## File e-4: ONLY PROSPECTIVE STUDIES PAIRWISE COMPARISONS

<u>Phenytoin (PHT) versus phenobarbital (PB).</u> There were no statistically significant differences in effectiveness between PHT and PB [0.68 (95% CI: 0.6-0.76) versus 0.79 (95% CI: 0.68-0.87), p = 0.125283].

Study	Proportion	95%-CI					
PHT							
Agarwal et al, 2007	0.84	[0.71; 0.93]				1	_
Alvarez et al, 2011	0.59	[0.46; 0.70]		_	1	-	
Chitsaz et al, 2013	0.60	[0.32; 0.84]			-		
Chakravarhi et al, 2015	0.68	[0.45; 0.86]		_	-		
Mundlarmuri et al, 2015	0.68	[0.53; 0.80]			-	_	
Gujjar et al, 2017	0.70	[0.51; 0.85]				+	
Random effects model		[0.60; 0.76]			-		
Heterogeneity: $I^2 = 43\% [0\%]$	77%]						
PB							
Malamiri et al, 2012	0.77	[0.58; 0.90]				<u> </u>	
Su et al, 2016	0.81	[0.65; 0.92]			_	-	-
Random effects model	0.79	[0.68; 0.87]			-		
Heterogeneity: $I^2 = 0\%$	2						
Test for subgroup difference	s: $\chi_1^2 = 2.35$ , df =		ı	I	I	ı	ı
		0	0.2	0.4	0.6	8.0	1

<u>Phenytoin (PHT) versus valproate (VPA).</u> There were no statistically significant differences in effectiveness between PHT and VPA [0.68 (95% CI: 0.6-0.76) versus 0.71 (95% CI: 0.6-0.8), p = 0.708281].

Study	Proportion	95%-CI	
PHT			
Agarwal et al, 2007	0.84	[0.71; 0.93]	
Alvarez et al, 2011	0.59	[0.46; 0.70]	<del>-   -   -   -   -   -   -   -   -   -  </del>
Chitsaz et al, 2013	0.60	[0.32; 0.84]	
Chakravarhi et al, 2015	0.68	[0.45; 0.86]	-
Mundlarmuri et al, 2015	0.68	[0.53; 0.80]	<del>-   -  </del>
Gujjar et al, 2017	0.70	[0.51; 0.85]	
Random effects mode		[0.60; 0.76]	<b>→</b>
Heterogeneity: $I^2 = 43\%$ [ 0%]	77%]		
VPA			
Agarwal et al, 2007	0.88	[0.76; 0.95]	<del></del>
Olsen et al, 2007	0.73	[0.56; 0.86]	
Alvarez et al, 2011	0.75	[0.62; 0.85]	<del></del>
Chen et al, 2011	0.50	[0.31; 0.69]	<del></del>
Malamiri et al, 2012	0.90	[0.73; 0.98]	<del></del>
Chitsaz et al, 2013	0.73	[0.45; 0.92]	
Mundlarmuri et al, 2015	0.68	[0.53; 0.80]	
Su et al, 2016	0.44	[0.28; 0.62]	
Misra et al, 2017	0.70	[0.51; 0.84]	
Random effects model	0.71	[0.60; 0.80]	•
Heterogeneity: $I^2 = 72\%$ [44%]		_	
Test for subgroup difference	es: $\chi_1^2 = 0.14$ , df =	$= 1 (p = 0.71)^{-1}$	1 1 1 1 1
	•	0	0.2 0.4 0.6 0.8 1

**Phenytoin** (PHT) versus levetiracetam (LEV). There were no statistically significant differences in effectiveness between PHT and VPA [0.68 (95% CI: 0.6-0.76) versus 0.64 (95% CI: 0.51-0.76), p = 0.5838824].

Study	Proportion	95%-CI					
PHT							
Agarwal et al, 2007	0.84	[0.71; 0.93]				-	_
Alvarez et al, 2011	0.59	[0.46; 0.70]		_		-	
Chitsaz et al, 2013	0.60	[0.32; 0.84]			-		
Chakravarhi et al, 2015	0.68	[0.45; 0.86]		_			
Mundlarmuri et al, 2015	0.68	[0.53; 0.80]			-		
Gujjar et al, 2017	0.70	[0.51; 0.85]			$\overline{}$	•	
Random effects model		[0.60; 0.76]			-		
Heterogeneity: $I^2 = 43\%$ [ 0%;	; 77%]						
LEV	-						
Eue et al, 2009	0.48	[0.31; 0.66]					
Alvarez et al, 2011	0.52	[0.38; 0.65]		-	+		
Atmaca et al, 2015	0.70	[0.35; 0.93]				1	_
Chakravarhi et al, 2015	0.59	[0.36; 0.79]			-		
Mundlarmuri et al, 2015	0.78	[0.64; 0.88]			_	-	
Gujjar et al, 2017	0.82	[0.60; 0.95]					_
Random effects model		[0.51; 0.76]				-	
Heterogeneity: $I^2 = 64\%$ [13%]	5; 85%]						
Test for subgroup difference	es: $\chi_1^2 = 0.30$ , df =	$= 1 (p = 0.59)^{-1}$	ı	- 1	ı	- 1	- 1
		0	0.2	0.4	0.6	8.0	1

**Phenytoin** (PHT) versus lacosamide (LAC). There were no statistically significant differences in effectiveness between PHT and VPA [0.68 (95% CI: 0.6-0.76) versus 0.66 (95% CI: 0.51-0.79), p = 0.8064959].

