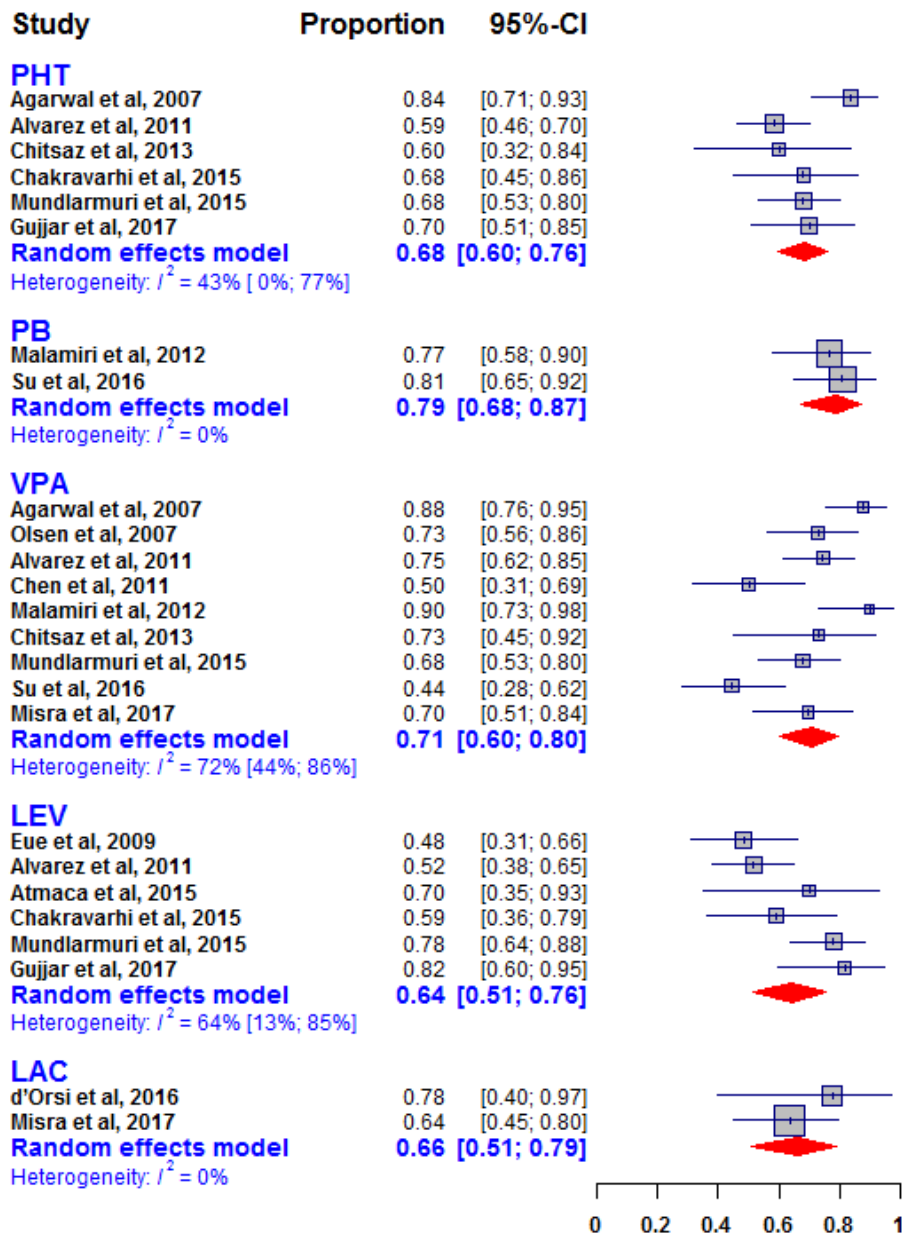# File e-3: ONLY PROSPECTIVE STUDIES

Considering only prospective studies showed that the most effective non-BZD AED was PB with a SS of 0.79 (95% CI: 0.68-0.87) followed by VPA 0.71 (95% CI: 0.6-0.8), PHT 0.68 (95% CI: 