# **BMJ Open**

#### Comparative neurological outcomes and safety of antiepileptic drugs during pregnancy and breastfeeding: a systematic review and network meta-analysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2017-017248
Article Type:	Research
Date Submitted by the Author:	10-Apr-2017
Complete List of Authors:	Veroniki, Areti Angeliki; Li Ka Shing Knowledge Institute, St. Michael's Hospital Rios, Patricia; Li Ka Shing Knowledge Institute, St. Michael's Hospital Cogo, Elise; Li Ka Shing Knowledge Institute, St. Michael's Hospital Straus, Sharon; Li Ka Shing Knowledge Institute, St. Michael's Hospital; University of Toronto, Department of Medicine Finkelstein, Yaron; The Hospital for Sick Children; University of Toronto, Department of Paediatrics Kealey, M.; Li Ka Shing Knowledge Institute, St. Michael's Hospital Reynen, Emily; Li Ka Shing Knowledge Institute, St. Michael's Hospital Soobiah, Charlene; Li Ka Shing Knowledge Institute, St. Michael's Hospital; University of Toronto, Institute for Health Policy Management & Evaluation Thavorn, Kednapa; University of Ottawa, School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine; The Ottawa Hospital Research Institute, Clinical Epidemiology Program Hutton, Brian; University of Ottawa, School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine; Ottawa Hospital Research Institute, Center for Practice Changing Research Hemmelgarn, BR; University of Calgary, Departments of Medicine and Community Health Sciences Yazdi, Fatemeh; Li Ka Shing Knowledge Institute, St. Michael's Hospital D'Souza, Jennifer; Li Ka Shing Knowledge Institute, St. Michael's Hospital MacDonald, Heather; Li Ka Shing Knowledge Institute, St. Michael's Hospital Tricco, Andrea; Li Ka Shing Knowledge Institute, St. Michael's Hospital; University of Toronto, Epidemiology Division, Dalla Lana School of Public Health
<b>Primary Subject Heading</b> :	Neurology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	multiple treatment meta-analysis, knowledge synthesis, Epilepsy < NEUROLOGY, pregnancy, infants, developmental delay



Comparative neurological out during pregnancy and breastf meta-analysis Areti Angeliki Veroniki, PhD, MSc <sup>1</sup> Patricia Rios, MSc <sup>1</sup> Elise Cogo, ND, MLIS <sup>1</sup>	comes and safety of anti-epileptic drugs reeding: a systematic review and network Email: <u>VeronikiA@smh.ca</u> Email: <u>RiosP@smh.ca</u>
during pregnancy and breastf meta-analysis Areti Angeliki Veroniki, PhD, MSc <sup>1</sup> Patricia Rios, MSc <sup>1</sup> Elise Cogo, ND, MLIS <sup>1</sup>	<b>Teeding: a systematic review and network</b> Email: <u>VeronikiA@smh.ca</u> Email: <u>RiosP@smh.ca</u>
<b>meta-analysis</b> Areti Angeliki Veroniki, PhD, MSc <sup>1</sup> Patricia Rios, MSc <sup>1</sup> Elise Cogo, ND, MLIS <sup>1</sup>	Email: <u>VeronikiA@smh.ca</u> Email: <u>RiosP@smh.ca</u>
Areti Angeliki Veroniki, PhD, MSc <sup>1</sup> Patricia Rios, MSc <sup>1</sup> Elise Cogo, ND, MLIS <sup>1</sup>	Email: <u>VeronikiA@smh.ca</u> Email: <u>RiosP@smh.ca</u>
Patricia Rios, MSc <sup>1</sup> Elise Cogo, ND, MLIS <sup>1</sup>	Email: <u>RiosP@smh.ca</u>
Elise Cogo, ND, MLIS <sup>1</sup>	
	Email: <u>CogoE@smh.ca</u>
Sharon E. Straus, MD, MSc <sup>1,2</sup>	Email: <u>Sharon.straus@utoronto.ca</u>
Yaron Finkelstein, MD <sup>3,4,5</sup>	Email: <u>Yaron.Finkelstein@sickkids.ca</u>
Ryan Kealey, PhD <sup>1</sup>	Email: <u>ryan.kealey@utoronto.ca</u>
Emily Reynen, MD, CM, PharmD <sup>1</sup>	Email: <u>ereynen@gmail.com</u>
Charlene Soobiah, PhD (Cand.) <sup>1,6</sup>	Email: <u>SoobiahC@smh.ca</u>
Kednapa Thavorn, PhD <sup>7,8,9</sup>	Email: <u>kthavorn@ohri.ca</u>
Brian Hutton, PhD, MSc <sup>7,10</sup>	Email: <u>bhutton@ohri.ca</u>
Brenda R. Hemmelgarn, MD, PhD <sup>11</sup>	Email: <u>Bhemmelg@ucalgary.ca</u>
Fatemeh Yazdi, MSc <sup>1</sup>	Email: <u>SabaghYazdiF@smh.ca</u>
Jennifer D'Souza, HBSc <sup>1</sup>	Email: jennifer.dsouza@mail.utoronto.ca
Heather MacDonald, MSc <sup>1</sup>	Email: <u>hrmacdonald@gmail.com</u>
Andrea C. Tricco, PhD, MSc <sup>1,12,*</sup>	Email: <u>TriccoA@smh.ca</u>
AUTHOR DETAILS	
<sup>1</sup> Li Ka Shing Knowledge Institute, St. M	lichael's Hospital, 209 Victoria Street, East Building,
Toronto, Ontario, M5B 1W8, Canada	
	Sharon E. Straus, MD, MSc <sup>1,2</sup> Yaron Finkelstein, MD <sup>3,4,5</sup> Ryan Kealey, PhD <sup>1</sup> Emily Reynen, MD, CM, PharmD <sup>1</sup> Charlene Soobiah, PhD (Cand.) <sup>1,6</sup> Kednapa Thavorn, PhD <sup>7,8,9</sup> Brian Hutton, PhD, MSc <sup>7,10</sup> Brenda R. Hemmelgarn, MD, PhD <sup>11</sup> Fatemeh Yazdi, MSc <sup>1</sup> Jennifer D'Souza, HBSc <sup>1</sup> Heather MacDonald, MSc <sup>1</sup> Andrea C. Tricco, PhD, MSc <sup>1,12,*</sup> <b>AUTHOR DETAILS</b> <sup>1</sup> Li Ka Shing Knowledge Institute, St. M Toronto, Ontario, M5B 1W8, Canada

2		
3 4	22	<sup>2</sup> Department of Medicine, University of Toronto, 27 King's College Circle, Toronto, Ontario
5 6 7	23	M5S 1A1, Canada
7 8 9	24	<sup>3</sup> The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canad
10 11	25	<sup>4</sup> Department of Paediatrics, University of Toronto, 172 St. George Street, Toronto, Ontario,
12 13 14	26	M5R 0A3, Canada
15 16	27	<sup>5</sup> Department of Pharmacology and Toxicology, University of Toronto, Medical Sciences
17 18 10	28	Building, Room 4207, 1 King's College Circle, Toronto, Ontario, M5S 1A8, Canada
20 21	29	<sup>6</sup> Institute for Health Policy Management & Evaluation, University of Toronto, 4th Floor,
22 23	30	155 College Street, Toronto, Ontario, M5T 3M6, Canada
24 25 26	31	<sup>7</sup> School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine,
27 28	32	University of Ottawa, Roger-Guindon Building, 451 Smyth Road, Ottawa, Ontario, K1H 8M5
29 30 21	33	Canada
32 33	34	<sup>8</sup> Clinical Epidemiology Program, Ottawa Hospital Research Institute, The Ottawa Hospital,
34 35	35	501 Smyth Road, Ottawa, Ontario, K1H 8L6, Canada
36 37 38	36	<sup>9</sup> Institute of Clinical and Evaluative Sciences (ICES uOttawa), 1053 Carling Avenue, Ottawa
39 40	37	Ontario, K1Y 4E9, Canada
41 42 43	38	<sup>10</sup> Ottawa Hospital Research Institute, Center for Practice Changing Research, The Ottawa
43 44 45	39	Hospital–General Campus, 501 Smyth Road, PO Box 201B, Ottawa, Ontario, K1H 8L6,
46 47	40	Canada.
48 49 50	41	<sup>11</sup> Departments of Medicine and Community Health Sciences, University of Calgary, TRW
51 52	42	Building, 3rd Floor, 3280 Hospital Drive NW, Calgary, Alberta, T2N 4Z6, Canada
53 54 55	43	<sup>12</sup> Epidemiology Division, Dalla Lana School of Public Health, University of Toronto, 6th
56 57	44	Floor, 155 College Street, Toronto, Ontario, M5T 3M7, Canada
58 59		
60		

### **\*Corresponding author**

- 46 Prof. Andrea C. Tricco, PhD
- 47 Scientist, Knowledge Translation Program,
- 48 Li Ka Shing Knowledge Institute, St. Michael's Hospital,
- 49 209 Victoria Street, East Building, Toronto, Ontario, M5B 1W8, Canada
  - 50 Phone: 416-864-6060, Fax: 416-864-5805, Email: <u>TriccoA@smh.ca</u>

- 52 Keywords: multiple treatment meta-analysis, knowledge synthesis, epilepsy, pregnancy,
- 53 infants, developmental delay.
- **Word count**: abstract (282 words); main text (3848 words); 1 table; 3 figures; 3 additional
  - 55 files; 41 references



1	
2	
2	
3	
4	
5	
6	
1	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
20	
21	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
<u>4</u> 8	
<u>40</u>	
50	
51	
52 50	
53	
54	
55	
56	
57	
58	
59	
60	

56	ABSTRACT
57	<b>Objectives</b> : To compare the safety of Anti-epileptic drugs (AEDs) on neurodevelopment of
58	infants/children exposed in-utero or during breastfeeding.
59	Design and Setting: Systematic review and Bayesian random-effects network meta-
60	analysis (NMA).
61	<b>Participants</b> : 27 cohort studies including 4,841 infants/children.
62	Interventions: Mono- and poly-therapy AEDs were included, including first-generation
63	(i.e., carbamazepine, clobazam, clonazepam, ethosuximide, phenobarbital, phenytoin,
64	primidone, valproate) and newer-generation (i.e., gabapentin, lamotrigine, levetiracetam,
65	oxcarbazepine, topiramate, vigabatrin) AEDs.
66	Primary and secondary Outcome measures: Cognitive developmental delay and
67	autism/dyspraxia were primary outcomes. Attention deficit hyperactivity disorder,
68	language delay, neonatal seizures, psychomotor developmental delay, and social
69	impairment were secondary outcomes.
70	Results: The NMA on cognitive developmental delay 10 cohort studies, 748 children, 14
71	AEDs and control (no AED) suggested valproate (arm sample size (N)=160, odds ratio
72	(OR)=8.63, 95% credible interval (CrI): 3.01-25.74) and the combination carbamazepine,
73	phenobarbital, and valproate (N=3, OR=17.31, CrI: $1.02-434.50$ ) were statistically
74	significantly associated with more children experiencing cognitive developmental delay. A
75	NMA was conducted on autism including 5 cohort studies, 2,551 children, 11 AEDs and
76	control; only oxcarbazepine (N=321, OR=13.51, CrI: 1.28-221.40), valproate (N=485,
77	OR=17.29, 95% CrI: 2.40-217.60), lamotrigine (N=745, OR=8.88, CrI: 1.28-112.00), and
78	lamotrigine+valproate (N=6, OR=132.70, CrI: 7.41-3851.00) were associated with a

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
4/	
48	
49	
50	
51	
52 50	
ວຽ 54	
54 57	
55	
56	
5/	
20	
59	
60	

79	significantly greater risk of autism compared with control. Psychomotor developmental
80	delay was the largest NMA of secondary outcomes (11 cohort studies, 1,145 children, 17
81	AEDs and control): valproate (N=137, OR=4.16, CrI: 2.04-8.75) and
82	carbamazepine+phenobarbital+valproate (N=3, OR=19.12, CrI: 1.49-337.50) were
83	associated with a significantly greater risk of psychomotor delay compared with control.
84	<b>Conclusions</b> : Across all outcomes, valproate alone or combined with another AED is
85	associated with the greatest risk, whereas oxcarbazepine and lamotrigine were associated
86	with increased occurrence of autism. Counselling is advised for women considering
87	pregnancy to tailor the safest regimen.
88	
89	Registration: PROSPERO database (CRD42014008925).
90	Keywords: multiple treatment meta-analysis, knowledge synthesis, epilepsy, pregnancy,
91	infants, developmental delay.
92	ARTICLE SUMMARY
93	Strengths and limitations of this study
94	• 27 cohort studies involving 4,841 children of women who took AEDs were included
95	in this systematic review. More evidence from long-term follow-up studies is
96	required.
97	• This study was the first that compared and ranked the safety of AEDs, including
98	comparative safety of treatments that have not been directly compared.

1 2		
3 4	99	• Across all neurological outcomes, valproate alone or combined with another AED is
5 6 7	100	associated with the greatest risk.
7 8 9	101	Oxcarbazepine and lamotrigine were associated with increased occurrence of
o 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 20	101 102	<ul> <li>Oxcarbazepine and lamotrigine were associated with increased occurrence of autism.</li> </ul>
$\begin{array}{c} 23\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 39\\ 40\\ 42\\ 43\\ 44\\ 56\\ 78\\ 90\\ 51\\ 52\\ 53\\ 55\\ 56\\ 78\\ 59\\ \end{array}$		

### **INTRODUCTION**

Anti-epileptic drugs (AEDs) are used by pregnant women for various conditions, such as epilepsy, pain syndromes, psychiatric disorders, and chronic migraine.<sup>1</sup> AED use during pregnancy is associated with risks to the fetus, as these drugs can cross the placenta or may be transferred to the infant through breastfeeding and may be associated with adverse neurodevelopment outcomes.<sup>2-4</sup> Two systematic reviews examined the association between AED exposure and neurodevelopment *in utero*, and reported that exposure to valproate was linked to significantly lower IQ scores and poorer overall neurodevelopmental outcomes in the children of women who used these medications.<sup>56</sup> No statistically significant associations were found between neurodevelopment and exposure to other AEDs such as carbamazepine, lamotrigine, or phenytoin.<sup>5-8</sup> However, there is a lack of sufficiently powered studies to assess the impact of AEDs on neurodevelopment in children of women exposed to these agents, especially for newer generation drugs, thus highlighting the need for a systematic review.910 The aim of this study was to compare the safety of AEDs and assess their impact on neurodevelopment in infants and children exposed in-utero or during breastfeeding, employing a systematic review and network meta-analysis (NMA). 

#### METHODS

The methods are briefly described here; details can be found in the published protocol (Additional File 1).<sup>11</sup> This study was registered with PROSPERO (CRD42014008925). We followed the ISPOR<sup>12</sup> guidelines for our NMA, and reported our findings using the PRISMA extension for NMA (Additional File 2).13

#### **Eligibility criteria**

All randomized clinical trials (RCTs), quasi-RCTs, and observational studies were eligible. Included studies assessed infants or children  $\leq 12$  years of age whose mothers consumed AEDs during pregnancy and/or while breastfeeding. Both mono- and poly-therapy AEDs were eligible, including first-generation (i.e., carbamazepine, clobazam, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproate) and newer-generation (i.e., marketed after 1990 including: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin), with no restrictions on AED dosage. Placebo, no AED, other AEDs alone or in combination, were considered as comparators. Duplicate studies that used the same registry or population sample (i.e., companion studies) were used for supplementary information only. No language or other restrictions were imposed. The primary neurological outcomes were cognitive developmental delay and autism/dyspraxia, and the secondary outcomes included attention deficit hyperactivity disorder (ADHD), language delay, neonatal seizures, psychomotor developmental delay. and social impairment (outcome measures and diagnostic scales used are provided in Additional File 3: Appendix A). Our initial intention was to evaluate all safety outcomes in infants and children who were exposed to AEDs *in-utero* or during breastfeeding in one publication. However, given the breadth of evidence we identified, we report results

related to risk of major congenital malformations, birth, and prenatal outcomes in a secondpaper (paper in preparation).

#### 145 Searching, screening, abstraction, appraisal of methodological quality

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials up to December 15, 2015, and identified additional studies from scanning references and contacting authors. Unpublished studies were sought by searching clinical trial registries and conference abstracts. After a calibration exercise, titles/abstracts and full-text papers were screened by two reviewers independently (further details reported in Additional File 3: Appendix B). Conflicts were resolved through discussion. The same approach was used for data abstraction and appraisal of methodological quality. Observational studies were only identified, and their methodological quality was appraised with the Newcastle-Ottawa Scale (Additional File 3: Appendix C).<sup>14</sup> For each outcome with 

 $155 \ge 10$  studies and treatment comparisons with different total numbers of patients, the comparison-adjusted funnel plot was used to assess reporting bias,<sup>15</sup> where the overall

157 treatment effect for each comparison was estimated under the fixed-effect meta-analysis

, 158 model.

#### **Synthesis of included studies**

We used the odds ratio (OR) for each dichotomous outcome, and outcome data were
pooled using hierarchical models and the Markov Chain Monte Carlo sampling method in a
Bayesian framework. To account for anticipated methodological and clinical heterogeneity
across studies, and to achieve the highest generalizability in the meta-analytical treatment
effects, we applied a random-effects model.<sup>16</sup>

Page 11 of 90

#### **BMJ Open**

For connected evidence networks, we applied a random-effects NMA hierarchical model.<sup>17</sup> The review team pre-specified the network nodes. Due to the complexity of the data and the studies' underreporting, differences in drug dosages could not be accounted for, and it was assumed that different dosages of the same AED were equally effective. When a study reported multiple dosages for the same treatment, we combined the data for this treatment. We assessed the transitivity assumption for each outcome a priori using the treatment effect modifiers: age, baseline risk, treatment indication, timing, and methodological quality. The mean of each continuous effect modifier and the mode of each categorical effect modifier for each pairwise comparison were presented in tables for each outcome.<sup>18</sup> The consistency assumption was evaluated for the entire network of each outcome using the design-by-treatment interaction model.<sup>19</sup> If inconsistency was identified, further examination for local inconsistency in parts of the network was completed using the loop-specific method.<sup>20 21</sup> Common within-network between-study variance ( $\tau^2$ ) across treatment comparisons was assumed in the conventional meta-analysis, NMA, and design-by-treatment interaction model, so that treatment comparisons including a single study can borrow strength from the remaining network. This assumption was clinically reasonable. as the treatments included were of the same nature. In the loop-specific approach, common within-loop  $\tau^2$  was assumed. For cognitive developmental delay and autism/dyspraxia outcomes, network meta-regression analyses for maternal age and baseline risk (i.e., using the control group) were conducted, when at least 10 studies provided relevant information, assuming a common

186 fixed coefficient across treatment comparisons. Sensitivity analyses for cognitive

187 developmental delay and autism/dyspraxia outcomes were performed for studies with the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2		
3 4	188	treatment indication of epilepsy, large study size (i.e., >300), maternal alcohol intake,
5 6 7	189	maternal tobacco use, only first-generation AEDs, and higher methodological quality for the
8 9	190	two items of the Newcastle-Ottawa Scale that had the highest percentage of low
10 11	191	methodological quality (adequacy of follow-up of cohorts and comparability of cohorts
12 13 14	192	items for cohort studies). Severity of epilepsy, which may be a risk factor variable as the
15 16	193	more severe the epilepsy the more necessary AED medications for the mother, <sup>22</sup> was not
17 18 10	194	evaluated in our analyses since this was not commonly reported. For autism/dyspraxia, a
20 21	195	sensitivity analysis on maternal IQ/psychiatric history was additionally conducted. We
22 23	196	measured the goodness of fit using the posterior mean of the residual deviance, the degree
24 25 26	197	of between-study heterogeneity, and the deviance information criterion. In a well-fitting
27 28	198	model the posterior mean residual deviance should be close to the number of data points. <sup>23</sup>
29 30 21	199	<sup>24</sup> A difference of 3 units in the deviance information criterion was considered important
32 33	200	and the lowest value of the deviance information criterion corresponded to the model with
34 35	201	the best fit. <sup>23 24</sup>
36 37 38	202	All analyses were conducted in OpenBUGS <sup>25</sup> assuming non-informative priors for all model
39 40	203	parameters and a half normal prior distribution for the between-study standard deviation
41 42 43	204	$(\tau \sim N(0,1), \tau > 0)$ . The first 10,000 iterations were discarded and then 100,000 simulations
44 45	205	were run with thinning of 10 values. Convergence was checked by visual inspection of the
46 47 48	206	evaluation of the mixing of two chains. The median and 95% CrI were calculated for each
40 49 50	207	parameter value, since medians are not overly influenced by outliers. The network
51 52	208	command <sup>26</sup> was used to apply the design-by-treatment interaction model.
53 54 55	209	For NMA estimates, a 95% predictive interval (PrI) is also reported to capture the
56 57	210	magnitude of the between-study variance ( $ au^2$ ) and present the interval within which the
58 59 60		11

1

#### **BMJ Open**

2
3
1
4
5
6
7
8
9
10
10
11
12
13
14
15
16
17
17
18
19
20
21
22
23
24
24
25
26
27
28
29
20
30
31
32
33
34
35
36
27
31
38
39
40
41
42
43
44
44
45
46
47
48
40
- <del>1</del> -0 50
50
51
52
53
54
55
56
50
5/
58
59
60

treatment effect of a future study is expected to lie.<sup>27 28</sup> The estimated safety of the included 211 212 AED medications was ranked using the surface under the cumulative ranking (SUCRA) 213 curve.<sup>29</sup> The larger the SUCRA for a treatment, the higher its safety rank among all the 214 available treatment options. A steep gradient in the cumulative ranking curve suggests that 215 the corresponding treatment is most likely the safest. SUCRA curve values are presented

216 along with 95% CrIs to capture the uncertainty in the parameter values.

### **RESULTS**

### 218 Literature search and included studies

Our literature search identified 5,305 titles and abstracts, which after the screening process yielded 642 articles potentially relevant for inclusion (Figure 1). After full-text review, 93 studies fulfilled eligibility criteria along with 17 studies identified through supplemental methods. Of the 110 total eligible studies in the complete review, 27 articles with nine companion reports or potentially overlapping studies included one or more relevant neurological outcomes (Additional File 3: Appendices D, E). Two of the included studies were conference abstracts with usable data, nine were non-English publications, and four studies, not captured in the original literature search, were identified through reference scanning. A table with the key excluded studies and a rationale for their exclusion is presented in Additional File 3: Appendix F. Study and patient characteristics We included 27 cohort studies (4,841 total patients) published between 1989 and 2015 (Table 1; Additional File 3: Appendices G, H). The number of patients included in each study ranged from 23 to 2,011 (median 69), and the number of arms compared in each study ranged from two to 12. Most studies (78%) were published after 2000, more than half of the studies (67%) included fewer than 100 patients, and 13 studies (48%) included a control group of pregnant/breastfeeding women with epilepsy who did not receive AEDs.

- The mean age of women ranged from 24 to 32 years. About half of the studies were funded
- through government/public research funding (52%).

### 238 Methodological quality results

1	
2	
3	
4	
5	
0 7	
י פ	
0 Q	
10	
11	
12	
13	:
14	
15	
16	
17	
18	
19	
20	
21	
23	
24	
25	
26	
27	
28	4
29	
30	
31	
32	
აა ვ∕I	
34	
36	-
37	
38	
39	
40	
41	
42	
43	
44 15	
40	
40 47	
48	
49	
50	4
51	
52	
53	
54	
55	
56	
5/	
20 50	
09 60	
00	

239	Twenty-seven observational studies were appraised using the Newcastle Ottawa Scale
240	(Additional File 3: Appendix I). All studies selected the non-exposed cohort from the same
241	community as the exposed cohort, 25 (93%) included a representative (or somewhat
242	representative) sample, 25 (93%) assessed outcomes independently, blindly or via a
243	record linkage (e.g., identified through database records), and 21 (78%) ascertained
244	exposure via secured records (e.g., database records) or structured interviews. No evidence
245	for reporting bias was identified by the visual inspection of the comparison-adjusted funnel
246	plots (Additional File 3: Appendix J).
247	Statistical analysis results
248	No important concerns were raised regarding the violation of the transitivity assumption
249	when mean maternal age, mean baseline risk, treatment indication, and timing were
250	assessed (Additional File 3: Appendix K). However, the average methodological quality
251	appraisal across treatment comparisons varied across treatment comparisons. The
252	evaluation of the consistency assumption using the design-by-treatment interaction model
253	suggested that there was no evidence of significant inconsistency across all outcomes
254	(Additional File 3: Appendix K).
255	In the following sections, we present the overall results of the NMA analyses for each
256	outcome, while the SUCRA curve values from all outcomes are presented in Additional File
257	3: Appendix L and depicted in a rank-heat plot ( <u>http://rh.ktss.ca/</u> ) <sup>30</sup> in Additional File 3:
258	Appendix M.
259	Cognitive developmental delay
260	The NMA for cognitive developmental delay (definitions in Additional File 3: Appendix A)
261	included ten cohort studies, 748 children, and examined 13 AEDs plus control (i.e., no

Page 16 of 90

1 2	
3 4	2
5 6 7	2
7 8 9	2
10 11	2
12 13	2
14 15 16	2
17 18	2
20 21	2
22 23	2
24 25 26	2
27 28	2
29 30 31	2
32 33	2
34 35 26	2
30 37 38	2
39 40	2
41 42 43	2
44 45	2
46 47	2
40 49 50	2
51 52	2
53 54 55	2
56 57	2
58 59 60	

262	exposure to AEDs). One study included children exposed to AEDs both <i>in-utero</i> and through
263	breastfeeding, and nine included children exposed to AEDs in-utero. Overall, 6% of the
264	treatment comparisons in the network reached statistical significance (Figure 2a;
265	Additional File 3: Appendices K, N). Valproate (OR=8.63, 95% CrI: 3.01-25.74) and
266	carbamazepine+phenobarbital+valproate (OR=17.31, 95% CrI: 1.02-434.50) were
267	statistically significantly associated with greater risk in children experiencing
268	developmental delay compared with control (Figure 3).
269	Restricting the NMA to 9 cohort studies including 725 offspring of women only with
270	epilepsy as their treatment indication, comparing 13 AEDs plus control produced results
271	that were generally in agreement with the overall results. The same was observed in a
272	network meta-regression model of baseline risk for offspring of women with epilepsy who
273	were not exposed to AEDs (estimated regression coefficient on OR scale: 0.94, 95% CrI:
274	$0.67-2.19$ ; $\tau^2=0.17$ , 95% CrI: 0.00-1.38; residual deviance= 40.26, data points= 42, deviance
275	information criterion= 71). Restricting the analysis to 6 cohort studies including 480
276	children comparing 11 first-generation AEDs, we found that valproate was statistically
277	significantly more harmful than control, phenytoin, and carbamazepine, yet
278	carbamazepine+phenobarbital+valproate was no longer statistically significant versus
279	control. The results were no longer statistically significant when restricted to two studies
280	of 319 offspring of women with a history of alcohol and tobacco use comparing 3 AEDs and
281	control. This result was consistent in sensitivity analyses including only higher
282	methodological quality studies in the 'comparability of cohorts' item on the Newcastle-
283	Ottawa Scale (2 studies, 181 children, 3 AEDs plus control) and the 'adequacy of follow-up
284	of cohorts' (4 studies, 283 children, 11 AEDs plus control).

