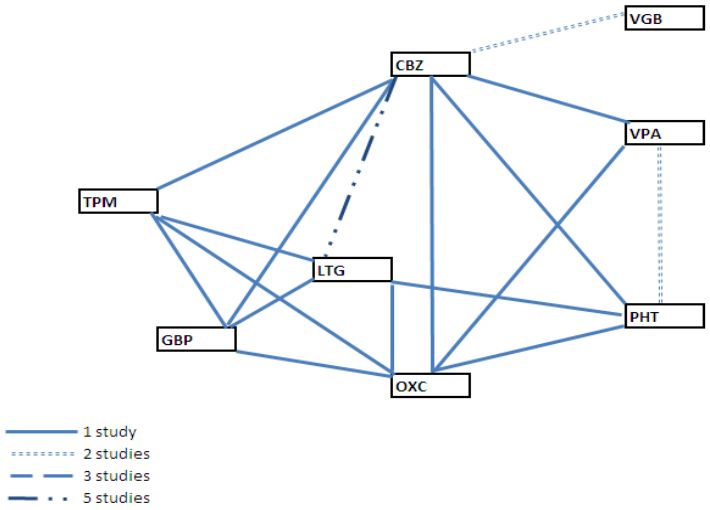
A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is *chance* and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

- Different populations (e.g. gender, age)
- Different interventions (doses)
- Different follow-up periods (1 year, 2 years)

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the odds ratios from the direct evidence (from pair-wise meta-analysis) to the odds ratios from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the odds ratio from the NMA did not fit within the confidence interval of the odds ratio from the direct comparison. Where inconsistency between observed treatment effects was identified, we sought to find the heterogeneity by examining the details of the study design, population, interventions and outcomes of the relevant trials.

1.4 Results

A total of 101 studies from the original evidence review met the inclusion criteria for at least one network. Figures 1a-1d show the 4 networks created by eligible comparisons for each NMA.



Figures 1a: Network 1: Monotherapy in newly diagnosed focal seizures- seizure freedom

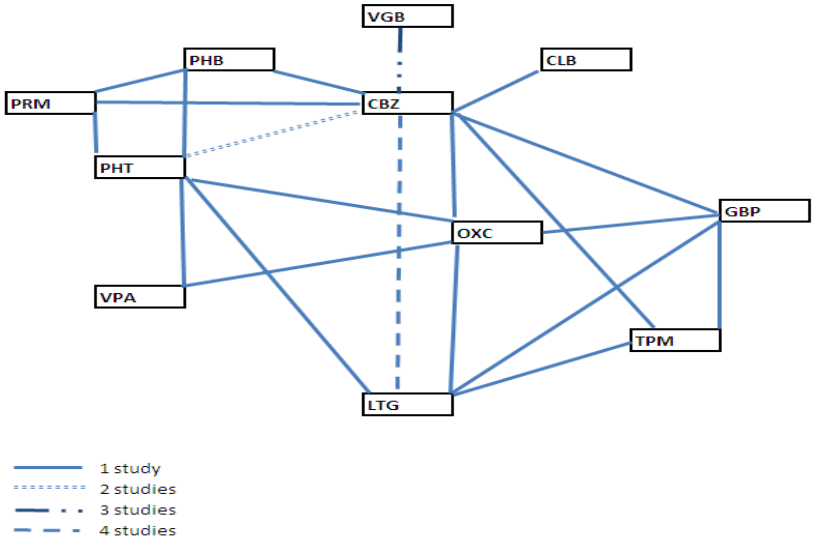


Figure 1b: Network 2: Monotherapy in newly diagnosed focal seizures- withdrawal due to adverse events.

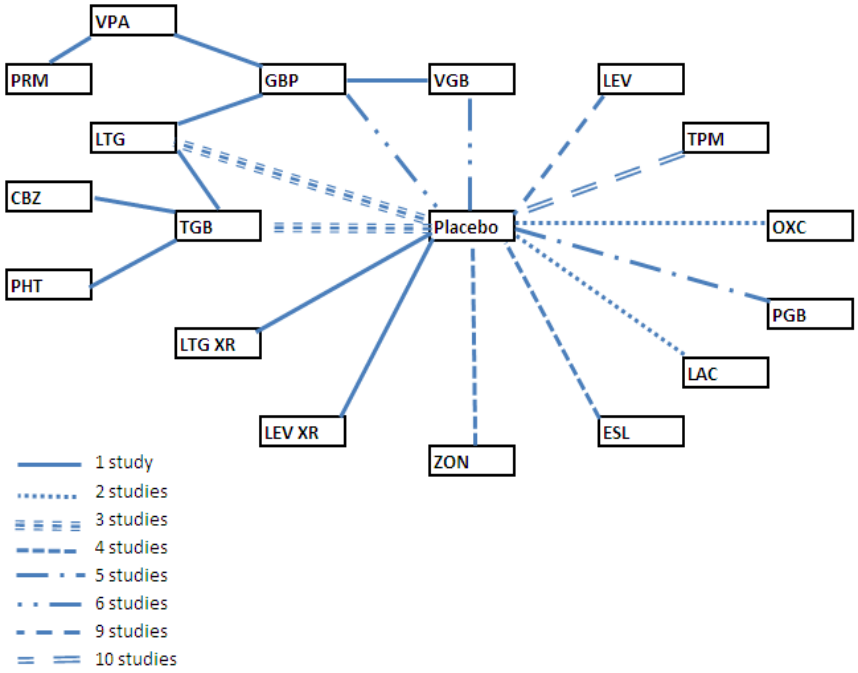


Figure 1c: Network 3: Adjunctive therapy in refractory focal seizures- 50% reduction in seizures.

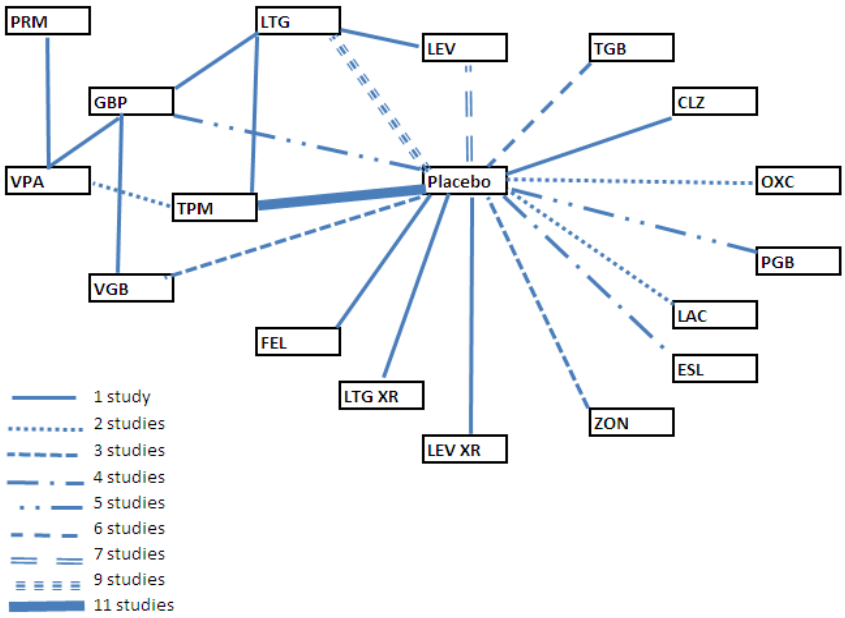


Figure 1d: Network 4: Adjunctive therapy in refractory focal seizures- Withdrawal due to adverse events.

The trial data from the 12 studies in people with newly diagnosed focal seizures who achieved seizure freedom on monotherapy are shown in Table 1. The trial data from the 15 studies of people with newly diagnosed focal seizures who withdrew (monotherapy) due to adverse events are presented in Table 2. The trial data from the 63 studies of people with refractory focal seizures who achieved 50% reduction in seizure frequency are presented in Table 3. Data from 67 studies relating to the proportion of patients with refractory focal seizures who withdrew (adjunctive) due to adverse events is included in Table 4.

Table 1: Trial data for seizure freedom (monotherapy for newly diagnosed focal seizures)

			Active treatment		Comparator	
Active Treatment	**Comparator**	**Study**	**N**	**NR**	**N**	**NR**
LTG	CBZ	Marson 2007 [4]	356	103	347	125
OXC	CBZ		189	66		
GBP	CBZ		337	81		
TPM	CBZ		338	112		
GBP	LTG		337	81	356	103
GBP	TPM		337	81	338	112
LTG	TPM		356	103	338	112
GBP	OXC		337	81	189	66
LTG	OXC		356	103	189	66
TPM	OXC		338	112	189	66
LTG	CBZ	Brodie 1995 [5]	73	16	73	23
		Nieto- Barrera 2001{Nieto-Barrera, 2001 4723 /id}	417	39	201	31
		Steinhof 2005{Steinhoff, 2005 4668 /id}	88	78	88	83
VGB	CBZ	Tanganelli 1996 [6]	26	12	25	14
		Kalviainen 1995{Kalviainen, 1995 4702 /id}	50	16	50	26
VPA	CBZ	Callaghan 1985 [7]	27	12	31	11
PHT	CBZ		21	12	31	11
PHT	VPA		21	12	27	12
LTG	PHT	Steiner 1999 [8]	44	9	46	11
OXC	VPA	Christe 1997 [9]	76	29	78	33
OXC	PHT	Bill 1997 [10]	84	39	98	55
VPA	PHT	Turnbull 1985 [11]	33	9	31	9
VPA	PHT	Rastogi 1991 [12]	14	6	13	2

1 N; number of participants, NR; number of responders

12 studies were included for the network of seizure freedom on monotherapy for newly diagnosed focal seizures (Table 1). The mean age of participants in these trials was 38.9 years (range 8- 91) with some studies also including elderly participants (Bill, 1997, Callaghan, 1985, Brodie, 1995 and Steiner, 1999). The minimum age of participants in all studies was 12 years with the exception of Rastogi (1991) and Callaghan (1985) that included children aged 8 years and older.

The duration of the treatment was comparable across the twelve trials included for this analysis; Brodie (1995), Steiner (1999), Christe (1997), Bill (1991) and Callaghan (1985), Kalviainen (1995) and Turnbull (1985) had set up a treatment period of 48 weeks, whereas Rastogi (1991) and Tanganelli (1996) followed participants for 8 and 4-24 weeks of treatment respectively. SANAD trial (Marson, 2007) was a pragmatic trial with a 6 year follow up period. For the NMA analysis, we used SANAD results at the end of first year to be consistent with the other data in the network (please see section 1.3 for limitations of this approach).

The majority of AEDs used in these 12 studies were used in accordance with the usual therapeutic dosages as recommended by the British National Formulary (BNF). However, sodium valproate in some studies was prescribed in lower doses than its usual therapeutic range; in Turnbull and Callaghan (600mg/daily) and in Rastogi (15mg/kg/day) (BNF recommended is 1-2 gr/day or 20-30 mg/kg/daily). The highest amount of phenytoin also given in Bill's trial was 800 mg/day whereas the highest BNF recommended threshold is 500 mg/daily. Finally, carbamazepine in both studies by Callaghan (1985) and Brodie (1997) were prescribed in lower doses than the ones recommended by BNF; carbamazepine was given in a dose of 600 mg/daily whereas the usual dosage is 0.8-1.2gr/day).

Table 2: Trial data of withdrawal due to adverse events (monotherapy for newly diagnosed focal seizures)

			Active treatment		Comparator	
Active Treatment	**Comparator**	**Study**	**N**	**NW**	**N**	**NW**
LTG	CBZ	Marson 2007 [4]	370	60	368	96
OXC	CBZ		202	46		
GBP	CBZ		366	62		
TPM	CBZ		366	95		
GBP	LTG		366	62	370	60
GBP	TPM		366	62	366	95
LTG	TPM		370	60	366	95
GBP	OXC		366	62	202	46
LTG	OXC		370	60	202	46
TPM	OXC		366	95	202	46
LTG	CBZ	Brodie 1995 [5]	131	19	129	35
		Steinhof 2005{Steinhoff, 2005 4668 /id}	88	7	88	17
		Nieto- Barrera 2001{Nieto-Barrera, 2001 4723 /id}	259	126	126	63
GBP	CBZ	Chadwick 1998 [13]	146	13	74	18
VGB	CBZ	Chadwick 1999 [14]	229	43	230	61
		Kalviaien 1995{Kalviainen, 1995 4702 /id}	50	0	50	12
VGB	CBZ	Tanganelli 1996 [6]	37	0	39	1
CLN	CBZ	Mikkelsen 1981 [15]	17	7	19	4
PHT	CBZ	Ramsay 1983 [16]	45	8	42	8
		Mattson 1985{Mattson, 1985 4651 /id}	110	18	101	12
PHB	CBZ	Mattson 1985{Mattson, 1985 4651 /id}	101	19	101	12
PRM	CBZ	Mattson 1985{Mattson, 1985 4651 /id}	109	36	101	12

LTG	PHT	Steiner 1999 [8]	86	13	95	18
OXC	VPA	Christe 1997 [9]	128	15	121	10
OXC	PHT	Bill 1997 [10]	143	5	144	16
PHB	PHT	Mattson 1985{Mattson, 1985 4651 /id}	101	19	110	18
PRM	PHT	Mattson 1985{Mattson, 1985 4651 /id}	109	36	110	18
PHB	PRM	Mattson 1985{Mattson, 1985 4651 /id}	101	19	109	36
VPA	PHT	Turnbull 1985 [11]	33	9	31	11

1 N; number of participants, NW; number of participants withdrawing

15 studies were included for the NMA of withdrawal due to adverse events on monotherapy for newly diagnosed focal seizures (Table 2). The mean age of participants in these trials was 40.0 years (range 6- 91), with all studies including also elderly participants except Turnbull (1985) and Christe (1997) that included participants up to the age of 65 years. The minimum age of participants in all studies was 12 years with the exception of Mikkelson (1981) that included children aged 6 years and older.