0.6-0.76), LAC 0.66 (95% CI: 0.51-0.79), and the least effective non-BZD AED was LEV 0.64 (95% CI: 0.51-0.76).
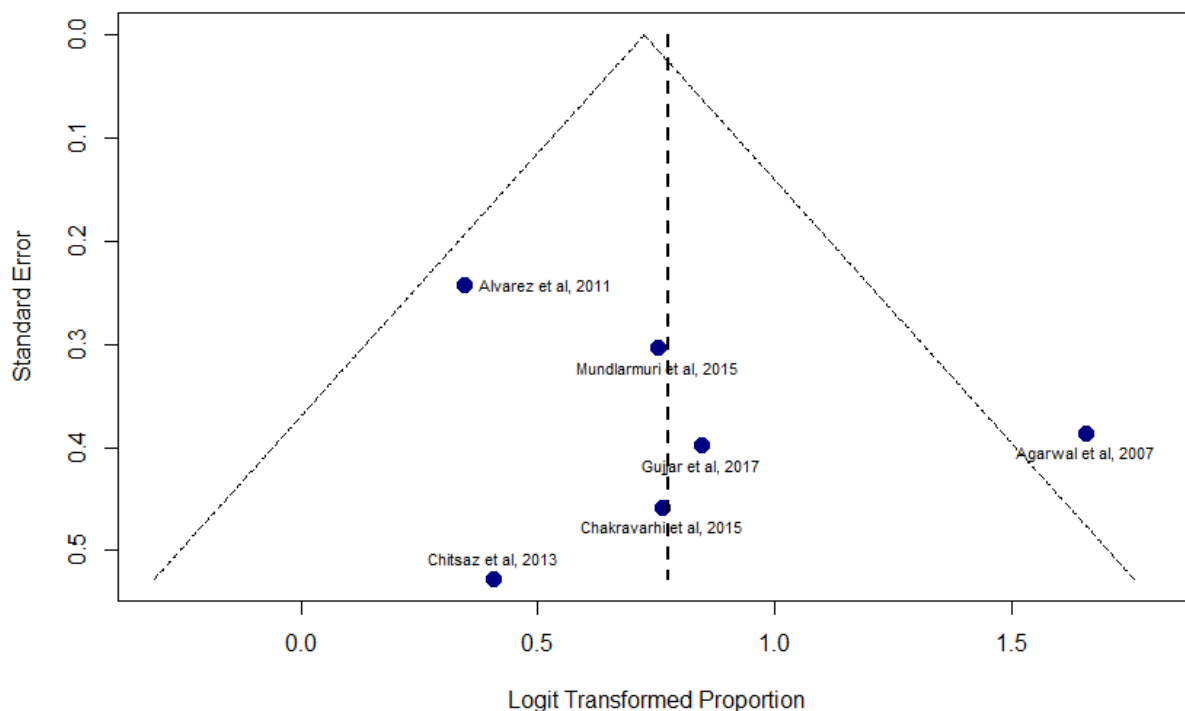
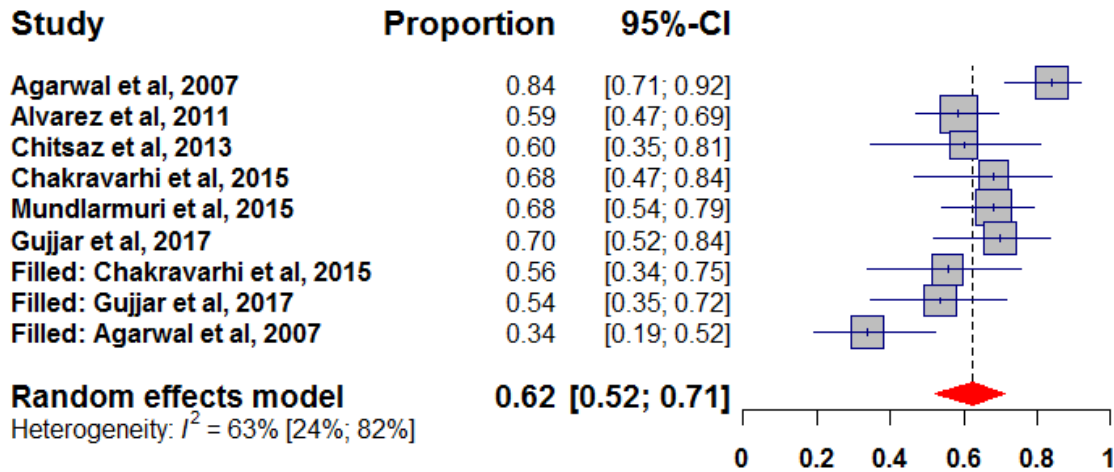## ADJUSTMENT FOR PUBLICATION BIAS IN ONLY PROSPECTIVE STUDIES