1		
2 3 4	285	Autism/dyspraxia
5 6 7	286	The NMA on autism/dyspraxia (definitions in Additional File 3: Appendix A) included five
7 8 9	287	cohort studies, 2,551 children exposed <i>in utero</i> , and examined 11 AEDs plus control (i.e., no
10 11	288	AED exposure). Overall, 9% of the treatment comparisons in the network reached
12 13 14	289	statistical significance (Figure 2b; Additional File 3: Appendices K, N). Compared with
15 16	290	control, only valproate (OR=17.29, 95% CrI: 2.40-217.60), oxcarbazepine (OR= 13.51,
17 18 19	291	95% CrI: 1.28-221.40), lamotrigine (OR= 8.88, 95% CrI: 1.28-112.00), and
20 21	292	lamotrigine+valproate (OR=132.70, 95% CrI: 7.41-3851.00) were significantly associated
22 23 24	293	with increased occurrence of autism/dyspraxia (Figure 3).
24 25 26	294	Restricting the NMA to studies including only women with epilepsy as their treatment
27 28	295	indication produced results that were generally in agreement with the overall results,
∠9 30 31	296	except that oxcarbazepine was no longer in the network (4 cohort studies, 540 children, 9
32 33	297	AEDs plus control). Two cohort studies of 404 offspring of women with a history of tobacco
34 35 36	298	use compared 3 AEDs and control and found similar results except that oxcarbazepine and
37 38	299	lamotrigine+valproate were no longer in the network. The results were in agreement in
39 40 41	300	sensitivity analyses including only higher methodological quality studies in the
41 42 43	301	'comparability of cohorts' item on the Newcastle-Ottawa Scale (4 studies, 2395 children, 11
44 45	302	AEDs plus control) and the 'adequacy of follow-up of cohorts' (3 studies, 2244 children, 9
46 47 48	303	AEDs plus control), except that lamotrigine was no longer statistically significant than
49 50	304	control for the latter.
51 52 53	305	Neonatal Seizure
54 55	306	One cohort study included 72 children who were exposed to AEDs in-utero as well as
56 57 5°	307	through breastfeeding reported on the incidence of neonatal seizures. The study compared
59 60		16

2	
3	
1	
4	
5	
6	
7	
8	
9	
10	
10	
11	
12	
13	
14	
15	
16	
10	
17	
18	
19	
20	
21	
21	
22	
23	
24	
25	
26	
27	
20	
20	
29	
30	
31	
32	
33	
24	
34	
35	
36	
37	
38	
30	
40	
40	
41	
42	
43	
44	
45	
40	
40	
47	
48	
49	
50	
51	
51	
5Z	
53	
54	
55	
56	
57	
57	
58	
59	

60

1

valproate against lamotrigine and found no statistically significant difference in neonatal
seizures between the two drugs (OR=0.18, 95% CrI: 0.01-3.70).

310 **Psychomotor developmental delay** 

The NMA on psychomotor developmental delay (definitions in Additional File 3: Appendix
A) included 11 cohort studies, 1,145 children exposed *in utero*, and examined 17 AEDs plus
control (i.e., no AED exposure). Overall, 4% of treatment comparisons in the network
reached statistical significance (Figure 2c; Additional File 3: Appendices K, N). Valproate
(OR=4.16, 95% CrI: 2.04-8.75) and carbamazepine+phenobarbital+valproate (OR=19.12,
95% CrI: 1.49-337.50) were statistically significantly more harmful than control (Figure 3).

317 Language delay

318 The NMA on language delay (definitions in Additional File 3: Appendix A) included five

319 cohort studies, 509 children, and examined four AEDs plus control (i.e., no AED exposure;

320 Figure 2d; Additional File 3: Appendices K, N). One study included children exposed to

321 AEDs *in-utero* and through breastfeeding, and four included children exposed to AEDs *in-*

322 *utero*. Compared with control, valproate was the only treatment significantly associated

323 with increased risk of language delay (OR=7.95, 95% CrI: 1.50-49.13; Figure 3).

324 Attention deficit hyperactivity disorder

The NMA on ADHD (definitions in Additional File 3: Appendix A) included four cohort
studies, 750 children, and examined five AEDs plus control (i.e., no AED exposure). One
study included children exposed to AEDs *in-utero* and through breastfeeding, while three
studies included children exposed to AEDs *in-utero*. None of the treatment comparisons
reached statistical significance (Figure 2e; Additional File 3: Appendices K, N).

330 Social Impairment

Page 19 of 90

1

60

2		
3 4	331	One cohort study included 422 children exposed to AEDs in-utero as well as through
5 6 7	332	breastfeeding. The children were exposed to carbamazepine (n=48), lamotrigine (n=71),
7 8 9	333	valproate (n=27) and control (n=278). No significant differences in social impairment were
10 11	334	identified. <sup>31</sup>
$\begin{array}{c}12\\13\\14\\56\\7\\89\\01\\22\\22\\22\\22\\22\\22\\22\\22\\22\\22\\22\\22\\22$	335	to beer to view only

#### **DISCUSSION**

Our results suggest that AEDs generally pose a risk for infants and children exposed *in*-*utero* or during breastfeeding. Valproate was statistically significantly associated with more children experiencing autism/dyspraxia, language, cognitive and psychomotor developmental delays versus children who were not exposed to AEDs. Oxcarbazepine, lamotrigine and lamotrigine+valproate were associated with increased occurrence of autism/dyspraxia, whereas for the cognitive developmental delay and psychomotor developmental delay outcomes, children exposed to the combination of carbamazepine, phenobarbital, and valproate were at a greater risk of harm than those who were not exposed to AEDs. However, due to the lack of data identified in these studies, we were unable to consider a number of factors, such as anticonvulsant dosing, severity of epilepsy, duration of exposure, serum concentrations of exposure, mother's IQ/education, which may all influence outcomes, and hence these results should be interpreted with caution. In addition, our subsequent analyses may be underpowered due to missing data (e.g., maternal age is not reported in 17 of the 27 studies, alcohol use is not reported in 23 of 27 studies, tobacco use is not reported in 22 of 27 studies, and epileptic control group was not included in 14 of 27 studies). NMA is a particularly useful tool for decision-makers because it allows the ranking of treatments for each outcome. However, the results of our SUCRA curves should be interpreted with caution, especially due to the small number of studies and children included in each NMA, which is also reflected in the high uncertainty around the SUCRA

357 values (Additional File 3: Appendix L).<sup>32</sup> The probability that a top AED is actually among

#### **BMJ Open**

י י	
2	
3	
4	
5	
6	
7	
0	
0	
9	
10	
11	
12	
13	
11	
14	
15	
16	
17	
18	
19	
20	
21	
21	
22	
23	
24	
25	
26	
27	
21	
28	
29	
30	
31	
32	
33	
27	
34	
35	
36	
37	
38	
30	
10	
40	
41	
42	
43	
44	
45	
46	
47	
47	
48	
49	
50	
51	
52	
52	
50	
04 55	
55	
56	
57	
58	
59	

60

358 the worst one is likely high,<sup>32</sup> as the SUCRA findings were unstable with overlapping 359 uncertainty intervals overlap.

360 Our results are consistent with a longitudinal study of 311 children that found exposure to 361 lamotrigine was associated with significantly higher IQ scores and verbal function at six 362 years of age compared to children exposed to valproate (Additional File 3: Appendix F).<sup>8</sup> As 363 indicated in Additional File 3: Appendix F, we were unable to include this study because the 364 outcome was reported as a continuous measure, where we focused on dichotomous 365 outcomes to ease interpretation. Our results are supported by findings from a cohort study 366 in the UK, which found that children exposed to levetiracetam were not at increased risk 367 for delayed development compared to unexposed children (Additional File 3: Appendix 368 F).<sup>33</sup> As indicated in Additional File 3: Appendix F, we were unable to include this study due 369 to the same reason as above. A NMA of 195 RCTs and 28,013 patients (including both males 370 and females) showed that gabapentin and levetiracetam showed the best tolerability 371 profile compared with other AEDs, whereas oxcarbazepine and topiramate had a higher 372 withdrawal rate, and lamotrigine an intermediate withdrawal rate.<sup>34</sup> 373 Across all outcomes, valproate alone or combined with another AED (even with a newer-374 generation agent, e.g., lamotrigine) was associated with the greatest risk. Similarly, two 375 previous systematic reviews that did not conduct a NMA found valproate was associated 376 with significantly lower IQ scores and poorer overall neurodevelopmental outcomes when 377 compared to an unexposed control group.<sup>56</sup> Also consistent with our results, a 2014 378 Cochrane review (with a meta-analysis of 10 studies) concluded that AED polytherapy led 379 to poorer developmental outcomes and IQ compared to healthy controls, epileptic controls, 380 and unspecified monotherapy.<sup>5</sup> This Cochrane review also concluded that insufficient data

exist for newer anti-epileptic drugs. These risks must be balanced with the need to control
seizure activity in pregnancy and thus informed decision making by patients and clinicians
is critical.

Strengths of our study include a comprehensive systematic review methodology that followed the Cochrane Handbook<sup>35</sup> and ISPOR<sup>12</sup> guidelines, and reported using the PRISMA extension for NMA.<sup>13</sup> To the best of our knowledge, our study was the first that compared and ranked the safety of AEDs. We evaluated the comparative safety of treatments that have not been directly compared head-to-head before. In addition, we calculated predictive intervals, which account for between-study variation and provide a predicted range for the treatment effect estimate, should a future study be conducted. On average, the predictive intervals suggested that our results are robust.

Our systematic review has a few limitations worth noting. First, when multiple doses were reported for the same treatment, we lumped the dosages because this information was not consistently reported across the included studies. However, this is common for cohort studies, which report on a number of different types of exposures amongst patients. Second, several polytherapies had high SUCRA estimates but with very wide CrIs, which is due to the small number of studies included for each drug combination with underpowered sample sizes. Evidence suggests that ranking probabilities for a treatment of being the best may be biased toward the treatments with the smallest number of studies, which may have influenced our SUCRA results.<sup>32 36</sup> As such, the effect sizes need to be taken into account when considering the SUCRA values. Third, due to the absence of evidence from RCTs, our conclusions were based on evidence from observational studies only, and inherent biases because of confounding and shortcomings of these studies may have impacted our findings.

Page 23 of 90

#### **BMJ Open**

For example, the included studies often failed to report important confounding variables. such as family history of autism, ADHD, and maternal IO, making it impossible for us to control these variables through subgroup analysis and meta-regression. Recent research papers have explored methods to incorporate non-randomized with randomized evidence in a NMA and have highlighted the need to carefully explore the level of confidence in the non-randomized evidence.<sup>37 38</sup> However, the use of observational studies allows the assessment of the safety profile of AED treatments and offers the opportunity to evaluate effects in pregnancy.<sup>39</sup> Future large-scale observational studies are needed to allow the evaluation of rare adverse events that otherwise cannot be adequately evaluated in RCTs, especially during pregnancy. Fourth, although no intransitivity for most treatment effect modifiers assessed was evident, there was an imbalance in the methodological study quality appraisal across treatment comparisons and most outcomes, which may impact our results. However, the assessment of consistency suggested no disagreement between the different sources of evidence in the network. Fifth, although the tendency towards publication bias is greater with observational studies than with randomized trials,<sup>40</sup> the assessment of publication bias and small-study effects using adjusted funnel plots suggested no evidence for their prevalence. Also, the majority of the included studies in this review compared multiple treatments inducing correlations in each funnel plot, which may mask asymmetry. Although we plotted data points corresponding to the study-specific basic parameters to reduce correlations, this issue may still exist. Sixth, we were unable to conduct sub-group analysis by type of exposure (breastfeeding versus *in utero*) due to the small number of studies included in the NMA and due to the poor reporting; 22 studies did

2	
3 4	42
567	42
7 8 9	42
10 11	42
12 13	43
14 15 16	43
17 18	43
19 20 21	43
21 22 23	43
24 25	43
26 27 28	43
29 30	13
31 32	тJ 42
33 34 35	40
36 37	43
38 39	
40 41 42	
42 43 44	
45 46	
47 48	
49 50 51	
52 53	
54 55	
56 57	
58 59 60	

6 not report whether exposure was also in breastfeeding (additional to *in utero*). Hence, we 7 included all studies in the analysis irrespective of the type of exposure. 8 More evidence from long-term follow-up studies is required to further delineate 9 neurodevelopmental risks in children. Registries should aim to include a suitable control 0 group and collect information on potential confounders, such as alcohol and tobacco use, 1 allowing researchers to identify the safest agents for different patient-level covariates, and 2 enhance decision-making for healthcare providers and patients. An individual patient data 3 NMA would likely provide further clarity to the field, which allows the tailoring of 4 management to specific patient characteristics.<sup>41</sup> 5 CONCLUSION 6 Across all outcomes, valproate alone or combined with another AED was associated with 7 the greatest risk, whereas oxcarbazepine and lamotrigine were associated with increased 8 occurrence of autism. Counselling is advised for women considering pregnancy to tailor the 9 safest regimen.

1 2		
3 4	440	LIST OF ABBREVIATIONS
5 6 7	441	AEDs: Anti-epileptic drugs; CrI: Credible interval; NMA: Network Meta-analysis; OR: Odds
8 9	442	ratio; PrI: Predictive interval; SUCRA curve: Surface under the cumulative ranking curve
10 11 12	443	ADDITIONAL FILES
13 14 15	444	Additional File 1: Protocol
16 17 18 19	445	Additional File 2: PRISMA NMA Checklist
20 21	446	Additional File 3: Supplementary Online Content (Appendices A-O)
22 23 24	447	Appendix A. Outcome measures and diagnostic scales used in analysis
25 26	448	Appendix B. Additional Information on Methods
27 28 29	449	Appendix C. Newcastle-Ottawa Scale scoring guide
30 31	450	Appendix D. List of included studies
32 33 34	451	Appendix E. Additional information on search results
35 36	452	Appendix F. Key Excluded Studies
37 38 39	453	Appendix G. Table of Individual Study Characteristics
40 41	454	Appendix H. Table of Patient Characteristics
42 43 44	455	Appendix I. Methodological quality of observational studies – Newcastle Ottawa Scale
45 46	456	Appendix J. Comparison-adjusted funnel plots
47 48 49	457	Appendix K. Statistically significant network meta-analysis results along with meta-
50 51	458	analysis results, transitivity, and inconsistency assessments
52 53 54	459	Appendix L. Frequencies, events and samples sizes, SUCRA values, and total group risks per
55 56 57 58 59	460	treatment and outcome

2	
3	
4	
5	
6	
7	
<i>'</i>	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
11	
18	
19	
20	
21	
22	
23	
24	
25	
20	
20	
21	
28	
29	
30	
31	
32	
33	
34	
35	
20	
30	
37	
38	
39	
40	
41	
42	
43	
44	
15	
40	
40	
47	
48	
49	
50	
51	
52	
53	
51	
54	
55	
56	
57	
58	
59	
60	

1

461 Appendix M. Rank-heat plot of cognitive developmental delay, autism/dyspraxia,

462 psychomotor developmental delay, language delay, and attention deficit hyperactivity

463 disorder outcomes

464 Appendix N. Number of studies and treatments per outcome

<text>

1 2		
2 3 4	465	FIGURE LEGENDS
5 6 7	466	Figure 1. Study flow diagram
8 9	467	Figure 2. Network diagrams for cognitive developmental delay, autism/dyspraxia,
10 11 12	468	psychomotor developmental delay, language delay, and attention deficit
13 14	469	hyperactivity disorder outcomes
15 16 17	470	Each treatment node is weighted according to the number of patients that have received the
18 19	471	particular treatment, and each edge is weighted according to the number of studies
20 21 22	472	comparing the treatments it connects.
23 24	473	<u>Abbreviations:</u> carbam - carbamazepine, clobaz - clobazam, clonaz - clonazepam, ethos -
25 26 27	474	ethosuximide, gabap - gabapentin, lamot - lamotrigine, levet - levetiracetam, oxcar -
27 28 29	475	oxcarbazepine, pheno - phenobarbital, pheny - phenytoin, primid - primidone, topir -
30 31	476	topiramate, valpro - valproate, vigab – vigabatrin
32 33 34	477	Figure 3. Forest plots for cognitive developmental delay, autism/dyspraxia,
35 36 37	478	psychomotor developmental delay, language delay, and attention deficit
38 39 40 41 42 43 44 546 47 48 49 51 52 354 55 56 57 58	479	hyperactivity disorder outcomes
59 60		2

#### DECLARATIONS

#### **CONTRIBUTORS**

AAV analysed the data, interpreted the results, and drafted the manuscript. ACT and SES conceived and designed the study, helped obtain funding, interpreted the results, and helped write sections of the manuscript. PR and EC coordinated the review, screened citations and full-text articles, abstracted data, appraised quality, resolved discrepancies, contacted authors, and edited the manuscript. CS provided methodological support and screened citations and full-text articles and edited the manuscript. RK, ER, FY, JDS, KT, and HM screened citations and full-text articles, abstracted data, and/or appraised quality. BH, BRH and YF helped conceive the study and edited the manuscript. All authors read and approved the final manuscript.

## ACKNOWLEDGEMENTS

We thank Dr. David Moher for providing his feedback on our protocol. We thank Dr. Laure Perrier for conducting the literature searches, Becky Skidmore for peer-reviewing the MEDLINE search, and Alissa Epworth for obtaining the full-text articles. We thank Alistair Scott, Wing Hui, and Geetha Sanmugalingham for screening some of the citations and/or abstracting some of the data for a few of the included studies, Misty Pratt and Mona Ghannad for helping scan reference lists, and Ana Guzman, Susan Le, and Inthuja Selvaratnam for contacting authors and formatting the manuscript. **FUNDING** 

This systematic review was funded by the Canadian Institutes for Health Research/Drug Safety and Effectiveness Network (CIHR/DSEN). AAV is funded by the Banting Postdoctoral

Fellowship Program from the CIHR. SES is funded by a Tier 1 Canada Research Chair in

1 2		
3 4	503	Knowledge Translation. BH is funded by a CIHR/DSEN New Investigator Award in
5 6 7	504	Knowledge Synthesis. BRH receives funding from the Alberta Heritage Foundation for
7 8 9	505	Medical Research. ACT is funded by a Tier 2 Canada Research Chair in Knowledge
10 11	506	Synthesis. The funder had no role in the design and conduct of the study; collection,
12 13 14	507	management, analysis, and interpretation of the data; preparation, review, or approval of
15 16	508	the manuscript; or decision to submit the manuscript for publication.
17 18 10	509	COMPETING INTERESTS
19 20 21	510	None declared.
22 23	511	ETHICS APPROVAL
24 25 26 27 28 29 30 31	512	Not applicable.
	513	PROVENANCE AND PEER REVIEW
	514	Not commissioned; externally peer reviewed.
32 33	515	DATA SHARING STATEMENT
34 35	516	All datasets generated and/or analysed during the current study are available from the
36 37 38	517	corresponding author on reasonable request.
39 40	518	OPEN ACCESS
41 42 43	519	This is an Open Access article distributed in accordance with the Creative Commons
44 45	520	Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute,
46 47 48	521	remix, adapt, build upon this work non-commercially, and license their derivative works on
48 49 50	522	different terms, provided the original work is properly cited and the use is non-
51 52	523	commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.
53 54 55		
56 57		
58 59 60		28
00		

#### REFERENCES

Spina E, Perugi G. Antiepileptic drugs: indications other than epilepsy. *Epileptic Disord*. 1. 2004;6(2):57-75. Harden CL, Pennell PB, Koppel BS, et al. Management issues for women with epilepsy-focus 2. on pregnancy (an evidence-based review): III. vitamin K, folic acid, blood levels, and breast-feeding: report of the quality standards subcommittee and therapeutics and technology assessment subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia. 2009:50(5):1247-55. Samren EB, van Duijn CM, Koch S, et al. Maternal use of antiepileptic drugs and the risk of 3. major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia*. 1997;38(9):981-90. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women 4. with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res.* 2008;81(1):1-13. Bromley R, Weston J, Adab N, et al. Treatment for epilepsy in pregnancy: 5. neurodevelopmental outcomes in the child. The Cochrane database of systematic reviews. 2014(10):Cd010236. Banach R, Boskovic R, Einarson T, Koren G. Long-term developmental outcome of children 6. of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. Drug Saf. 2010;33(1):73-9. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of 7. autism spectrum disorders and childhood autism. JAMA. 2013;309(16):1696-703. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive 8. outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12(3):244-52. Wlodarczyk BJ, Palacios AM, George TM, Finnell RH, Antiepileptic drugs and pregnancy 9. outcomes. Am J Med Genet A. 2012;158a(8):2071-90. Velez-Ruiz NJ, Meador KJ. Neurodevelopmental effects of fetal antiepileptic drug exposure. 10. Drug Saf. 2015;38(3):271-8. 11. Tricco AC, Cogo E, Veroniki AA, et al. Comparative safety of anti-epileptic drugs among infants and children exposed in utero or during breastfeeding: protocol for a systematic review and network meta-analysis. Syst Rev. 2014;3:68. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-12. analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014;17(2):157-73. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of 13. systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-84. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the 14. quality of nonrandomised studies in meta-analyses Ottawa, Canada: Ottawa Hospital Research Institute: 2000. Available from: http://www.ohri.ca/programs/clinical epidemiology/oxford.asp. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network 15. meta-analysis in STATA. PLoS One. 2013;8(10):e76654. Furukawa TA, Guyatt GH, Griffith LE. Can we individualize the 'number needed to treat'? An 16. empirical study of summary effect measures in meta-analyses. Int J Epidemiol. 2002;31(1):72-6. 