The duration of the treatment varied across the 15 trials included for this analysis ; Brodie (1995), Steiner (1999), Christe (1997), Bill (1991), Mikkelson (1981) and Chadwick (1999) had set up a treatment period of 1 year (48-52 weeks), whereas Tanganelli (1996) and Chadwick (1998) followed participants for 8, 16 and 24 weeks of treatment respectively. SANAD (Marson, 2007) was a pragmatic trial with a 6 year follow up period. For the purposes of our NMA, we used the SANAD results at the end of first year to be consistent with other data in this network (please see section 1.3 for limitations of this approach). Of the remaining studies, the longest were conducted by Ramsay (1983),Turnbull (1985) and Matson (1985) which lasted up to 2 years.

The majority of drugs used in these 15 studies were consistently in accordance with the usual therapeutic dosages as recommended by the BNF. However, sodium valproate in Turnbull was prescribed in lower doses (600mg/daily) than its usual therapeutic range (BNF recommended is 1-2 gr/day or 20-30 mg/kg/daily); carbamazepine also in both studies by Chadwick (1998, 1999)) and Brodie (1995) were prescribed in lower doses than the ones recommended by BNF; carbamazepine was given in a dose of 600 mg/daily whereas the usual dosage is 0.8-1.2gr/day. The highest amount of phenytoin also given in Bill's trial was 800 mg/day whereas the highest BNF recommended threshold is 500 mg/daily. Finally, the maximum dosage of vigabatrin given in Chadwick (1999) was 4 gr/daily although the maximum recommended by the BNF is 3gr in daily basis.

Table 3: Trial data of 50% reduction in seizure frequency (adjunctive treatment for refractory focal seizures)

			Active treatment		Comparator	
Active Treatment	**Comparator**	**Study**	**N**	**NR**	**N**	**NR**
ESC	Placebo	**Elger 2009** [61]	300	93	102	15
ESC	Placebo	**Elger 2007** [62]	97	46	47	13
ESC	Placebo	**Gil Nagel 2009{Gil-Nagel, 2009 5082 /id}**	165	58	87	19
ESC	Placebo	**Ben- Menachem 2010{Ben-Menachem, 2010 5077 /id}**	295	92	100	13
GBP	Placebo	**Yamauchi 2006** [36]	127	20	82	5
GBP	Placebo	**US Gabapentin group 1993** [37]	155	30	98	8
GBP	Placebo	**UK Gabapentin group 1990** [38]	61	14	66	6
GBP	Placebo	**Sivenius 1991** [39]	27	5	18	3
GBP	Placebo	**Anhut 1994** [40]	163	36	109	10
GBP	Placebo	**Appleton 1999{Appleton, 1999 4604 /id}**	119	25	128	23
LSM	Placebo	**Halasz 2009** [55]	322	120	163	41
LSM	Placebo	**Ben Menachem 2007** [56]	215	79	97	21
LTG	Placebo	**Loiseau 1990** [65]	23	7	23	1
LTG	Placebo	**Schapel 1993** [66]	41	9	41	0
LTG	Placebo	**Binnie 1989** [67]	34	2	34	0
LTG	Placebo	**Matsuo 1993** [17]	143	33	73	12
LTG	Placebo	**Duchowny 1999{Duchowny, 1999 4611 /id}**	98	41	101	16
LTG XR	Placebo	**Naritoku 2007** [18]	121	49	122	29
LEV	Placebo	**Zhou 2008** [21]	14	8	14	2
LEV	Placebo	**Xiao 2009** [22]	28	13	28	11
LEV	Placebo	**Tsai 2006** [23]	47	20	47	5
LEV	Placebo	**Ben-Menachem 2000** [24]	181	72	105	17
LEV	Placebo	**Cereghino 2000** [25]	199	76	95	7

LEV	Placebo	**Wu 2009** [26]	103	57	103	26
LEV	Placebo	**Shorvon 2000** [27]	212	53	112	11
LEV	Placebo	**Levisohn 2009 {Levisohn, 2009 51 /id}**	64	40	34	14
LEV	Placebo	**Glauser 2006{Glauser, 2006 382 /id}**	101	45	97	19
LEV XR	Placebo	**Peltola 2009** [20]	79	34	79	23
OXC	Placebo	**Barcs 2000** [63]	521	205	173	22
OXC	Placebo	**Glauser 2000**	138	55	129	28
PGB	Placebo	**French 2003** [50]	267	108	100	14
PGB	Placebo	**Elger 2005** [51]	268	103	73	8
PGB	Placebo	**Lee 2009** [52]	119	55	59	19
PGB	Placebo	**Arroyo 2004** [53]	191	54	97	6
PGB	Placebo	**Beydoun 2005** [54]	215	98	98	9
TGB	Placebo	**Uthman 1998** [44]	145	33	91	4
TGB	Placebo	**Sachdeo 1997** [45]	211	54	107	9
TGB	Placebo	**Kalviainen 1998** [46]	77	11	77	5
TPM	Placebo	**Korean Topiramate Group 1999** [28]	91	45	86	11
TPM	Placebo	**Yen 2000** [29]	23	11	23	3
TPM	Placebo	**Guberman 2002** [30]	171	75	92	22
TPM	Placebo	**Sharief 1996** [31]	23	8	24	2
TPM	Placebo	**Tassinari 1996** [32]	30	14	30	3
TPM	Placebo	**Ben-Menachem 1996** [33]	28	12	28	0
TPM	Placebo	**Faught 1996** [34]	136	54	45	8
TPM	Placebo	**Privitera 1996** [35]	96	40	47	4
TPM	Placebo	**Elterman 1999{Elterman, 1999 4608 /id}**	41	16	45	9
TPM	Placebo	**Novotny 2010{Novotny, 2010 5087 /id}**	112	37	37	10
VGB	Placebo	**Dean 1999** [47]	43	22	45	3
VGB	Placebo	**French 1996** [48]	93	40	90	17

VGB	Placebo	**Grunewald 1994** [49]	22	9	23	4
ZNM	Placebo	**Brodie 2005** [57]	174	74	120	21
ZNM	Placebo	**Sackellares 2004** [58]	78	21	74	12
ZNM	Placebo	**Schmidt 1993** [59]	71	20	68	6
ZNM	Placebo	**Faught 2001** [60]	118	41	85	16
GBP	LTG	**Sethi 2002** [41]	27	21	25	23
GBP	VGB	**Lindberger 2000** [42]	50	27	52	34
GBP	VPA	**Maton 1998**[43]	10	2	15	6
LTG	TGB	**Chmielewska 2001** [19]	22	11	26	11
PRM	VPA	**Sun 2009{Sun, 2009 5091 /id}**	68	23	68	35
TGB	PHT	**Cramer 2001** [64]	105	23	101	28
TGB	CBZ	**Cramer 2001** [64]	67	14	76	33

N; number of participants, NR; number of responders

61 studies were included for the NMA for 50% reduction in seizure frequency in adjunctive therapy in refractory focal seizures (Table 3). The mean age (of participants in all trials was 16.9 years (range 1-77). The youngest participants were included in Novotny (2010) study with a mean age of 1 years old.

The duration of treatment for the majority of studies in this network was 18- 20 weeks. However, Cereghino (2000), Zhou (2008), Matsuo (1993), Lindberger (2000) and two cross over studies (Loiseau (1990) and Schapel (1993)) had set up a treatment period up to 32 weeks. The shortest study in this network was Novotny (2010) and the longest study was conducted by Cereghino (2000) which lasted 38 weeks.

The majority of drugs used in these 61 studies were consistently in accordance with the usual therapeutic dosages as recommended by the BNF. However, the highest amount of topiramate given in Privitera's trial was 1000 mg/day whereas the highest BNF recommended threshold is 800 mg/daily. One of the zonisamide's doses in Brodie (2005) trial (100mg/daily) was lowest than the recommended range of dosage by the BNF (300-500 mg/daily), whereas tiagabine in Uthman study was given in

higher dose (56 mg/daily) than the maximum recommended (45 mg/daily). Lastly, vigabatrin was given in some studies (Lindberger and Dean) in higher doses, 4 and 6 gr/daily respectively, than the maximum recommended by the BNF for this drug (3gr/daily).

Table 4: Trial data of withdrawal due to adverse events (adjunctive treatment for focal seizures)

			Active treatment		Comparator	
Active Treatment	**Comparator**	**Study**	**N**	**NR**	**N**	**NR**
CLO	Placebo	**Koeppen 1987** [69]	129	3	129	0
ESC	Placebo	**Elger 2009** [61]	300	32	102	4
ESC	Placebo	**Elger 2007** [62]	97	7	47	4
ESC	Placebo	**Gil Nagel 2009{Gil-Nagel, 2009 5082 /id}**	165	16	87	5
ESC	Placebo	**Ben-Menachem 2010{Ben-Menachem, 2010 5077 /id}**	295	57	100	3
FEL	Placebo	**Bourgeois 1993** [70]	30	2	34	0
GBP	Placebo	**US Gabapentin group 1993** [37]	155	4	98	1
GBP	Placebo	**UK Gabapentin group 1990** [38]	61	7	66	4
GBP	Placebo	**Yamuauchi 1993** [36]	127	7	82	1
GBP	Placebo	**Anhut 1994** [40]	163	11	109	4
GBP	Placebo	**Appleton 1999{Appleton, 1999 4604 /id}**	119	6	128	3
LTG	Placebo	**Matsuo 1993** [17]	143	13	73	1
GBP	Placebo		211	54		
LSM	Placebo	**Halasz 2009** [55]	322	34	163	8
LSM	Placebo	**Ben-Menachem 2007 {1615}**	215	36	97	5
LTG	Placebo	**Matsuo 1996** [68]	8	1	4	0
LTG	Placebo	**Duchowny 1999{Duchowny, 1999 4611 /id}**	98	5	101	6
LTG	Placebo	**Messenheimer 1994** [78]	98	4	98	1
LTG	Placebo	**Sander 1990** [79]	20	1	19	1
LTG	Placebo	**Jawad 1989** [80]	24	1	24	0
LTG	Placebo	**Schacter 1995** [81]	334	28	112	9
LTG	Placebo	**Stolarek 1994** [82]	22	0	**22**	**1**
LTG	Placebo	**Binnie 1989** [67]	34	1	34	**0**
LTG XR	Placebo	**Naritoku 2007** [18]	121	12	122	2
LEV	Placebo	**Tsai 2006** [23]	47	3	47	1

LEV	Placebo	**Cereghino 2000** [25]	199	13	95	5
LEV	Placebo	**Wu 2009** [26]	103	0	103	2
LEV	Placebo	**Shorvon 2000** [27]	212	23	112	6
LEV	Placebo	**Levisohn 2009 {Levisohn, 2009 51 /id}**	64	7	34	2
LEV	Placebo	**Glauser 2006{Glauser, 2006 382 /id}**	101	5	97	9
LEV	Placebo	**Ben-Menachem 2000** [24]	181	17	105	9
LEV XR	Placebo	**Peltola 2009** [20]	79	5	79	2
OXC	Placebo	**Barcs 2000** [63]	521	200	173	15
OXC	Placebo	**Glauser 2000{Glauser, 2000 4603 /id}**	138	14	129	4
PGB	Placebo	**French 2003** [50]	267	35	100	5
PGB	Placebo	**Lee 2009** [52]	119	7	59	0
PGB	Placebo	**Arroyo 2004** [53]	191	27	97	6
PGB	Placebo	**Beydoun 2005** [54]	215	48	98	7
PGB	Placebo	**Elger 2005** [51]	268	61	73	5
VPA	Placebo	**Meador 2003** [71]	29	2	13	1
TGB	Placebo	**Uthman 1998** [44]	145	22	91	7
TGB	Placebo	**Sachdeo 1997** [45]	211	24	107	7
TGB	Placebo	**Kalviainen 1998** [46]	77	17	77	2
TPM	Placebo	**Ben-Menachem 1996** [33]	28	6	28	0
TPM	Placebo	**Korean Topiramate Group 1999** [28]	91	7	86	3
TPM	Placebo	**Guberman 2002** [30]	171	13	92	2
TPM	Placebo	**Sharief 1996** [31]	23	6	24	1
TPM	Placebo	**Tassinari 1996** [32]	30	4	30	1
TPM	Placebo	**Faught 1996** [34]	136	12	45	3
TPM	Placebo	**Privitera 1996** [35]	96	15	47	1
TPM	Placebo	**Yen 2000** [29]	23	2	23	2
TPM	Placebo	**Elterman 1999{Elterman, 1999 4608 /id}**	41	0	45	1

TPM	Placebo	**Novotny 2010{Novotny, 2010 5087 /id}**	112	4	37	2
TPM	Placebo	**Meador 2003**	34	6	13	1
VGB	Placebo	**Dean 1999** [47]	43	5	45	1
VGB	Placebo	**French 1996** [48]	93	7	90	2
VGB	Placebo	**Loiseau 1990** [65]	23	2	23	0
VGB	Placebo	**Tartara 1986** [75]	23	1	23	0
VGB	Placebo	**McKee 1993** [76]	24	1	24	0
VGB	Placebo	**Tassinari 1997** {4712}	31	1	31	0
ZNM	Placebo	**Brodie 2005** [57]	174	36	120	8
ZNM	Placebo	**Sackellares 2004** [58]	78	12	74	1
ZNM	Placebo	**Brodie 2004**	73	5	71	1
GBP	VGB	**Lindberger 2000** [42]	50	7	52	7
GBP	VPA	**Maton 1998** [43]	10	5	15	2
LTG	LEV	**Labiner 2009** [74]	132	14	136	24
PRM	VPA	**Sun 2009{Sun, 2009 5091 /id}**	68	7	68	3
TPM	LTG	**Blum 2006** [73]	96	24	96	20
TPM	VPA	**Aldenkamp 2000** [72]	29	6	30	2
TPM	VPA	**Meador 2003 {602}**	34	6	29	2

1 N; number of participants, NW; number of participants withdrawing

67 studies were included for the NMA of adjunctive therapy for withdrawal due to adverse events in refractory focal seizures (Table 4). The mean age of participants in all trials were 17 years (range 1-77).