__Phenytoin (PHT).__ The distribution of prospective studies evaluating the effectiveness of PHT showed evidence of publication bias and, therefore, adjustment for publication bias with Duval and Tweedie's trim and fill method resulted in a different estimation of SS than the original one.
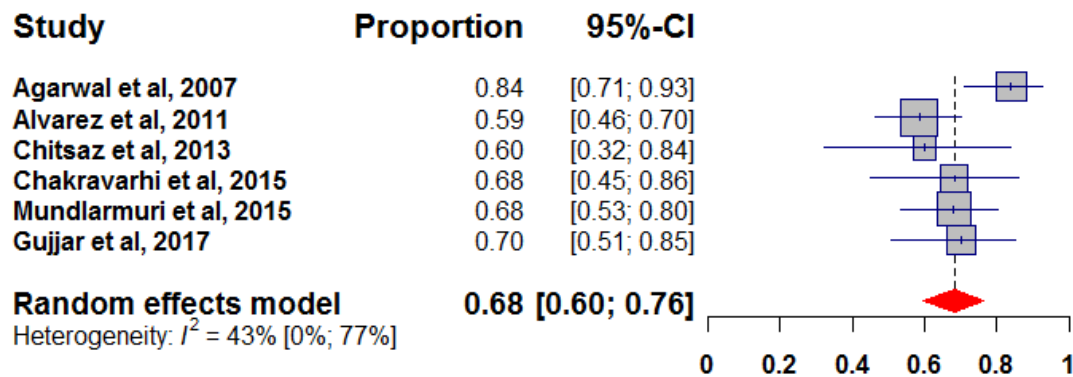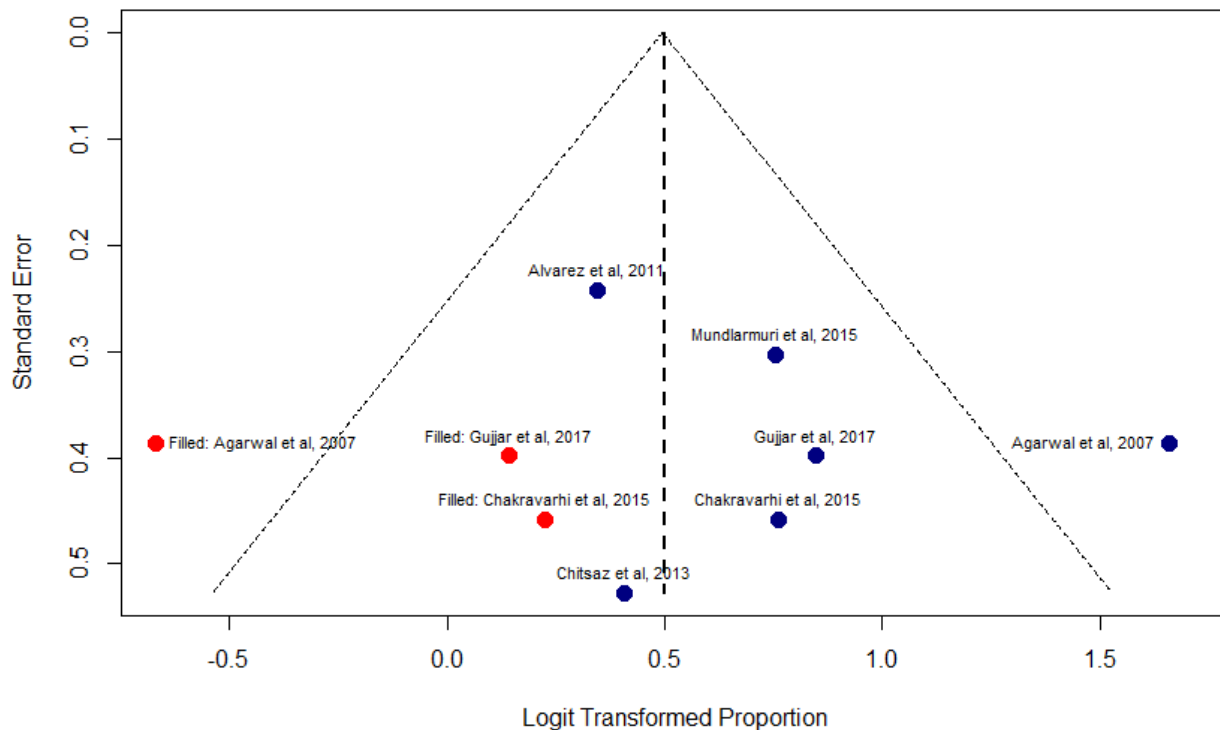

Original forest plot of the effectiveness of PHT. The probability of stopping seizures (SS) is 0.68 (95% CI: 0.6-0.76).

Funnel plot showing evidence of publication bias.

Study | **Proportion** | **95%-CI**

Study	Proportion	95%-CI
Agarwal et al, 2007	0.84	[0.71; 0.92]
Alvarez et al, 2011	0.59	[0.47; 0.69]
Chitsaz et al, 2013	0.60	[0.35; 0.81]
Chakravarhi et al, 2015	0.68	[0.47; 0.84]
Mundlarmuri et al, 2015	0.68	[0.54; 0.79]
Gujjar et al, 2017	0.70	[0.52; 0.84]
Filled: Chakravarhi et al, 2015	0.56	[0.34; 0.75]
Filled: Gujjar et al, 2017	0.54	[0.35; 0.72]
Filled: Agarwal et al, 2007	0.34	[0.19; 0.52]
Random effects model	**0.62 [0.52; 0.71]**	

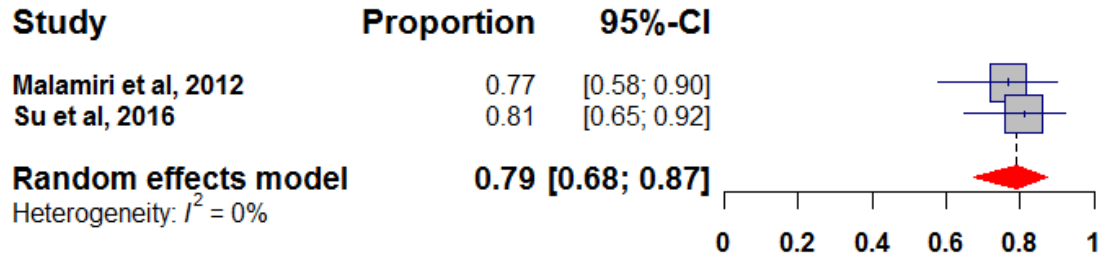Heterogeneity: $I^2 = 63\%$ [24%; 82%]