Page 31 of 90

1

2		
3	569	17. Lu G. Ades AE. Combination of direct and indirect evidence in mixed treatment
4	570	comparisons. <i>Stat Med.</i> 2004:23(20):3105-24.
5	571	18. Jansen IP. Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It
0 7	572	all depends on the distribution of effect modifiers. <i>BMC Med</i> . 2013:11:159.
8	573	19. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-
9	574	analysis: model estimation using multivariate meta-regression. <i>Res Synth Methods</i> . 2012:3(2):111-
10	575	25.
11	576	20. Song F. Altman DG. Glenny AM. Deeks II. Validity of indirect comparison for estimating
12	577	efficacy of competing interventions: empirical evidence from published meta-analyses. <i>BMI</i> .
13	578	2003:326(7387):472.
14	579	21. Veroniki AA. Vasiliadis HS. Higgins IP. Salanti G. Evaluation of inconsistency in networks of
15	580	interventions. Int   Epidemiol. 2013;42(1):332-45.
10	581	22. Dalessio DJ. Seizure Disorders and Pregnancy. <i>N Engl J Med.</i> 1985;312(9):559-63.
18	582	23. Welton NJ, Sutton AJ, Cooper N, Abrams KR, Ades A. Evidence synthesis for decision making
19	583	in healthcare. New York: Wiley; 2012.
20	584	24. Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model
21	585	complexity and fit. J R Stat Soc Ser B Stat Methodol. 2002;64(4):583-639.
22	586	25. Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: Evolution, critique and future
23	587	directions. <i>Stat Med</i> . 2009;28(25):3049-67.
24	588	26. Palmer T, Sterne J. Meta-Analysis in Stata: An Updated Collection from the Stata Journal.
25	589	White I, editor. Texas: Stata Press; 2016.
20 27	590	27. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. <i>BMJ</i> .
28	591	2011;342:d549.
29	592	28. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis.
30	593	J R Stat Soc Ser A Stat Soc. 2009;172(1):137-59.
31	594	29. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for
32	595	presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin
33	596	<i>Epidemiol.</i> 2011;64(2):163-71.
34	597	30. Veroniki AA, Straus SE, Fyraridis A, Tricco AC. The rank-heat plot is a novel way to present
30	598	the results from a network meta-analysis including multiple outcomes. <i>J Clin Epidemiol</i> . 2016.
37	599	31. Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic
38	600	drugs prenatally and through breastfeeding: a prospective cohort study on children of women with
39	601	epilepsy. <i>JAMA neurology</i> . 2013;70(11):1367-74.
40	602	32. Trinquart L, Attiche N, Bafeta A, Porcher R, Ravaud P. Uncertainty in Treatment Rankings:
41	603	Reanalysis of Network Meta-analyses of Randomized Trials. <i>Ann Intern Med.</i> 2016;164(10):666-73.
42	604	33. Shallcross R, Bromley RL, Irwin B, Bonnett LJ, Morrow J, Baker GA. Child development
43	605	following in utero exposure: levetiracetam vs sodium valproate. <i>Neurology</i> . 2011;76(4):383-9.
44 45	606	34. Zaccara G, Giovannelli F, Giorgi FS, Franco V, Gasparini S, Benedetto U. Tolerability of new
40 46	607	antiepileptic drugs: a network meta-analysis. Eur J Clin Pharmacol. 2017.
40 47	608	35. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions.
48	609	5.1.0 ed: The Cochrane Collaboration; 2009.
49	610	36. Kibret T, Richer D, Beyene J. Bias in identification of the best treatment in a Bayesian
50	611	network meta-analysis for binary outcome: a simulation study. <i>Clin Epidemiol</i> . 2014;6:451-60.
51	612	37. Efthimiou O, Mavridis D, Debray TP, et al. Combining randomized and non-randomized
52	613	evidence in network meta-analysis. <i>Stat Med</i> . 2017.
53	614	38. Schmitz S, Adams R, Walsh C. Incorporating data from various trial designs into a mixed
54	615	treatment comparison model. <i>Stat Med</i> . 2013;32(17):2935-49.
00 56	616	39. Cameron C, Fireman B, Hutton B, et al. Network meta-analysis incorporating randomized
57	617	controlled trials and non-randomized comparative cohort studies for assessing the safety and
58	618	effectiveness of medical treatments: challenges and opportunities. <i>Syst Rev.</i> 2015;4:147.
59		
60		30

1

2 3	(10	
4 5	619 620	<ul> <li>40. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research.</li> <li><i>Lancet.</i> 1991;337(8746):867-72.</li> <li>41. Venenilei AA, Strawa SE, Sachiah C, Elliett ML Triage AC, A securing regions of in direct</li> </ul>
6 7	621 622	41. Veroniki AA, Straus SE, Soobiah C, Elliott MJ, Tricco AC. A scoping review of indirect comparison methods and applications using individual patient data. <i>BMC Med Res Methodol</i> .
8 9 10	623 624	2016;16(1):47.
10 11 12		
13 14		
15 16		
17 18 19		
20 21		
22 23		
24 25 26		
27 28		
29 30		
31 32 33		
34 35		
36 37 28		
30 39 40		
41 42		
43 44 45		
43 46 47		
48 49		
50 51 52		
52 53 54		
55 56		
57 58		
59		

Table 1. Summary Characteristics of in	cluded studies	
Study/Patient Characteristic	# of Studies (n=27)	% of Studies
Year of publication		
1980-1989	1	3.70
1990-1999	6	22.22
2000-2009	5	18.52
2010-2015	14	51.85
NR	1	3.70
Continent (of country of study conduct)		
Europe	18	66.67
North America	5	18.52
Asia	1	3.70
Australia	2	7.41
Trans-Continental	1	3.70
Study design		
Observational cohort	27	100.00
Case-control	0	0.00
Randomized clinical trial	0	0.00
Registry study		
Yes	10	37.04
No	17	62.96
Sample size		
0-99	17	62.96
100-299	8	29.63
300-499	1	3.70
500-699	0	0.00
700-999	0	0.00
1000+	1	3.70
Number of interventions		
2	4	14.81
3	5	18.52
4	8	29.63
5-7	7	25.93
8-10	2	7.41
11+	1	3.70
Outcomes <sup>*,†</sup>		
Cognitive Developmental Delay	11	40.74
Autism/Dyspraxia	5	18.52
	r -	10 50

Study/Patient Characteristic	# of Studies (n=27)	% of Studies
ADHD	4	14.81
Psychomotor Developmental Delay	11	40.74
Neonatal Seizures	2	7.41
Social Impairment	1	3.70
Funding		
Public	14	51.85
Private	0	0.00
Mixed public and private	4	14.81
NR/Unclear	9	33.33
Treatment indication 🦯		
Epilepsy	21	77.78
Mixed indications <sup>‡</sup>	0	0.00
Not reported	6	22.22
Epileptic control group <sup>§</sup>		
Yes	13	48.15
No/NR/NA	14	51.85
Mean maternal age	4	
24-26 y	2	7.41
27-29 y	5	18.52
30-32 y	3	11.11
Not reported	17	62.96
AED exposure during pregnancy		
Reported as during 1 <sup>st</sup> trimester	6	22.22
Reported as any time during pregnancy	6	22.22
Not reported	15	55.56
Alcohol use during pregnancy		
Yes	4	14.81
NR	23	85.19
Tobacco use during pregnancy		
Yes	5	18.52
NR	22	81.48

\*Values in this category do not match totals as some studies report more than one outcome

<sup>†</sup>Percentage of total number of included studies (n=27)

<sup>‡</sup> Includes individuals taking AEDs for psychiatric disorders, migraine, and

neuropathic/neurological pain

<sup>§</sup> Consisted of women with Epilepsy who did not take AEDs during pregnancy



\*27 publications reporting 28 included studies.

Figure 1. Study flow diagram

171x128mm (300 x 300 DPI)


Figure 2. Network diagrams for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes.

 $\| + \| +$  Each treatment node is weighted according to the number of patients that have received the particular treatment, and each edge is weighted according to the number of studies comparing the treatments it connects. $\| + \| +$ 

Abbreviations: carbam - carbamazepine, clobaz - clobazam, clonaz - clonazepam, ethos - ethosuximide, gabap - gabapentin, lamot - lamotrigine, levet - levetiracetam, oxcar - oxcarbazepine, pheno phenobarbital, pheny - phenytoin, primid - primidone, topir - topiramate, valpro - valproate, vigab vigabatrin!! +

171x128mm (300 x 300 DPI)





# Figure 3. Forest plots for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes

171x128mm (300 x 300 DPI)



**Open Access** 

# Comparative safety of anti-epileptic drugs among infants and children exposed *in utero* or during breastfeeding: protocol for a systematic review and network meta-analysis

Andrea C Tricco<sup>1</sup>, Elise Cogo<sup>1</sup>, Veroniki A Angeliki<sup>1</sup>, Charlene Soobiah<sup>1,2</sup>, Brian Hutton<sup>3</sup>, Brenda R Hemmelgarn<sup>4</sup>, David Moher<sup>3</sup>, Yaron Finkelstein<sup>5,6,7</sup> and Sharon E Straus<sup>1,8\*</sup>

### Abstract

**Background:** Epilepsy affects about 1% of the general population. Anti-epileptic drugs (AEDs) prevent or terminate seizures in individuals with epilepsy. Pregnant women with epilepsy may continue taking AEDs. Many of these agents cross the placenta and increase the risk of major congenital malformations, early cognitive and developmental delays, and infant mortality. We aim to evaluate the comparative safety of AEDs approved for chronic use in Canada when administered to pregnant and breastfeeding women and the effects on their infants and children through a systematic review and network meta-analysis.

**Methods:** Studies examining the effects of AEDs administered to pregnant and breastfeeding women regardless of indication (e.g., epilepsy, migraine, pain, psychiatric disorders) on their infants and children will be included. We will include randomized clinical trials (RCTs), quasi-RCTs, non-RCTs, controlled before-after, interrupted time series, cohort, registry, and case-control studies. The main literature search will be executed in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. We will seek unpublished literature through searches of trial protocol registries and conference abstracts. The literature search results screening, data abstraction, and risk of bias appraisal will be performed by two individuals, independently. Conflicts will be resolved through discussion. The risk of bias of experimental and quasi-experimental studies will be appraised using the Cochrane Effective Practice and Organization of Care Risk-of-Bias tool, methodological quality of observational studies will be appraised using the Newcastle-Ottawa Scale, and quality of reporting of safety outcomes will be conducted using the McMaster Quality Assessment Scale of Harms (McHarm) tool. If feasible and appropriate, we will conduct random effects meta-analysis. Network meta-analysis will be considered for outcomes that fulfill network meta-analysis assumptions.

The primary outcome is major congenital malformations (overall and by specific types), while secondary outcomes include fetal loss/miscarriage, minor congenital malformations (overall and by specific types), cognitive development, psychomotor development, small for gestational age, preterm delivery, and neonatal seizures. (Continued on next page)

Full list of author information is available at the end of the article



© 2014 Tricco et al.; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

<sup>\*</sup> Correspondence: sharon.straus@utoronto.ca

<sup>&</sup>lt;sup>1</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria Street,

East Building, Toronto, Ontario M5B 1 T8, Canada

<sup>&</sup>lt;sup>8</sup>Department of Geriatric Medicine, University of Toronto, 172 St. George Street,

Toronto, Ontario M5R 0A3, Canada

Tricco et al. Systematic Reviews 2014, 3:68 http://www.systematicreviewsjournal.com/content/3/1/68

#### (Continued from previous page)

**Discussion:** Our systematic review will address safety concerns regarding the use of AEDs during pregnancy and breastfeeding. Our results will be useful to healthcare providers, policy-makers, and women of childbearing age who are taking anti-epileptic medications.

Systematic review registration: PROSPERO CRD42014008925.

**Keywords:** Anti-epileptic drug, Breastfeeding, Comparative safety, Congenital malformation, Epilepsy, Fetus, Infant, Network meta-analysis, Pregnancy, Systematic review

#### Background

Epilepsy is the most common chronic neurological condition, affecting 0.6 to 1% of the population [1,2]. Individuals with uncontrolled epilepsy experience recurrent seizures, which can have psychosocial and physical consequences, including a compromised life expectancy [3,4]. The goal of anti-epileptic treatment is to improve quality of life and health outcomes by reducing the frequency of seizures [4].

Anti-epileptic medications decrease seizures by reducing excitation and enhancing inhibition of neurons [5-7]. Many of these medications target different channels, including calcium, sodium, and glutamate, and are broadly classified as first generation agents (e.g., phenobarbitone, phenytoin, carbamazepine, sodium valproate, ethosuximide) and second generation agents (e.g., lamotrigine, levetiracetam, topiramate, gabapentin, vigabatrin, oxcarbazepine, clobazam, clonazepam, zonisamide, lacosamide, rufinamide, primidone) [8]. Due to the broad and varied mechanisms of action, the indications for some of these medications also include pain syndromes, psychiatric disorders, and migraine headaches [8].

Many clinical practice guidelines recommend that women of childbearing age continue to take their anti-epileptic medications; however, medications with lower risk of teratogenic events are advised [9,10] since anti-epileptic drugs (AEDs) cross the placenta or transfer through breast milk, posing risks to the fetus and infant [9,11,12].

Some AEDs have been associated with increased risk of harm to the fetus and infants. For example, exposure to valproate has led to increased risk of major congenital malformations [10], cognitive delay, and minor congenital abnormalities [13-16]. Phenobarbital has been associated with minor congenital abnormalities and developmental delay [17,18]. Carbamazepine and lamotrigine have been associated with minor congenital abnormalities [19-22]. However, other than studies of the use of valproate, many studies have produced inconsistent findings regarding harm to the fetus and infant with use of other agents [23]. As such, our objective is to evaluate the comparative safety of AEDs for infants and children who were exposed *in utero* or during breastfeeding through a systematic review and network meta-analysis.

### Methods/Design

#### Protocol

A systematic review protocol was developed and registered with the PROSPERO database (CRD42014008925, available at: http://www.crd.york.ac.uk/PROSPERO/display\_record. asp?ID=CRD42014008925). It was revised with feedback from the decision-makers who posed the query within Health Canada, healthcare practitioners, content experts, and research methodologists. The reporting of our systematic review protocol was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols [24].

#### Eligibility criteria

We will include studies examining the effects of AEDs on infants and children who were exposed in utero or during breastfeeding. We will include experimental studies (randomized clinical trials [RCTs], quasi-RCTs, non-RCTs), guasi-experimental studies (controlled before and after studies, interrupted time series), and observational studies (cohort, case-control, registry studies) of pregnant women at any stage of pregnancy and breastfeeding women and their infants/children. The rationale for including other study designs in addition to RCTs is that there are ethical issues in conducting RCTs of AEDs in pregnancy, so RCT evidence might not exist for some or all of these drugs. Given that our review includes rare outcomes, including observational evidence is crucial. In contrast to efficacy evaluation, safety assessment usually requires very large sample sizes to be able to detect adverse events. Therefore, while RCTs have lower risk of bias, they usually do not have the statistical power needed to adequately evaluate uncommon/rare safety outcomes due to Type II (i.e., false negative) error [25]. Given that our review includes rare outcomes, including observational evidence is crucial [26]. Additionally, observational studies can often provide more generalizable evidence due to the strict participant inclusion criteria in most RCTs [27]. Real-world safety evidence that has external validity is important for the assessment of the possible risks of AEDs in pregnant and breastfeeding women.

The diagnosis of neurodevelopmental delay related to *in utero* exposure is made before adolescence, and

hence, we will limit inclusion to children up to 12 years of age. AEDs that are approved for chronic use in Canada will be included. Drugs that are only used acutely or those that are not currently approved for use in Canada will be excluded, as the focus of this review is on the Canadian setting [28-32]. However, most of the medications we will examine are available in other countries as well. The relevant 16 medications and their synonyms are listed in Additional file 1, and the excluded drugs are listed in Additional file 2. Studies of all combinations and doses of these medications are eligible for inclusion. Since we are only interested in exposures that occur in *utero* or during breastfeeding, studies examining AEDs administered directly to infants or children will be excluded. All indications for AEDs will be included such as epilepsy, migraine, pain, and psychiatric disorders.

In order to be included, studies must compare an antiepileptic medication against another included anti-epileptic medication, placebo, a 'no intervention' control group, or combinations of two or more anti-epileptic medications. Only studies providing results for our outcomes of interest will be included. Our primary outcome is major congenital malformations (overall and by specific type, such as craniofacial defects and neural tube defects). Secondary outcomes include minor congenital malformations (overall and by specific type, such as epicanthal folds and microstomia), cognition (e.g., global cognitive functioning and specific cognitive domains such as attention), psychomotor development (e.g., autism, dyspraxia), small for gestational age, preterm delivery, neonatal seizures, and fetal loss/miscarriage. No other limitations will be imposed on the eligibility criteria, including published/unpublished material, language of dissemination, duration of follow-up, or year of publication. The draft eligibility criteria can be found in Additional file 3.

#### Information sources and literature search

Our main literature search will be executed in the MED-LINE database. The search terms were drafted by an experienced librarian and can be found in Additional file 4. The search was peer reviewed by another librarian using the Peer Review of Electronic Search Strategies checklist [33].

In addition to MEDLINE, we will also search the EMBASE and the Cochrane Central Register of Controlled Trials databases. We will follow the MEDLINE search strategy for these databases, and the search terms will be adjusted accordingly. The electronic database search will be supplemented by searching for unpublished literature [34]. This will be accomplished through exploring conference abstracts, clinical trial registries, and contacting manufacturers of AEDs. We will also scan the reference lists of included studies and previous reviews in the area [23,35,36].

#### Study selection process

The eligibility criteria screening form will be pilot-tested by the team and is presented in Additional file 3. We will calculate inter-rater reliability from the pilot-test and screening will only commence after high agreement (e.g., kappa statistic  $\geq$ 60%) is observed [37]. Subsequently, two reviewers will screen each title/abstract and potentially relevant full-text articles from the literature search results, independently. Conflicts will be resolved through discussion. All screening will occur using our online screening software (synthesi.SR) [38].

#### Data items and data collection process

We will abstract data on the PICOS elements [39], including patient characteristics (e.g., age of the mother and infant/child, indication for anti-epileptic treatment, co-morbidities, concomitant medications), intervention details (e.g., type of anti-epileptic treatment, dose, route of administration, duration of treatment, timing [trimester] of treatment during pregnancy), comparator details (e.g., comparator agent, dose, route of administration), outcome results (e.g., major congenital abnormality, minor congenital abnormality, cognitive function, psychomotor development) at the longest duration of follow-up, and study characteristics (e.g., study design, country of conduct, year of conduct, sample size, setting). These characteristics will be abstracted using a data abstraction form created in Excel with an accompanying "cheat sheet" that will guide the reviewers with this process. The data abstraction form and cheat sheet will be pilot-tested and data abstraction will only commence when high agreement (e.g., kappa statistic ≥60%) [37] is observed. Each included study will be abstracted by two team members, independently, who will resolve disagreements through discussion.

#### Methodological quality/risk of bias appraisal

We will use various tools to assess the methodological quality/risk of bias of each of the studies that fulfill our eligibility criteria. This will be conducted by two reviewers, independently, and conflicts will be resolved through discussion. First, we will appraise the risk of bias of experimental and quasi-experimental studies using the Cochrane Effective Practice and Organization of Care Risk-of-Bias tool [40]. Second, we will assess the methodological quality of observational studies using the Newcastle-Ottawa Scale [41]. Third, the quality of reporting of harms will be appraised using the McMaster Quality Assessment Scale of Harms (McHarm) tool [42].

#### Synthesis of included studies

A narrative summary of study results will be presented along with evidence summary tables. When sufficient data are available, we will conduct random effects meta-

5

6

7

8

9

10

11

12

5

6

7

8

9

10

11

12

13 14

15

16 17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50 51

52

53

54

55

56

57

58

59

60

analysis to calculate pooled odds ratios for dichotomous data and pooled mean differences for continuous data [43,44]. Direct (pairwise) meta-analysis will be performed with RCTs alone in order to examine whether the data are consistent between direct and indirect evidence. If the large majority of included studies are observational, we will also conduct additional meta-analyses including observational studies alone. Analyses will be stratified by treatment indication (e.g., epilepsy, pain, etc.) to reduce clinical heterogeneity between different study populations whenever possible; for example, epilepsy itself in pregnant women is related to an increased baseline risk of certain neonatal adverse outcomes. Statistical, clinical, and methodological heterogeneity will be examined prior to conducting the meta-analysis. Funnel plots will be drawn for outcomes including at least 10 studies to explore asymmetry that might be explained by clinical, statistical, and methodological heterogeneity. The proportion of statistical heterogeneity will be examined using the  $I^2$  measure [45] and the magnitude of statistical heterogeneity will be calculated using the restricted maximum likelihood [46]. Meta-regression will be conducted for clinically relevant subgroups or when extensive statistical heterogeneity is observed (e.g.,  $I^2 \ge$ 75%) [47]. This will allow the examination of the impact of important factors on our results, such as maternal age, dose, duration and timing (e.g., trimester) of antiepileptic treatment, co-morbidities, concomitant medications, risk of bias results, and sample size (due to Type II statistical power errors with rare adverse events). To ensure the meta-regression analysis is intuitive, the number of covariates examined will be less than 10% of the number of studies included in the meta-analysis for the particular outcome.

We anticipate that many of these outcomes will be rare. To deal with studies reporting zero events in one treatment arm, 0.5 will be added to the numerator and 1 will be added to the denominator. We will exclude studies reporting zero events in all treatment arms for a particular outcome [48,49]. We also anticipate that we will encounter missing data in the included studies. We will contact the study authors for this data and if we are unable to receive the data, we will impute missing data (e.g., measures of variance) using established methods [50]. To ensure that our imputations do not bias our results, we will conduct a sensitivity analysis [51]. The meta-analysis and meta-regression will be analyzed in R using the *metafor* command [52].

A random-effects network meta-analysis will be conducted to make inferences regarding the comparative safety of the various AEDs [15], as well as rank their safety using rankograms and the surface under the cumulative ranking curve [53]. We will ensure the following factors are present prior to conducting network meta-analysis: i) transitivity (i.e., comparable distribution of effect modifiers across comparisons), which will be examined using boxplots or percentages to visually inspect potential effect modifiers of treatment effect [54]; ii) consistency between direct and indirect data, which will be examined locally (i.e., in certain paths of the network) using the loop-specific method [55,56] and the node-splitting method [57], and globally (i.e., evaluating the network as a whole), using the design-by-treatment interaction model [58]; and iii) we will quantify the amount of variability attributed to heterogeneity and inconsistency rather than sampling error, by calculating the  $I^2$  [59]. We will estimate the amount of heterogeneity using the restricted maximum likelihood method and assuming common within-network heterogeneity. We will compare the magnitude of heterogeneity between consistency and inconsistency models, as well as between meta-regression and network meta-analysis models to determine how much heterogeneity will be explained by inconsistency or the explanatory variable, respectively. We will first use the design-by-treatment model for the evaluation of inconsistency in a network as a whole and then, if inconsistency is detected, we will employ the loop-specific and node-splitting methods to identify which piece of evidence is responsible for inconsistency. As mentioned above, analyses will be stratified by treatment indication when clinically appropriate. Important heterogeneity and inconsistency will be explored using network metaregression using the same methods as described above, as necessary.

Prior to conducting the network meta-analysis, we will hold a team meeting to finalize which treatment nodes will be included in the analysis since we are unclear about the indications, dosages, patient populations, and outcomes reported in all of the studies. We will discuss issues, including conducting a class versus independent drug analysis, inclusion of drug routes of administration and dosages, as well as timing of drug administration. These decisions will be examined through a sensitivity analysis in which we will classify treatment nodes using a different classification to see how stable our results are. The network meta-analysis results will be presented as summary treatment effects for each pair of treatments. Network meta-analysis will be conducted in Stata with the *mvmeta* routine [60].

A sequential approach will be used for the network meta-analysis. We will first restrict our analysis to RCTs, which will be the primary analysis of interest. We will then include data from quasi-experimental studies, and finally, data from observational studies. This will provide an understanding of the contribution of each type of study design to our summary estimates, providing us with information on how these agents work above and beyond clinical trials.

### Discussion

Epilepsy is the most common chronic neurological condition, affecting 0.6 to 1% of the population [1,2]. Given that approximately a third of patients receiving AEDs are of reproductive age and almost half of pregnancies are unplanned [61], the fetus may be exposed to these in the first trimester of pregnancy, including during the critical stage of embryogenesis [62].

The comparative safety of these agents is currently unknown and our results will be important for policymakers, healthcare providers, and women of childbearing age. To ensure our results have wide dissemination and uptake, we will publish our results in open access journals, present our findings at scientific conferences, conduct dissemination meetings with key stakeholders (including policy-makers and healthcare providers), and produce policy briefs for Health Canada, the organization that posed this query.

### **Additional files**

Additional file 1: List of relevant medications. Additional file 2: Excluded drugs. Additional file 3: Draft eligibility criteria. Additional file 4: MEDLINE literature search.

#### Abbreviations

AEDs: Anti-epileptic drugs; RCTs: Randomized clinical trials.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

ACT conceived and designed the study, helped obtain funding for the study, and helped write the draft protocol. EC registered the protocol with the PROSPERO database and edited the draft protocol. AV helped write the draft protocol. CS edited the draft protocol. BH, BRH, DM, and YF provided input into the design, helped obtain funding for the study, and edited the draft protocol. SES conceived the study, designed the study, obtained the funding, and helped write the draft protocol. All authors read and approved the final protocol.

#### Acknowledgements

This systematic review was funded by the Canadian Institutes of Health Research/Drug Safety and Effectiveness Network (CIHR/DSEN). ACT and BH are funded by a CIHR/DSEN New Investigator Award in Knowledge Synthesis. BRH receives funding from the Alberta Heritage Foundation for Medical Research. DM is funded by a University of Ottawa Research Chair. SES is funded by a Tier 1 Canada Research Chair in Knowledge Translation. We thank Laure Perrier for conducting the literature searches and Becky Skidmore for peer reviewing the MEDLINE search strategy. We also thank Dr. Joseph Beyene for providing feedback on our original proposal and Wing Hui and Judy Tran for formatting the paper.