The duration of treatment for the majority of studies in this network was 12-18 weeks. However, Uthman's study lasted 20 weeks, Kalviainen's trial 22 weeks and, Brodie , Barcs, Matsuo, and Lindberger 's trials had set up a treatment period of 24 weeks. The longest study was conducted by Cereghino (2000) which lasted 38 weeks. The shortest study in this network was Novotny (2010).

The majority of drugs used in these 67 studies were given consistently with the usual therapeutic dosages as recommended by the BNF. However, the highest amount of topiramate given in Privitera's trial was 1000 mg/day whereas the highest BNF recommended threshold is 800 mg/daily. One of the zonisamide's doses in Brodie (2005) trial (100mg/daily) was lowest than the recommended range of dosage by the BNF (300-500 mg/daily), whereas tiagabine in Uthman study was given in higher dose (56 mg/daily) than the maximum recommended (45 mg/daily). Lastly, vigabatrin was given in some studies (Lindberger and Dean) in higher doses, 4 and 6 gr/daily respectively, than the maximum recommended by the BNF for this drug (3gr/daily).

The clinical evidence reviews considered the quality of the outcome measures according to the modified GRADE evidence profiles. The clinical evidence reviews showed the methodological quality of the outcome measures included in the NMA was moderate to very low.

Network 1: Seizure freedom in monotherapy for newly diagnosed focal seizures

Table 5 summarises the results of the conventional meta-analyses in terms of odds ratios generated from studies directly comparing different interventions. Table 5 also presents the results of the NMA in terms of odds ratios for every possible treatment comparison.

Table 5: Effectiveness (seizure freedom) of interventions in newly diagnosed population focal seizures, results of conventional and network meta-analyses

Carbamazepine	0.76 (0.60, 0.95)	0.96 (0.63-1.45)	**0.56 (0.32-0.78)**	0.88 (0.64-1.20)	**0.51 (0.26, 0.97)**	1.44 (0.51-4.16)	2.43 (0.78, 7.69)
0.77 (0.54-1.08)	Lamotrigine	1.31 (0.91, 1.92)	0.78 (0.55, 1.09)	1.22 (0.88, 1.67)			1.22 (0.45-3.33)
0.99 (0.61-1.62)	1.29 (0.80-2.12)	Oxcarbazepine	**0.59 (0.40, 0.87)**	0.92 (0.63, 1.34)		1.19 (0.63-2.27)	1.47 (0.82-2.63)
0.58 (0.34-0.98)	0.75 (0.45-1.30)	0.59 (0.33-1.05)	Gabapentin	**1.56 (1.08, 1.75)**			
0.91 (0.54-1.53)	1.18 (0.70-2.01)	0.92 (0.51-1.63)	1.58 (0.87-2.80)	Topiramate			
0.50 (0.24-1.06)	0.65 (0.29-1.51)	0.51 (0.22-1.25)	0.86 (0.36-2.19)	0.54 (0.22-1.37)	Vigabatrin		
1.34 (0.70-2.63)	1.75 (0.90-3.57)	1.35 (0.76-2.50)	2.31 (1.08-5.06)	1.48 (0.70-3.22)	2.69 (0.97-7.20)	Valproate	0.99 (0.49, 2.00)
1.35 (0.73-2.39)	1.75 (0.96-3.19)	1.36 (0.79-2.30)	2.34 (1.12-4.60)	1.48 (0.73-2.93)	**2.71 (1.03-6.65)**	1.01 (0.52-1.81)	Phenytoin

Results in white are the odds ratios and 95% confidence intervals from the conventional meta-analyses of direct comparisons between the column-defining treatment and the row-defining treatment. Odds ratios greater than 1 favour the column-defining treatment.
Results in gray are the median odds ratios and credible intervals from the NMA of direct and indirect comparisons between the row-defining treatment and the column-defining treatment. Odds ratios greater than 1 favour the row-defining treatment.
Numbers in bold highlight statistically significant results (P<0.05).

Based on the direct comparisons (in white in Table 5), efficacy as assessed by seizure freedom in newly diagnosed focal seizures favours carbamazepine over lamotrigine gabapentin and vigabatrin. In addition, oxcarbazepine was more effective than gabapentin but gabapentin was more effective when compared to topiramate. No other treatment effects reached statistical significance. The random effects model used for the NMA fit well, with a residual deviance of 26.12 reported. This corresponds well to the total number of trial arms, 22.

Based on the results of the NMA (in grey in Table 5), no AED treatment was found to be significantly more effective in achieving seizure freedom as a monotherapy for newly diagnosed focal seizures than carbamazepine. The only treatment effects that reached significance were; gabapentin was significantly less effective than carbamazepine and phenytoin was significantly more effective in achieving seizure freedom when compared to vigabatrin.

When we compared the results from the direct analysis and NMA we found no inconsistencies for any comparison. All the median odds ratios of AEDs compared to carbamazepine from the NMA lie within the 95% confidence interval from the direct comparison of the same AEDs.

Table 6 presents the relative risk of each intervention compared to carbamazepine. It also gives the probability that each intervention is most effective. Based on point estimates, distribution of rank and proportion of simulations in which they are the most effective AEDs, phenytoin and valproate were the most effective AEDs in achieving seizure freedom (they were the optimal strategy in 45.9% and 44.2% of simulations respectively).

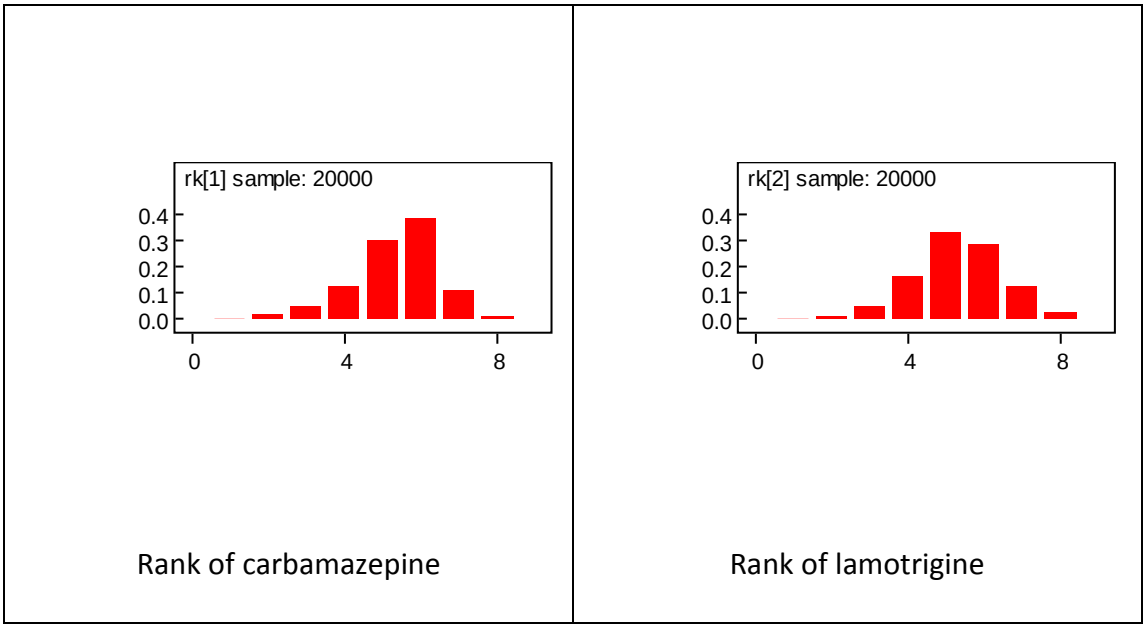
Table 6: Effectiveness of interventions in network 1 compared to carbamazepine

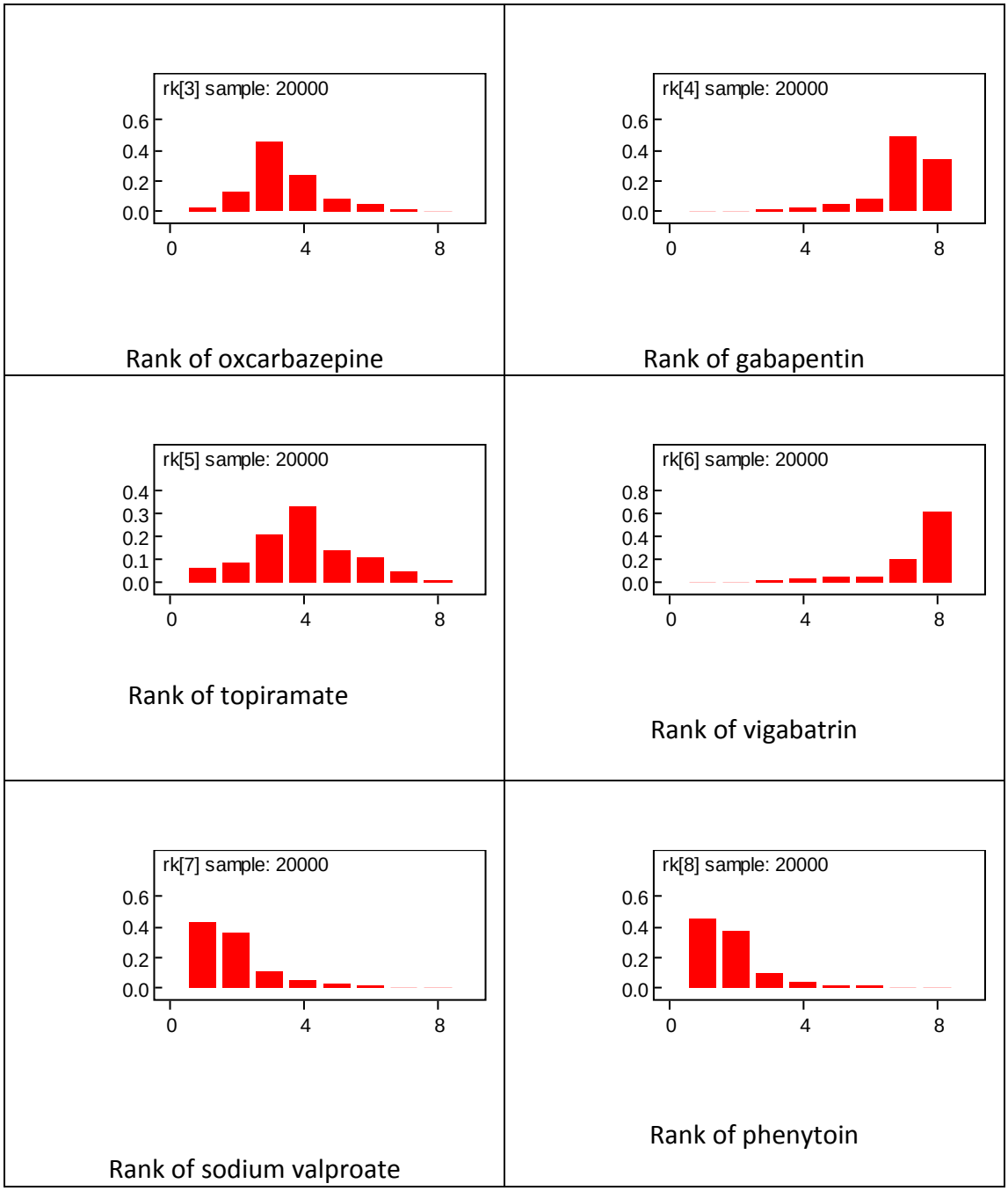
AED*	^Median relative risk (95% Credible Interval)	Probability intervention is most effective (%)
Carbamazepine	-	0.3%
Vigabatrin	0.76 (0.44, 1.20)	0.8%
Gabapentin	0.84 (0.57, 1.14)	0.2%
Lamotrigine	1.00 (0.80, 1.21)	0.4%
Topiramate	1.10 (0.79, 1.42)	5.4%
Oxcarbazepine	1.15 (0.86, 1.46)	2.8%
Valproate	1.34 (0.95, 1.73)	44.2%
Phenytoin	1.35 (0.97, 1.68)	45.9%

^ Median RR<1, Carbamazepine was more effective compared to the AED
SANAD data dichotomized from time to 12 month remission (year 1) to seizure freedom.

Figure 3 shows the distribution of probabilities of each intervention being ranked at each of 8 positions.

Figure 3: Ranking of interventions in network 1





Ranking is based on the relative risk compared to no treatment and indicates the probability of being the best treatment, second best, third best and so on among the 12 different interventions being evaluated.

Network 2: Withdrawal due to adverse events in monotherapy for newly diagnosed focal seizures

Table 7 summarises the results of the conventional meta-analyses in terms of odds ratios generated from studies directly comparing different interventions. Table 7 also presents the results of the NMA in terms of odds ratios for every possible treatment comparison.