Forest plot of the effectiveness of PHT after applying Duval and Tweedie's trim and fill method. The probability of stopping seizures (SS) is 0.62 (95% CI: 0.52-0.71).
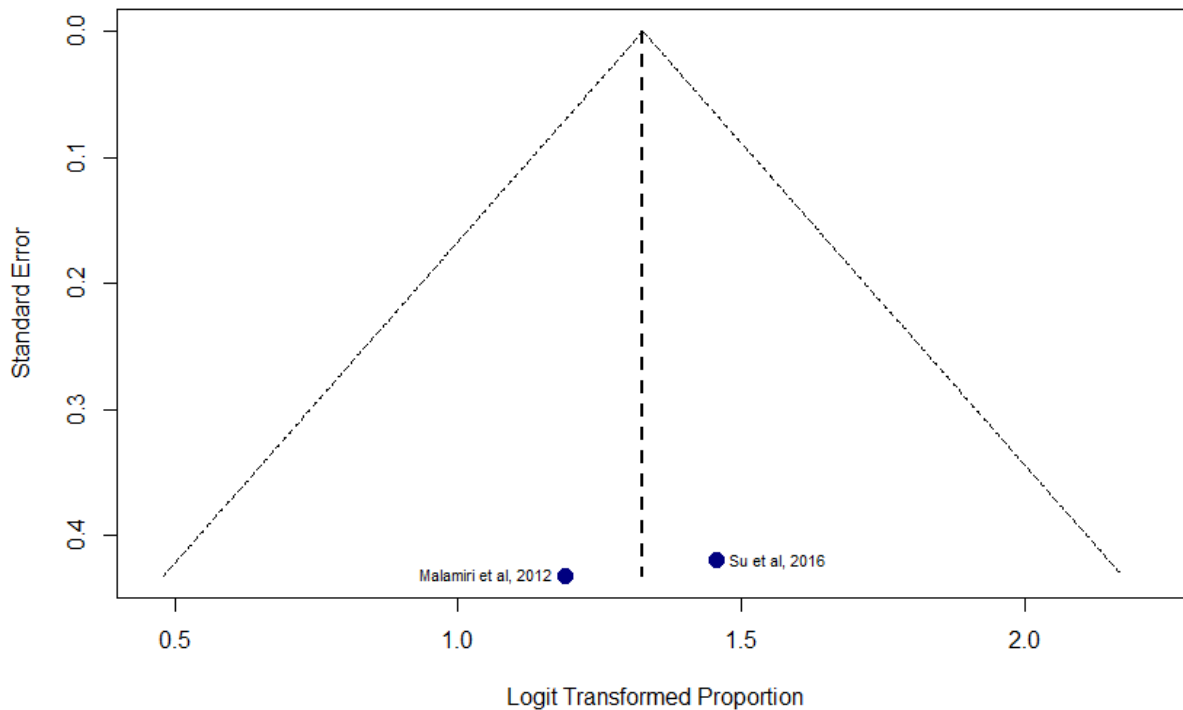

Funnel plot showing the imputed study after applying Duval and Tweedie's trim and fill method, adjusting for publication bias.

Phenobarbital (PB). The distribution of prospective studies evaluating the effectiveness of PB showed no evidence of publication bias and, correction for publication bias with Duval and Tweedie's trim and fill method is not possible with only two studies.

Study	Proportion	95%-CI	
Malamiri et al, 2012	0.77	[0.58; 0.90]	
Su et al, 2016	0.81	[0.65; 0.92]	
Random effects model	**0.79 [0.68; 0.87]**		
Heterogeneity: $I^2 = 0\%$			

Original forest plot of the effectiveness of PB. The probability of stopping seizures (SS) is 0.79 (95% CI: 0.68-0.87).
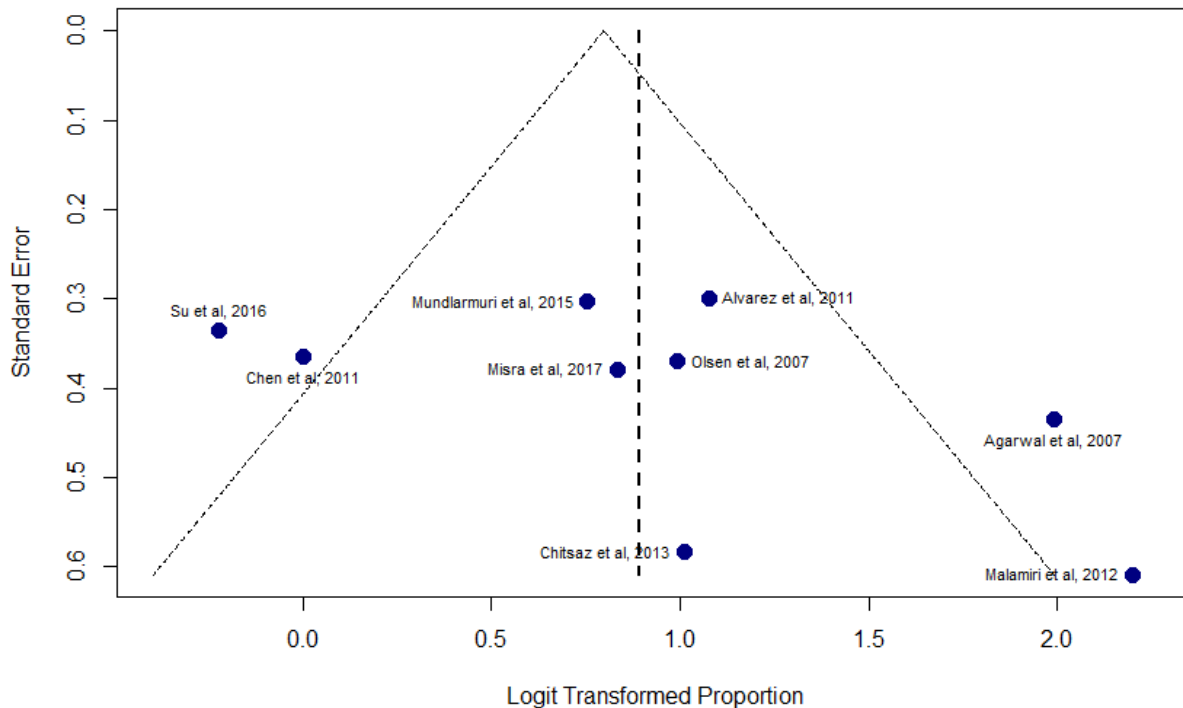