#### Author details

<sup>1</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria Street, East Building, Toronto, Ontario M5B 1 T8, Canada. <sup>2</sup>Institute of Health Policy Management and Evaluation, University of Toronto, Health Sciences Building, 155 College Street, Suite 425, Toronto, Ontario M5T 3 M6, Canada. <sup>3</sup>Clinical Epidemiology Program, Centre for Practice-Changing Research, Ottawa Hospital Research Institute, The Ottawa Hospital – General Campus and University of Ottawa, 501 Smyth Road, Box 711, Ottawa, Ontario K1H 8 L6, Canada. <sup>4</sup>Departments of Medicine and Community Health Sciences, University of Calgary, TRW Building, 3rd Floor, 3280 Hospital Drive NW, Calgary, Alberta T2N 4Z6, Canada. <sup>5</sup>The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. <sup>6</sup>Department of Pediatrics, University of Toronto, 172 St. George Street, Toronto, Ontario M5R 0A3, Canada. <sup>7</sup>Department of Pharmacology and Toxicology, University of Toronto, Medical Sciences Building, 1 King's College Circle, Room 4207, Toronto, Ontario M5S 1A8, Canada. <sup>8</sup>Department of Geriatric Medicine, University of Toronto, 172 St. George Street, Toronto, Ontario M5R 0A3, Canada.

#### Received: 9 April 2014 Accepted: 17 June 2014 Published: 25 June 2014

#### References

- Hauser WA, Hesdorffer D: Epilepsy, Frequency, Causes and Consequences. New York: Demos Publications; 1990.
- Wiebe S, Bellhouse DR, Fallahay C, Eliasziw M: Burden of epilepsy: the Ontario Health Survey. Can J Neurol Sci 1999, 26(4):263–270.
- Sperling MR: The consequences of uncontrolled epilepsy. CNS Spectr 2004, 9(2):98–101. 106–109.
- 4. Jones MW: Consequences of epilepsy: why do we treat seizures? Can J Neurol Sci 1998, 25(4):S24–S26.
- Dickenson AH, Ghandehari J: Anti-convulsants and anti-depressants. Handb Exp Pharmacol 2007, 177:145–177.
- Stefani A, Spadoni F, Bernardi G: Voltage-activated calcium channels: targets of antiepileptic drug therapy? *Epilepsia* 1997, 38(9):959–965.
- Snutch TP, Reiner PB: Ca<sup>2+</sup> channels: diversity of form and function. Curr Opin Neurobiol 1992, 2(3):247–253.
- Spina E, Perugi G: Antiepileptic drugs: indications other than epilepsy. Epileptic Disord 2004, 6(2):57–75.
- 9. Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, Hopp J, Ting TY, Hauser WA, Thurman D, Kaplan PW, Robinson JN, French JA, Wiebe S, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Shafer PO, Le Guen CL, American Academy of Neurology; American Epilepsy Society: Management issues for women with epilepsy–focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: report of the quality standards subcommittee and therapeutics and technology assessment subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009, 50(5):1247–1255.
- Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA, Wiebe S, Thurman D, Koppel BS, Kaplan PW, Robinson JN, Hopp J, Ting TY, Gidal B, Hovinga CA, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Hirtz D, Le Guen C, American Academy of Neurology; American Epilepsy Society: Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009, 50(5):1237–1246.
- Samren EB, van Duijn CM, Koch S, Hiilesmaa VK, Klepel H, Bardy AH, Mannagetta GB, Deichl AW, Gaily E, Granstrom ML, Meinardi H, Grobbee DE, Hofman A, Janz D, Lindhout D: Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 1997, 38(9):981–990.
- Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C: Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res* 2008, 81(1):1–13.
- Adab N, Jacoby A, Smith D, Chadwick D: Additional educational needs in children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2001, 70(1):15–21.
- Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, Coyle H, Fryer A, Gorry J, Gregg J, Mawer G, Nicolaides P, Pickering L, Tunnicliffe L, Chadwick DW: The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004, 75(11):1575–1583.
- Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M, Matila R, Kotila M, Nylund T, Bardy A, Kaaja E, Granstrom ML: Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology* 2004, 62(1):28–32.
- Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW, for the NEAD Study Group: Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 2009, 360(16):1597–1605.

Page 5 of 6

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

Tricco et al. Systematic Reviews 2014, 3:68 http://www.systematicreviewsjournal.com/content/3/1/68

- Holmes LB, Wyszynski DF, Lieberman E: The AED (antiepileptic drug) pregnancy registry: a 6-year experience. *Arch Neurol* 2004, 61(5):673–678.
- Reinisch JM, Sanders SA, Mortensen EL, Rubin DB: In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA 1995, 274(19):1518–1525.
- Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, Irwin B, McGivern RC, Morrison PJ, Craig J: Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2006, 77(2):193–198.
- Meador KJ, Baker GA, Finnell RH, Kalayjian LA, Liporace JD, Loring DW, Mawer G, Pennell PB, Smith JC, Wolff MC, NEAD Study Group: In utero antiepileptic drug exposure: fetal death and malformations. *Neurology* 2006, 67(3):407–412.
- Vajda FJ, Hitchcock A, Graham J, Solinas C, O'Brien TJ, Lander CM, Eadie MJ: Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur J Neurol* 2006, 13(6):645–654.
- Holmes LB, Baldwin EJ, Smith CR, Habecker E, Glassman L, Wong SL, Wyszynski DF: Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 2008, 70(22 Pt 2):2152–2158.
- Meador KJ, Penovich P, Baker GA, Pennell PB, Bromfield E, Pack A, Liporace JD, Sam M, Kalayjian LA, Thurman DJ, Moore E, Loring DW, NEAD Study Group: Antiepileptic drug use in women of childbearing age. *Epilepsy Behav* 2009, 15(3):339–343.
- Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L: Reporting Guidelines for Systematic Review Protocols. In 19th Cochrane Colloaujum: 19–22 October 2011: Madrid. Spain.
- Ross CJ, Visscher H, Sistonen J, Brunham LR, Pussegoda K, Loo TT, Rieder MJ, Koren G, Carleton BC, Hayden MR, CPNDS Consortium: The Canadian Pharmacogenomics Network for Drug Safety: a model for safety pharmacology. *Thyroid* 2010, 20(7):681–687.
- Eypasch E, Lefering R, Kum CK, Troidl H: Probability of adverse events that have not yet occurred: a statistical reminder. *BMJ* 1995, 311(7005):619–620.
- 27. Atkins D: Creating and synthesizing evidence with decision makers in mind: integrating evidence from clinical trials and other study designs. *Med Care* 2007, **45**(10 Supl 2):S16–S22.
- Health Canada: Drug Product Database. http://www.hc-sc.gc.ca/dhp-mps/ prodpharma/databasdon/index-eng.php.
- 29. United States National Library of Medicine's ChemIDPlus Lite Database. http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp.
- 30. Canadian Pharmacists Association: E-CPS (Compendium of Pharmaceuticals and Specialties). http://www.e-therapeutics.ca/home.whatsnew.action.
- Epilepsy Canada: Anticonvulsant Medications. http://www.epilepsy.ca/en-CA/ Diagnosis-and-Treatment/Anticonvulsant-Medications.html.
- Epilepsy Ontario: Anticonvulsant/Anti-Seizure Medication from A to Z. http://epilepsyontario.org/anticonvulsantanti-seizure-medication-from-a-to-z/.
- Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C: An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol 2009, 62(9):944–952.
- Canadian Agency for Drugs and Technologies in Health: Grey Matters: A Practical Search Tool for Evidence-Based Medicine. http://www.cadth.ca/ resources/grey-matters.
- Adab N, Tudur SC, Vinten J, Williamson P, Winterbottom J: Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database Syst Rev 2004, 3:CD004848.
- Banach R, Boskovic R, Einarson T, Koren G: Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. Drug Saf 2010, 33(1):73–79.
- 37. Landis JR, Koch GG: The measurement of observer agreement for categorical data. *Biometrics* 1977, **33**(1):159–174.
- 38. Synthesi.SR. http://knowledgetranslation.ca/sysrev/login.php.
- Stone PW: Popping the (PICO) question in research and evidence-based practice. Appl Nurs Res 2002, 15(3):197–198.
- 40. Cochrane Effective Practice and Organization of Care Group Draft Risk of Bias Tool. http://epoc.cochrane.org/epoc-author-resources.
- The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. http://www.ohri.ca/programs/clinical\_epidemiology/ oxford.asp.

- Santaguida PL, Raina P, Ismaila A: The Development of the McHarm Quality Assessment Scale for Adverse Events. Hamilton, Ontario: McMaster University; 2008.
- Raudenbush SW: Analyzing Effect Sizes: Random Effects Models. In *The* Handbook of Research Synthesis and Meta-analysis. 2nd edition. Edited by Cooper H, Hedges LV, Valentine JC. New York: Russell Sage Foundation; 2009:295–315.
- 44. Viechtbauer W: Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat* 2005, **30**(3):261–293.
- 45. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002, **21**(11):1539–1558.
- 46. Viechtbauer W: Confidence intervals for the amount of heterogeneity in meta-analysis. *Stat Med* 2007, **26**(1):37–52.
- Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2009. http://www.cochrane.org/ handbook.
- Sweeting MJ, Sutton AJ, Lambert PC: What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004, 23(9):1351–1375.
- Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A: Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007, 26(1):53–77.
- Littell JH, Corcoran J, Pillai V: Systematic Reviews and Meta-Analysis. New York: Oxford University Press; 2008.
- Carpenter J, Rucker G, Schwarzer G: Assessing the sensitivity of meta-analysis to selection bias: a multiple imputation approach. *Biometrics* 2011, 67(3):1066–1072.
- Conducting Meta-Analyses in R with the metafor Package. http://www.jstatsoft.org/v36/i03/.
- Salanti G, Ades AE, Ioannidis JP: Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011, 64(2):163–171.
- 54. Salanti G: Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012, 3(2):80–97.
- Song F, Altman DG, Glenny AM, Deeks JJ: Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003, 326(7387):472.
- Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G: Evaluation of inconsistency in networks of interventions. Int J Epidemiol 2013, 42(1):332–345.
- 57. Dias S, Welton NJ, Caldwell DM, Ades AE: Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010, **29**(7–8):932–944.
- White IR, Barrett JK, Jackson D, Higgins JPT: Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012, 3(2):111–125.
- Jackson D, Barrett JK, Stephen R, White IR, Higgins JPT: A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. Stat Med 2014, In press.
- 60. White IR: Multivariate random-effects meta-regression: updates to mvmeta. *Stata J* 2011, 11(2):255–270.
- Centers for Disease Control and Prevention: Unintended Pregnancy Prevention. http://www.cdc.gov/reproductivehealth/unintendedpregnancy/.
- Yerby MS: Pregnancy, teratogenesis, and epilepsy. Neurol Clin 1994, 12(4):749–771.

#### doi:10.1186/2046-4053-3-68

**Cite this article as:** Tricco *et al.*: Comparative safety of anti-epileptic drugs among infants and children exposed *in utero* or during breastfeeding: protocol for a systematic review and network meta-analysis. *Systematic Reviews* 2014 **3**:68.

## PRISMA NMA Checklist

Section/Topic	Item #	Checklist Item <sup>*</sup>	Reported on Page #
TITLE			8
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	1
ABSTRACT			
Structured summary 2		<ul> <li>Provide a structured summary including, as applicable:</li> <li>Background: main objectives</li> <li>Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis.</li> <li>Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</li> <li>Discussion/Conclusions: limitations; conclusions and implications of findings.</li> <li>Other: primary source of funding; systematic review registration number with registry name.</li> </ul>	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	7
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information.	8

4
2
3
4
4
5
6
7
1
8
9
10
10
11
12
13
10
14
15
16
17
17
18
19
20
20
21
22
22
23
24
25
26
27
27
28
29
20
30
31
32
33
33
34
35
36
50
37
38
39
40
40
41
42
42
11
44
45
46
17
41
48
49
50
50
51
52
52
55
54
55
56
57
5/
58
59
60
00

		including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in</i> <i>the treatment network, and note whether any have</i> <i>been clustered or merged into the same node</i> (with justification).	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9 (see also Appendix C)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Additional File 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta- analysis).	9 (see also Appendix C)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9 (see also Appendix C)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Additional File 1
Geometry of the network	<b>S</b> 1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	9-12 (see also Appendix C)
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present	9-12

2	
3	
4	
5	
5	
6	
7	
8	
0	
9	
10	
11	
12	
40	
13	
14	
15	
16	
47	
17	
18	
19	
20	
20	
21	
22	
23	
24	
24	
25	
26	
27	
20	
20	
29	
30	
31	
32	
52	
33	
34	
35	
36	
00	
37	
38	
39	
40	
40	
41	
42	
43	
44	
17	
40	
46	
47	
48	
10	
49	
50	
51	
52	
52	
03	
54	
55	
56	
57	
57	
58	
59	
60	

		summary findings from meta-analyses.	
Planned methods of analysis	14	<ul> <li>Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to:</li> <li><i>Handling of multi-arm trials;</i></li> <li><i>Selection of variance structure;</i></li> <li><i>Selection of prior distributions in Bayesian analyses; and</i></li> <li><i>Assessment of model fit.</i></li> </ul>	9-12 (see also Appendix C)
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	10 (see also Appendix C)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9 (see also Appendix C)
Additional analyses	16	<ul> <li>Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul> <li>Sensitivity or subgroup analyses;</li> <li>Meta-regression analyses;</li> <li>Alternative formulations of the treatment network; and</li> <li>Use of alternative prior distributions for Bayesian analyses (if applicable).</li> </ul> </li> </ul>	10-12 (see also Appendix C)
<b>RESULTS<sup>†</sup></b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	13 and Figure 1
Presentation of network structure	<b>S</b> 3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	14-18 (see also Appendix L)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS,	Table 1, Appendices H

		follow-up period) and provide the citations.	and I
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Appendix J
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified</i> <i>approaches may be needed to deal with</i> <i>information from larger networks</i> .	N/A (data can be provided by the corresponding author)
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger</i> <i>networks, authors may focus on comparisons</i> <i>versus a particular comparator (e.g. placebo or</i> <i>standard care), with full findings presented in an</i> <i>appendix. League tables and forest plots may be</i> <i>considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	Figure 3, Appendices L, M, O
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	14 (see also Appendix L)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	14 (see also Appendix K)
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied</i> , <i>alternative choice of prior distributions for Bayesian analyses</i> , and so forth).	Appendix M
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	19-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the</i> <i>assumptions, such as transitivity and consistency.</i> <i>Comment on any concerns regarding network</i>	21-23

2	
3	
4	
, F	
5	
6	
7	
1	
8	
0	
9	
10	
11	
11	
12	
13	
10	
14	
15	
10	
10	
17	
10	
10	
19	
20	
20	
21	
22	
~~	
23	
24	
<u> </u>	
25	
26	
27	
21	
28	
20	
29	
30	
31	
01	
32	
33	
00	
34	
35	
26	
30	
37	
20	
30	
39	
10	
40	
41	
42	
40	
43	
44	
<u> </u>	
40	
46	
17	
41	
48	
ΔQ	
-10	
50	
51	
E 0	
52	
53	
51	
04	
55	
56	
57	
58	
50	
59	
60	

Conclusions	26	<i>geometry (e.g., avoidance of certain comparisons).</i> Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	27-28

Abbreviations: PICOS - population, intervention, comparators, outcomes, study design \* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

# **Supplementary Online Content**

Appraisal of selection bias using the comparison-adjusted funnel plot Additional details on the synthesis of included studies References Appendix C. Newcastle-Ottawa Scale scoring guide Appendix D. List of included studies Appendix E. Additional information on search results Appendix F. Key excluded studies References	
Additional details on the synthesis of included studies References	
Appendix C. Newcastle-Ottawa Scale scoring guide Appendix D. List of included studies Appendix E. Additional information on search results Appendix F. Key excluded studies References	
Appendix D. List of included studies	
Appendix E. Additional information on search results Appendix F. Key excluded studies References	
Appendix F. Key excluded studies	
References	
Appendix G. Table of Individual Study characteristics	
Appendix H. Table of Patient characteristics	
Appendix I. Methodological quality of observational studies - Newcastle Otta	wa Scal
Appendix J. Comparison-adjusted funnel plots*	
Appendix K. Statistically significant network meta-analysis results along with results, transitivity, and inconsistency assessments	meta-ar
Appendix L. Frequencies, events and samples sizes, SUCRA values, and total treatment and outcome	group r
Appendix M. Rank-heat plot of cognitive developmental delay, autism/dyspra developmental delay, language delay, and attention deficit hyperactivity disor	xia, psy der outco
Appendix N. Number of studies and treatments per outcome	

# Appendix A. Outcome measures and diagnostic scales used in analysis

Cognitive developmental delay	
Bayley Scales of Infant Development (children ≤42 mo.)	Score $\geq 2$ standard deviations below the mean
Griffiths Scale of Infant Development (children >42 mo.)	Score $\geq 2$ standard deviations below the mean
McCarthy Scales of Children's Abilities (children >30 mo.)	Score $\geq 1$ standard deviations below the mean
Stanford-Binet IV Intelligence scale for children	Intelligence quotient <u>&lt;</u> 80
Touwen's Test	Above average number of items rated abnormal in one or more domains
Wechsler Scale of Preschool and Primary Intelligence	Intelligence quotient <90
Wechsler Intelligence Scale for Children - III	Intelligence quotient <80; verbal intelligence quotient <69
Developmental Assessment	Confirmed diagnosis by developmental pediatrician or pediatric neurologist
Autism/dyspraxia	
Developmental Assessment	Diagnosis confirmed by developmental specialists at 2 years of age
Medical Records	Confirmed diagnosis recorded in medical history; registry records (ICD-10 codes F84.0, F84.1, F84.5, F84.8, and F84.9)
Modified checklist for autism in toddlers	Scored positive for $\geq 2$ out of 6 critical items OR $\geq 3$ any items of the total scale
Psychomotor developmental delay	
Ages and Stages Questionnaire	>3 standard deviations from the test mean
Bayley Scales of Infant Development – Psychomotor Index	>2 standard deviations below the standardized mean for the test
Touwen's Test	Demonstrated dysfunctions in fine motor balance, fine motor functions, and coordination of extremities
Schedule of Growing Skills II	Scored as 'delayed' in $\geq 1$ domain of the test
Developmental Assessment	Infant scored >2 negative items (administered by general practitioner or pediatrician); diagnosis of neuromotor deficit confirmed by a trained nurse practitioner; infant failing to sit by 10 months or walk by 18 months
Health/Medical Records	Diagnosis of psychomotor delay recorded in medical records
	· · ·

Page	51 (	of	90
------	------	----	----

**BMJ Open** 

Language Delay			
Ages and Stages Questionnaire	>3 standard deviations from the test mean		
Clinical Evaluation of Language Fundamentals – 4 <sup>th</sup> Edition	Score <70 in core language domain; score <84 overall		
Learning Accomplishment Profile	Below average performance in expressive speech (adjusted for age)		
Comprehensive Language Assessment (Peabody Picture Vocabulary Test; Receptive Expressive Emergent Language Scale; Expressive One Word Picture Vocabulary Test, or Sequenced Inventory of	Scores/assessment indicate a >6 moth delay in age appropriate language development		
Communication Development)			
ADHD			
Attention Problems and Hyperactivity Scales	Score >1 standard deviations from the test mean		
Child Behaviour Checklist	≥6 positive items on checklist		
Diagnostic and Statistical Manual – IV	$\geq$ 5 positive items on checklist		
Medical Records	Confirmed diagnosis in hospital/medical records made by a pediatrician or child psychiatrist		
Neonatal Seizure			
Medical records	Record of seizures during 1 <sup>st</sup> year; confirmation of neonatal seizure by electroencephalography or diagnosis		
Social Impairment			
Developmental Assessment (Ages and Stages Questionnaire [6 and 18 months]; Child Behaviour Checklist [36 months])	Scores dichotomized into 'normal' or 'adverse' range based on pre-defined values used by scale, for scales without pre-defined values cut-off was set at a score >2 standard deviations outside the test mean		
L			

## Appendix B. Additional Information on the Methods

### **Information sources**

An experienced librarian executed search strategies for MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The search strategy for MEDLINE was peer reviewed by another librarian using the PRESS checklist,<sup>1</sup> and is available in the protocol.<sup>2</sup> The literature search was initially conducted from inception to March 18, 2014, and a rapid search update of these databases was subsequently conducted on December 15, 2015. Authors of AED studies were contacted for unpublished study data, and the reference lists of all included studies were scanned to identify additional studies.

### Study selection and data collection

Prior to screening, two pilot-tests were conducted to assess the eligibility criteria and screening form. Once reviewers reached  $\geq$ 80% agreement, pairs of reviewers independently screened titles and abstracts (level 1) and later screened potentially relevant full-text articles (level 2). Upon completion of title and abstract screening, 6% of citations were discrepant between reviewer pairs and had to be resolved by discussion or a third reviewer. At the conclusion of full-text screening, 16% of articles were discrepant and had to be resolved by discussion. The same process was used for data abstraction and quality appraisal. Three rounds of pilot testing were conducted prior to data abstraction to train reviewers and refine the data abstraction form. For studies published in the last 10 years, authors were contacted to request clarification or additional data.

### Appraisal of selection bias using the comparison-adjusted funnel plot

All eligible medications were ordered from oldest to newest using their international market approval dates. To overcome some of the correlations induced by multi-arm studies, which may possibly cause overestimation and mask funnel plot asymmetry, we plotted data points corresponding to the study-specific basic parameters (treatment comparisons with common comparator). In each study, we used the control group as the common comparator or if this was missing, we used the oldest treatment comparator against the remaining AEDs. We used the fixed-effect model, as the random-effects model gives more weight to smaller studies and this may impact the assessment of small-study effects. We planned to explore observed asymmetry through subgroup analysis or meta-regression.

### Additional details on the synthesis of included studies

Due to the complexity of the data and the studies' underreporting, differences in drug dosages could not be accounted for, and it was assumed that different dosages of the same AED were equally effective. When a study reported multiple dosages for the same treatment, we combined the data for this treatment. We assessed the transitivity assumption for each outcome *a priori* using the treatment effect modifiers: age, baseline risk, treatment indication, timing, and methodological quality. The mean of each continuous effect modifier and the mode of each categorical effect modifier for each pairwise comparison were presented in tables for each outcome.<sup>3</sup> The consistency assumption was evaluated for the entire network of each outcome

### **BMJ Open**

using the design-by-treatment interaction model.<sup>4</sup> If inconsistency was identified, further examination for local inconsistency in parts of the network was completed using the loopspecific method.<sup>5 6</sup> Common within-network between-study variance ( $\tau^2$ ) across treatment comparisons was assumed in the conventional meta-analysis, NMA, and design-by-treatment interaction model, so that treatment comparisons including a single study can borrow strength from the remaining network. This assumption was clinically reasonable, as the treatments included were of the same nature. In the loop-specific approach, common within-loop  $\tau^2$  was assumed.

For cognitive developmental delay and autism/dyspraxia outcomes, network meta-regression analyses for maternal age and baseline risk (i.e., using the control group) were conducted, when at least 10 studies provided relevant information, assuming a common fixed coefficient across treatment comparisons. Sensitivity analyses for cognitive developmental delay and autism/dyspraxia outcomes were performed for studies with the treatment indication of epilepsy, large study size (i.e., >300), maternal alcohol intake, maternal tobacco use, only first-generation AEDs, and higher methodological quality for the two items of the Newcastle-Ottawa Scale that had the highest percentage of low methodological quality (adequacy of follow-up of cohorts and comparability of cohorts items for cohort studies). Severity of epilepsy, which may be a risk factor variable, was not evaluated in our analyses since this was not commonly reported. For autism/dyspraxia, a sensitivity analysis on maternal IQ/psychiatric history was additionally conducted. We measured the goodness of fit using the posterior mean of the residual deviance, the degree of between-study heterogeneity, and the deviance information criterion. In a wellfitting model the posterior mean residual deviance should be close to the number of data points.<sup>7</sup> <sup>8</sup> A difference of 3 units in the deviance information criterion was considered important and the lowest value of the deviance information criterion corresponded to the model with the best fit.<sup>78</sup>

All analyses were conducted in OpenBUGS,<sup>9</sup> assuming non-informative priors for all model parameters and a half normal prior distribution for the between-study standard deviation  $(\tau \sim N(0,1), \tau > 0)$ . The first 10,000 iterations were discarded and then 100,000 simulations were run with thinning of 10 values. Convergence was checked by visual inspection of the evaluation of the mixing of two chains. The median and 95% CrI were calculated for each parameter value, since medians are not overly influenced by outliers. The *network* command<sup>10</sup> was used to apply the design-by-treatment interaction model.

### References

1. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol*. 2016;75:40-6.

2. Tricco AC, Cogo E, Angeliki VA, et al. Comparative safety of anti-epileptic drugs among infants and children exposed in utero or during breastfeeding: protocol for a systematic review and network meta-analysis. *Syst Rev.* 2014;3:68.

3. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC Med.* 2013;11:159.

 White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network metaanalysis: model estimation using multivariate meta-regression. *Res Synth Methods*. 2012;3(2):111-25.
 Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ*. 2003;326(7387):472.

BMJ Open

6. Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol*. 2013;42(1):332-45.

7. Welton NJ, Sutton AJ, Cooper N, Abrams KR, Ades A. Evidence synthesis for decision making in healthcare. New York: Wiley; 2012.

8. Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Ser B Stat Methodol*. 2002;64(4):583-639.

9. Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: Evolution, critique and future directions. *Stat Med*. 2009;28(25):3049-67.