Study	Proportion	95%-CI					
PHT							
Agarwal et al, 2007	0.84	[0.71; 0.93]				-	_
Alvarez et al, 2011	0.59	[0.46; 0.70]		_	1	-	
Chitsaz et al, 2013	0.60	[0.32; 0.84]			- 0		
Chakravarhi et al, 2015	0.68	[0.45; 0.86]		_	1	<del></del>	
Mundlarmuri et al, 2015	0.68	[0.53; 0.80]			-	<del></del>	
Gujjar et al, 2017	0.70	[0.51; 0.85]				+	
Random effects model Heterogeneity: $I^2 = 43\%$ [ 0%;	<b>0.68</b>	[0.60; 0.76]			<b>-</b>		
LAC							
d'Orsi et al, 2016	0.78	[0.40; 0.97]				•	
Misra et al, 2017	0.64	[0.45; 0.80]		_	-		
Random effects model	0.66	[0.51; 0.79]			-		
Heterogeneity: $I^2 = 0\%$	2						
Test for subgroup difference	s: $\chi_1^2 = 0.06$ , df =	$= 1 (p = 0.80)^{-1}$	ı	- 1	ı	- 1	ı
	•	0	0.2	0.4	0.6	8.0	1

<u>Phenobarbital (PB) versus valproate (VPA).</u> There were no statistically significant differences in effectiveness between PB and VPA [0.79 (95% CI: 0.68-0.87) versus 0.71 (95% CI: 0.6-0.8), p = 0.2597667].

Study	Proportion	95%-CI					
PB							
Malamiri et al, 2012	0.77	[0.58; 0.90]					
Su et al, 2016	0.81	[0.65; 0.92]			_	4	-
Random effects model		0.68; 0.87]			-	<b>—</b>	
Heterogeneity: $I^2 = 0\%$		•					
VPA							
Agarwal et al, 2007	0.88	[0.76; 0.95]				-	_
Olsen et al, 2007	0.73	[0.56; 0.86]				1	
Alvarez et al, 2011	0.75	[0.62; 0.85]				1	
Chen et al, 2011	0.50	[0.31; 0.69]		$\overline{}$	+		
Malamiri et al, 2012	0.90	[0.73; 0.98]					-
Chitsaz et al, 2013	0.73	[0.45; 0.92]		_			-
Mundlarmuri et al, 2015	0.68	[0.53; 0.80]			-	<del>                                     </del>	
Su et al, 2016	0.44	[0.28; 0.62]	-	1			
Misra et al, 2017	0.70	[0.51; 0.84]					
Random effects model	0.71	0.60; 0.80]			-		
Heterogeneity: $I^2 = 72\%$ [44%]	; 86%]	_					
Test for subgroup difference	es: χ <sub>1</sub> = 1.27, df =	1 $(p = 0.26)$	ı	ı	1	1	ı
	-	0	0.2	0.4	0.6	8.0	1

<u>Phenobarbital (PB) versus levetiracetam (LEV).</u> There were no statistically significant differences in effectiveness between PB and VPA [0.79 (95% CI: 0.68-0.87) versus 0.64 (95% CI: 0.51-0.76), p = 0.07098913].

Study	Proportion	95%-CI					
PB							
Malamiri et al, 2012	0.77	[0.58; 0.90]				-	
Su et al, 2016	0.81	[0.65; 0.92]			_		-
Random effects mode	0.79	[0.68; 0.87]			-		
Heterogeneity: $I^2 = 0\%$		•					
LEV							
Eue et al, 2009	0.48	[0.31; 0.66]		-			
Alvarez et al, 2011	0.52	[0.38; 0.65]		-	1		
Atmaca et al, 2015	0.70	[0.35; 0.93]				•	_
Chakravarhi et al, 2015	0.59	[0.36; 0.79]			1		
Mundlarmuri et al, 2015	0.78	[0.64; 0.88]			_	1	
Gujjar et al, 2017	0.82	[0.60; 0.95]				1	_
Random effects mode		[0.51; 0.76]			-	-	
Heterogeneity: $I^2 = 64\%$ [13%]	5; 85%]						
Test for subgroup difference	es: χ <sub>1</sub> = 3.26, df =		- 1	I	ı	ı	ı
		0	0.2	0.4	0.6	8.0	1

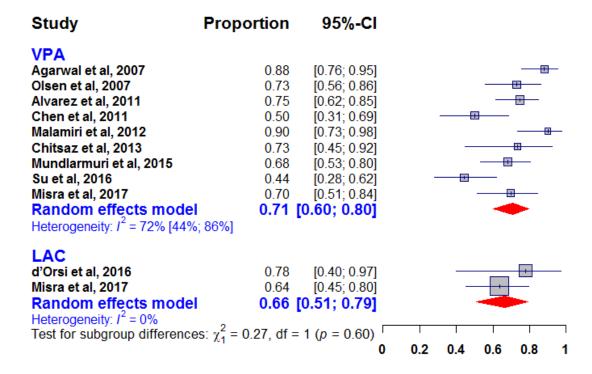
<u>Phenobarbital (PB) versus lacosamide (LAC).</u> There were no statistically significant differences in effectiveness between PB and VPA [0.79 (95% CI: 0.68-0.87) versus 0.66 (95% CI: 0.51-0.79), p = 0.1463393].