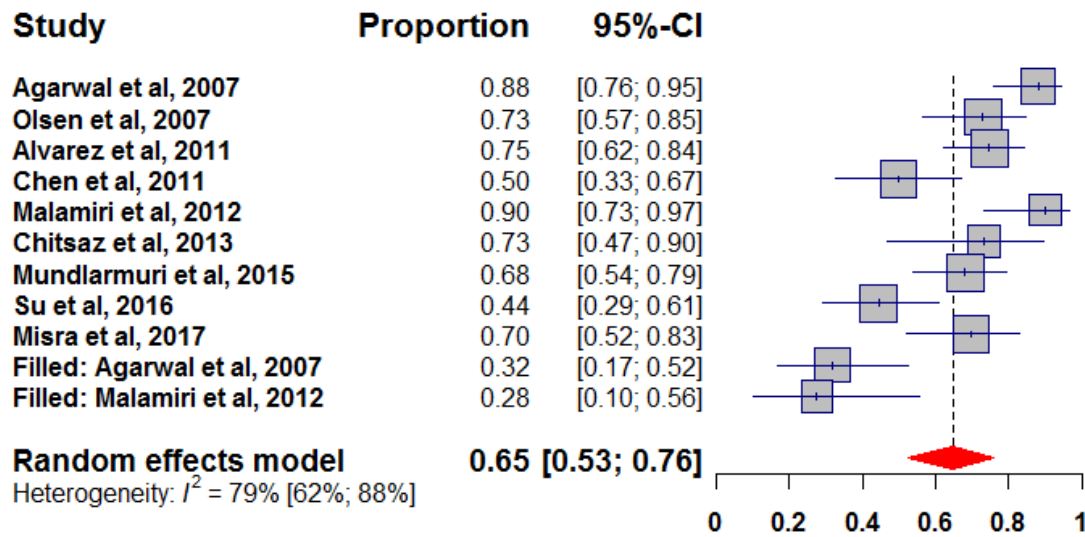**Funnel plot showing no evidence of publication bias.**

Valproate (VPA). The distribution of prospective studies evaluating the effectiveness of VPA showed evidence of publication bias and, therefore, correction for publication bias with Duval and Tweedie's trim and fill method resulted in a different estimation of SS than the original one.
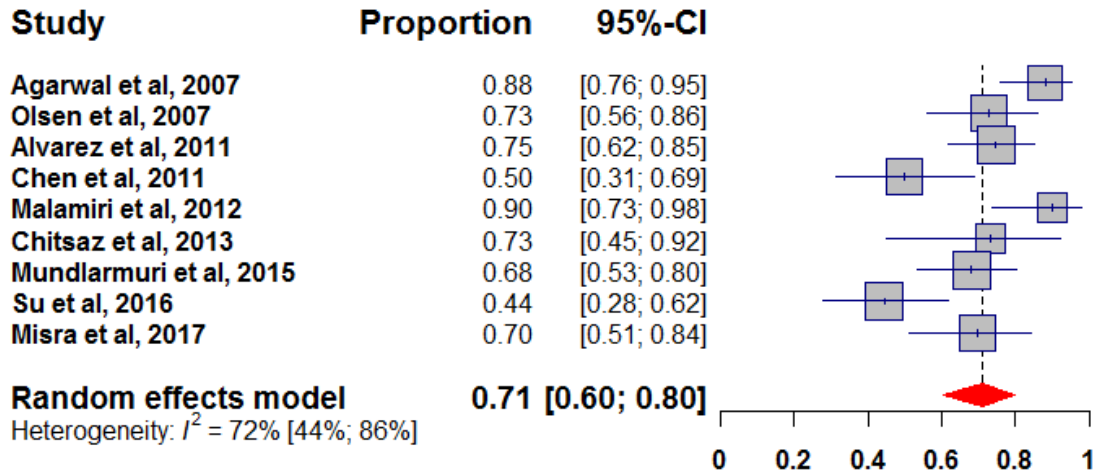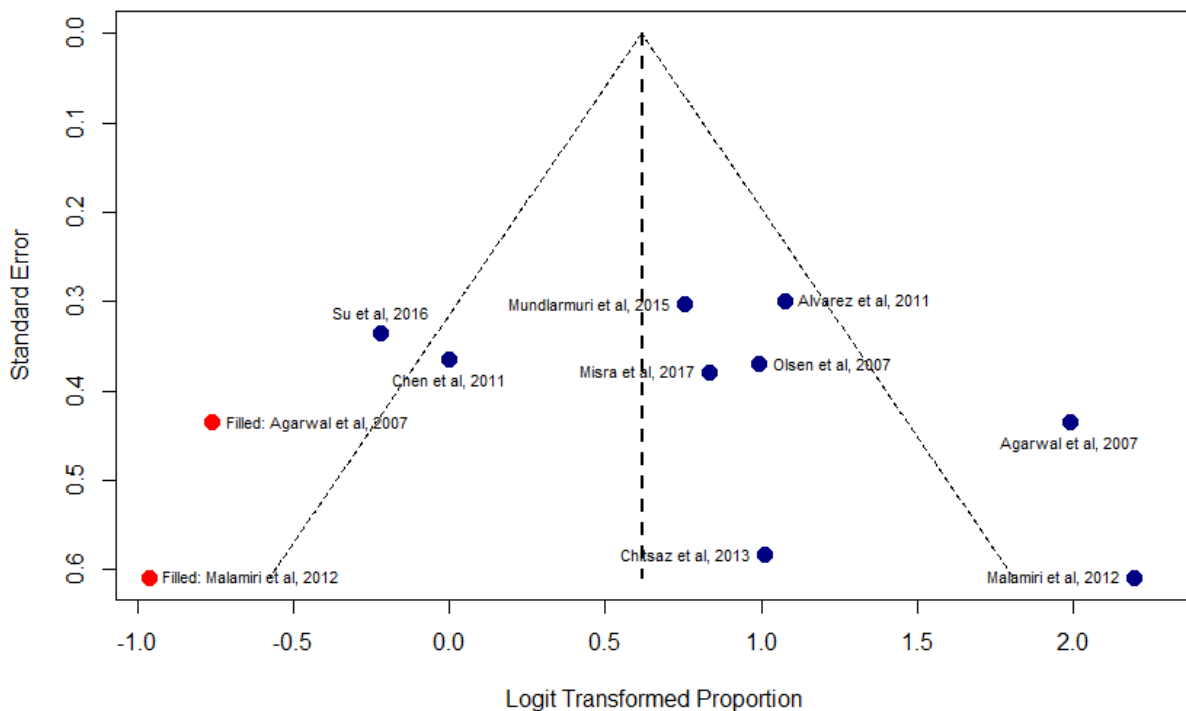