10. Palmer T, Sterne J. Meta-Analysis in Stata: An Updated Collection from the Stata Journal. White I, editor. Texas: Stata Press; 2016.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

# Appendix C. Newcastle-Ottawa Scale scoring guide

# **COHORT Studies**

Excel Column	NOS* Answer Options**	NOS Coding Manual*
RefID	Enter the report's RefID.	
DA	Enter your initials.	
First author	Enter the first author's last name.	
Year of publication	Enter the year of the publication.	
SELECTION:	-	
1) Representative-	a) truly representative of the	Item is assessing the representativeness of exposed individuals in the
ness of the exposed	average pregnant woman	community, not the representativeness of the sample of women from
cohort	<ul> <li>taking AEDs in the community</li> <li>b) somewhat representative of the average pregnant woman taking AEDs in the community</li> <li>c) selected group of users e.g., nurses, volunteers</li> <li>d) no description of the derivation of the cohort</li> </ul>	some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of estrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of estrogen). <u>Note:</u> Truly representative (A) is a population-based cohort at the provincial or
		<ul><li>national levels (e.g., a sample from 2 cities is not enough). We need very 'broad' sample of the population.</li><li>Somewhat representative (B) includes private clinics, hospital-based, or</li></ul>

		community-based
2) Selection of the	a) drawn from the same	Note:
non-exposed cohort	<ul> <li>a) drawn from the same community as the exposed cohort</li> <li>b) drawn from a different source</li> <li>c) no description of the derivation of the non-exposed cohort</li> </ul>	In our review of mostly multi-arm studies, this question pertains to the study's comparator group(s) – including "active" controls (for example, a less teratogenic AED). Therefore, this will often be 'A' for our studies.
3) Ascertainment of exposure	<ul> <li>a) secure record (e.g., surgical records)</li> <li>b) structured interview</li> <li>c) written self-report</li> <li>d) no description</li> </ul>	Note:         Option 'A' includes patient hospital records, prescription drug database, or hospital/clinic visits (e.g., patient is asked about "current" AED use during a visit with their doctor).         Option 'B' includes a hospital/clinic visit, but the patients are asked to remember their AED use during pregnancy (e.g., retrospectively ascertained exposure).
		'A'.
4) Demonstration that outcome of interest was not present at start of study	a) yes b) no	In the case of mortality studies, outcome of interest is still the presence of a disease/incident, rather than death. That is to say that a statement of 'no history of disease or incident' earns a star (i.e. option 'A'). Note: Since our review is on program twomen this question is 'A' for all
		Please email us if a study involves breastfeeding women
COMPARABILITY	•	Trease chian as it a study involves breastreeuning women.
1) Comparability of cohorts on the basis of the design or analysis	<ul> <li>a) answer is BOTH B &amp; C (i.e. study controls for age and one other important factor)</li> <li>b) study controls for age of the women</li> </ul>	Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

c)	study controls for any other important factor	Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable
d)	study does not control for any important factor or it is not	on each variable used in the adjustment.
	described	There may be multiple ratings for this item for different categories of
		exposure (e.g., ever vs. never, current vs. previous or never). [A maximum of 2 stars can be allotted in this category].
		Note:
		The study should have initially matched the groups or presented adjuste
		odds ratios, AND in addition, since in our review we are analyzing each
		AED arm separately (instead of the whole exposed conort), the study must also report the factor of interest for 'each AED arm' (or state that
		<b>'each AED arm'</b> is matched).
		Thus, there are 2 parts to this question:
		1) The study should have matched/adjusted for age at whatever level
		of groups they were focused on (even if they aren't our abstracted AED
		arms); AND
		2) Then the study should also have reported the age for each AED ar
		If they haven't done both of these 2 things, it's a 'D' here (unless they
		happen to combine these by reporting adjusted ORs for each of our AEI
		<u>arms).</u>
		For our review, this generally pertains to <b>the comparability of the</b>
		<b>MOTHERS.</b> The exception here is in studies of cognitive/psychomotor development
		disorders in children - when age of the children should be comparable.
		The "other important factors" here are any one of these:

		<ul> <li>history of congenital malformations (CMs), fetal losses, preterm deliveries or small babies.</li> <li>family history of genetic problems or CMs.</li> <li>alcohol use.</li> <li>nutritional deficiencies (e.g., lack of folic acid).</li> <li>Example:         <ul> <li>Option 'B' indicates that the study initially matched groups based on the women's age (or reported adjusted ORs) AND they report the mean women's age for EACH of our arms (e.g., for Tx1, Tx2, etc.).</li> </ul> </li> </ul>
OUTCOME: 1) Assessment of outcome	<ul> <li>a) independent OR blind assessment</li> <li>b) record linkage</li> <li>c) self-report</li> <li>d) no description</li> </ul>	<ul> <li>For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.</li> <li>a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.)</li> <li>b) Record linkage (e.g. identified through ICD codes on database records)</li> <li>c) Self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)</li> <li>d) No description.</li> </ul> Note: Blind (A) is if they tell us that the outcome assessors were blinded to exposures; or if the outcome is objective. For our purposes, we will focus on the primary outcome of interest of our systematic review, which is major malformations (an objective outcome).

		So most of ours will be A, unless the study is only on a secondary
		outcome (e.g., cognitive development) and is based on the mother's self-
		report of their child (e.g., not a clinical examination).
2) Was follow-up	a) yes	An acceptable length of time should be decided before quality assessment
long enough for	b) no	begins (e.g. 5 yrs. for exposure to breast implants)
outcomes to occur		
		Note:
		For this component, focus only on the outcomes that are reported in the
		results.
		For our purposes, we will focus on the primary outcome of interest of our
		systematic review, which is major malformations.
		• For studies focusing on 'birth' outcomes (i.e. malformations, preterm,
		fetal losses, born small), the answer is 'A' if they follow the groups
		until birth.
		• For studies focusing on cognitive developmental disorders, an
		adequate follow-up period (i.e. child's age) is 4 years.
		• For studies focusing on psychomotor delays, an adequate follow-up
		period is the earliest point of detection of the disorder.
		• For studies focusing on neonatal seizures, an adequate follow-up
		period (i.e. infant's age) is 6 months.
3) Adequacy of	a) complete follow up - all	This item assesses the follow-up of the exposed and non-exposed cohorts
follow up of	subjects accounted for	to ensure that losses are not related to either the exposure or the outcome.
cohorts	b) subjects lost to follow up	
	unlikely to introduce bias -	Note:
	small number lost (see	Especially check ones that start their total sample size (or figure
	'Note'), or description	diagram) with only the ones who had "complete" data (or only those
	provided of those lost	who they had "successfully" recruited), as these are often a 'D' (since
	c) follow up rate is inadequate	they don't report on the ones NOT followed up).
	(see 'Note') and no	
	description of those lost	• For a prospective study, $\geq 90\%$ follow-up rate per year is adequate
	d) no statement	(e.g., 10% dropout or less for 1 year, 20% for 2 years of follow-up.
		etc.). This includes missing or incomplete data, etc.
		/ / ····· / ····· / ····· / ····

• For a retrospective cohort study, ≥80% follow-up rate is adequate; including the ones that they could NOT recruit or who would NOT participate.
• For a survey/mail questionnaire, $\geq$ 75% response rate is adequate. (For
a survey, a dropout rate is congruent to a survey response rate).
12

# **CASE-CONTROL Studies**

Excel Column	NOS* Answer Options**	NOS Coding Manual*
RefID	Enter the report's RefID.	
DA	Enter your initials.	
First author	Enter the first author's last name.	
Year of publication	Enter the year of the publication.	
SELECTION:		
1) Is the case definition adequate?	<ul> <li>a) yes, with independent validation</li> <li>b) yes, e.g., record linkage or based on self-reports</li> <li>c) no description</li> </ul>	<ul> <li>a) Requires some independent validation (e.g. &gt;1 person/record/time/ process to extract information, or reference to primary record source such as x-rays or medical/hospital records)</li> <li>b) Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record</li> <li>c) No description</li> </ul> <u>Note:</u> This question is assessing the group of infants that have the outcome of interest (e.g., CMs) – i.e. the "cases" in a case-control study design.
2) Representative- ness of the cases	<ul><li>a) consecutive or obviously representative series of cases</li><li>b) potential for selection biases, or not stated</li></ul>	<ul> <li>a) All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample)</li> <li>b) Not satisfying requirements in part (a), or not stated.</li> <li><u>Note:</u> Option 'A' is a population-based sample.</li> </ul>
3) Selection of controls	<ul><li>a) community controls</li><li>b) hospital controls</li><li>c) no description</li></ul>	This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.

		a) Community controls (i.e. same community as cases and would be
		cases II had outcome)
		b) Hospital controls, within same community as cases (i.e. not another aity) but derived from a hospitalized nonulation
		a) No description
		c) No description
		Note:
		This question is assessing the group of infants that don't have the
		outcome (e.g., CMs) – i.e. the "controls" in a case-control study design.
	6	
		Community controls (A) includes a population-based sample.
4) Definition of	a) no history of disease	a) If cases are first occurrence of outcome, then it must explicitly state
controls	(endpoint)	that controls have no history of this outcome. If cases have new (not
	b) no description of source	necessarily first) occurrence of outcome, then controls with previous
		occurrences of outcome of interest should not be excluded.
		b) No mention of history of outcome
		Nata
		$\frac{1NO(C.)}{Cince a variantia on fatal affects this question is (A) for all studies$
		Since our review is on retai effects, this question is A for an studies.
		Thease email us in a study involves exposure during breastreeding.
COMPARABILITY		
1) Comparability	a) answer is BOTH B & C (i e	Fither cases and controls must be matched in the design and/or
of cases and	study controls for age and one	confounders must be adjusted for in the analysis Statements of no
controls on the	other important factor)	differences between groups or that differences were not statistically
hasis of the design	b) study controls for age of the	significant are not sufficient for establishing comparability
or analysis	women	significant are not sufficient for establishing comparability.
	c) study controls for any other	Note: If the odds ratio for the exposure of interest is adjusted for the
	important factor	confounders listed, then the groups will be considered to be comparable
	d) study does not control for any	on each variable used in the adjustment.
	important factor or it is not	
	described	There may be multiple ratings for this item for different categories of
		exposure (e.g. ever vs. never, current vs. previous or never). [A maximum

		of 2 stars can be allotted in this category].
		<ul> <li><u>Note:</u> The study should have initially matched the groups, AND in addition, since in our review we are analyzing each AED arm separately (instead of the whole cases group), the study must also report the factor of interest for 'each AED arm' (or state that 'each AED arm' is matched).</li> <li>For our review, this generally pertains to the comparability of the MOTHERS of the cases and controls. The exception here is in studies of cognitive/psychomotor development disorders in children - when age of the children should be comparable.</li> <li>The "other important factors" here are any one of these:</li> <li>history of congenital malformations (CMs), fetal losses, preterm deliveries or small babies.</li> <li>family history of genetic problems or CMs.</li> <li>alcohol use.</li> <li>nutritional deficiencies (e.g., lack of folic acid).</li> <li>For example, Option 'B' indicates that the study initially matched groups based on the women's age AND they report the mean women's age for EACH arm (e.g., for Tx1, Tx2, etc.).</li> </ul>
EXPOSURE:		
1) Assessment of exposure	<ul> <li>a) secure record (e.g., surgical records)</li> <li>b) structured interview where blind to case/control status</li> <li>c) interview not blinded to case/control status</li> <li>d) written self-report or medical</li> </ul>	Note: Option 'A' includes patient hospital records, prescription drug database, or hospital/clinic visits (e.g., patient is asked about "current" AED use during a visit with their doctor). "Interview" here includes a hospital/clinic visit, but the patients are asked to remember their AED use during pregnancy (e.g., retrospectively

	record only	ascertained exposure).
	e) no description	
2) Same method of	a) yes	Note:
ascertainment for	b) no	This question is asking whether the method of ascertainment of exposure
cases and controls		was the same for 'cases' (with the outcome) and 'controls' (without the
		outcome; in this case-control study design).
3) Non-response	a) same rate for both groups	Note:
rate	b) non-respondents described	For our review, this pertains to either the infants or the mothers of the
	c) rate different and no	case and control groups.
	designation	
	e o	We're allowing 10% dropout per year for a prospective study $- e.g., 10\%$
		for 1 year, 20% for 2 years of follow-up, etc.
		For a survey, we allow for a 75% response rate in order for it be adequate.
		For a survey, a dropout rate is congruent to a survey response rate.

\*Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: <u>http://www.ohri.ca/programs/clinical\_epidemiology/oxford.asp</u> \*\*In the **"NOS Coding Manual" column**, the first section for each item is copied straight from the NOS documentation while the lower portions in each item are our "Notes" tailored for the AED review.

## Appendix D. List of included studies

1. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry*. 2004;75(11):1575-83.

2. Vinten J, Bromley RL, Taylor J, Adab N, Kini U, Baker GA. The behavioral consequences of exposure to antiepileptic drugs in utero. *Epilepsy Behav.* 2009;14(1):197-201.

3. Mawer G, Clayton-Smith J, Coyle H, Kini U. Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. *Seizure*. 2002;11(8):512-8.

4. Arkilo D, Hanna J, Dickens D, et al. Pregnancy and neurodevelopmental outcomes with in-utero antiepileptic agent exposure. A pilot study. *Eur J Paediatr Neurol*. 2015;19(1):37-40.

5. Bromley R, Baxter N, Calderbank R, Mawer G, Clayton-Smith J, Baker G. A comprehensive review of the language abilities of children exposed to valproate or carbamazepine in utero. American Epilepsy Society; Texas2010.

6. Bromley RL, Mawer GE, Briggs M, et al. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry*. 2013;84(6):637-43.

7. Bromley RL, Mawer G, Clayton-Smith J, Baker GA. Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology*. 2008;71(23):1923-4.

8. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA*. 2013;309(16):1696-703.

9. Cohen MJ, Meador KJ, Browning N, et al. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6 years. *Epilepsy Behav*. 2013;29(2):308-15.

 Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child*. 2011;96(7):643-7.
 Tomson T, Battino D, Bonizzoni E, et al. Antiepileptic drugs and intrauterine death: A prospective

11. Tomson T, Battino D, Bonizzoni E, et al. Antiepileptic drugs and intrauterine death: A prospective observational study from EURAP. *Neurology*. 2015;85(7):580-8.

 Dean JCS, Hailey H, Moore SJ, Lloyd DJ, Turnpenny PD, Little J. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. *J Med Genet*. 2002;39(4):251-9.
 Rasalam AD, Hailey H, Williams JH, et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. *Dev Med Child Neurol*. 2005;47(8):551-5.

14. D'Souza SW, Robertson IG, Donnai D, Mawer G. Fetal phenytoin exposure, hypoplastic nails, and jitteriness. *Arch Dis Child*. 1991;66(3):320-4.

15. Eriksson K, Viinikainen K, Mönkkönen A, et al. Children exposed to valproate in utero— Population based evaluation of risks and confounding factors for long-term neurocognitive development. *Epilepsy Res.* 2005;65(3):189-200.

16. Viinikainen K, Eriksson K, Monkkonen A, et al. The effects of valproate exposure in utero on behavior and the need for educational support in school-aged children. *Epilepsy Behav.* 2006;9(4):636-40.

17. Gaily E. Development and growth in children of epileptic mothers: a prospective controlled study. Helsinki, Finland: University of Helsinki; 1990.

18. Gaily EK, Granstrom ML, Hillesmaa VK, Bardy AH. Head circumference in children of epileptic mothers: contributions of drug exposure and genetic background. *Epilepsy Res.* 1990;5(3):217-22.

19. Hiilesmaa V. A prospective study on maternal and fetal outcome in 139 women with epilepsy. Helsinki: University of Helsinki; 1982.

20. Hiilesmaa VK, Bardy A, Teramo K. Obstetric outcome in women with epilepsy. *Am J Obstet Gynecol*. 1985;152(5):499-504.

21. Gogatishvili N, Ediberidze T, Lomidze G, Tatishvili N, Kasradze S. PO-0834 Long-term Developmental Outcome Of Children Prenatally Exposed To Antiepileptic Drugs. *Arch Dis Child*. 2014;99(Suppl 2):A526.

22. Gogatishvili N, Ediberidze T, Lomidze G, Tatishvili N, Kasradze S. Cognitive outcomes of children with fetal antiepileptic drug exposure at the age of 3-6 years-preliminary data. 1st Congress of the European Academy of Neurology; Berlin: European Journal of Neurology; 2015. p. 329.

23. Jones KL, Lacro RV, Johnson KA, Adams J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med*. 1989;320(25):1661-6.

**BMJ Open** 

 Katz JM, Pacia SV, Devinsky O. Current Management of Epilepsy and Pregnancy: Fetal Outcome, Congenital Malformations, and Developmental Delay. *Epilepsy Behav*. 2001;2(2):119-23.
 Koch S, Jager-Roman E, Losche G, Nau H, Rating D, Helge H. Antiepileptic drug treatment in pregnancy: drug side effects in the neonate and neurological outcome. *Acta Paediatr*. 1996;85(6):739-46.
 Lacroix I, Hurault-Delarue C, Guitard C, et al. Psychomotor effects of in utero exposure to psychotropic medications: A comparative study in EFEMERIS database. Congrès de Physiologie Pharmacologie et Thérapeutique: Dijon, France2012.

27. Miskov S, Juraski RG, Fucic A, et al. Croatian Pregnant Women with Epilepsy and Effects of Antiepileptic Drugs Exposure in their Offspring - seven years of prospective surveillance. American Epilepsy Society; Texas2010.

 Nadebaum C, Anderson VA, Vajda F, Reutens DC, Barton S, Wood AG. Language skills of school-aged children prenatally exposed to antiepileptic drugs. *Neurology*. 2011;76(8):719-26.
 Rihtman T, Parush S, Ornoy A. Developmental outcomes at preschool age after fetal exposure to

valproic acid and lamotrigine: cognitive, motor, sensory and behavioral function. *Reprod Toxicol.* 2013;41:115-25.

30. Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. *JAMA*. 1994;271(10):767-70.

 Shankaran S, Woldt E, Nelson J, Bedard M, Delaney-Black V. Antenatal phenobarbital therapy and neonatal outcome. II: Neurodevelopmental outcome at 36 months. *Pediatrics*. 1996;97(5):649-52.
 van der Pol MC, Hadders-Algra M, Huisjes HJ, Touwen BC. Antiepileptic medication in pregnancy: late effects on the children's central nervous system development. *Am J Obstet Gynecol*.

1991;164(1 Pt 1):121-8.
33. Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. *JAMA neurology*. 2013;70(11):1367-74.

34. Veiby G, Daltveit AK, Schjolberg S, et al. Exposure to antiepileptic drugs in utero and child development: a prospective population-based study. *Epilepsia*. 2013;54(8):1462-72.

35. Wood AG, Nadebaum C, Anderson V, et al. Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy. *Epilepsia*. 2015;56(7):1047-55.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

### Appendix E. Additional information on search results

Of the included 110 studies, nine were written in languages other than English and three were conference abstracts or letter to the editor with usable data. Scanning of reference lists of included articles and related reviews identified 13 additional studies. Forty-eight percent of contacted authors (22/46) provided clarification or additional data. Additionally, 29% (13/45) of authors of conference abstracts provided additional unpublished data. We were unable to contact 11 authors due to non-working email addresses. One author provided a manuscript and three authors provided unpublished data that were included in the analysis.

# Appendix F. Key excluded studies

Author, Year	Research Group	Title	Reason for Exclusion
Meador, 2009 <sup>1</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs	Outcomes only reported as continuous variables
Meador, 2010 <sup>2</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Effects of breastfeeding in children of women taking antiepileptic drugs	Outcomes only reported as continuous variables
Meador, 2011 <sup>3</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age	Outcomes only reported as continuous variables
Meador, 2012 <sup>4</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Effects of fetal antiepileptic drug exposure: Outcomes at age 4.5 years	Outcomes only reported as continuous variables
Meador, 2013 <sup>5</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study	Outcomes only reported as continuous variables
Shallcross, 2011 <sup>6</sup>	Liverpool and Manchester Neurodevelopment Group and The UK Epilepsy and Pregnancy Register	Child development following in utero exposure: Levetiracetam vs. sodium valproate	Outcomes only reported as continuous variables
Shallcross, 2014 <sup>7</sup>	Liverpool and Manchester	In utero exposure to levetiracetam vs. valproate: Development and language at 3 years of age	Outcomes only reported as continuous variables

	Neurodevelopment Group and The UK Epilepsy and Pregnancy				
References	Register				
1.         Mead           2009;360(16)         2.         Mead           2010;75(22):'         3.         Mead           3.         Mead         2012;75(22):'           3.         Mead         2012;75(16):'           5.         Mead         2012;78(16):'           5.         Mead         2012;78(16):'           6.         Shalle         sodium valprof           7.         Shalle         age. Neurolog	or KJ, Baker GA, Browning N, (1597-605. or KJ, Baker GA, Browning N, 954-60. or KJ, Baker GA, Browning N, 34(Pt 2):396-404. or KJ, Baker GA, Browning N, 207-14. or KJ, Baker GA, Browning N, bservational study. <i>Lancet Ne</i> cross R, Bromley RL, Irwin B, bate. <i>Neurology</i> . 2011;76(4):38 cross R, Bromley RL, Cheyne <i>gy</i> . 2014;82(3):213-21.	et al. Cognitive function at et al. Effects of breastfeed et al. Foetal antiepileptic of et al. Effects of fetal antiepileptic dr <i>urol.</i> 2013;12(3):244-52. Bonnett LJ, Morrow J, Bak 33-9. CP, et al. In utero exposur	t 3 years of age after fetal ding in children of women t drug exposure and verbal v pileptic drug exposure: out rug exposure and cognitive er GA. Child development re to levetiracetam vs valpr	exposure to antiepileptic taking antiepileptic drugs versus non-verbal abiliti comes at age 4.5 years e outcomes at age 6 yea following in utero expos roate: development and	c drugs. <i>N Engl J Me</i> s. <i>Neurology</i> . es at three years of a <i>Neurology</i> . ars (NEAD study): a sure: levetiracetam vs language at 3 years

**BMJ Open** 

Author, Year	Country of conduct	Registry or Setting	Study period	Interventions	Outcomes	Funding
Adab, 2004 <sup>1</sup> [CR: Vinten, 2009 <sup>2</sup> ; Mawer, 2002 <sup>3*</sup>	UK	Mersey Regional Epilepsy Clinic; Epilepsy Clinic at the Manchester Royal Infirmary; Antenatal clinic at St Mary's Hospital, Manchester	2000- 2001	Carbam, Control, Valpro	Cognitive Developmental Delay, Psychomotor Developmental Delay	NR
Arkilo, 2015 <sup>4</sup>	USA	Minnesota Epilepsy Group	2006- 2011	Carbam, Lamot, Levet, Pheny, Valpro	Autism/Dyspraxia, Psychomotor Developmental Delay	NR
Bromley, 2010 <sup>5</sup>	UK	Liverpool and Manchester Neurodevelopment Group	NR	Carbam, Valpro	Language Delay	NR
Bromley, 2013 <sup>6</sup> [CR: Bromley, 2008 <sup>7</sup> ]	UK	Liverpool and Manchester Neurodevelopment group	2000- 2004	Carbam, Control, Lamot, Valpro	Autism/Dyspraxia, ADHD	mixed public & private
Christensen, 2013 <sup>8</sup> †	Denmark	Danish Civil Registration System; Danish Prescription Register; Danish Psychiatric Central Register; Danish Birth Register; Danish National Hospital Register	1996- 2006	Carbam, Clonaz, Lamot, Oxcar, Valpro	Autism/Dyspraxia	public