Study	Proportion	95%-CI					
PB Malamiri et al, 2012 Su et al, 2016 Random effects model Heterogeneity: $I^2 = 0\%$	0.77 0.81 <b>0.79</b>	[0.58; 0.90] [0.65; 0.92] <b>[0.68; 0.87]</b>				•	-
LAC d'Orsi et al, 2016 Misra et al, 2017 Random effects model Heterogeneity: $I^2 = 0\%$	0.78 0.64 <b>0.66</b>	[0.40; 0.97] [0.45; 0.80] <b>[0.51; 0.79]</b>			_	1	
Test for subgroup difference	s: $\chi_1^2 = 2.11$ , df	= 1 (p = 0.15)	0.2	0.4	0.6	0.8	1

<u>Valproate (VPA) versus levetiracetam (LEV).</u> There were no statistically significant differences in effectiveness between VPA and LEV [0.71 (95% CI: 0.6-0.8) versus 0.64 (95% CI: 0.51-0.76), p = 0.4095867].

Study	Proportion	95%-CI	
VPA			
Agarwal et al, 2007	0.88	[0.76; 0.95]	<del></del>
Olsen et al, 2007	0.73	[0.56; 0.86]	
Alvarez et al, 2011	0.75	[0.62; 0.85]	
Chen et al, 2011	0.50	[0.31; 0.69]	-
Malamiri et al, 2012	0.90	[0.73; 0.98]	
Chitsaz et al, 2013	0.73	[0.45; 0.92]	
Mundlarmuri et al, 2015	0.68	[0.53; 0.80]	
Su et al, 2016	0.44	[0.28; 0.62]	
Misra et al, 2017	0.70	[0.51; 0.84]	
Random effects model	0.71	[0.60; 0.80]	•
Heterogeneity: $I^2 = 72\%$ [44%]	; 86%]	•	
LEV			
Eue et al, 2009	0.48	[0.31; 0.66]	
Alvarez et al, 2011	0.52	[0.38; 0.65]	<del>- ] -  </del>
Atmaca et al, 2015	0.70	[0.35; 0.93]	
Chakravarhi et al, 2015	0.59	[0.36; 0.79]	
Mundlarmuri et al, 2015	0.78	[0.64; 0.88]	
Gujjar et al, 2017	0.82	[0.60; 0.95]	-
Random effects model	0.64	[0.51; 0.76]	
Heterogeneity: $I^2 = 64\%$ [13%]		- · -	
Test for subgroup difference	s: $\chi_1^2 = 0.68$ , df =	= 1 (p = 0.41)	
_ <u>-</u>		0	0.2 0.4 0.6 0.8 1

<u>Valproate (VPA) versus lacosamide (LAC).</u> There were no statistically significant differences in effectiveness between VPA and LEV [0.71 (95% CI: 0.6-0.8) versus 0.66 (95% CI: 0.51-0.79), p = 0.6033318].



<u>Levetiracetam (LEV) versus lacosamide (LAC).</u> There were no statistically significant differences in effectiveness between LEV and LAC [0.64 (95% CI: 0.51-0.76) versus 0.66 (95% CI: 0.51-0.79), p = 0.8414806].

Study	Proportion	95%-CI					
LEV							
Eue et al, 2009	0.48	[0.31; 0.66]		+			
Alvarez et al, 2011	0.52	[0.38; 0.65]			1		
Atmaca et al, 2015	0.70	[0.35; 0.93]				1	_
Chakravarhi et al, 2015	0.59	[0.36; 0.79]			1		
Mundlarmuri et al, 2015	0.78	[0.64; 0.88]			_	1	
Gujjar et al, 2017	0.82	[0.60; 0.95]				1	_
Random effects model		[0.51; 0.76]			•	-	
Heterogeneity: $I^2 = 64\%$ [13%]	; 85%]						
LAC							
d'Orsi et al, 2016	0.78	[0.40; 0.97]				-	
Misra et al, 2017	0.64	[0.45; 0.80]		_	-		
Random effects model	0.66	0.51; 0.79]			-		
Heterogeneity: $I^2 = 0\%$		· ·					
Test for subgroup difference	s: $\chi_1^2 = 0.04$ , df =	1 $(p = 0.84)$		T			
<b>.</b>	~1	0	0.2	0.4	0.6	8.0	1