Original forest plot of the effectiveness of VPA. The probability of stopping seizures (SS) is 0.71 (95% CI: 0.6-0.8).

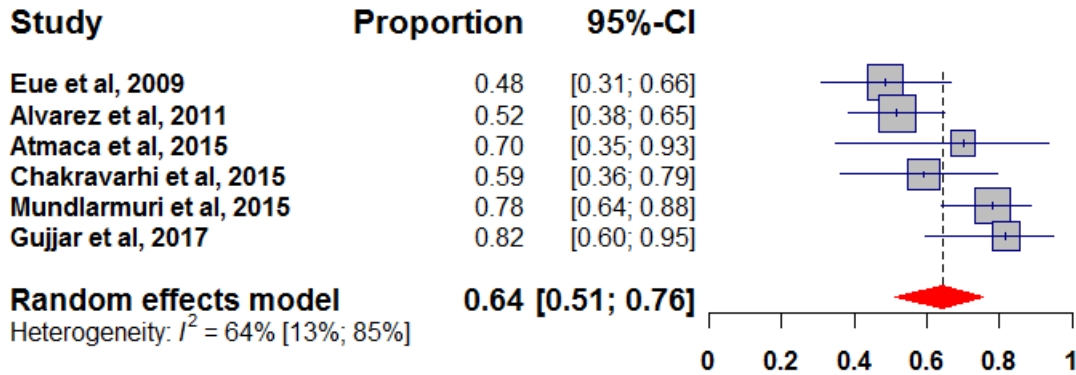**Funnel plot showing evidence of publication bias.**

Forest plot of the effectiveness of VPA after applying Duval and Tweedie's trim and fill method. The probability of stopping seizures (SS) is 0.65 (95% CI: 0.53-0.76).
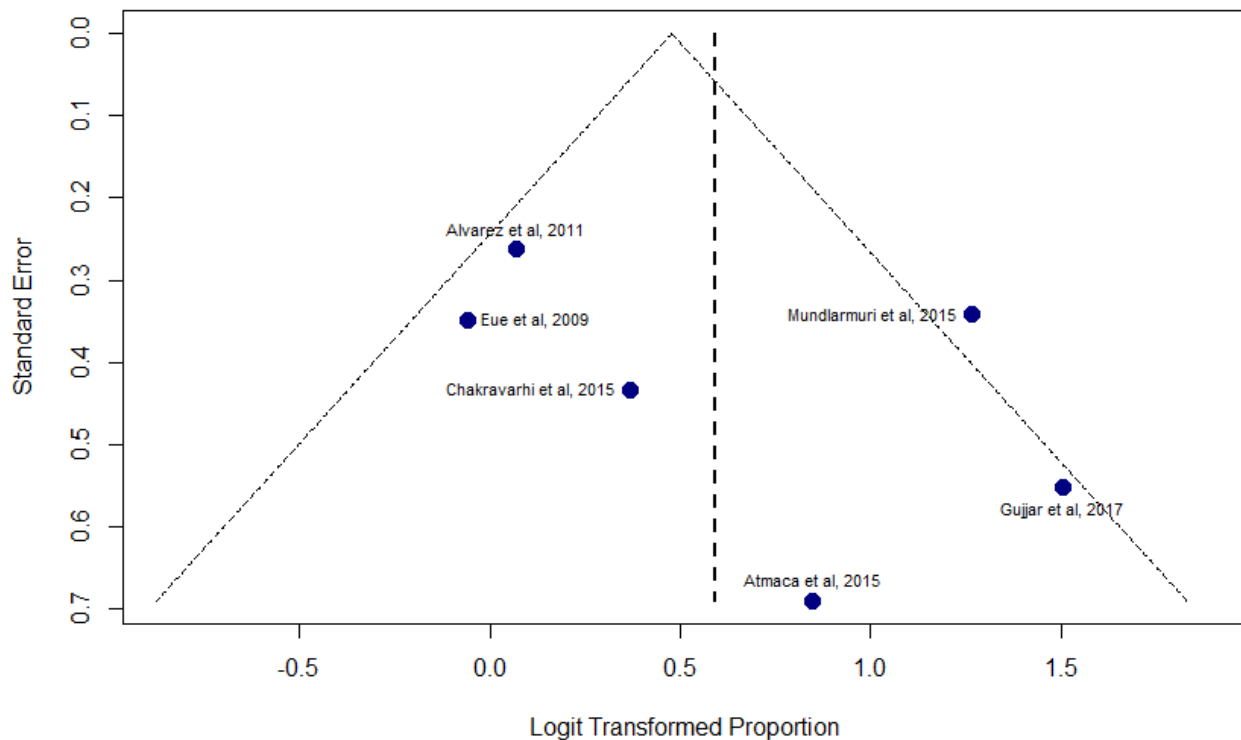