Appendix G. Table of Individual Study characteristics

Page 71 of 90

### BMJ Open

Cohen, 2013 <sup>9</sup>	USA;UK	Neurodevelopmental Effects of Antiepileptic Drugs Study Group	1999- 2004	Carbam, Lamot, Pheny, Valpro,	ADHD	public
Cummings, 2011 <sup>10</sup> † [CR: Tomson, 2015 <sup>11</sup> ]	Northern Ireland	UK Epilepsy and Pregnancy Register (Northern Ireland); Northern Ireland Child Health System	1996- 2005	Carbam, Lamot, Valpro,	Cognitive Developmental Delay	public
Dean, 2002 <sup>12</sup> [CR: Rasalam, 2005 <sup>13</sup> ]	Scotland	Aberdeen Maternity Hospital	1976- 2000	Carbam, Carbam+Pheno, Carbam+Pheny, Carbam+Valpro, Control, Ethos, Pheno, Pheno+Pheny, Pheno+Valpro, Pheny, Primid, Valpro	Psychomotor Developmental Delay, ADHD	NR
D'Souza, 1991 <sup>14</sup>	United Kingdom	St Mary's Hospital	1980- 1982	Carbam, Control, Pheno, Pheny, Valpro	Cognitive Developmental Delay	public
Eriksson, 2005 <sup>15</sup> † [CR: Viinikainen, 2006 <sup>16</sup> ]	Finland	Kuopio University Hospital	1989- 2000	Carbam, Control, Valpro	Cognitive Developmental Delay, Psychomotor Developmental Delay	public
Gaily, 1990 <sup>17</sup> [CR: Gaily, 1990 <sup>18</sup> ; Hiilesmaa, 1982 <sup>19</sup> ; Hiilesmaa, 1985 <sup>20</sup> ]	Finland	Helsinki University Central Hospital	1975- 1979	Carbam, Carbam+Pheno+Pheny, Carbam+Pheny, Carbam+Valpro, Control, Ethos+Pheny, Pheno+Pheny, Pheny, Pheny+Primid, Pheny+Valpro	Cognitive Developmental Delay , Psychomotor Developmental Delay	mixed public private
Gogatishvili, 2014 <sup>21</sup>	Georgia	Georgian National AED- Pregnancy Registry	NR	Carbam, Lamot, Valpro	Cognitive Developmental	public
					Delay	
-------------------------------------	---------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------	------------------------------------------------------------------	-------------------------------------------------------------------------------	--------
Gogatishvili, 2015 <sup>22</sup>	Georgia	Georgian National AED- Pregnancy Registry	NR	Carbam, Carbam+Levet, Lamot, Pheno, Valpro	Language Delay	public
Jones, 1989 <sup>23</sup> †	US	California Teratogen Registry	1979- 1988	Carbam, Carbam+Pheno, Carbam+Pheno+Valpro, Carbam+Primid	Cognitive Developmental Delay, Psychomotor Developmental Delay	public
Katz, 2001 <sup>24</sup>	USA	Mount Sinai Comprehensive Epilepsy Center	1990- 2000	Carbam, Control, Lamot, Pheno, Pheny, Primid, Valpro	Cognitive Developmental Delay	NR
Koch, 1996 <sup>25</sup>	Germany	NR	1976- 1983	Pheno, Pheny, Primid, Valpro	Cognitive Developmental Delay	public
Lacroix, 2012 <sup>26</sup>	France	EFEMERIS database - Caisse Primaire d'Assurance Maladie of Haute-Garonne and Maternal and Infant Protection Service; Antenatal Diagnostic Centre	2004- 2008	Carbam, Clobaz, Clonaz, Gabap, Lamot, Pheno, Topir, Valpro	Psychomotor Developmental Delay	NR
Mawer, 2002 <sup>3</sup>	England	Manchester Royal Infirmary	1990- 1999	Carbam, Lamot, Pheny, Valpro	Cognitive Developmental Delay	NR

Page	73	of	90
------	----	----	----

Miskov, 2010 <sup>27</sup>	Croatia	NR	2003- 2010	Carbam, Control, Gabap, Lamot, Valpro	Psychomotor Developmental Delay, Neonatal Seizures	NR
Nadebaum, 2011 <sup>28</sup> †	Australia	Australian Registry of Antiepileptic Drug Use in Pregnancy	Australian Registry of Antiepileptic Drug Use in 2007- 2009 Carbam, Lamot, Valpro Pregnancy		Language Delay	mixed public & private
Rihtman, 2013 <sup>29</sup>	Israel	Israeli Teratogen Information Service	NR	Lamot, Valpro	Neonatal Seizure	mixed public & private
Scolnik, 1994 <sup>30</sup>	Canada	Hospital for Sick Children - Motherisk Program; North York General Hospital; Toronto Hospital; Oshawa General Hospital	1987- 1992	Carbam, Pheny	Cognitive Developmental Delay	public
Shankaran, 1996 <sup>31</sup>	USA	Children's Hospital of Michigan	NR	Control, PHENO,	Psychomotor Developmental Delay, Language Delay	public
Van der Pol, 1991 <sup>32</sup>	Netherlands	Groningen University Hospital	1973- 1981	Carbam, Carbam+Pheno, Control, Pheno	Psychomotor Developmental Delay	public
Veiby, 2013a <sup>33</sup> †	Norway	Norwegian Institute of Public Health- Mother and Child Cohort Study	1999- 2009	Carbam, Control, Lamot, Valpro	Social Impairment	public
Veiby, 2013b <sup>34</sup> †	Norway	Medical Birth Registry of Norway	1999- 2008	Carbam, Control, Lamot, Valpro	Psychomotor Developmental Delay, Autism/Dyspraxia,	public

				Language Delay, ADHD	
Wood, 2015 <sup>35</sup> † Australia	Australian Registry of Antiepileptic Drug Use in Pregnancy	2007- 2010	Carbam, Carbam+Clonaz, Carbam+Lamot, Carbam+Pheny, Lamot+Valpro, Valpro	Autism/Dyspraxia	public
Abbreviations: ADHD – Atte	ention Deficit Hyperactivity D	Disorder;	NR – Not Reported		
Carbam = Carbamazepine; Cl Lamotrigine; Levet = Levetira Topir = Topiramate; Valpro =	obaz = Clobazam; Clonaz = C acetam; Oxcar = Oxcarbazepin Valproate; Vigab = Viagabat	Clonazepa ne; Phenc trin	um; Ethos = Ethosuximide; Gab o = Phenobarbital; Pheny = Phe	ap = Gabapentin; Lamo nytoin; Pridmid = Prim	ot = idone;
*Single publication reporting †Registry Studies	on two separate cohorts				
		27			

### Appendix H. Table of Patient characteristics

Author, Year	Indication	Sample Size*	Mean Age (Women)	Mean Age (Children)/ Follow-up period†	AED Exposure Timing	Maternal Alcohol Use n/N‡	Maternal Tobacco Use n/N‡
Adab, 2004a <sup>1</sup> § [CR: Vinten, 2009 <sup>2</sup> ; Mawer, 2002 <sup>3</sup> ]	Epilepsy	177	26.1	9-10.5	NR	24/279‡	68/249‡
Adab, 2004b <sup>1</sup> § [CR: Vinten, 2009 <sup>2</sup> ; Mawer, 2002 <sup>3</sup> ]	Epilepsy	81	26.1	3-3.33	NR	24/279‡	68/249‡
Arkilo, 2015 <sup>4</sup>	Epilepsy	59	NR	NA	First trimester	NR	NR
Bromley, 2010 <sup>5</sup>	NR	60	NR	6-7	Whole pregnancy	NR	NR
Bromley, 2013 <sup>6</sup> [CR: Bromley, 2008 <sup>7</sup> ]	Epilepsy	156	28	6	NR	28/156	42/156
Christensen, 2013 <sup>8</sup>	NR	2011	NR	NR	Whole pregnancy	NR	NR
Cohen, 2013 <sup>9</sup>	Epilepsy	108	30	6	NR	12/192‡	NR
Cummings, 2011 <sup>10</sup> [CR: Tomson, 2015 <sup>11</sup> ]	Epilepsy	142	NR	2-3	Whole pregnancy	32/108‡	19/108‡
Dean, 2002 <sup>12</sup> [CR: Rasalam, 2005 <sup>13</sup> ]	Epilepsy	287	27	3.75-15.5	First trimester	NR	NR
D'Souza, 1991 <sup>14</sup>	Epilepsy	42	26.5	2.5-3.5	Whole pregnancy	NR	NR
Eriksson, 2005 <sup>15</sup> [CR: Viinikainen, 2006 <sup>16</sup> ]	Epilepsy	39	28.2	NR	NR	NR	NR

Gaily, 1990 <sup>17</sup> [CR: Gaily, 1990 <sup>18</sup> ; Hiilesmaa, 1982 <sup>19</sup> ; Hiilesmaa, 1985 <sup>20</sup>	Epilepsy	134	27.8	5.5	First trimester	NR	NR
Gogatishvili, 2014 <sup>21</sup>	NR	39	NR	2 to 4	NR	NR	NR
Gogatishvili, 2015 <sup>22</sup>	NR	23	NR	3 to 6	NR	NR	NR
Jones, 1989 <sup>23</sup>	Epilepsy	63	NR	NR	Whole pregnancy	NR	NR
Katz, 2001 <sup>24</sup>	Epilepsy	51	31	NR	NR	NR	NR
Koch, 1996 <sup>25</sup>	Epilepsy	40	NR	6	First trimester	NR	NR
Lacroix, 2012 <sup>26</sup>	NR	109	NR	0.75	NR	NR	NR
Mawer, 2002 <sup>3</sup>	Epilepsy	52	NR	NR	NR	NR	NR
Miskov, 2010 <sup>27</sup>	Epilepsy	55	NR	NR	NR	NR	NR
Nadebaum, 2011 <sup>28</sup>	Epilepsy	66	31.6	7.4	First trimester	NR	5/66
Rihtman, 2013 <sup>29</sup>	Epilepsy	72	NR	NR	Whole pregnancy	NR	NR
Scolnik, 1994 <sup>30</sup>	Epilepsy	75	NR	1.5-3	1st trimester	NR	NR
Shankaran, 1996 <sup>31</sup>	NR	96	NR	NR	NR	NR	NR
Van der Pol, 1991 <sup>32</sup>	Epilepsy	57	NR	6-13	NR	NR	NR
Veiby, 2013a <sup>33</sup>	Epilepsy	422	NR	0.5	NR	NR	NR
Veiby, 2013b <sup>34</sup>	Epilepsy	248	28.9	3	NR	NR	68/726‡
Wood, 2015 <sup>35</sup>	Epilepsy	77	NR	6-8	NR	NR	NR
Abbrowistions NA N	at amplicable.	ID Mat	non out od				

Abbreviations: NA – Not applicable; NR – Not reported

\* Sample size used for analysis; ineligible treatment arms (i.e. treatment arms with excluded drugs or unspecified polytherapy) are not included in the count

<sup>†</sup> The mean age for children/follow-up period data were only collected for outcomes related to cognitive and/or psychomotor development

‡ Total sample size is based on the number of women enrolled in the study; may differ from the sample size used for analysis

§ Single publication reporting on two separate cohorts

Page 77 of 90

BMJ Open

Appendix I. Methodological qualit	y of observational studies -	- Newcastle Ottawa Scale results
-----------------------------------	------------------------------	----------------------------------

First Author, Year	Representativen ess of the exposed cohort	Selection of the non- exposed cohort	Ascertainme nt of exposure	Demonstratio n that outcome of interest was not present at start of study	Comparabili ty of cohorts on the basis of the design or analysis	Assessmen t of outcome	Was follow-up long enough for outcomes to occur	Adequac y of follow up of cohorts
Adab, 2004 <sup>1</sup>	В	А	А	А	С	А	А	С
Arkilo, 2015 <sup>4</sup>	В	А	В	А	D	А	А	С
Bromley, 2010 <sup>5</sup>	D	А	D	А	D	D	В	D
Bromley, 2013 <sup>6</sup>	А	А	A	A	А	А	А	С
Christensen , 2013 <sup>8</sup>	А	А	А	A	А	В	А	В
Cohen, 2013 <sup>9</sup>	А	А	D	A	A	А	А	С
Cummings, 2011 <sup>10</sup>	А	А	А	А	А	А	А	С
Dean, 2002 <sup>12</sup>	В	А	А	А	D	А	А	С
D'Souza, 1991 <sup>14</sup>	В	А	A	A	D	A	А	А
Eriksson, 2005 <sup>15</sup>	В	А	А	А	В	А	А	D
Gaily, 1990 <sup>17</sup>	В	А	А	А	D	А	А	А
Gogatishvil i, 2014 <sup>21</sup>	А	А	D	А	D	А	А	D

1	
2	
3	
4	
5	
6	
7	
0	
0	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
30	
<u>4</u> 0	
40 ∕11	
41 10	
4∠ ∕\?	
43	
44	
45	
46	
47	
48	
10	

Gogatishvil i, 2015 <sup>22</sup>	А	А	D	А	D	А	А	D
Jones, 1989 <sup>23</sup>	А	А	В	А	D	А	А	В
Katz, 2001 <sup>24</sup>	В	А	А	А	D	А	А	D
Koch, 1996 <sup>25</sup>	В	А	В	А	D	А	А	C
Lacroix, 2012 <sup>26</sup>	А	А	А	А	А	А	А	A
Mawer, 2002 <sup>3</sup>	В	A	A	A	D	А	А	В
Miskov, 2010 <sup>27</sup>	D	А	D	А	D	D	А	D
Nadebaum, 2011 <sup>28</sup>	А	А	A	A	А	А	А	В
Rihtman, 2013 <sup>29</sup>	А	В	А	А	А	А	А	С
Scolnik, 1994 <sup>30</sup>	В	А	А	A	D	А	А	А
Shankaran, 1996 <sup>31</sup>	В	А	А	А	D	А	А	В
Van der Pol, 1991 <sup>32</sup>	В	А	D	А	А	А	А	В
Veiby, 2013a <sup>33</sup>	А	А	А	А	А	А	А	D
Veiby, 2013b <sup>34</sup>	А	А	А	А	А	А	А	С
Wood, 2015 <sup>35</sup>	А	А	А	А	D	А	А	С

30 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



## Log-odds ratio centered at comparison-specific pooled effect

\* Funnel plots have been produced only for outcomes with  $\geq 10$  studies. For multi-arm studies we plot data points from each study-specific basic parameter (treatment comparisons with a study-specific common comparator)

Appendix K. Statistically significant network meta-analysis results along with meta-analysis results, transitivity, and
inconsistency assessments

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatme nt Indicatio n	Timin g	Comparabili ty of cohorts	Adequac y of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)			
Cognitive Developmental Delay (10 studies, 748 patients, 14 treatments)											
Carbam+Pheno+V alpro vs Control	NA	NR	NR	NR	NR	NR	NA	17.31 (1.03-434.50) (0.86- 488.60)			
Lamot vs Valpro	4 (NA)	140 (31.00)	Epilepsy	NR	Н	Н	0.17 (0.02- 0.80)	0.13 (0.02-0.57) (0.01- 0.79)			
Valpro vs Carbam	1 (NA)	23 (31.00)	Epilepsy	NR	Н	Н	0.44 (0.00- 11.07)	3.69 (1.72-7.63) (0.94- 13.88)			
Valpro vs Control	3 (0.06)	165 (28.80)	Epilepsy	NR	Н	Н	10.45 (3.42- 33.73)	8.63 (3.01-25.74) (1.82- 38.93)			
Valpro vs Pheno	3 (NA)	36 (31.00)	Epilepsy	1st trimest er	Н	Н	4.41 (0.79- 38.91)	5.87 (1.26-42.27) (0.93- 56.07)			
Valpro vs Pheny	3 (NA)	58 (31.00)	Epilepsy	1st trimest er	Н	Н	3.28 (0.81- 14.38)	3.01 (1.06-9.18) (0.71- 14.27)			
Common between-s	tudy varian	ce across tre	atment com	parisons			0.13 (0.00- 1.01)	0.15 (0.00-1.25) (NA)			
Residual deviance: 4 Data points: 42	40										

Page 81 of 90

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatme nt Indicatio n	Timin g	Comparabili ty of cohorts	Adequac y of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
DIC: 69								
				Chi-	square test:			
Evaluation of consis	tency using	the design-	by-treatment	13.3	3	P- value: 0.	64	
interaction model				Deg	rees of	Heterogene	eity: 0	
				Free	edom: 16			
		Autism	n Dyspraxia	(5 studie	es, 2551 patients	s, 12 treatme	ents)	
Lamot vs Control	2 (0.00)	254 (27.75)	Epilepsy	1st trimest er	Н	Н	13.77 (2.06- 188.00)	8.88 (1.29-112.00) (0.94 146.80)
Lamot+Valpro vs Carbam	1 (NA)	40 (NR)	Epilepsy	NR	L	L	15.02 (2.04- 171.90)	22.89 (2.58-219.00) (1.90 282.20)
Lamot+Valpro vs Clonaz	NA	NR	NR	NR	NR	NR	NA	20.21 (1.48-351.30) (1.15 455.00)
Lamot+Valpro vs Control	NA	NR	NR	NR	NR	NR	NA	$   \begin{array}{r} 132.70 \\   (7.41-3.9 \times 10^3) \\   (5.82-4.6 \times 10^3)   \end{array} $
Lamot+Valpro vs Lamot	NA	NR	NR	NR	NR	NR	NA	14.61 (1.51-149.10) (1.14 196.80)
Oxcar vs Control	NA	NR	NR	NR	NR	NR	NA	13.51 (1.28-221.40) (0.86 267.40)
Valpro vs Carbam	5 (NA)	1003 (27.83)	Epilepsy	1st trimest	L	L	3.20 (1.20- 8.68)	3.02 (1.09-8.40) (0.57-

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatme nt Indicatio n	Timin g	Comparabili ty of cohorts	Adequac y of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
				er				14.31)
Valpro vs Control	2 (0.00)	249 (27.75)	Epilepsy	1st trimest er	Н	Н	9.19 (1.14- 132.10)	17.29 (2.40-217.60) (1.61- 274.90)
Common between-st	tudy variand	ce across tre	atment comp	parisons			0.12 (0.00- 1.37)	0.16 (0.00-1.95) (NA)
Residual deviance: 2 Data points: 24 DIC: 44	24		-6				, , , , , , , , , , , , , , , , , , ,	
				Chi	square test.			
Evaluation of consis interaction model	tency using	the design-	by-treatment	t 3.79 Deg Free	rees of dom: 5	P- value: 0. Heterogene	57 ity: 0	
Evaluation of consis interaction model	tency using	the design-	by-treatment	t 3.79 Deg Free al Delay (	rees of dom: 5 11 studies, 114	P- value: 0. Heterogene 5 patients, 18	57 ity: 0 8 treatments)	
Evaluation of consis interaction model Carbam+Pheno+V alpro vs Control	tency using Psyc NA	the design- homotor Do NR	by-treatment evelopmenta NR	t 3.79 Deg Free al Delay (	rees of dom: 5 11 studies, 114 NR	P- value: 0. Heterogene <b>5 patients, 1</b> NR	57 ity: 0 <b>8 treatments)</b> NA	19.12 (1.49-337.50) (1.34- 370.40)
Evaluation of consis interaction model Carbam+Pheno+V alpro vs Control Carbam+Pheno+V alpro vs Pheno	tency using Psyc NA NA	the design- homotor Do NR NR	by-treatment evelopment: NR NR	t 3.79 Deg Free al Delay ( NR	rees of dom: 5 11 studies, 114 NR NR	P- value: 0. Heterogene <b>5 patients, 1</b> NR NR	57 ity: 0 8 treatments) NA NA	19.12 (1.49-337.50) (1.34- 370.40) 19.86 (1.38-393.60) (1.26- 423.30)
Evaluation of consis interaction model Carbam+Pheno+V alpro vs Control Carbam+Pheno+V alpro vs Pheno Levet vs Carbam+Pheno+V alpro	tency using Psyc NA NA NA	the design-	by-treatment evelopmenta NR NR NR	t 3.79 Deg Free al Delay ( NR NR	rees of dom: 5 11 studies, 114 NR NR NR	P- value: 0. Heterogene <b>5 patients, 1</b> NR NR NR	57 ity: 0 8 treatments) NA NA NA	$19.12 \\ (1.49-337.50) (1.34-370.40) \\ 19.86 \\ (1.38-393.60) (1.26-423.30) \\ 0.01 \\ (0.00-0.58) (0.00-0.62) \\ 0.62)$
Evaluation of consis interaction model Carbam+Pheno+V alpro vs Control Carbam+Pheno+V alpro vs Pheno Levet vs Carbam+Pheno+V alpro Valpro vs Carbam	tency using Psyc NA NA NA 7 (NA)	the design- homotor Do NR NR NR 331 (27.80)	by-treatment evelopments NR NR NR Epilepsy	t 3.79 Deg Free al Delay ( NR NR NR Ist trimest er	rees of dom: 5 11 studies, 114 NR NR NR H	P- value: 0. Heterogene <b>5 patients, 13</b> NR NR NR H	57 ity: 0 8 treatments) NA NA NA 2.72 (1.39- 5.67)	$ \begin{array}{r}     19.12 \\     (1.49-337.50) (1.34-370.40) \\     19.86 \\     (1.38-393.60) (1.26-423.30) \\     0.01 \\     (0.00-0.58) (0.00-0.62) \\     2.45 \\     (1.27-4.88) (0.95-6.77) \\ \end{array} $

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatme nt Indicatio n	Timin g	Comparabili ty of cohorts	Adequac y of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
		(28.38)		trimest er			8.64)	(2.04-8.75) (1.52- 12.05)
Valpro vs Pheno	2 (NA)	141 (NR)	Epilepsy	1st trimest er	Н	Н	3.68 (1.17- 12.30)	4.32 (1.72-11.20) (1.34- 14.51)
Common between-s	study variance	ce across tre	atment comp	parisons			0.05 (0.00- 0.49)	0.06 (0.00-0.63) (NA
Residual deviance: Data points: 51 DIC: 78	45							
Evaluation of consist interaction model	stency using	the design-l	by-treatment	Chi- 13.4 Deg Free	square test: 6 rees of cdom: 21	P- value: 0. Heterogene	89 ity: 0	
		Lang	guage Delay	(5 studie	es, 509 patients,	, 5 treatment	s)	
Valpro vs Control	1 (0.03)	173 (28.90)	Epilepsy	NR	L	Н	6.96 (1.14- 37.03)	7.95 (1.50-49.13) (0.96- 74.52)
Common between-s	study variance	ce across tre	atment comp	parisons			0.15 (0.00- 1.85)	0.16 (0.00-2.15) (NA
Residual deviance: Data points: 14 DIC: 23	12							
Evaluation of consist interaction model	stency using	the design-l	by-treatment	Chi- 2.33 Deg Free	rees of edom: 3	P- value: 0. Heterogene	50 ity: 0	
	F	or peer revi	ew only - http	o://bmjop	<sup>35</sup> en.bmj.com/site/	/about/guideli	nes.xhtml	

Page 83 of 90

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatme nt Indicatio n	Timin g	Comparabili ty of cohorts	Adequac y of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
			ADHD (4 st	udies, 75	50 patients, 6 tro	eatments)		
Residual deviance: Data points: 17 DIC: 22	:12							
Abbreviations: A high risk of bias; I PrI - Predictive Int	DHD - Atten 2 - low risk of erval; ROB -	tion Deficit f bias; MA - Risk of Bia	Hyperactivit Meta-analys	y Disorde sis; NA -	er; CrI - Credible Not applicable; ]	e Interval; DI NMA - Netw	C - Deviance Inf ork Meta-analys	ormation Criterion; H- is; NR- Not Reported;
Carbam = Carbam Lamotrigine; Leve Topir = Topiramat	azepine; Clol et = Levetirac e; Valpro = V	oaz = Cloba: etam; Oxcai /alproate; V	zam; Clonaz z = Oxcarbaz ïigab = Viaga	= Clonaz epine; Ph abatrin	zepam; Ethos = H neno = Phenobar	Ethosuximide bital; Pheny =	e; Gabap = Gabar = Phenytoin; Pric	pentin; Lamot = Imid = Primidone;
					36			
	F	For peer revi	ew only - http	p://bmjop	en.bmj.com/site/	about/guideli	ines.xhtml	

Appendix L. Frequencies, events and samples size	es, SUCRA values, and total group risks
per treatment and outcome	

Treatment	Frequency of treatment in network	Total # events/Total Sample size	Median SUCRA (95% CrI)	Total Group Risk Median (IQR)					
Cognitive Developmental Delay									
Carbamazepine+Levetiraceta	1	0/2	0.86 (0.07-	0.00 (0.00-					
<u>m</u>			1.00)	0.00)					
Carbamazepine+Phenobarbita	1	0/3	0.86 (0.14-	0.00 (0.00-					
1			1.00)	0.00)					
Control	4	8/125	0.79 (0.43-	0.04 (0.00-					
			0.93)	0.09)					
Lamotrigine	4	0/43	0.71 (0.29-	0.00 (0.00-					
		0, 10	1.00)	0.00)					
Phenobarbital+Phenytoin	1	0/15	0.71 (0.07-	0.00 (0.00-					
		0/10	1.00)	0.00)					
Phenobarbital	3	1/12	0.64 (0.21-	0.00 (0.00-					
	3	1/ 12	1.00)	0.33)					
Carbamazenine	9	29/238	0.50 (0.29-	0.15 (0.05-					
	,	29/238	0.79)	0.20)					
Primidone	2	2/13	0.50 (0.14-	0.09 (0.00-					
	2	2,15	0.93)	0.18)					
Dhonytoin	5	11/111	0.43 (0.21-	0.10 (0.00-					
	5	11/111	0.79)	0.21)					
Dhanutain+Valproata	1	0/5	0.36 (0.00-	0.00 (0.00-					
r nenytom+ v aproate	1	0/3	1.00)	0.00)					
Carbamazepine+Phenobarbita	1	0/4	0.29 (0.00-	0.00 (0.00-					
l+Phenytoin	1	0/4	1.00)	0.00)					
Eth a gravingi da   Dh anartain	1	0/2	0.21 (0.00-	0.00 (0.00-					
EthosuxImide+Phenytoin	1	0/3	1.00)	0.00)					
Value at a	7	50/1/0	0.21 (0.00-	0.35 (0.25-					
valproate	/	50/160	0.43)	0.50)					
	1	1/11	0.14 (0.00-	0.09 (0.09-					
Carbamazepine+Pnenytoin	1	1/11	0.79)	0.09)					
Carbamazepine+Phenobarbita	1	2/2	0.07 (0.00-	0.67 (0.67-					
l+Valproate	1	2/3	0.71)	0.67)					
Autism/Dyspraxia									
Cantral	2	1/100	0.91 (0.55-	0.00 (0.00-					
Control	2	1/180	1.00)	0.01)					
I	1	0/11	0.73 (0.09-	0.00 (0.00-					
Levetiracetam	1	0/11	1.00)	0.00)					
Carbamazepine	5	8/518	0.64 (0.36-	0.03 (0.01-					
<b>I</b>		-	(	(					