Table 7: Tolerability (withdrawal due to adverse events) of interventions in a newly diagnosed population with focal seizures, results of conventional and network meta-analyses

Carbamazepine	0.51 (0.39, 0.65)	0.96 (0.62, 1.44)	**0.52 (0.37-0.78)**	0.99 (0.71-1.38)	**0.52 (0.34, 0.78)**	2.63 (0.61, 11.37)	1.23 (0.66-2.32)	**3.66 (1.78, 7.54)**	1.72 (0.79, 3.76)	
0.51 (0.25-0.98)	Lamotrigine	1.51 (0.99, 2.32)	1.05 (0.71, 1.55)	1.05 (0.71, 1.54)			1.32 (0.59-2.86)			
0.62 (0.19-1.58)	1.23 (0.37-3.27)	Oxcarbazepine	0.69 (0.45, 1.06)	**1.19 (0.79, 1.78)**			**3.45 (1.23-10.0)**			0.68 (0.29-1.59)
0.45 (0.16-1.10)	0.87 (0.29-2.39)	0.72 (0.22-2.59)	Gabapentin	**1.72 (1.20, 2.44)**						
0.87 (0.25-2.73)	1.70 (0.47-5.56)	1.38 (0.38-5.81)	1.93 (0.53-7.24)	Topiramate						
0.33 (0.06-0.75)	0.66 (0.10-1.72)	0.55 (0.07-1.85)	0.76 (0.10-2.33)	0.40 (0.05-1.38)	Vigabatrin					
2.98 (0.43-21.45)	5.88 (0.78-48.5)	4.87 (0.58-49.94)	6.71 (0.83-64.22)	3.52 (0.37-36.83)	**9.29 (1.27 -133.2)**	Clonazepam				
1.18 (0.48-2.72)	2.31 (0.90-5.83)	1.91 (0.69-6.38)	2.67 (0.80-9.20)	1.37 (0.35-5.51)	**3.52 (1.19-24.37)**	0. 39 (0.05-3.13)	Phenytoin	**2.5 (1.32, 4.76)**	1.19 (0.58, 2.38)	0.68 (0.24, 1.96)
3.38 (0.87-12.98)	**6.60 (1.55- 28.3)**	5.47 (1.24-30.5)	**7.64 (1.60- 40.85)**	3.94 (0.70 - 24.69)	**10.05 (2.53- 104.6)**	1.13 (0.10 - 12.31)	2.86 (0.79 - 11.4)	Primidone		
1.56 (0.39-6.06)	3.06 (0.70-13.55)	2.53 (0.55-14.85)	3.58 (0.69- 19.78)	1.81 (0.31-11.29)	**4.7 (1.15 - 47.98)**	0.53 (0.05-5.80)	1.33 (0.35-5.39)	0.47 (0.11- 1.98)	Phenobarbital	
0.41 (0.06- 2.35)	0.80 (0.11-4.99)	0.67 (0.14-3.13)	0.92 (0.12- 6.47)	0.48 (0.06-3.65)	1.23 (0.19 - 16.66)	0.14 (0.008-1.86)	0.35 (0.05-2.21)	0.12 (0.01- 1.02)	0.26 (0.02 - 2.33)	Valproate

- Results in white are the odds ratios and 95% confidence intervals from the conventional meta-analyses of direct comparisons between the column-defining treatment and the row-defining treatment. Odds ratios greater than 1 favour the row-defining treatment.
- Results in gray are the median odds ratios and credible intervals from the NMA of direct and indirect comparisons between the row-defining treatment and the column-defining treatment. Odds ratios greater than 1 favour the column-defining treatment.
- Numbers in bold highlight statistically significant results (P<0.05).

Based on the direct comparisons (in white in Table 7), tolerability as assessed by withdrawal due to adverse events favours significantly lamotrigine, gabapentin and vigabatrin over carbamazepine, carbamazepine over primidone, gabapentin over topiramate, oxcarbazepine over phenytoin and phenytoin over primidone. No other treatment effects reached statistical significance.

The random effects model used for the NMA fit well, with a residual deviance of 37.29 reported. This corresponds well to the total number of trial arms, 31. No inconsistencies were identified in this network.

Based on the results of the NMA (in grey in Table 7), lamotrigine and vigabatrin were more tolerable as assessed by less withdrawals due to adverse events over carbamazepine. Primidone was also found in the NMA to perform worst in tolerability when compared to lamotrigine, gabapentin and vigabatrin, although there is uncertainty over the magnitude of these effects (very wide confidence intervals). Table 8 presents the relative risk of each intervention compared to carbamazepine. It also gives the probability that each intervention is most effective.

Table 8: Tolerability of interventions in network 2 compared to carbamazepine

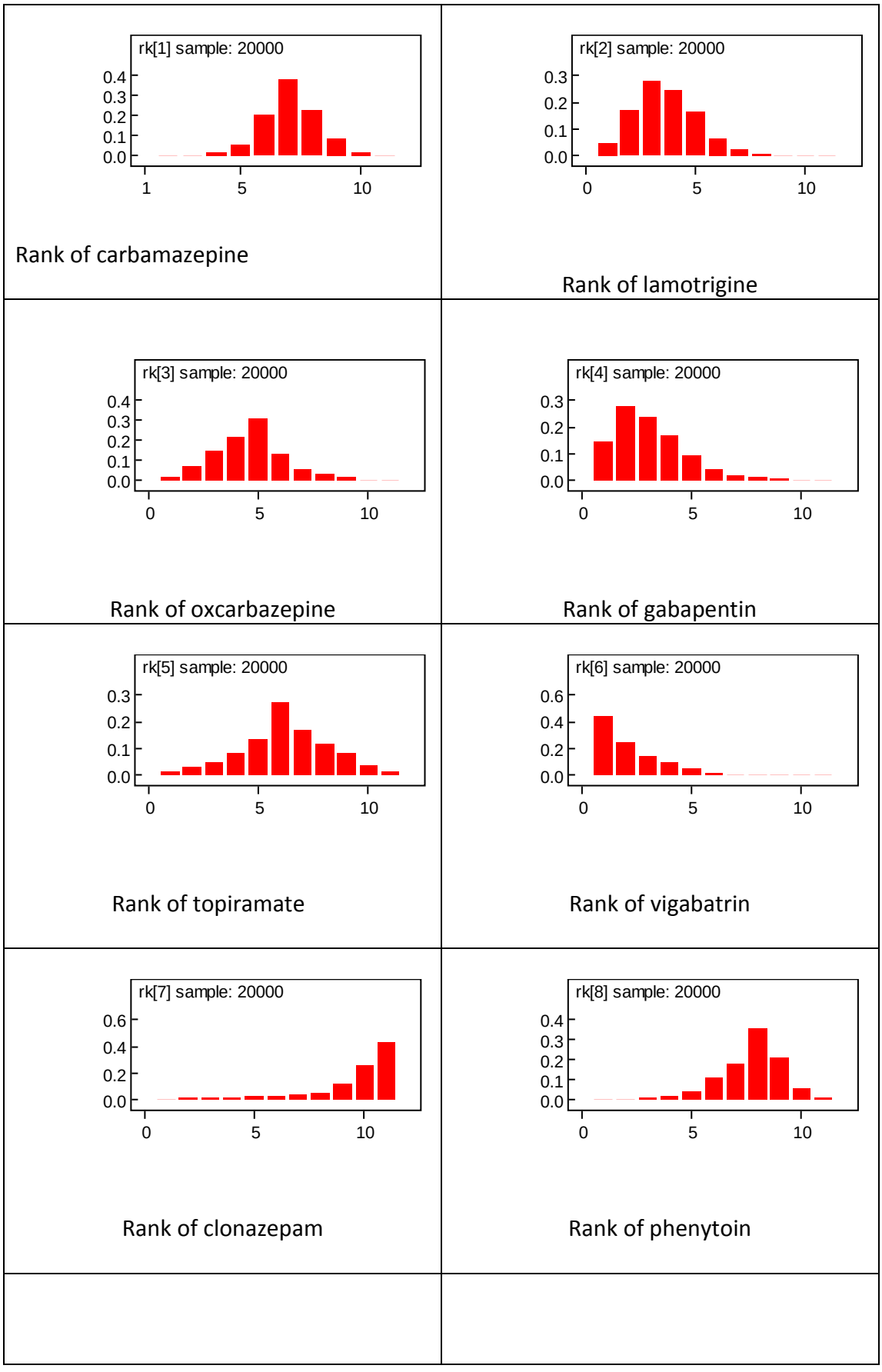
AED*	^Median relative risk (95% Credible Interval)	Probability intervention is most tolerable (%)
Carbamazepine	-	0
Lamotrigine	0.58 (0.30, 0.99)	4.52%
Oxcarbazepine	0.68 (0.24, 1.39)	1.62%
Gabapentin	0.51 (0.20, 1.08)	14.31%
Topiramate	0.90 (0.30, 1.95)	1.19%
Vigabatrin	0.40 (0.08, 0.80)	43.9%
Clonazepam	2.04 (0.50, 3.73)	0.54%
Phenytoin	1.13 (0.55, 1.95)	0.06%
Primidone	2.18 (0.90, 3.43)	0.06%
Phenobarbital	1.38 (0.45, 2.79)	0.46%
Valproate	0.48 (0.07, 1.79)	33.36%

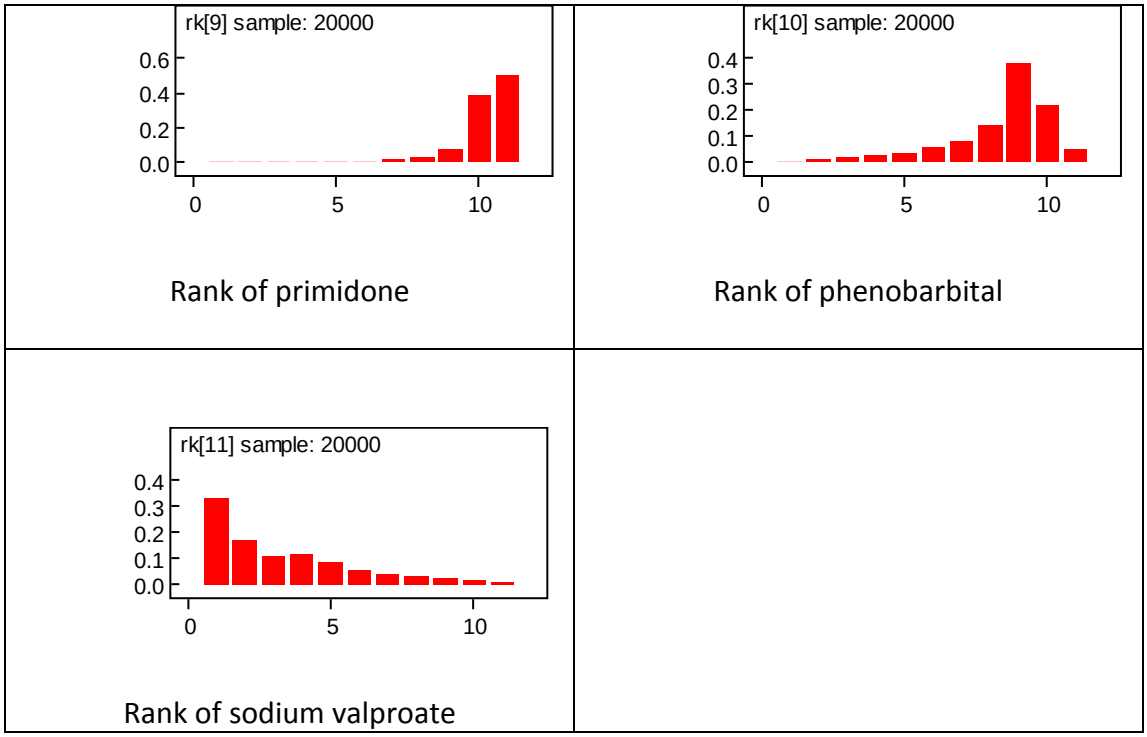
^ Median RR<1, Carbamazepine was less tolerable compared to the AED
SANAD data dichotomized from time to 12 month remission (year 1) to seizure freedom.

Based on point estimates, distribution of rank and proportion of simulations in which they are the most tolerable AEDs, vigabatrin and sodium valproate were the most tolerable AEDs (they were the optimal strategy in 43.9% and 33.4% of simulations respectively).

Figure 4 shows the distribution of probabilities of each intervention being ranked at each of 9 positions.

Figure 4: Ranking of interventions in network 2





Network 3: Adjunctive therapy for refractory focal seizures- 50% reduction in seizure frequency

Table 9 summarises the results of the conventional meta-analyses in terms of odds ratios generated from studies directly comparing different interventions. Table 9 also presents the results of the NMA in terms of odds ratios for every possible treatment comparison.