Funnel plot showing the imputed studies after applying Duval and Tweedie's trim and fill method, adjusting for publication bias.
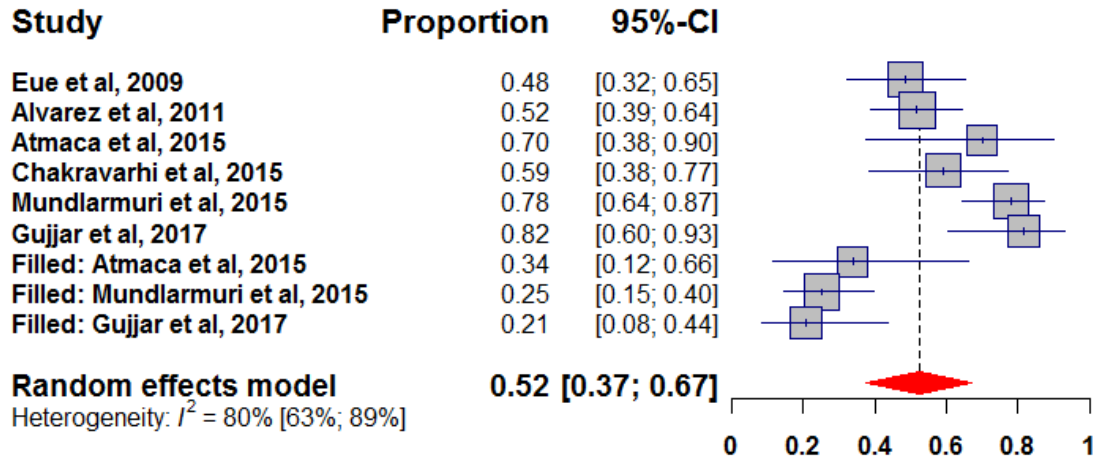
Levetiracetam (LEV). The distribution of prospective studies evaluating the effectiveness of LEV showed evidence of publication bias and, therefore, correction for publication bias with Duval and Tweedie's trim and fill method resulted in a different estimation of SS than the original one.


Study	Proportion	95%-CI
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]
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%; 85%]

Original forest plot of the effectiveness of LEV. The probability of stopping seizures (SS) is 0.64 (95% CI: 0.51-0.76).

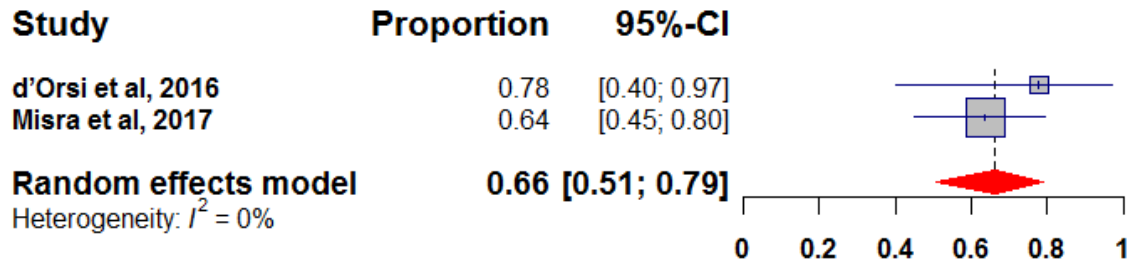**Funnel plot showing evidence of publication bias.**