Treatment	Frequency of treatment in network	Total # events/Total Sample size	Median SUCRA (95% CrI)	Total Group Risk Median (IQR)
			0.91)	0.06)
Carbamazepine+Lamotrigine	1	0/5	0.64 (0.00- 1.00)	0.00 (0.00- 0.00)
Clonazenam	1	3/269	0.64 (0.18-	0.01 (0.01-
	-	0/202	0.91)	0.01)
Carbamazepine+Phenytoin	1	0/3	0.55 (0.00- 1 00)	0.00 (0.00- 0.00)
		o / =	0.55 (0.00-	0.00 (0.00-
Phenytoin	1	0/5	1.00)	0.00)
Carbamazenine+Clonazenam	1	0/3	0.45 (0.00-	0.00 (0.00-
Carbanazepine - Cionazepan		0/5	1.00)	0.00)
Lamotrigine	4	14/745	0.45 (0.18-	0.04 (0.01-
Luniourgine		11// 10	0.82)	0.08)
Oxcarbazepine		7/321	0.36 (0.09-	0.02 (0.02-
F			0.82)	0.02)
Valproate	5	21/485	0.27 (0.09-	0.05 (0.03-
			0.55)	0.08)
Lamotrigine+Valproate	1	3/6	0.00 (0.00-0.27)	0.50 (0.50- 0.50)
Neonatal Seizure			,	
Lamotrigine	1	3/42	NA	0.07 (NA)
Valproate	1	0/30	NA	0.00 (NA)
<b>Psychomotor Developmental</b>	Delay			
Levetiracetam	1	0/11	0.94 (0.29-	0.00 (0.00-
	1	0/11	1.00)	0.00)
Phenobarbital+Phenytoin	1	0/15	0.82 (0.12-	0.00 (0.00-
Thenobulottur Thenytom	I	0/10	1.00)	0.00)
Carbamazepine+Phenvtoin	1	0/11	0.76 (0.06-	0.00 (0.00-
			1.00)	0.00)
Control	8	21/323	0.76 (0.53-	0.06 (0.03-
			0.94)	0.10)
Phenobarbital	4	11/117	0.76 (0.47-	0.07 (0.02-
			0.94)	0.17
Carbamazepine	10	32/249	0.39 (0.33-	0.10 (0.00-
Carbamazenine+Phenobarbita			0.59 (0.18-	0.13 (0.00-
	2	3/15	0.94)	0 25)
			0.53 (0.24-	0.09(0.06-
Lamotrigine	4	11/126	0.82)	0.12)
	1	4/27	0.47 (0.12-	0.15 (0.15-
Cionazepam	1	4/2/	0.88)	0.15)

Treatment	Frequency of treatment in network	Total # events/Total Sample size	Median SUCRA (95% CrI)	Total Group Risk Median (IQR)
Phenytoin+Valproate	1	0/5	0.47 (0.00-	0.00 (0.00-
Carbamazepine+Phenobarbita l+Phenytoin	1	0/4	0.41 (0.00- 1.00)	0.00 (0.00- 0.00)
Clobazam	1	1/6	0.41 (0.00-0.94)	0.17 (0.17-0.17)
Phenytoin	3	10/83	0.41 (0.12-0.71)	0.04 (0.00-0.33)
Ethosuximide+Phenytoin	1	0/3	0.35 (0.00- 1.00)	0.00 (0.00- 0.00)
Topiramate	2	1/6	0.29 (0.00- 0.88)	0.13 (0.00-0.25)
Valproate	7	36/137	0.24 (0.06- 0.53)	0.28 (0.11- 0.38)
Gabapentin	2	1/4	0.12 (0.00- 0.76)	0.25 (0.00- 0.50)
Carbamazepine+Phenobarbita l+Valproate	1	2/3	0.06 (0.00- 0.59)	0.67 (0.67- 0.67)
Language Delay				
Control	2	17/209	0.75 (0.50- 1.00)	0.13 (0.03- 0.24)
Phenobarbital	1	10/41	0.75 (0.00- 1.00)	0.24 (0.24- 0.24)
Carbamazepine	4	17/117	0.50 (0.00- 0.75)	0.15 (0.06- 0.25)
Lamotrigine	3	6/59	0.50 (0.00- 1.00)	0.00 (0.00- 0.14)
Valproate	4	21/83	0.00 (0.00- 0.50)	0.22 (0.12- 0.35)
ADHD				
Phenytoin	2	2/41	1.00 (0.20- 1.00)	0.05 (0.04- 0.06)
Control	3	6/218	0.80 (0.20- 1.00)	0.03 (0.00- 0.05)
Phenobarbital	1	4/61	0.60 (0.00- 1.00)	0.07 (0.07- 0.07)
Lamotrigine	3	7/105	0.40 (0.00- 0.80)	0.07 (0.00-0.13)
Carbamazepine	4	17/182	0.20 (0.00- 0.60)	0.09 (0.04-0.13)
Valproate	4	12/143	0.20 (0.00-	0.08 (0.03-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2	
3	
4	
4	
5	
6	
7	
۰ ۵	
0	
9	
10	
11	
12	
12	
13	
14	
15	
16	
17	
40	
IÖ	
19	
20	
21	
22	
22	
23	
24	
25	
26	
20	
21	
28	
29	
30	
31	
20	
32	
33	
34	
35	
36	
30	
37	
38	
39	
40	
40	
41	
42	
43	
44	
45	
40	
46	
47	
48	
49	
F0	
50	
51	
52	
53	
54	
54	
55	
56	
57	
58	
EO	
59	
60	

Treatment	Frequency of treatment in network	Total # events/Total Sample size	Median SUCRA (95% CrI)	Total Group Risk Median (IQR)
			0.80)	0.16)
Social Impairment				
Carbamazepine	1	6/48	NA	0.13 (NA)
Control	1	37/276	NA	0.13 (NA)
Lamotrigine	1	9/71	NA	0.13 (NA)
Valproate	1	1/27	NA	0.04 (NA)

**Abbreviations:** ADHD - attention deficit hyperactivity disorder; CrI - Credible Interval; IQR - interquartile range; NA - Not applicable; SUCRA - surface under the cumulative ranking curve

Carbam = Carbamazepine; Clobaz = Clobazam; Clonaz = Clonazepam; Ethos = Ethosuximide; Gabap = Gabapentin; Lamot = Lamotrigine; Levet = Levetiracetam; Oxcar = Oxcarbazepine; Pheno = Phenobarbital; Pheny = Phenytoin; Pridmid = Primidone; Topir = Topiramate; Valpro = Valproate; Vigab = Viagabatrin

## Appendix M. Rank-heat plot of cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes\*



**Abbreviations:** carbam - carbamazepine, clobaz - clobazam, clonaz - clonazepam, ethos - ethosuximide, gabap - gabapentin, lamot - lamotrigine, levet - levetiracetam, oxcar - oxcarbazepine, pheno - phenobarbital, pheny - phenytoin, primid - primidone, topir - topiramate, valpro - valproate, vigab - vigabatrin

\*Rank-heat plot of cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes (5 circles) and 25 treatments (25 radii). Each sector is coloured according to the surface under the cumulative ranking curve value of the corresponding treatment and outcome using the transformation of three colours red (0%), For Deer review only yellow (50%), and green (100%).

Total studies	Range of study arms	# of treatments	# of patients	# of direct treatment comparisons	# of NMA treatment comparisons	Statistically significant NMA treatment effects	# of studies with zero events in all arms	# of studies with ineligible outcome definition*
<b>Cognitive Dev</b>	elopmental	Delay						
10	(2,8)	14	748	53	105	6	0	5
Autism/Dyspr	axia							
5	(4,6)	12	2551	34	66	8	0	4
Neonatal Seizi	ıre							
1	(2,2)	2	69	1	0	0	1	1
<b>Psychomotor</b>	Developme	ntal Delay						
11	(2,8)	18	1145	74	153	6	0	5
Language Dela	ay							
5	(2,4)	5	509	7	10	1	0	3
ADHD								
4	(4,5)	6	750	14	15	0	0	0
Social Impair	ment							
1	(4,4)	4	422	1	0	0	0	0

# **BMJ Open**

#### Comparative safety of anti-epileptic drugs for neurological development in children exposed during pregnancy and breastfeeding: a systematic review and network metaanalysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2017-017248.R1
Article Type:	Research
Date Submitted by the Author:	25-May-2017
Complete List of Authors:	Veroniki, Areti Angeliki; Li Ka Shing Knowledge Institute, St. Michael's Hospital Rios, Patricia; Li Ka Shing Knowledge Institute, St. Michael's Hospital Cogo, Elise; Li Ka Shing Knowledge Institute, St. Michael's Hospital Straus, Sharon; Li Ka Shing Knowledge Institute, St. Michael's Hospital; University of Toronto, Department of Medicine Finkelstein, Yaron; The Hospital for Sick Children; University of Toronto, Department of Paediatrics Kealey, M.; Li Ka Shing Knowledge Institute, St. Michael's Hospital Reynen, Emily; Li Ka Shing Knowledge Institute, St. Michael's Hospital Soobiah, Charlene; Li Ka Shing Knowledge Institute, St. Michael's Hospital; University of Toronto, Institute for Health Policy Management & Evaluation Thavorn, Kednapa; University of Ottawa, School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine; The Ottawa Hospital Research Institute, Clinical Epidemiology Program Hutton, Brian; University of Ottawa, School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine; Ottawa Hospital Research Institute, Center for Practice Changing Research Hemmelgarn, BR; University of Calgary, Departments of Medicine and Community Health Sciences Yazdi, Fatemeh; Li Ka Shing Knowledge Institute, St. Michael's Hospital D'Souza, Jennifer; Li Ka Shing Knowledge Institute, St. Michael's Hospital MacDonald, Heather; Li Ka Shing Knowledge Institute, St. Michael's Hospital Tricco, Andrea; Li Ka Shing Knowledge Institute, St. Michael's Hospital; University of Toronto, Epidemiology Division, Dalla Lana School of Public Health
<b>Primary Subject Heading</b> :	Neurology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	multiple treatment meta-analysis, knowledge synthesis, Epilepsy < NEUROLOGY, pregnancy, infants, developmental delay



2
2
3
4
5
6
7
0
8
9
10
11
40
12
13
14
15
16
10
17
18
19
20
20
21
22
23
2/
24 05
25
26
27
28
20
29
30
31
32
02
33
34
35
36
07
37
38
39
40
11
41
42
43
44
15
40
46
47
48
10
73
50
51
52
52
55
54
55
56
57
50
20
59
60

1

2

3

# Comparative safety of anti-epileptic drugs for neurological development in children exposed during pregnancy and breastfeeding: a systematic review and network meta-analysis Areti Angeliki Veroniki, PhD, MSc<sup>1</sup> Email: VeronikiA@smh.ca

4	Areti Angeliki Veroniki, PhD, MSc <sup>1</sup>	Email: <u>VeronikiA@smh.ca</u>
5	Patricia Rios, MSc <sup>1</sup>	Email: <u>RiosP@smh.ca</u>
6	Elise Cogo, ND, MLIS <sup>1</sup>	Email: <u>CogoE@smh.ca</u>
7	Sharon E. Straus, MD, MSc <sup>1,2</sup>	Email: <u>Sharon.straus@utoronto.ca</u>
8	Yaron Finkelstein, MD <sup>3,4,5</sup>	Email: <u>Yaron.Finkelstein@sickkids.ca</u>
9	Ryan Kealey, PhD <sup>1</sup>	Email: <u>ryan.kealey@utoronto.ca</u>
10	Emily Reynen, MD, CM, PharmD <sup>1</sup>	Email: <u>ereynen@gmail.com</u>
11	Charlene Soobiah, PhD (Cand.) <sup>1,6</sup>	Email: <u>SoobiahC@smh.ca</u>
12	Kednapa Thavorn, PhD <sup>7,8,9</sup>	Email: <u>kthavorn@ohri.ca</u>
13	Brian Hutton, PhD, MSc <sup>7,10</sup>	Email: <u>bhutton@ohri.ca</u>
14	Brenda R. Hemmelgarn, MD, PhD <sup>11</sup>	Email: <u>Bhemmelg@ucalgary.ca</u>
15	Fatemeh Yazdi, MSc <sup>1</sup>	Email: <u>SabaghYazdiF@smh.ca</u>
16	Jennifer D'Souza, HBSc <sup>1</sup>	Email: jennifer.dsouza@mail.utoronto.ca
17	Heather MacDonald, MSc <sup>1</sup>	Email: <u>hrmacdonald@gmail.com</u>
18	Andrea C. Tricco, PhD, MSc <sup>1,12,*</sup>	Email: <u>TriccoA@smh.ca</u>
19	AUTHOR DETAILS	

- 20 <sup>1</sup> Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria Street, East Building,
- 21 Toronto, Ontario, M5B 1W8, Canada

#### BMJ Open

2		
3 4	22	<sup>2</sup> Department of Medicine, University of Toronto, 27 King's College Circle, Toronto, Ontario
5 6 7	23	M5S 1A1, Canada
7 8 9	24	<sup>3</sup> The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canad
10 11	25	<sup>4</sup> Department of Paediatrics, University of Toronto, 172 St. George Street, Toronto, Ontario,
12 13 14	26	M5R 0A3, Canada
15 16	27	<sup>5</sup> Department of Pharmacology and Toxicology, University of Toronto, Medical Sciences
17 18 10	28	Building, Room 4207, 1 King's College Circle, Toronto, Ontario, M5S 1A8, Canada
20 21	29	<sup>6</sup> Institute for Health Policy Management & Evaluation, University of Toronto, 4th Floor,
22 23	30	155 College Street, Toronto, Ontario, M5T 3M6, Canada
24 25 26	31	<sup>7</sup> School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine,
27 28	32	University of Ottawa, Roger-Guindon Building, 451 Smyth Road, Ottawa, Ontario, K1H 8M5
29 30 21	33	Canada
32 33	34	<sup>8</sup> Clinical Epidemiology Program, Ottawa Hospital Research Institute, The Ottawa Hospital,
34 35	35	501 Smyth Road, Ottawa, Ontario, K1H 8L6, Canada
36 37 38	36	<sup>9</sup> Institute of Clinical and Evaluative Sciences (ICES uOttawa), 1053 Carling Avenue, Ottawa
39 40	37	Ontario, K1Y 4E9, Canada
41 42 43	38	<sup>10</sup> Ottawa Hospital Research Institute, Center for Practice Changing Research, The Ottawa
43 44 45	39	Hospital–General Campus, 501 Smyth Road, PO Box 201B, Ottawa, Ontario, K1H 8L6,
46 47	40	Canada.
48 49 50	41	<sup>11</sup> Departments of Medicine and Community Health Sciences, University of Calgary, TRW
51 52	42	Building, 3rd Floor, 3280 Hospital Drive NW, Calgary, Alberta, T2N 4Z6, Canada
53 54 55	43	<sup>12</sup> Epidemiology Division, Dalla Lana School of Public Health, University of Toronto, 6th
56 57	44	Floor, 155 College Street, Toronto, Ontario, M5T 3M7, Canada
58 59		
60		

## **\*Corresponding author**

- 46 Prof. Andrea C. Tricco, PhD
- 47 Scientist, Knowledge Translation Program,
- 48 Li Ka Shing Knowledge Institute, St. Michael's Hospital,
- 49 209 Victoria Street, East Building, Toronto, Ontario, M5B 1W8, Canada
  - 50 Phone: 416-864-6060, Fax: 416-864-5805, Email: <u>TriccoA@smh.ca</u>

- **Keywords:** multiple treatment meta-analysis, knowledge synthesis, epilepsy, pregnancy,
- 53 infants, developmental delay.
- **Word count**: abstract (300 words); main text (4,000 words); 2 tables; 3 figures; 3
- 55 additional files; 51 references

Page 5 of 90

**BMJ Open** 

1		
2 3 4	56	ABSTRACT
5 6 7	57	Objectives: Compare the safety of anti-epileptic drugs (AEDs) on neurodevelopment of
8 9	58	infants/children exposed in-utero or during breastfeeding.
10 11 12	59	Design and Setting: Systematic review and Bayesian random-effects network meta-
13 14	60	analysis (NMA). Medline, EMBASE, and the Cochrane Central Register of Controlled Trials
15 16 17	61	were searched until April 27 <sup>th</sup> , 2017. Screening, data abstraction, and quality appraisal
18 19	62	were completed in duplicate by independent reviewers.
20 21 22	63	<b>Participants</b> : 29 cohort studies including 5,100 infants/children.
22 23 24	64	Interventions: Mono- and poly-therapy AEDs including first-generation (carbamazepine,
25 26	65	clobazam, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproate) and
27 28 29	66	newer-generation (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate,
30 31	67	vigabatrin) AEDs. Epileptic women who did not receive AEDs during pregnancy or
32 33 34	68	breastfeeding served as the control group.
35 36	69	Primary and secondary Outcome measures: Cognitive developmental delay and
37 38 20	70	autism/dyspraxia were primary outcomes. Attention deficit hyperactivity disorder,
39 40 41	71	language delay, neonatal seizures, psychomotor developmental delay, and social
42 43	72	impairment were secondary outcomes.
44 45 46	73	Results: The NMA on cognitive developmental delay (11 cohort studies, 933 children, 18
47 48	74	treatments) suggested among all AEDs only valproate was statistically significantly
49 50	75	associated with more children experiencing cognitive developmental delay when compared
52 53	76	with control (odds ratio (OR)=7.40, 95% credible interval (CrI): 3.00-18.46). The NMA on
54 55	77	autism (5 cohort studies, 2,551 children, 12 treatments), suggested that oxcarbazepine
56 57 58	78	(OR=13.51, CrI: 1.28-221.40), valproate (N=485, OR=17.29, 95% CrI: 2.40-217.60),
59 60		4

lamotrigine (OR=8.88, CrI: 1.28-112.00), and lamotrigine+valproate (OR=132.70, CrI:
7.41-3,851.00) were associated with significantly greater odds of developing autism
compared with control. The NMA on Psychomotor developmental delay (11 cohort studies,
1,145 children, 18 treatments) found that valproate (OR=4.16, CrI: 2.04-8.75) and
carbamazepine+phenobarbital+valproate (OR=19.12, CrI: 1.49-337.50) were associated
with significantly greater odds of psychomotor delay compared with control.
Conclusions: Valproate alone or combined with another AED is associated with the
greatest odds of adverse neurodevelopmental outcomes compared with control.
Oxcarbazepine and lamotrigine were associated with increased occurrence of autism.
Counselling is advised for women considering pregnancy to tailor the safest regimen.
Registration: PROSPERO database (CRD42014008925).
Keywords: multiple treatment meta-analysis, knowledge synthesis, epilepsy, pregnancy,
infants, developmental delay.
ARTICLE SUMMARY
Strengths and limitations of this study
Strengths and minutions of this study
• 29 cohort studies involving 5,100 children of women who took AEDs were included
in this systematic review. More evidence from long-term follow-up studies is
required.
• This study was the first that compared and ranked the safety of AEDs, including
comparative safety of treatments that have not been directly compared.

1 2			
2 3 4	100	٠	Across all neurological outcomes and treatments compared with control, valproate
5 6 7	101		alone or combined with another AED is associated with the greatest odds of adverse
7 8 9	102		development.
10 11	103	•	Oxcarbazepine and lamotrigine were associated with increased occurrence of
$\begin{array}{c} 12\\ 13\\ 14\\ 56\\ 17\\ 89\\ 02\\ 12\\ 23\\ 45\\ 26\\ 78\\ 90\\ 12\\ 33\\ 33\\ 35\\ 37\\ 38\\ 90\\ 14\\ 23\\ 45\\ 67\\ 89\\ 01\\ 22\\ 35\\ 55\\ 55\\ 56\\ \end{array}$	104		autism.

**INTRODUCTION** 

Anti-epileptic drugs (AEDs) are used by pregnant women for various conditions, such as epilepsy, pain syndromes, psychiatric disorders, and chronic migraine.<sup>1</sup> AED use during pregnancy is associated with risks to the fetus, as these drugs can cross the placenta or may be transferred to the infant through breastfeeding and may be associated with adverse neurodevelopment outcomes.<sup>2-4</sup> Two systematic reviews examined the association between AED exposure and neurodevelopment *in utero*, and reported that exposure to valproate was linked to significantly lower IQ scores and poorer overall neurodevelopmental outcomes in the children of women who used these medications.<sup>56</sup> No significant associations were found between neurodevelopment and exposure to other AEDs such as carbamazepine, lamotrigine, or phenytoin.<sup>5-8</sup> However, there is a lack of sufficiently powered studies to assess the impact of AEDs on neurodevelopment in children of women exposed to these agents, especially for newer generation drugs, thus highlighting the need for a systematic review.910 The aim of this study was to compare the safety of AEDs and assess their impact on neurodevelopment in infants and children exposed *in-utero* or during breastfeeding, employing a systematic review and network meta-analysis (NMA). 

# METHODS The methods are briefly described here; details can be found in the published protocol (Additional File 1).<sup>11</sup> This study was registered with PROSPERO (CRD42014008925). We followed the ISPOR<sup>12</sup> guidelines for our NMA, and reported our findings using the PRISMA extension for NMA (Additional File 2).<sup>13</sup> Eligibility criteria All randomized clinical trials (RCTs), quasi-RCTs, and observational studies were eligible.

Included studies assessed infants or children  $\leq 12$  years of age whose mothers consumed AEDs during pregnancy and/or while breastfeeding. Both mono- and poly-therapy AEDs were eligible, including first-generation (i.e., carbamazepine, clobazam, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproate) and newer-generation (i.e., marketed >1990: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin), with no restrictions on AED dosage. Placebo, no AED, other AEDs alone or in combination, were considered as comparators. Duplicate studies that used the same registry or population sample (i.e., companion studies) were used for supplementary information only. No language or other restrictions were imposed. The primary neurological outcomes were cognitive developmental delay and autism/dyspraxia, and the secondary outcomes included attention deficit hyperactivity disorder (ADHD), language delay, neonatal seizures, psychomotor developmental delay, and social impairment. Table 2 shows the outcome measures and diagnostic scales used. We initially intended to evaluate all safety outcomes in infants/ children exposed to AEDs *in-utero* or during breastfeeding in one publication, but given the breadth of evidence we

1 2			
2 3 4	144	identified, we report results related to risk of major congenital malformations, birth, and	
5 6 7	145	prenatal outcomes in a companion paper. <sup>14</sup>	
7 8 9	146	Information sources	
10 11	147	An experienced librarian executed search strategies for MEDLINE, EMBASE, and the	
12 13 14	148	Cochrane Central Register of Controlled Trials up to March 18, 2014, and then updated the	ì
15 16	149	search in April 27 <sup>th</sup> 2017. The search strategy for MEDLINE was peer-reviewed by another	ſ
17 18 19	150	librarian using the PRESS checklist, <sup>15</sup> and is available in the protocol. <sup>11</sup> Additional studies	
20 21	151	were identified by scanning references and contacting authors. Unpublished studies were	
22 23 24	152	sought by searching clinical trial registries and conference abstracts.	
24 25 26	153	Study selection and data collection	
27 28	154	After a calibration exercise, titles/abstracts (level 1) and full-text papers (level 2) were	
29 30 31	155	screened by two reviewers independently. Upon completion of level 1, 6% of citations wer	e
32 33	156	discrepant between reviewer pairs, whereas at the conclusion of level 2, 16% of articles	
34 35 36	157	were discrepant. Conflicts were resolved through discussion or by a third reviewer. The	
37 38	158	same approach was used for data abstraction and appraisal of methodological quality.	
39 40	159	Three rounds of pilot testing were conducted prior to data abstraction to train reviewers	
41 42 43	160	and refine the data abstraction form. For studies published in the last 10 years, authors	
44 45	161	were contacted to request clarification or additional data.	
46 47 48	162	Appraisal of methodological quality	
49 50	163	Only observational studies were identified and included for analysis, and their	
51 52 53	164	methodological quality was appraised with the Newcastle-Ottawa Scale (NOS) (Additional	
54 55	165	File 3: Appendix A). <sup>16</sup> For each outcome with $\geq$ 10 studies, the comparison-adjusted funnel	
56 57	166	plot was used to assess small-study effects, <sup>17</sup> where the overall treatment effect for each	
50 59 60			9

1 2		
3 4	167	comparison was estimated under the fixed-effect meta-analysis model. All eligible
5 6 7	168	medications were ordered from oldest to newest using their international market approval
8 9	169	dates. Hence, the comparison-adjusted funnel plot additionally assesses the hypothesis that
10 11	170	newer AEDs are favoured over older ones. To overcome some of the correlations induced
12 13 14	171	by multi-arm studies, which may cause overestimation and mask funnel plot asymmetry,
15 16	172	we plotted data points corresponding to the study-specific basic parameters (treatment
17 18 10	173	comparisons with common comparator). In each study, we used the control group as the
20 21	174	common comparator or if this was missing, we used the oldest treatment comparator
22 23	175	against the remaining AEDs.
24 25 26	176	Synthesis of included studies
27 28	177	We used the odds ratio (OR) for each dichotomous outcome, and outcome data were
29 30 31	178	pooled using hierarchical meta-analysis and NMA models and the Markov Chain Monte
32 33	179	Carlo sampling method in a Bayesian framework. To account for anticipated
34 35 26	180	methodological and clinical heterogeneity across studies, and to achieve the highest
36 37 38	181	generalizability in the meta-analytical treatment effects, we applied a random-effects
39 40	182	model. <sup>18</sup>
41 42 43	183	A NMA was applied for connected evidence networks and pre-specified treatment nodes. <sup>19</sup>
44 45	184	We assessed the transitivity assumption for each outcome <i>a priori</i> using the effect
46 47 48	185	modifiers: age, baseline risk, treatment indication, timing, and methodological quality. The
49 50	186	mean of each continuous effect modifier and the mode of each categorical effect modifier
51 52	187	for each pairwise comparison were presented in tables for each outcome. <sup>20</sup> The consistency
53 54 55	188	assumption was evaluated for the entire network of each outcome using the random-
56 57	189	effects design-by-treatment interaction model when multiple studies were available in
ວຽ 59 60		10