1 Table 9: Effectiveness (50% reduction in seizure frequency) of interventions in an adjunctive population with focal seizures, results of
2 conventional and network meta-analyses

Placebo	**3.15 (1.99, 4.97)**	**4.45 (2.61, 7.58)**	**2.12 (1.50, 2.99)**	**3.65 (2.83, 4.71)**	**3.70 (2.76, 4.95)**	**3.49 (2.45, 4.98)**	**4.45 (3.25-6.08)**	**1.88 (1.35, 2.63)**	**2.47 (1.80-3.40)**		1.84 (0.95-3.55)	**2.18 (1.26-3.79)**	**4.00 (2.35-6.81)**				
4.11 (2.40-7.35)	Lamotrigine		0.30 (0.06-1.68)										0.74 (0.23-2.27)				
4.48 (2.53-8.13)	1.08 (0.48-2.34)	Vigabatrin	0.62 (0.28-1.38)														
2.20 (1.46-3.36)	0.54 (0.27-0.99)	0.49 (0.26-0.92)	Gabapentin											2.63 (0.41-16.66)			
3.68 (2.64-5.23)	0.89 (0.46-1.67)	0.83 (0.42, 1.60)	1.68 (0.97-2.88)	Levetiracetam													
4.15 (2.87-6.1)	1.00 (0.51-1.88)	0.93 (0.45, 1.81)	**1.89 (1.07-3.25)**	1.12 (0.68-1.89)	Topiramate												
3.37 (1.90-6.04)	0.82 (0.35-1.74)	0.75 (0.32, 1.70)	1.54 (0.73-3.06)	0.91 (0.47-1.81)	0.81 (0.40-1.62)	Oxcarbazepine											
4.51 (2.98-7.00)	1.09 (0.53-2.11)	1.01 (0.49-2.04)	2.05 (1.14-3.66)	1.22 (0.72-2.12)	1.09 (0.62-1.90)	1.34 (0.65-2.72)	Pregabalin										
1.90 (1.09-3.38)	0.46 (0.20-0.97)	**0.43 (0.18, 0.94)**	0.87 (0.43, 1.73)	0.51 (0.26-0.99)	**0.46 (0.23, 0.90)**	0.57 (0.25-1.28)	**0.43 (0.21-0.86)**	Lacosamide									
2.47 (1.60-3.98)	0.60 (0.29-1.18)	0.55 (0.26, 1.14)	1.12 (0.60-2.06)	0.67 (0.38-1.19)	0.60 (0.33-1.08)	0.73 (0.35-1.56)	0.55 (0.29-1.02)	1.30 (0.62-2.70)	Eslicarbazepine Acetate								

2.83 (1.76-4.63)	0.69 (0.32-1.37)	0.64 (0.29-1.35)	1.29 (0.68-2.40)	0.77 (0.43, 1.4)	0.68 (0.37-1.26)	0.84 (0.40-1.79)	0.63 (0.33-1.18)	1.49 (0.71-3.13)	1.15 (0.58-2.21)	Zonisamide							
1.81 (0.74-4.7)	0.44 (0.14-1.25)	0.41 (0.14-1.19)	0.82 (0.30-2.27)	0.49 (0.19-1.33)	0.44 (0.17-1.18)	0.53 (0.19-1.62)	0.39 (0.15-1.13)	0.95 (0.33-2.89)	0.74 (0.26-2.07)	0.64 (0.23-1.82)	Levetiracetam XR						
2.18 (0.95-5.18)	0.53 (0.19-1.39)	0.49 (0.17-1.39)	0.99 (0.38-2.58)	0.59 (0.24-1.50)	0.53 (0.20-1.31)	0.65 (0.23-1.85)	0.48 (0.18-1.25)	1.15 (0.41-3.21)	0.88 (0.34-2.32)	0.77 (0.29-2.06)	1.21 (0.34-4.17)	Lamotrigine XR					
3.89 (2.21 - 7.02)	0.94 (0.45-1.88)	0.86 (0.39-1.99)	1.77 (0.89-3.56)	1.05 (0.54-2.08)	0.94 (0.46-1.87)	1.15 (0.51-2.69)	0.86 (0.42-1.79)	2.05 (0.91-4.54)	1.57 (0.74-3.34)	1.38 (0.64, 2.91)	2.14 (0.72-6.33)	1.78 (0.64-4.93)	Tiagabine		**2.94 (1.38-6.25)**	1.36 (0.72-2.56)	
7.75 (1.08-77.54)	1.86 (0.23-19.49)	1.75 (0.22-18.22)	3.49 (0.51-34.42)	2.10 (0.28-21.82)	1.89 (0.24-18.93)	2.33 (0.29-23.75)	1.72 (0.22-18.59)	4.11 (0.50-41.84)	3.11 (0.42-32.11)	2.76 (0.36-28.98)	4.30 (0.47-50.21)	3.58 (0.39-40.2)	2.02 (0.26-22.37)	Valproate			0.48 (0.24, 0.96)
11.68 (3.81-36.27)	2.84 (0.82-9.21)	2.60 (0.72-9.36)	**5.33 (1.63-17.19)**	3.17 (0.98-10.49)	2.84 (0.86-9.31)	3.46 (0.97-12.51)	2.60 (0.77-8.55)	**6.15 (1.75-21.75)**	**4.72 (1.41-16.38)**	4.13 (1.18-14.01)	**6.43 (1.53-27.45)**	**5.36 (1.30-21.74)**	**3.02 (1.13-8.11)**	1.50 (0.11-14.17)	Carbamazepine		
5.32 (1.79-16.04)	1.29 (0.39, 3.95)	1.18 (0.35-4.12)	2.42 (0.76-7.63)	1.44 (0.47-4.50)	1.28 (0.40-4.10)	1.56 (0.46-5.5)	1.18 (0.36-3.78)	2.80 (0.83-9.51)	2.14 (0.67-7.11)	1.87 (0.56-6.16)	2.91 (0.69-12.16)	2.43 (0.60-9.82)	1.37 (0.56-3.43)	0.68 (0.05-6.56)	0.45 (0.11-1.73)	Phenytoin	
3.75 (0.42-43.98)	0.90 (0.09, 11.44)	0.84 (0.09-10.35)	1.70 (0.19-19.57)	1.02 (0.11-12.15)	0.91 (0.10-11.13)	1.12 (0.11-13.43)	0.83 (0.08-10.42)	1.98 (0.20-24.13)	1.51 (0.16-18.54)	1.33 (0.14-16.44)	2.08 (0.19-28.64	1.72 (0.16-22.75)	0.98 (0.10, 12.41)	0.48 (0.19, 1.22)	0.33 (0.03, 5.11)	0.72 (0.06, 10.26)	Primidone

1 Results in white are the odds ratios and 95% confidence intervals from the conventional meta-analyses of direct comparisons between the column-defining treatment and the row-defining
2 treatment. Odds ratios greater than 1 favour the column-defining treatment.
3 Results in gray are the median odds ratios and credible intervals from the NMA of direct and indirect comparisons between the row-defining treatment and the column-defining treatment.
4 Odds ratios greater than 1 favour the row-defining treatment.
5 Numbers in bold highlight statistically significant results (P<0.05).

Based on the direct comparisons (in white in Table 9), all AEDs included in the third network with the exception of levetiracetam extended release were more effective in reducing 50% seizure frequency when compared individually to placebo. In addition, carbamazepine was more effective in reducing 50% seizure frequency than tiagabine and primidone was less effective than valproate.

The random effects model used for this NMA fit reasonably well, with a residual deviance of 133.9 reported. This corresponds well to the total number of trial arms, 104.

Based on the results of the NMA (in grey in Table 9), all AEDs included in the network of achieving more than 50% of seizure reduction in adjunctive focal seizures were more effective in reducing at least 50% seizure frequency when compared individually to placebo with the exception of levetiracetam extender release, lamotrigine extended release and sodium valproate. Topiramate was more effective than gabapentin and lacosamide was less effective when compared to vigabentin, topiramate and pregabalin. Topiramate was also more effective than gabapentin and carbamazepine was more effective compared to gabapentin, lacosamide, eslicarbazepine acetate, zonisamide, levetiracetam and lamotrigine extended release and tiagabine.

Table 10 presents the relative risk of each intervention compared to no treatment (placebo). It also gives the probability that each intervention is the most effective.

Table 10: Probability of achieving 50% reduction in seizure frequency by using one of the following AEDs compared to no treatment (placebo)

AED*	^Median relative risk (95% Credible Interval)	Probability intervention is most effective (%)
Placebo		0
Levetiracetam XR	1.61 (0.77, 2.96)	0.27%
Lacosamide	1.66 (1.07, 2.45)	0.02%
Lamotrigine XR	1.84 (0.95, 3.11)	0.48%
Gabapentin	1.85 (1.36, 2.44)	0
Eslicarbazepine Acetate	2.00 (1.46, 2.71)	0.01%
Zonisamide	2.20 (1.57, 2.94)	0.16%
Oxcarbazepine	2.45 (1.66, 3.36)	1.37%
Levetiracetam	2.59 (2.10, 3.13)	0.56%
Primidone	2.61 (0.46, 5.64)	17.64%
Tiagabine	2.67 (1.85, 3.60)	1.29%
Topiramate	2.77 (2.21, 3.38)	2.41%
Lamotrigine	2.76 (2.02, 3.67)	3.86%
Vigabatrin	2.89 (2.04, 3.82)	7.33%
Pregabaline	2.90 (2.27, 3.59)	5.83%
Phenytoin	3.16 (1.59, 4.75)	19.71%
Valproate	3.75 (1.07, 5.92)	20.47%
Carbamazepine	4.35 (2.64, 5.51)	18.58%

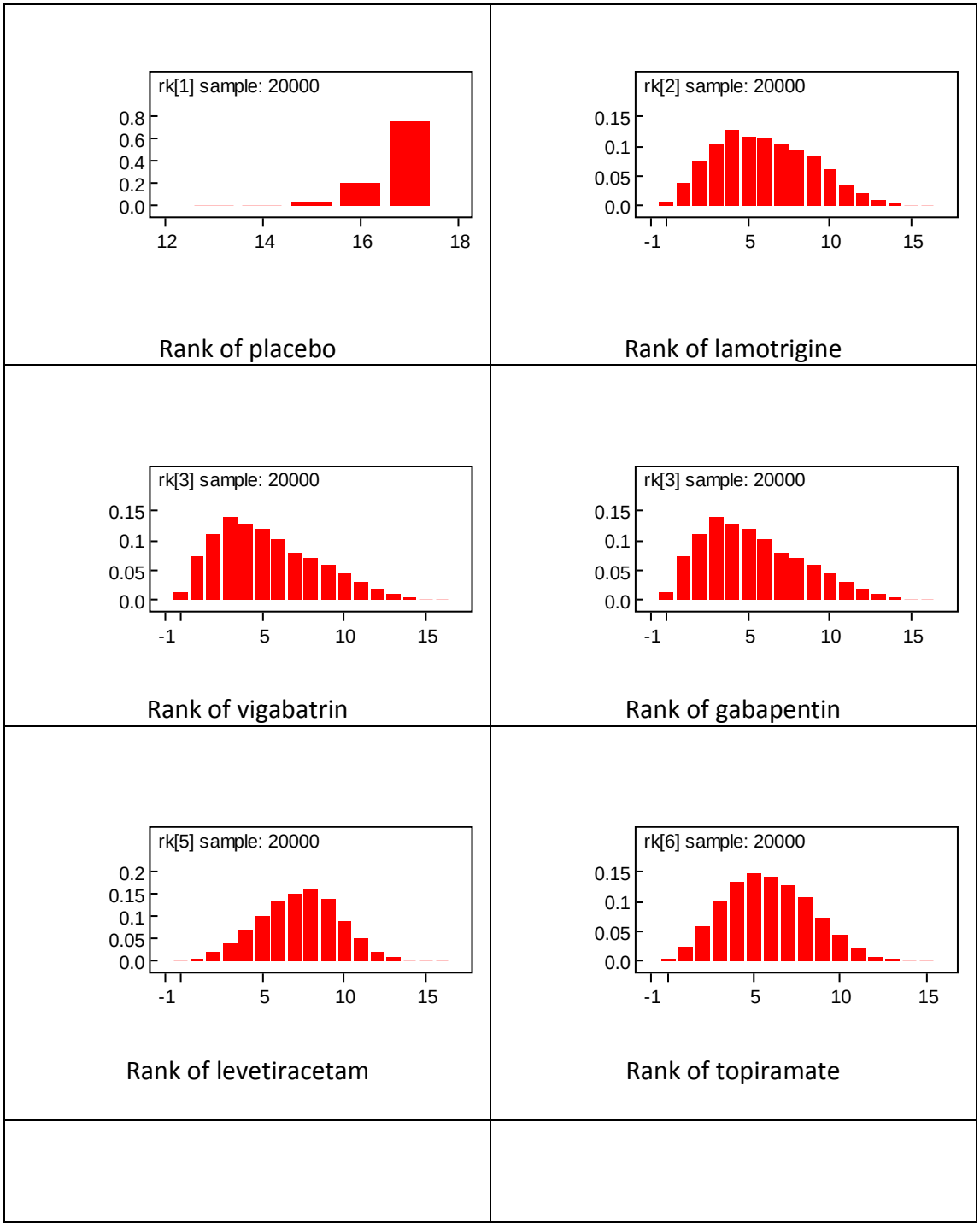
*compared against the placebo

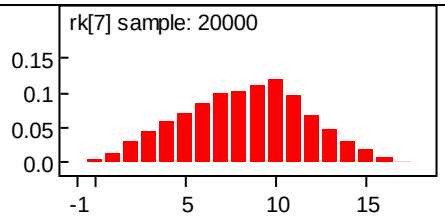
^ Median RR>1, AED was more effective compared to placebo

Based on point estimates, distribution of rank and proportion of simulations in which they are the most effective AEDs, sodium valproate, phenytoin, carbamazepine and primidone were the most effective in achieving a reduction of at least 50% seizure frequency (they were the optimal strategy in 20.5%, 19.7%, 18.6% and 17.6% of simulations respectively).

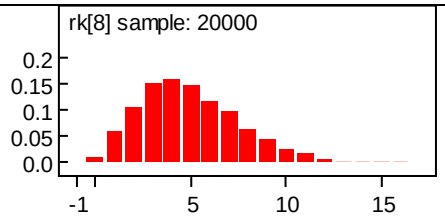
Figure 5 shows the distribution of probabilities of each intervention being ranked at each of 17 positions.