Forest plot of the effectiveness of LEV after applying Duval and Tweedie's trim and fill method. The probability of stopping seizures (SS) is 0.52 (95% CI: 0.37-0.67).
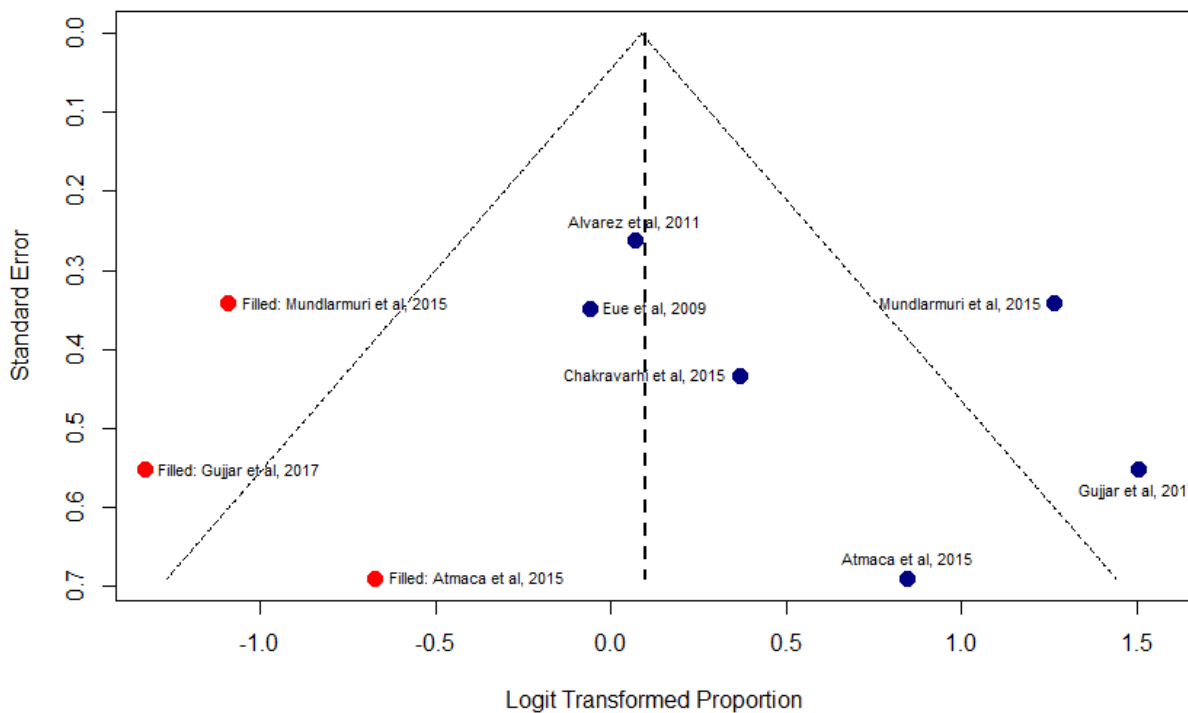

Funnel plot showing the imputed studies after applying Duval and Tweedie's trim and fill method, adjusting for publication bias.

Lacosamide (LAC). The distribution of prospective studies evaluating the effectiveness of LAC showed no evidence of publication bias and, correction for publication bias with Duval and Tweedie's trim and fill method is not possible with only two studies.

Study   **Proportion**   **95%-CI**

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: $I^2 = 0\%$

Original forest plot of the effectiveness of LAC. The probability of stopping seizures (SS) is 0.66 (95% CI: 0.51-0.79).
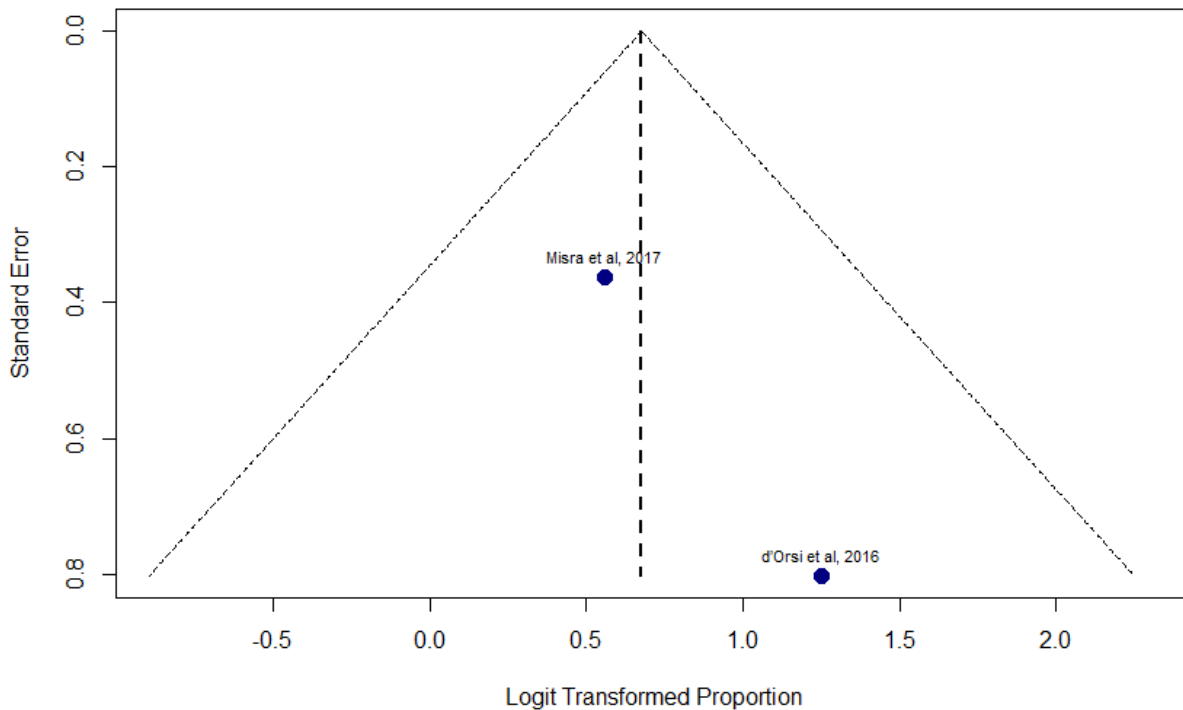
Funnel plot showing no evidence of publication bias.

In summary, considering only prospective studies and after correcting for publication bias the most effective non-BZD AED was PB with a SS of 0.79 (95% CI: 0.68-0.87) followed by LAC 0.66 (95% CI: 0.51-0.79), VPA 0.65 (95% CI: 0.53-0.76), PHT 0.62 (95% CI: 0.52-0.71), and the least effective non-BZD AED was LEV 0.52 (95% CI: 0.37-0.67).