Figure 5: Ranking of interventions in network 3

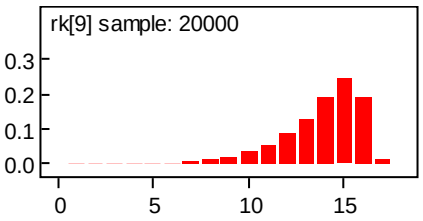




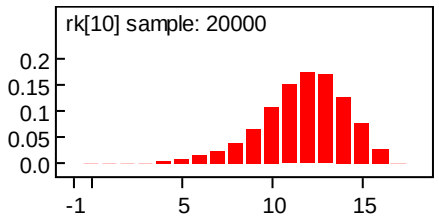
Rank of oxcarbazepine



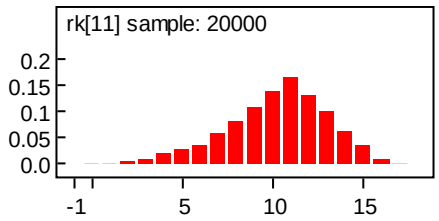
Rank of pregabalin



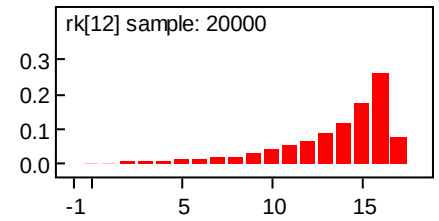
Rank of lacosamide



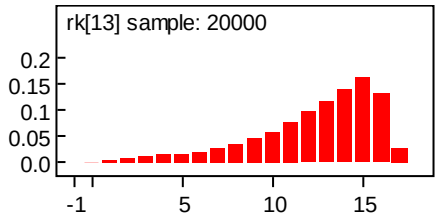
Rank of eslicarbazepine acetate



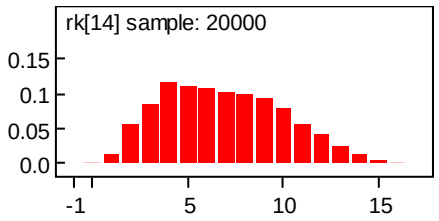
Rank of zonisamide



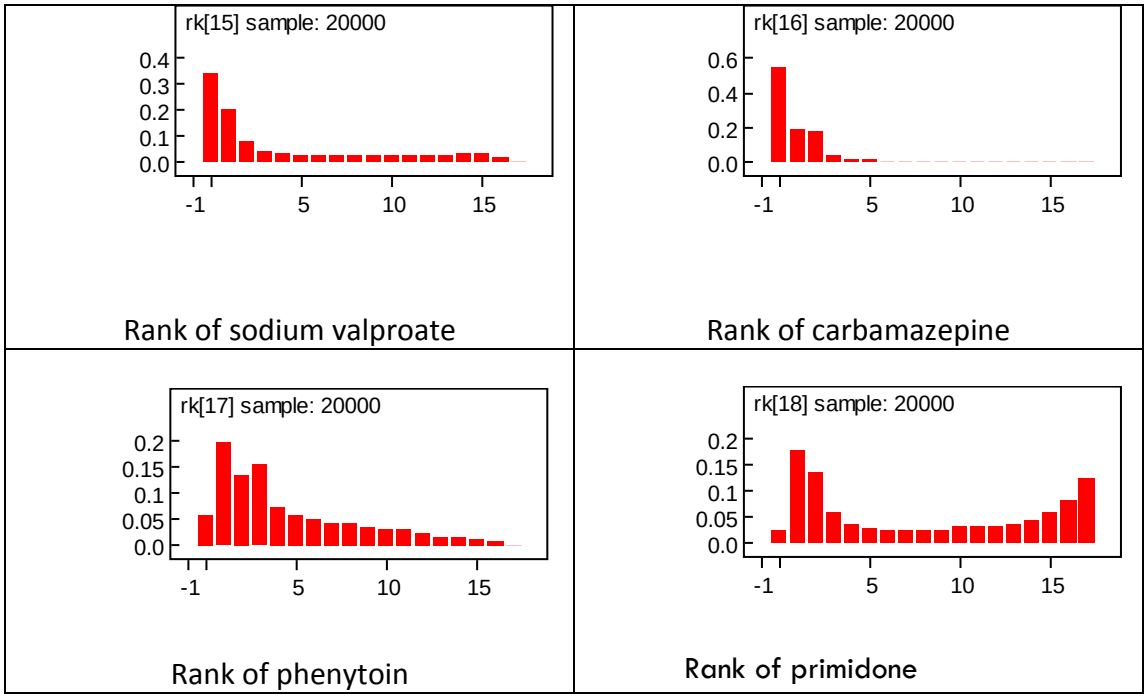
Rank of levetiracetam XR



Rank of lamotrigine XR



Rank of tiagabine



Network 4: Adjunctive therapy for refractory focal seizures- withdrawal due to adverse events

Table 11 summarises the results of the conventional meta-analyses in terms of odds ratios generated from studies directly comparing different interventions. Table 11 also presents the results of the NMA in terms of odds ratios for every possible treatment comparison.

1 Figure 11: Tolerability (withdrawal due to adverse events) of adjunctive treatment in refractory focal seizures, results of conventional and
2 network meta-analyses

Placebo	7.17 (0.37-140.14)	**5.92 (3.59, 9.76)**	**3.38 (2.16-5.30)**	**2.77 (1.58-4.87)**	**2.82 (1.53-5.20)**	**2.93 (1.70-5.04)**	**4.70 (2.33, 9.46)**	**14.85 (3.42-64.38)**	2.60 (0.49-13.83)	6.05 (0.28-131.25)	0.89 (0.07, 10.77)	**2.73 (1.61, 4.64)**	1.48 (0.87, 2.51)	1.23 (2.83, 4.71)	**2.31 (1.19, 4.46)**	**4.04 (1.48-10.99)**	
23.68 (0.98-155.2)	Clobazam																
5.71 (2.77-12.1)	0.25 (0.03-6.26)	Oxcarbazepi															
3.60 (2.12-6.35)	0.15 (0.02-3.70)	0.62 (0.25-1.60)	Pregabalin														
2.97 (1.54-6.05)	0.13 (0.02-3.15)	0.52 (0.19, 1.51)	0.83 (0.35-2.00)	Tiagabine													
3.01 (1.40-6.73)	0.13 (0.02-3.16)	0.53 (0.18-1.49)	0.85 (0.33-2.11)	1.02 (0.33-3.42)	Lacosamide												
2.94 (1.53-5.52)	0.13 (0.02-3.27)	0.52 (0.19, 1.29)	0.82 (0.35-1.84)	0.98 (0.37-2.43)	0.96 (0.36-2.67)	Eslicarbazepine acetate											
5.15 (2.47-12.47	0.23 (0.03-5.42)	0.90 (0.33-2.87)	1.45 (0.57-4.02)	1.76 (0.63-5.21)	1.70 (0.55-5.59)	1.76 (0. 69-5.34)	Zonisamide										
7.70 (1.7-50.79)	0.36 (0.02-12.76)	1.34 (0.25, 9.95)	2.16 (0.40-15.3)	2.70 (0.48-19.21)	2.59 (0.48, 18.73)	2.61 (0.51-20.08)	1.57 (0.25-10.88)	Lamotrigine XR									
3.07 (0.57-26.5)	0.14 (0.008-5.55)	0.55 (0.08, 4.98)	0.87 (0.15-7.74)	1.01 (0.16-9.62)	1.06 (0.16-9.58)	1.08 (0.18-9.70)	0.61 (0.08-5.37)	0.40 (0.03-5.30)	Levetiracetam XR								

22.43 (0.81-148.6)	0.88 (0.01-46.05)	3.86 (0.13-30.97)	6.29 (0.21-46.11)	7.15 (0.25, 60.88)	7.52 (0.26-62.38)	7.83 (0.29-57.03)	4.18 (0.14-36.63)	2.60 (0.05-39.6)	6.67 (0.15-98.9)	Felbamate						
0.63 (0.18-1.84)	**0.03 (0.00-0.65)**	**0.10 (0.03-0.44)**	**0.18 (0.05-0.57)**	**0.21 (0.05-0.75)**	**0.21 (0.05-0.83)**	**0.22 (0.06-0.77)**	**0.12 (0.03-0.44)**	**0.08 (0.01-0.53)**	0.19 (0.02-1.57)	**0.03 (0.00-0.91)**	Valproate	3.25 (0.98-10.72)			6.50 (0.94-45.11)		2.49 (0.62, 10.05)
2.55 (1.55-4.27)	**0.11 (0.01-2.49)**	0.45 (0.18-1.08)	0.71 (0.34-1.47)	0.85 (0.37-1.99)	0.83 (0.36-2.12)	0.87 (0.38-2.02)	0.50 (0.18-1.20)	0.33 (0.04-1.68)	0.81 (0.09-5.03)	0.11 (0.01-3.27)	**3.94 (1.46-14.05)**	Topiramate	0.79 (0.40-1.55)				
1.47 (0.93-2.37)	0.06 (0.00-1.44)	**0.26 (0.11-0.63)**	**0.41 (0.20-0.84)**	0.49 (0.21-1.11)	0.48 (0.21-1.22)	0.51 (0.23-1.14)	**0.28 (0.10-0.68)**	**0.19 (0.03-0.97)**	0.47 (0.05-2.81)	0.07 (0.00-1.87)	2.2 (0.77-8.51)	0.58 (0.32-1.04)	Lamotrigine	1.81 (0.89-3.70)			
1.51 (0.93 - 2.39)	0.06 (0.00-1.54)	**0.27 (0.11-0.61)**	**0.43 (0.20-0.85)**	0.51 (0.21-1.16)	0.50 (0.21-1.20)	0.52 (0.24-1.11)	**0.29 (0.10-0.70)**	0.19 (0.03-0.97)	0.48 (0.05-2.79)	0.07 (0.00-1.89)	2.44 (0.72-8.55)	0.60 (0.29-1.15)	1.02 (0.56-1.8)	Levetiracetam			
2.88 (1.54-5.68)	0.12 (0.02-3. 07)	0.52 (0.19-1.33)	0.81 (0.34-1.87)	0.97 (0.38-2.80)	0.94 (0.36-2.73)	1.00 (0.40-2.57)	0.57 (0.19-1.50)	0.37 (0.05-2.02)	0.91 (0.09-6.01)	0.13 (0.01-3.79)	**4.54 (1.50-15.94)**	1.13 (0.51-2.60)	1.97 (0.90-4.46)	1.95 (0.88-4.42)	Gabapentin	0.95 (0.00-2.94)	
4.16 (1.67-11.74)	0.18 (0.02-5.48)	0.72 (0.23-2.55)	1.17 (0.41-3.67)	1.40 (0.44-5.31)	1.38 (0.43-5.15)	1.43 (0.48-4.93)	0.79 (0.22-2.85)	0.55 (0.07-3.51)	1.32 (0.14-9.93)	0.19 (0.02-6.39)	**7.02 (1.46-32.02)**	1.66 (0.57-5.14)	2.86 (0.97-8.82)	2.75 (1.03-8.83)	1.46 (0.56-3.85)	Vigabatrin	
1.57 (0.25-12.11)	0.06 (0.00-2.75)	0.28 (0.04-2.32)	0.44 (0.06-3.66)	0.52 (0.07-4.41)	0.51 (0.07-4.80)	0.55 (0.08-4.44)	0.30 (0.04-2.52)	0.20 (0.02-2.37)	0.48 (0.03-7.57)	0.08 (0.00 - 3.69)	2.43 (0.58 - 14.42)	0.63 (0.10-4.66)	1.06 (0.16-8.39)	1.03 (0.16-8.59)	0.52 (0.08-4.23)	0.37 (0.04-3.51)	Primidone

- Results in white are the odds ratios and 95% confidence intervals from the conventional meta-analyses of direct comparisons between the column-defining treatment and the row-defining treatment. Odds ratios greater than 1 favour the row- defining treatment (lower proportion of participants withdrawn due to adverse events).
- Results in gray are the median odds ratios and 95% credible intervals from the NMA of direct and indirect comparisons between the row-defining treatment and the column-defining treatment. Odds ratios greater than 1 favour the column- defining treatment (lower proportion of participants withdrawn due to adverse events).
- Numbers in bold highlight statistically significant results (P<0.05).

Based on the direct comparisons (in white in table 11), oxcarbazepine, pregabalin, tiagabine, lacosamide, eslicarbazepine acetate, zonisamide, lamotrigine extended release, topiramate, gabapentin and vigabatrin were less tolerable as assessed by withdrawal due to adverse events when compared to no treatment (placebo).

The random effects model used for this NMA fit reasonably well, with a residual deviance of 139.3 reported. This corresponds reasonably well to the total number of trial arms 119.

Based on the results of the NMA (in grey in Table 11) clobazam, oxcarbazepine, pregabalin, tiagabine, lacosamide, acetate, zonisamide, lamotrigine extended release, topiramate, gabapentin and vigabatrin were significantly less tolerable compared to placebo. Valproate in the NMA analysis was found to be more tolerable when compared individually to clobazam, oxcarbazepine, pregabalin, tiagabine, lacosamide, zonisamide and lamotrigine extended release. Topiramate was also more tolerable as defined by a lower proportion of withdrawals due to adverse events compared to clobazam but less tolerable when compared to sodium valproate. Lastly, oxcarbazepine was less tolerable when compared to lamotrigine and levetiracetam.

No inconsistency was identified between the direct and NMA analysis results between the comparisons of any adjunctive treatment.

Table 12 presents the relative risk of each intervention compared to a baseline risk of no treatment (placebo). It also gives a probability of the intervention that an intervention has the highest risk of withdrawal due to adverse events (or least tolerable). Based on point estimates, distribution of rank and proportion of simulations in which they are the most tolerable AEDs, valproate was the most tolerable, (it was the optimal strategy in 64.2% of simulations).

Table 12: Probability of withdrawal due to adverse events by using one of the following AEDs compared to no treatment (placebo)

AED*	Median RR^	Upper CI
		Probability intervention is most tolerable (%)
Placebo		17.87%
Valproate	0.64 (0.19, 1.78)	64.17%
Lamotrigine	1.44 (0.93, 2.25)	0.68%
Levetiracetam	1.48 (0.93, 2.26)	0.97%
Primidone	1.54 (0.25, 8.38)	9.54%
Topiramate	**2.40 (1.51, 3.77)**	0
Gabapentin	**2.68 (1.51, 4.79)**	0.01%
Eslicarbazepine acetate	**2.73 (1.50, 4.67)**	0.035%
Tiagabine	**2.75 (1.51, 5.03)**	0.005%
Lacosamide	**2.79 (1.38, 5.47)**	0.095%
Levetiracetam XR	2.84 (0.57, 13.13)	3.86%
Pregabalin	**3.25 (2.03, 5.22)**	0
Vigabatrin	**3.69 (1.63, 8.21)**	0.005%
Zonisamide	**4.42 (2.33, 8.55)**	0
Oxcarbazepine	**4.80 (2.58, 8.38)**	0.01%
Lamotrigine XR	**6.07 (1.65, 16.98)**	0.13%
Felbamate	12.08 (0.81, 21.52)	1.68%
Clobazam	12.42 (0.99, 21.65)	0.92%

*compared against the placebo

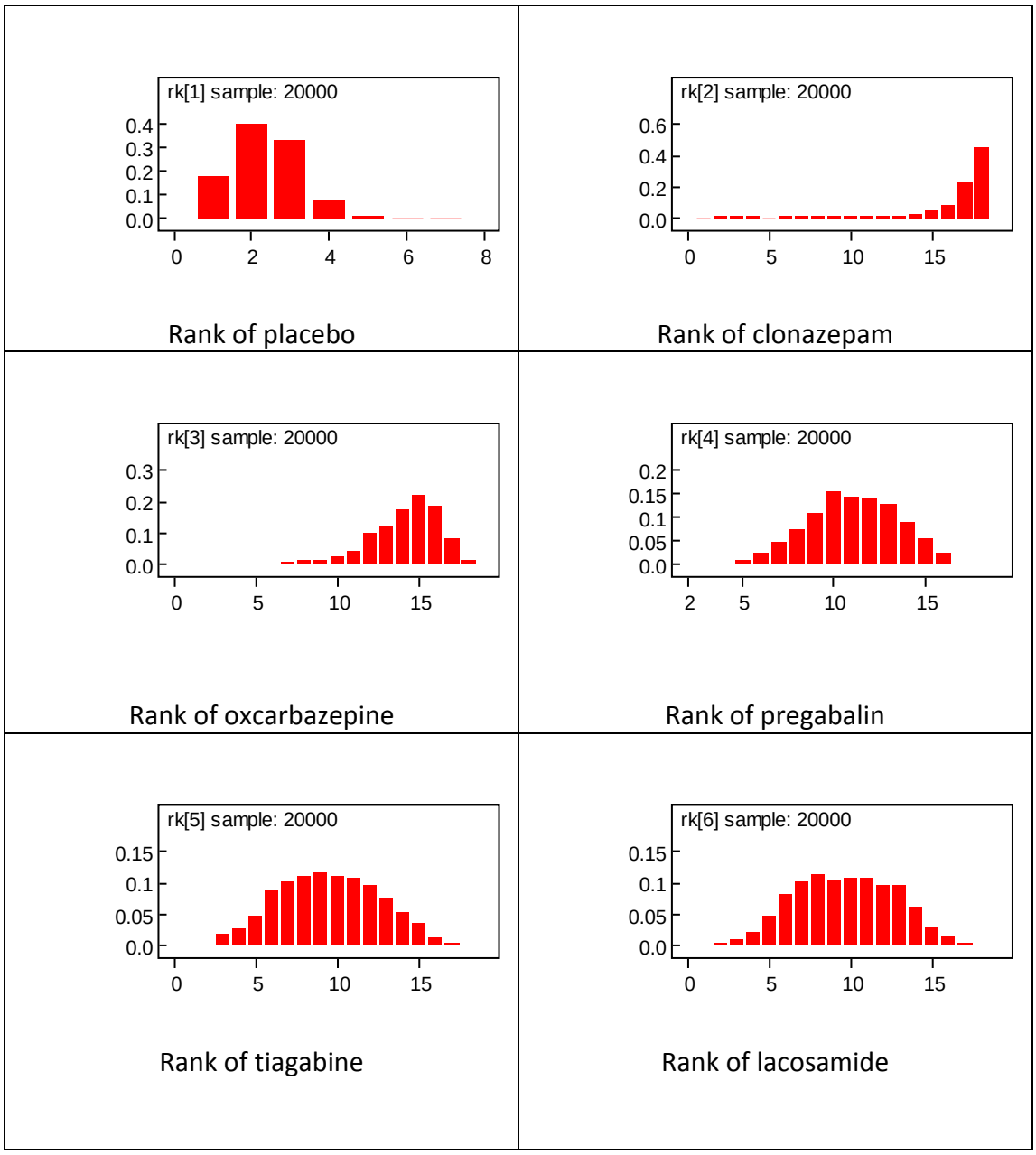
^ Median RR>1, AED was less tolerable compared to placebo

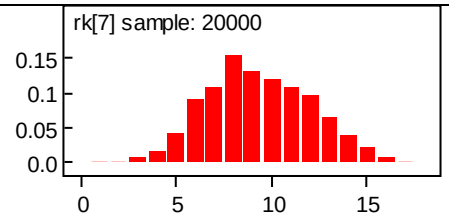
Oxcarbazepine, pregabalin, tiagabine, lacosamide, zonisamide, lamotrigine extended release, topiramate, gabapentin and vigabatrin were all found to be significantly less tolerable in relation to withdrawals due to adverse events compared to no treatment (placebo).

Based on point estimates, distribution of rank and proportion of simulations in which they are the most tolerable AEDs, valproate was the most tolerable AED (it were the optimal strategy in 64.2% of simulations).

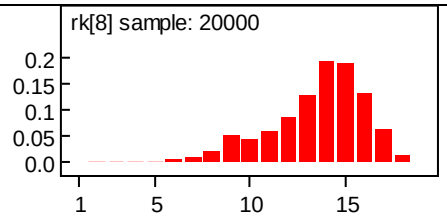
Figure 6 shows the distribution of probabilities of each intervention being ranked at each of 17 positions.

Figure 6: Ranking of interventions in network 4

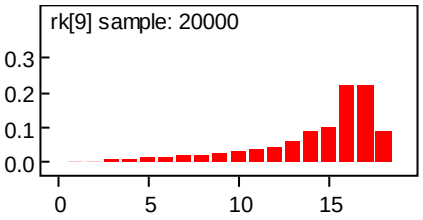




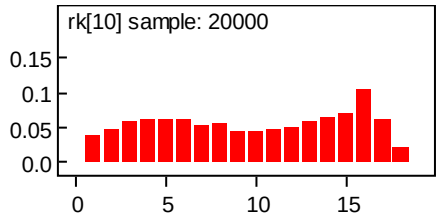
Rank of eslicarbazepine acetate



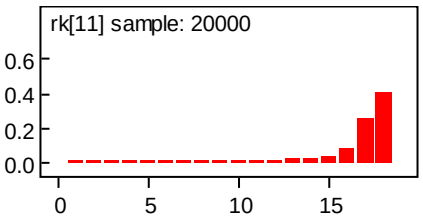
Rank of zonisamide



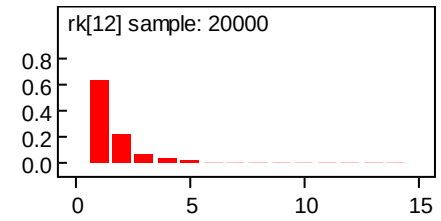
Rank of lamotrigine XR



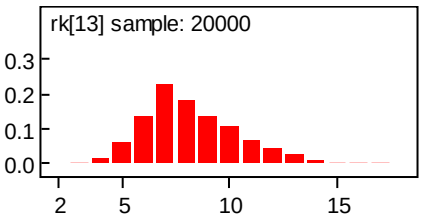
Rank of levetiracetam XR



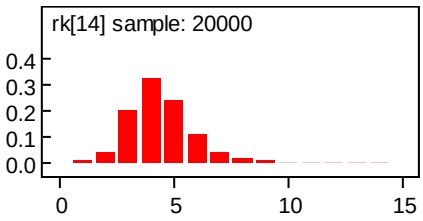
Rank of felbamate



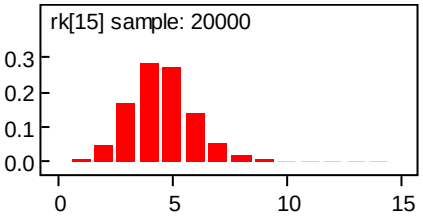
Rank of sodium valproate



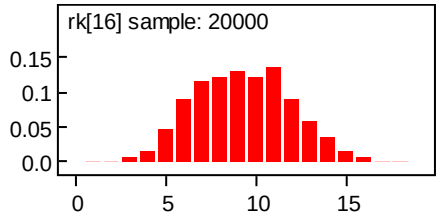
Rank of topiramate



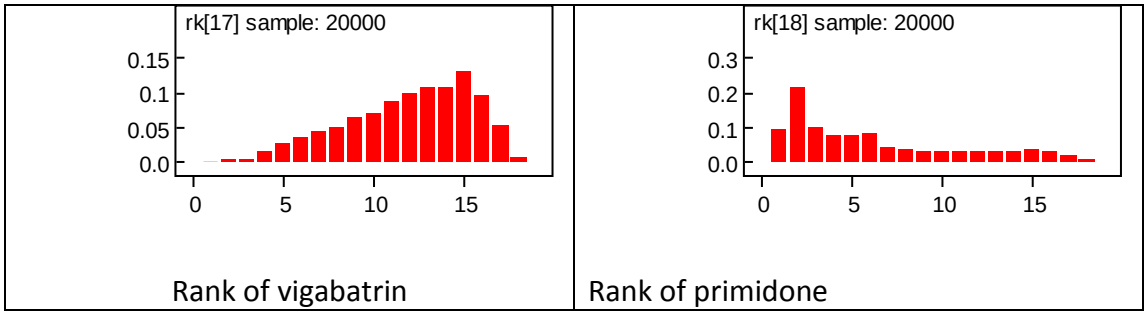
Rank of lamotrigine



Rank of levetiracetam



Rank of gabapentin



The number of patients randomised was used as the denominator in our data extraction for all parallel studies, except where it was not reported. In these situations other figures which could be used as the denominator may be available (for example, the "per protocol analysis" population or "safety population"), depending on the statistical analysis plan of the studies. In these situations, the largest number available was used as the denominator for withdrawal due to adverse events.

Based on the same principle, the number of patients entering each phase of the trial was used as the denominator whenever possible in cross over trials. However, there were instances where this information was not available, and the number of patients participating in the study was used. There was a concern that in cross over trials where the timing of drop outs are not clearly reported, there was a risk of bias from imputing number of patients randomised as the denominator; particularly when drop out rates are high, or unbalanced. If more participants from one of the arms withdrew in phase I, there will be fewer participants available to cross over to the second phase of the trial. Therefore, there will be fewer patients exposed to the drug with less withdrawals compared to the drug with more withdrawals. This could inflate the difference in proportion of patients dropping out between the two arm and may affect conclusions. Therefore, sensitivity analysis was conducted to test the robustness of including cross over trials in the NMA. The following scenarios were tested in a sensitivity analysis:

1. Including all cross over studies, regardless of drop out rates (base case)
2. Excluding cross over studies with >20% drop outs
3. Excluding cross over studies with >10% drop outs
4. Including only parallel studies, excluding any cross-over studies

Using 80,000 burn-in and 40,000 simulations (simulation was stopped when MC error/SD was 5% or less for each parameter), we found no important difference in the results between all the scenarios in terms of goodness of fit [83]and discrepancy or consistency of results [84,85]. Therefore, the results from the base case analysis were used.

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

During the literature review we identified two analyses of Individual Patient Data (IPD). The first IPD analysis compared the efficacy of carbamazepine versus sodium valproate in five monotherapy trials [86]. The second IPD was a summary of IPD evidence from randomized controlled trials of eight different AEDs (carbamazepine, sodium valproate, phenytoin, phenobarbitone, oxcarbazepine, lamotrigine) in monotherapy of focal seizures [87].

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 results [1]. The two IPD analyses were considered as supplementary evidence in monotherapy for focal seizures as they followed different reviewing protocols than those used in the guideline evidence reviews.

The main differences in the protocols set by our NMA and the two IPD analyses lie in the age profile of included population and the selection of outcomes measures. Our protocol set out separate reviews for monotherapy trials for adults and children whereas the IPD analysis reviewed evidence independently of age (trials in adults and children were combined together). The two IPD analyses carried out time to event analyses using: time to treatment failure (including both withdrawal due to adverse events and lack of efficacy), time to 12 months remission and time to first seizure. In our protocol, we set out seizure freedom and withdrawal due to adverse events as the most representative outcomes of efficacy and tolerability.

It is also important to highlight that the two types of meta-analyses (IPD and our network meta-analysis using summary data) share some common inclusion criteria; double, single and unblinded studies were included in both and the comparator drug was carbamazepine. In the second IPD analysis [87] seven common drugs were included in the two types of meta-analyses of monotherapy trials (carbamazepine, oxcarbazepine, phenytoin, lamotrigine, topiramate, valproate, gabapentin). This analysis included more studies than our network meta-analysis; 14 studies were meta-analyzed for the outcome of time to 12 months remission and 17 studies for the time to treatment failure, whereas our network meta-analysis included 12 and 15 studies for the outcomes of seizure freedom and withdrawal due to adverse events respectively. Six studies were included in both types of meta-analyses.

Table 13. Studies included in our NMA and in the second IPD analysis (Tudur Smith et al, 2007)

		IPD analysis		
	NMA (NCGC)	**Carbamazepine versus sodium evaporate monotherapy for epilepsy{Marson, 2000 5164 /id}**	**Multiple treatment comparisons in epilepsy monotherapy trials {Tudur Smith, 2007 5292 /id}**	**Exclusion reason from NMA (NCGC)**
Callaghan 1985	√			
Rastogi 1991	√			
Bill 1997	√		√	
Christe 1997	√			
Turnbull 1985	√		√	
Steiner 1999	√			
Brodie 1995	√		√	
Tanganelli 1996	√			
Marson 2007	√			
Nieto-Barrera 2001	√		√	
Chadwick 1998	√			
Chadwick 1999	√			

Kalviainen 1995	√			
Mikkelsen 1981	√			
Ramsay 1983	√		√	
Mattson 1985	√		√	
Steinhof 2005	√			
Heller 1995		√	√	Contamination; focal seizures < 80%
De Silva 1996		√	√	Contamination; partial seizures 50%
Mattson 1992		√	√	Unable to extrapolate data
Richens 1994		√	√	No efficacy data reported for placebo group
Verity 1995		√	√	Children, generalized tonic clonic population
Reunamen 1996			√	mixed partial and/or generalized seizures- no proportions are given (can not assess contamination)
Craig 1994			√	elderly
Placencia 1993			√	Contamination; focal seizures < 80%
Brodie 1999			√	elderly
Guerreiro 1997			√	children
Pal 1998			√	children

In relation to the findings, common results were revealed in our NMA and the two IPD analyses (Marson et al, 2000, Tudur Smith et al, 2007). In all analyses, no single drug was significantly more effective than carbamazepine in achieving seizure freedom and to time to 12 months remission. The only difference in results was found when data were compared for carbamazepine versus sodium valproate. In our NMA, although there was no significant difference between carbamazepine and valproate in achieving seizure freedom (median RR (95% C.I.); 1.34 (0.95, 1.73)), sodium valproate came as the most effective drug in achieving seizure freedom in

64.17% of networks' simulations. No significant difference was also found between carbamazepine and sodium valproate in achieving time to 12 months remission in the first IPD analysis [86] (HR (95% C.I); 0.87 (0.74, 1.02)). On the contrary, the second IPD analysis [87] found that sodium valproate was significantly less effective than carbamazepine (95% CI :1.01-1.42) in achieving time to 12 months remission. This difference in the results for the comparison of carbamazepine versus valproate is originated from the different studies contributing to the networks of NMA and the two IPD analyses. Studies included in the IPD analyses were excluded from our NMA on the basis of contamination on seizure types and the age distribution (Table 13). The GDG considered the IPD analyses in addition to the clinical and cost effectiveness and NMA findings in the decision making process and concluded that these did not change the recommendations. The GDG considered that valproate should still be included as a first line option along with carbamazepine, lamotrigine, and oxcarbazepine.

1.6 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in chapter 10 and appendix N, deciding upon the most effective intervention for the monotherapy and adjunctive treatment in focal seizures for newly diagnosed and refractory population is difficult. First, most interventions have not been directly compared to one another in a randomised controlled trial and second, there are many instances of overlapping comparisons that could potentially give inconsistent estimates of effect. In order to overcome the difficulty of interpreting the conclusions from these numerous separate comparisons and to identify any inconsistency within estimated treatment effects, NMA of the direct evidence were performed.

Our analyses were based on a total of 101 studies, randomised to 22 different interventions used for monotherapy and adjunctive treatment. These studies formed four networks of evidence, which were differentiated by seizure type and outcome. The first two networks were formed using data from studies that included only newly diagnosed focal seizures. The first network was used to assess

effectiveness of monotherapy in achieving seizure freedom and the second network was used to evaluate tolerability of monotherapy as defined by the proportion of people withdrawing due to adverse events. The third and fourth networks were formed using the data from the studies including refractory focal seizures; the third network was used to assess effectiveness of adjunctive treatment in achieving at least 50% reduction in seizure frequency, and, lastly, the fourth network evaluated tolerability as defined by the proportion of people withdrawing from adjunctive treatment due adverse events. The findings from the NMA have been used to facilitate decision-making for the GDG such that they could develop recommendations directed to the monotherapy and adjunctive treatment for newly diagnosed and refractory focal seizures in an adult population respectively, based on the best available direct and indirect evidence.

In the first network of monotherapy for assessing seizure freedom in newly diagnosed population, no AED (lamotrigine, oxcarbazepine, gabapentin, topiramate, vigabatrin, valproate and phenytoin) was found to be significantly different in terms of efficacy compared to carbamazepine.

In the second network of monotherapy assessing tolerability as defined by the proportion of people withdrawing due to adverse events, both lamotrigine and vigabatrin were more tolerable when compared to carbamazepine. Although the analysis was able to generate probabilities of a given intervention being the most tolerable treatment, defined as having the greatest relative risk compared to baseline drug, carbamazepine in this case, the probability estimates illustrate the considerable uncertainty around which intervention is truly optimal. For example, vigabatrin comes out as the treatment with the lowest relative risk compared to carbamazepine for withdrawing due to adverse event but it is only the best tolerable in 43.9% of simulations. This means that some other intervention or interventions are best in 56.1.% of simulations.

Similarly, when examining the results from the third network on adjunctive treatment for assessing the proportion of people achieving at least 50% reduction in seizure frequency, several AEDs (lamotrigine, vigabatrin, gabapentin, levetiracetam,

topiramate, oxcarbazepine, pregabalin, lacosamide, eslicarbazepine acetate, zonisamide, tiagabine, valproate, carbamazepine and phenytoin) were found to be significantly more effective than placebo. However, for some of these AEDs, for example lacosamide and gabapentin, the probability of being the most effective treatment was as low as 0.0%. The two most effective AEDs in achieving a reduction of at least 50% seizure frequency, based on point estimates, distribution of rank and proportion of simulations, were valproate and carbamazepine, (they were the optimal strategy in 20.5% and 18.6% of simulations respectively).

In the fourth network, all AEDs found to be significantly less tolerable than placebo in conventional meta-analysis were confirmed also in NMA, namely oxcarbazepine, pregabalin, tiagabine, lacosamide, eslicarbazepine acetate, zonisamide, lamotrigine extended release, topiramate, gabapentin and vigabatrin. Clobazam and levetiracetam were found to be significantly less tolerable than placebo only in the NMA, with valproate found to be the most tolerable in a probability of 64.17%.

All four networks seem to fit well, as demonstrated by residual deviance and no inconsistencies in the networks were found.

In summary, there are several outcome measures that could be used to evaluate the effectiveness of different interventions used in the treatment of focal seizures, but only two were used in this analysis; proportion of people achieving seizure freedom in a newly diagnosed population and the proportion of people achieving at least 50% reduction in seizures.

In addition to summarising the direct evidence into single measures of relative risk compared to no treatment, another aim of the NMA was to inform the effectiveness parameters in the economic model built to evaluate the cost-effectiveness of different AEDs used as monotherapy and adjunctive therapy in the treatment of focal epilepsy. Although not all of the interventions included in the NMA were included in the economic model, they collectively formed a network of evidence that was used to derive the best estimates of effect for those interventions that were included in the model.

A cost-effectiveness analysis (CEA) may be deterministic or probabilistic. If it is deterministic then only the point estimates for the effect sizes are used in the CEA. If it is probabilistic, a distribution will be used for each effect size instead of a point estimate. A probabilistic cost-effectiveness analysis is based on simulations as is the NMA.

The median estimates of relative risk from the network meta-analysis for effectiveness (assessed by seizure freedom in newly diagnosed focal seizures and by at least 50% reduction in seizure frequency in refractory focal seizures) and tolerability (assessed by withdrawal due to adverse events in both populations) were used in the deterministic cost-effectiveness analysis (presented in appendix P). For the probabilistic sensitivity analysis, we took the 20,000 sets of odds ratios from the network meta-analysis and we then sampled from this 'data' set for each of 10,000 Monte Carlo simulations. In each probabilistic simulation, a set of odds ratios were selected (one for each intervention) from the same NMA simulation, thereby preserving the joint posterior distributions and incorporating all uncertainty and correlation of treatment effects.

1.7 Conclusion

The first network for newly diagnosed focal seizures demonstrated that no AED was significantly more effective than carbamazepine in achieving seizure freedom. However, phenytoin and valproate ranked as the most effective AEDs in achieving seizure freedom (they were the optimal strategy in 45.9% and 44.2% of simulations respectively). Vigabatrin and sodium valproate were the most tolerable AEDs (they were the optimal strategy in 43.9% and 33.4% of simulations respectively)..

In refractory focal seizures, most AEDs were significantly more effective in reducing at least 50% seizure frequency compared to placebo. Sodium valproate, phenytoin, carbamazepine and primidone were the most effective in achieving a reduction of at least 50% seizure frequency , with a probability of 20.47 %, 19.71%, 18.58% and 17.64% respectively.

For withdrawal due to adverse events, most of the AEDs were significantly less tolerable compared to placebo, with sodium valproate found to be the most tolerable in a probability of 64.17%.

WinGUGS codes for the random effects model for the monotherapy treatment of focal seizures: multi-arm trials (any number of arms)

```
1
2   model{
3   for(i in 1:9){
4           w[i,1] <-0
5                   delta[i,t[i,1]]<-0
6                   mu[i] ~ dnorm(0,.0001)                                  # vague priors for trial
7   baselines
8                   for (k in 1:na[i])  {
9                       r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])                       # binomial
10  likelihood
11                                  logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]
12                                  # model
13  #Deviance residuals for data i
14        rhat[i,k] <- p[i,t[i,k]] * n[i,k]
15        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))  +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) -
16  log(n[i,k]-rhat[i,k])))
17                          }
18
19              sdev[i]<- sum(dev[i,1:na[i]])
20
21                          for (k in 2:na[i]) {
22                  delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])I(-5,5)          # trial-specific
23  LOR distributions
24                  md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]]  + sw[i,k]               # mean of LOR
25  distributions
26                  taud[i,t[i,k]] <- tau *2*(k-1)/k                            #precision of LOR
27  distributions
28                  w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])        #adjustment, multi-arm
29  RCTs
30                  sw[i,k] <-sum(w[i,1:k-1])/(k-1) }               # cumulative adjustment for
31  multi-arm trials
32    }
33
34  d[1]<-0
35  for (k in 2:8){d[k] ~ dnorm(0,.0001) }                  #  vague priors for basic parameters
36
37  sd~dunif(0,2)                                   #  vague prior for random effects standard
38  deviation
39  tau<-1/pow(sd,2)
40
41  A<-0.363
42  for (k in 2:8) {logit(T[k])<-logit(A)+d[k]}
43
44  rr[1]<-1
45  for (k in 2:8)  {logit(v[k])<-logit(0.363)+d[k]
46  rr[k]<-v[k]/0.363 }                         # calculate relative risk
47
```

```
sumdev <- sum(sdev[])                                   # Calculate residual
deviance

# Ranking and prob{treatment k is best}
 for (k in 1:8) {
            rk[k]<-9-rank(rr[],k)
best[k]<-equals(rank(rr[],k),8)}


# pairwise ORs
for (c in 1:(8-1))
        {  for (k in (c+1):8)
             {  lor[c,k] <- d[k] - d[c]
               log(or[c,k]) <- lor[c,k]
             }
         }
}



# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of
treatments
#        per trial in the dataset. In this dataset M is 4.


# NT=8 NS=9  BR=0.363



list(
d=c(NA,1,2,3, 4,5,6,7), # one for each treatment
sd=1,
mu=c(1,2,3,4,5,  6,7,8,9) # one for each trial

)


)

list(
d=c(NA,0.1,-1,-0.2),
sd=.2,
mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

WinGUGS codes for the random effect model for the adjunctive treatment of focal seizures : includes correlation structure for 3-arm trials

```
model{
sw[1] <- 0
for(i in 1:104)  {
    logit(p[i])<-mu[s[i]]+ delta[i]  * (1-equals(t[i],b[i]))                    #
model
    r[i]~dbin(p[i],n[i])                                                  #  binomial
likelihood
     delta[i] ~ dnorm(md[i],taud[i])I(-5,5)                              # trial-specific LOR
distributions
     taud[i] <- tau * (1 + equals(m[i],3) /3)                    # precisions of LOR
distributions
    md[i] <- d[t[i]] - d[b[i]]  +  equals(m[i],3) * sw[i]              # means of LOR
distributions

#Deviance residuals for data i
    rhat[i] <- p[i] * n[i]
    dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))

   }

sumdev <- sum(dev[])                                          # Calculate residual
deviance


for (i in 2:104)  {   sw[i] <- (delta[i-1] -  d[t[i-1]] + d[b[i-1]])/2}          # adjustment for
3-arm trials

for(j in 1:52){ mu[j]~dnorm(0,.0001) }                        # vague priors for NS trial
baselines

d[1]<-0
for (k in 2:17)  {d[k] ~ dnorm(0,.0001) }                     # vague priors for basic
parameters

sd~dunif(0,2)                          #  vague prior for random effects standard
deviation
tau<-1/pow(sd,2)

rr[1]<-1
for (k in 2:17)  {logit(v[k])<-logit(0.150)+d[k]
```

```
rr[k]<-v[k]/0.150 }                    # calculate relative risk

# Ranking and prob{treatment k is best}
 for (k in 1:17) {
            rk[k]<-18-rank(rr[],k)
best[k]<-equals(rank(rr[],k),17)}

# Pairwise ORs
for (c in 1:(17-1))
        {  for (k in (c+1):17)
             {  lor[c,k] <- d[k] - d[c]
               log(or[c,k]) <- lor[c,k]
             }
         }
}


#initial 1
list(
d=c(NA,-0.5,-1,-0.2, 0,-0.5,-1,-0.2, 0,-0.5,-1,-0.2, 0,-0.5,-1,-0.2, 2), # one for each
treatment
sd=1.2,
mu=c(-2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6,  -
2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6, -2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-
2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-
2.6,  -2.2,-2.3), # one for each trial
delta=c(0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-
0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-
0.2,-0.4,-0.6,-0.8, 0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,
0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-
0.8,  0,-0.2,-0.4,-0.6,-0.8, 0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-
0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6) # one for each data point
)

#initial 2
list(
d=c(NA,0,1,0), # one for each treatment
sd=.1,
mu=c(0,1,0,1,0,  -1,0,-1,0,-1,  0,1,0,1,0,  -1,0,-1,0,-1,  0,1,0,1),  # one for each trial
delta=c(0,1,0,1,0,  -1,0,-1,0,-1,  0,1,0,1,0,  -1,0,-1,0,-1,  0,1,0,1,0,  -1,0,-1,0,-1,
0,1,0,1,0,  -1,0,-1,0,-1, 0,1,0,1) # one for each data point
)
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