1
2
3
4
5
5
6
7
8
à
10
10
11
12
13
14
14
15
16
17
18
10
19
20
21
22
23
23
24
25
26
27
21
28
29
30
31
20
32
33
34
35
26
30
37
38
39
40
40
41
42
43
11
45
46
47
48
40
49
50
51
52
52
55
54
55
56
57
57
58
59
60

1

190 each network design or the fixed-effect design-by-treatment interaction model when a 191 single study informed each network design.<sup>21</sup> If inconsistency was identified, further 192 examination for local inconsistency in parts of the network was completed using the loopspecific method.<sup>22 23</sup> Common within-network between-study variance ( $\tau^2$ ) across 193 194 treatment comparisons was assumed in the meta-analysis, NMA, and design-by-treatment 195 interaction model, so that treatment comparisons including a single study can borrow 196 strength from the remaining network. This assumption was clinically reasonable, as the 197 treatments included were of the same nature. In the loop-specific approach, common 198 within-loop  $\tau^2$  was assumed. 199 For cognitive developmental delay and autism/dyspraxia outcomes, network meta-200 regression analyses for maternal age and baseline risk (i.e., using the control group) were 201 conducted, when  $\geq 10$  studies provided relevant information, assuming a common fixed 202 coefficient across treatment comparisons for AEDs vs. control. Sensitivity analyses for 203 cognitive developmental delay and autism/dyspraxia outcomes were performed for 204 treatment indication of epilepsy, large study size (i.e., >300), maternal alcohol intake, 205 maternal tobacco use, only first-generation AEDs, and methodological quality. The 206 sensitivity analysis for methodological quality was restricted to studies with low risk of 207 bias for the two items on the NOS where the greatest proportion of studies received a low-208 quality score: adequacy of follow-up of cohorts and comparability of cohorts. For 209 autism/dyspraxia, a sensitivity analysis on maternal IQ/psychiatric history was 210 additionally conducted. We measured the goodness of fit using the posterior mean of the 211 residual deviance, the degree of  $\tau^2$ , and the deviance information criterion (DIC). In a well-212 fitting model the posterior mean residual deviance should be close to the number of data

Page 13 of 90

1

 $\begin{array}{r} 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 55\\ 56\\ 57\\ 58\\ 59\\ \end{array}$ 

60

#### **BMJ Open**

2		
3 4	213	points. <sup>24 25</sup> A difference of 3 units in the DIC between a NMA and a network meta-
5 6 7	214	regression model was considered important and the lowest value of the DIC corresponded
8 9	215	to the model with the best fit. <sup>24 25</sup>
10 11	216	All analyses were conducted in OpenBUGS <sup>26</sup> assuming non-informative priors for all model
12 13 14	217	parameters, and $\tau \sim N(0,1)$ , $\tau > 0$ . The first 10,000 iterations were discarded and then
15 16	218	100,000 simulations were run with thinning of 10 values. Convergence was checked by
17 18 10	219	visual inspection of the evaluation of the mixing of two chains. The median and 95% CrI
20 21	220	were calculated for each parameter value. The <i>network</i> command <sup>27</sup> was used to apply the
22 23	221	design-by-treatment interaction model.
24 25 26	222	For NMA estimates, a 95% predictive interval (PrI) is also reported to capture the
27 28	223	magnitude of $ au^2$ and present the interval within which the treatment effect of a future
29 30	224	study is expected to lie. <sup>28 29</sup> The estimated safety of the included AEDs was ranked using the
31 32 33	225	surface under the cumulative ranking (SUCRA) curve. <sup>30</sup> The larger the SUCRA for a
34 35	226	treatment, the higher its safety rank among all the available treatment options. SUCRA
36 37 38	227	values are presented along with 95% CrIs to capture the uncertainty in the parameter
39 40	228	values. <sup>31</sup>
41 42		
43 44		

#### RESULTS

#### Literature search and included studies

Our literature search identified 5,707 titles and abstracts, which after the screening process yielded 681 articles potentially relevant for inclusion (Figure 1). After full-text review, 95 studies fulfilled eligibility criteria along with 17 studies identified through supplemental methods. Of the 112 total eligible studies in the complete review,<sup>14</sup> 29 articles with seven companion reports and two potentially overlapping registry studies included one or more relevant neurological outcomes (Additional File 3: Appendix B). Four of the studies included in this analysis were conference abstracts with usable data.<sup>32-35</sup> and four studies,<sup>36-39</sup> not captured in the original literature search, were identified through reference scanning. A table with the key excluded studies and a rationale for their exclusion is presented in Additional File 3: Appendix C. Study and patient characteristics We included 29 cohort studies (5,100 patients) published between 1989 and 2016 (Table 1; Additional File 3: Appendix D, E). The number of patients included in each study ranged from 23 to 2,011 (median 74.5). Most studies (76%) were published after 2000, 62% of the studies included fewer than 100 patients, and the 52% of the studies included a control group of pregnant/breastfeeding women with epilepsy who did not receive AEDs. The mean maternal age ranged from 24 to 34 years. About half of the studies (52%) were funded through government/public research funding. 

Methodological quality results 

Twenty-nine observational studies were appraised using the NOS (Additional File 3:

Appendix F). Overall, the studies were of good methodological quality and were rated as

#### **BMJ Open**

3 4	252	high quality across most items: 28 studies (97%) selected the non-exposed cohort from	the
5 6 7	253	same community as the exposed cohort, 26 (90%) included a representative or somewhat	at
7 8 9	254	representative sample, 27 (93%) assessed outcomes independently, with blinding, or via	a
10 11	255	record linkage (e.g., identified through database records), and 23 (79%) ascertained	
12 13 14	256	exposure via secured records (e.g., database records) or structured interviews. The	
15 16	257	comparability of cohorts and adequacy of follow-up were the lowest scoring items acros	S
17 18	258	the studies with only 12 (41%) and 10 (34%) studies rated as high quality on these item	s.
19 20 21	259	No evidence for small-study effects was identified by the visual inspection of the	
22 23	260	comparison-adjusted funnel plots (Additional File 3: Appendix G).	
24 25 26	261	Statistical analysis results	
20 27 28	262	No important concerns were raised regarding the violation of the transitivity assumption	n
29 30	263	when maternal age, baseline risk, treatment indication, and timing were assessed	
31 32 33	264	(Additional File 3: Appendix H). However, the average methodological quality appraisal	
34 35	265	across treatment comparisons varied across treatment comparisons. The evaluation of the	he
36 37 38	266	consistency assumption using the design-by-treatment interaction model suggested that	-
39 40	267	there was no evidence of significant inconsistency across all outcomes (Additional File 3	:
41 42 42	268	Appendix H).	
43 44 45	269	In the following sections, we present the significant NMA results by outcome for AEDs	
46 47	270	compared with control (i.e., no exposure to AEDs), while the SUCRA values from all	
48 49 50	271	outcomes are presented in Figure 2 and depicted in a rank-heat plot ( <u>http://rh.ktss.ca/</u> ) <sup>4</sup>	40
50 51 52	272	in Additional File 3: Appendix I.	
53 54	273	Cognitive developmental delay	
55 56 57			
58 59			1 /
60			14
2			
----------	---		
3			
4	4		
5			
6	4		
7			
8	2		
9 10			
10			
12			
12			
14	4		
15			
16	4		
17			
18	2		
19			
20			
21	4		
22			
23	4		
24			
25	2		
26			
27	;		
28	-		
29			
30 31	4		
32			
33	4		
34			
35	2		
36			
37			
38	•		
39			
40	4		
41			
42	2		
43			
44 45	2		
45 46			
40 17			
47 78	4		
40 40			
50	4		
51			
52	2		
53			
54	:		
55	•		
56			
57			
58			
59			
60			

1

274	The NMA for cognitive developmental delay (definitions in Table 1) included 11 cohort
275	studies, 933 children, and examined 18 treatments (Figure 3a; Additional File 3: Appendix
276	J; $\tau^2$ =0.12, 95% CrI: 0.00-1.15). One study included children exposed to AEDs both <i>in-utero</i>
277	and through breastfeeding, and ten included children exposed to AEDs in-utero. Across all
278	AEDs, only valproate was associated with significantly increased odds of cognitive
279	developmental delay when compared with control (odds ratio (OR)=7.40, 95% credible
280	interval (CrI): 3.00-18.46; Figure 2a; Additional File 3: Appendix H).
281	The same results were observed in a network meta-regression of baseline risk for offspring
282	of women with epilepsy who were not exposed to AEDs (estimated regression coefficient
283	on OR scale: 1.01, 95% CrI: 0.76-1.56; τ²=0.16, 95% CrI: 0.00-1.24; residual deviance=
284	45.27, data points= 47, DIC= 80.17). Similarly, the sensitivity analyses restricted to: a)
285	studies that only included women receiving AEDs to treat epilepsy (10 studies, 910
286	children, 17 treatments; $\tau^2$ =0.16, 95% CrI: 0.00-1.36), b) studies comparing only first-
287	generation AEDs (6 studies, 480 children, 13 treatments; $\tau^2$ =0.28, 95% CrI: 0.00-2.97), c)
288	studies that reported maternal alcohol or tobacco use (3 studies, 504 children, 7
289	treatments; $\tau^2$ =0.27, 95% CrI: 0.00-3.29), and d) studies with high methodological quality
290	on NOS item 'comparability of cohorts' (3 studies, 366 children, 7 treatments; $\tau^2$ =0.38, 95%
291	CrI: 0.00-4.14), were consistent with the NMA results (Additional File 3: Appendix K). The
292	sensitivity analysis with studies of high methodological quality on the NOS item 'adequacy
293	of follow-up' found no statistically significant results (4 studies, 283 patients, 12
294	treatments; $\tau^2$ =1.01, 95% CrI: 0.01-5.85; Additional File 3: Appendix K).
295	Autism/dyspraxia

Page 17 of 90

1

## **BMJ Open**

2	
3 ₄	2
4 5	
6	2
7 8	2
9	2
10 11	2
12	
13 14	3
15	2
16 17	5
18	3
19	
20 21	3
22	3
23 24	0
25	3
26 27	2
28	3
29 30	3
31	
32 33	3
34	2
35 36	З
37	3
38 39	
40	3
41 42	3
43	0
44 45	3
46	0
47 48	3
49	3
50 51	-
52	3
53 54	n
55	3
56	
ว/ 58	
59	
60	

296	The NMA on autism/dyspraxia (definitions in Table 1) included five cohort studies, 2,551
297	children exposed <i>in utero</i> , and examined 12 treatments ( $\tau^2$ =0.16, 95% CrI: 0.00-1.95;
298	Figure 3b; Additional File 3: Appendix H). Compared with control, only valproate
299	(OR=17.29, 95% CrI: 2.40-217.60), oxcarbazepine (OR= 13.51, 95% CrI: 1.28-221.40),
300	lamotrigine (OR= 8.88, 95% CrI: 1.28-112.00), and lamotrigine+valproate (OR=132.70,
301	95% CrI: 7.41-3851.00) were significantly associated with increased occurrence of
302	autism/dyspraxia (Figure 2b).
303	Restricting the NMA to studies including only women with epilepsy as their treatment
304	indication produced results that were generally in agreement with the NMA results, except
305	that oxcarbazepine was no longer in the network (4 cohort studies, 540 children, 10
306	treatments; $\tau^2$ =0.31, 95% CrI: 0.00-304). Two cohort studies of 404 offspring of women
307	with a history of tobacco use compared 4 treatments and found similar results except that
308	oxcarbazepine and lamotrigine+valproate were no longer in the network ( $ au^2$ =0.39, 95%
309	CrI: 0.00-4.47). The results were in agreement in sensitivity analyses including only higher
310	methodological quality studies in the 'comparability of cohorts' item on the NOS (4 studies,
311	2,395 children, 12 treatments; $\tau^2$ =0.19, 95% CrI: 0.00-2.43) and the 'adequacy of follow-up
312	of cohorts' (3 studies, 2244 children, 10 treatments; $\tau^2$ =0.23, 95% CrI: 0.00-2.88), except
313	that lamotrigine was no longer statistically significant than control for the latter
314	(Additional File 3: Appendix K).
315	Neonatal Seizure
316	One cohort study included 72 children who were exposed to AEDs in-utero as well as
317	through breastfeeding reported on the incidence of neonatal seizures. The study compared

2		
3 4	318	valproate against lamotrigine and found no significant difference in neonatal seizures
5 6 7	319	between the two drugs (OR=0.18, 95% CI: 0.01-3.70).
7 8 9	320	Psychomotor developmental delay
10 11	321	The NMA on psychomotor developmental delay (definitions in Table 1) included 11 cohort
12 13 14	322	studies, 1,145 children exposed <i>in utero</i> , and examined 18 treatments ( $\tau^2$ =0.06, 95% CrI:
15 16	323	0.00-0.63; Figure 3c; Additional File 3: Appendices H, J). Valproate (OR=4.16, 95% CrI:
17 18 10	324	2.04-8.75) and carbamazepine+phenobarbital+valproate (OR=19.12, 95% CrI: 1.49-
20 21	325	337.50) were significantly more harmful than control (Figure 2c).
22 23	326	Language delay
24 25 26	327	The NMA on language delay (definitions in Table 1) included five cohort studies, 509
20 27 28	328	children, and examined five treatments ( $\tau^2$ =0.16, 95% CrI: 0.00-2.15; Figure 3d; Additional
29 30	329	File 3: Appendices H, J). One study included children exposed to AEDs <i>in-utero</i> and through
31 32 33	330	breastfeeding, and four included children exposed to AEDs in-utero. Compared with
34 35	331	control, valproate was the only treatment significantly associated with increased odds of
36 37 38	332	language delay (OR=7.95, 95% CrI: 1.50-49.13; Figure 2d).
39 40	333	Attention deficit hyperactivity disorder
41 42 43	334	The NMA on ADHD (definitions in Table 1) included five cohort studies, 816 children, and
44 45	335	examined seven treatments ( $\tau^2$ =0.11, 95% CrI: 0.00-1.29). One study included children
46 47	336	exposed to AEDs in-utero and through breastfeeding, while four studies included children
48 49 50	337	exposed to AEDs in-utero. None of the treatment comparisons reached statistical
51 52	338	significance (Figure 3e; Figure 2e; Additional File 3: Appendices H, J).
53 54 55	339	Social Impairment
56 57 58		
59 60		17

1

Page 19 of 90

## **BMJ Open**

2		
3 4	340	One cohort study included 422 children exposed to AEDs in-utero as well as through
5 6 7	341	breastfeeding. The children were exposed to carbamazepine (n=48), lamotrigine (n=71),
7 8 9	342	valproate (n=27) and control (n=278). No significant differences in social impairment were
10 11	343	identified. <sup>41</sup>
$\begin{array}{c}12\\13\\14\\56\\78\\90\\12\\22\\22\\22\\22\\22\\22\\22\\22\\22\\22\\22\\22\\$	344	

## **DISCUSSION**

Our results suggest that AEDs generally pose a risk for infants and children exposed *in*-*utero* or during breastfeeding. Valproate was significantly associated with more children experiencing autism/dyspraxia, language, cognitive and psychomotor developmental delays versus children who were not exposed to AEDs. Oxcarbazepine, lamotrigine and lamotrigine+valproate were associated with increased occurrence of autism/dyspraxia, whereas for the cognitive developmental delay and psychomotor developmental delay outcomes, children exposed to the combination of carbamazepine, phenobarbital, and valproate were at greater odds of harm than those who were not exposed to AEDs. However, these results should be interpreted with caution, as a number of factors (e.g., anticonvulsant dosing, severity of epilepsy, duration of exposure, serum concentrations of exposure, mother's IQ/education) that may all influence outcomes were not identified in these studies. Also, our subsequent analyses may be underpowered due to missing data (e.g., 17 of the 27 studies did not report maternal age, 23 of 27 studies did not report alcohol use, 22 of 27 studies did not report tobacco use, and 14 of 27 studies did not include control group). NMA is a particularly useful tool for decision-makers because it allows the ranking of

361 NMA is a particularly useful tool for decision-makers because it allows the ranking of
362 treatments for each outcome. However, the results of our SUCRA curves should be
363 interpreted with caution, especially due to the small number of studies and children
364 included in each NMA, which is also reflected in the high uncertainty around the SUCRA
365 values (Figure 2).<sup>31</sup>

366 Our results are consistent with a longitudinal study of 311 children that found exposure to
367 lamotrigine was associated with significantly higher IQ scores and verbal function at six

Page 21 of 90

### **BMJ Open**

years of age compared to children exposed to valproate (Additional File 3: Appendix C).<sup>7</sup> As indicated in Additional File 3: Appendix C, we were unable to include this study because the outcome was reported as a continuous measure, where we focused on dichotomous outcomes to facilitate interpretation. Our results are supported by findings from a cohort study, which found that children exposed to levetiracetam were not at increased risk for delayed development compared to unexposed children (Additional File 3: Appendix C).<sup>42</sup> As indicated in Additional File 3: Appendix C, we were unable to include this study due to the same reason as above. A NMA of 195 RCTs (including 28,013 both male and female patients) showed that gabapentin and levetiracetam showed the best tolerability profile compared with other AEDs, whereas oxcarbazepine and topiramate had a higher withdrawal rate, and lamotrigine an intermediate withdrawal rate.<sup>43</sup> Across all outcomes, valproate alone or combined with another AED (even with a newer-generation agent, e.g., lamotrigine) was associated with the greatest odds. Similarly, two previous systematic reviews that did not conduct a NMA found valproate was associated with significantly lower IQ scores and poorer overall neurodevelopmental outcomes when compared to an unexposed control group.<sup>56</sup> Also consistent with our results, a 2014 Cochrane review including 28 studies (10 of these studies were included in the meta-analyses; with a maximum number of five studies per meta-analysis) concluded that AED polytherapy led to poorer developmental outcomes and IO compared to healthy controls, epileptic controls, and unspecified monotherapy.<sup>5</sup> This Cochrane review also concluded that insufficient data exist for newer AEDs. However, unlike our review, it included and analysed fewer studies, and did not differentiate between specific polytherapy regimens, and thus did not compare these regimens versus each other or specific monotherapy AEDs.

These risks must be balanced with the need to control seizure activity in pregnancy and 6 thus informed decision-making by patients and clinicians is critical. Strengths of our study include a comprehensive systematic review methodology that followed the Cochrane Handbook<sup>44</sup> and ISPOR<sup>12</sup> guidelines, and reported using the PRISMA extension for NMA.<sup>13</sup> To the best of our knowledge, our study was the first that compared and ranked the safety of AEDs. We evaluated the comparative safety of treatments that have not been directly compared head-to-head before. In addition, we calculated predictive intervals, which account for between-study variation and provide a predicted range for the treatment effect estimate, should a future study be conducted. On average, the predictive intervals suggested that our results are robust. Our systematic review has a few limitations worth noting. First, due to the complexity of the data and the studies' underreporting, differences in drug dosages could not be accounted for, and it was assumed that different dosages of the same AED were equally effective. When a study reported multiple dosages for the same treatment, we combined the data for this treatment. This is common for cohort studies, which report on a number of different types of exposures amongst patients. Second, several polytherapies had high SUCRA estimates but very wide CrIs, which is due to the small number of studies included for each drug combination with underpowered sample sizes. Evidence suggests that ranking probabilities for a treatment of being the best may be biased toward the treatments with the smallest number of studies, which may have influenced our SUCRA results.<sup>31 45</sup> As such, the effect sizes need to be taken into account when considering the SUCRA values. Third, due to the absence of evidence from RCTs, our conclusions were based on evidence from observational studies only, and inherent biases because of 

Page 23 of 90

### **BMJ Open**

confounding and shortcomings of these studies may have impacted our findings. For example, the included studies often failed to report important confounding variables,<sup>46</sup> such as family history of autism, ADHD, and maternal IQ, severity of epilepsy making it impossible for us to control these variables through subgroup analysis and meta-regression. Recent research has explored methods to incorporate non-randomized with randomized evidence in a NMA and have highlighted the need to carefully explore the level of confidence in the non-randomized evidence.<sup>47 48</sup> The use of observational studies allows the assessment of the safety profile of AED treatments and offers the opportunity to evaluate effects in pregnancy.<sup>49</sup> Future large-scale observational studies are needed to allow the evaluation of rare adverse events that otherwise cannot be adequately evaluated in RCTs, especially during pregnancy. Fourth, although no intransitivity for most effect modifiers assessed was evident, there was an imbalance in the methodological study quality appraisal across treatment comparisons and most outcomes, which may impact our results. Unknown factors or factors that could not be assessed due to dearth of data may pose the risk of residual confounding bias, and hence risk the validity of the transitivity assumption. However, the assessment of consistency suggested no disagreement between the different sources of evidence in the network. Fifth, although the tendency towards small-study effects is greater with observational studies than with randomized trials,<sup>50</sup> the assessment of small-study effects using adjusted funnel plots suggested no evidence for their prevalence. Also, the majority of the included studies in this review compared multiple treatments inducing correlations in each funnel plot, which may mask asymmetry. Although we plotted data points corresponding to the study-specific basic parameters to reduce correlations, this issue may still exist. Sixth, we were unable to conduct subgroup

1 2		
3 4	437	analysis by type of exposure (breastfeeding versus <i>in utero</i> ) due to the small number of
5 6 7	438	studies included in the NMA and due to the poor reporting; 22 studies did not report
7 8 9	439	whether exposure was also in breastfeeding (additional to <i>in utero</i> ). Hence, we included all
10 11	440	studies in the analysis irrespective of the type of exposure.
12 13 14	441	More evidence from long-term follow-up studies is required to further delineate
15 16	442	neurodevelopmental risks in children. Future studies should assess the genetic
17 18 10	443	contribution from the biological father, maternal seizures during pregnancy, exposure
20 21	444	through breastfeeding only, types of epilepsy, and maternal family history. Registries
22 23	445	should aim to include a suitable control group and collect information on potential
24 25 26	446	confounders, such as alcohol and tobacco use, allowing researchers to identify the safest
27 28	447	agents for different patient-level covariates, and enhance decision-making for healthcare
29 30 31	448	providers and patients. A critical evaluation of the validity of the control group is also
32 33	449	necessary, in order to examine potential differences between the treated and the not
34 35 26	450	treated populations. An individual patient data NMA would likely provide further clarity to
36 37 38	451	the field, which allows the tailoring of management to specific patient characteristics. <sup>51</sup>
39 40	452	CONCLUSION
41 42 43	453	Across all outcomes and treatments compared with control, valproate alone or combined
44 45	454	with another AED was associated with the greatest odds, whereas oxcarbazepine and
46 47 48	455	lamotrigine were associated with increased occurrence of autism. Counselling is advised
49 50	456	for women considering pregnancy to tailor the safest regimen.
51 52 53		
53 54 55		
56		
57 58		

59

1 2 3 4	457	LIST OF ABBREVIATIONS	
5 6 7	458	AEDs: Anti-epileptic drugs; CrI: Credible interval; NMA: Network Meta-analysis; OR: Od	ds
7 8 9	459	ratio; PrI: Predictive interval; SUCRA curve: Surface under the cumulative ranking curve	Э
10 11 12	460	ADDITIONAL FILES	
13 14	461	Additional File 1: Protocol	
15 16 17 18 19	462	Additional File 2: PRISMA NMA Checklist	
20 21	463	Additional File 3: Supplementary Online Content (Appendices A-O)	
22 23 24	464	Appendix A. Newcastle-Ottawa Scale scoring guide	
25 26	465	Appendix B. List of included studies	
27 28 29	466	Appendix C. Key Excluded Studies	
30 31	467	Appendix D. Table of Individual Study Characteristics	
32 33 34	468	Appendix E. Table of Patient Characteristics	
35 36	469	Appendix F. Methodological quality of observational studies – Newcastle Ottawa Scale	
37 38 20	470	Appendix G. Comparison-adjusted funnel plots	
39 40 41	471	Appendix H. Statistically significant network meta-analysis results along with meta-	
42 43	472	analysis results, transitivity, and inconsistency assessments	
44 45 46	473	Appendix I. Rank-heat plot of cognitive developmental delay, autism/dyspraxia,	
47 48	474	psychomotor developmental delay, language delay, and attention deficit hyperactivity	
49 50 51	475	disorder outcomes	
52 53	476	Appendix J. Number of studies and treatments per outcome	
54 55	477	Appendix K. Sensitivity and network meta-regression analyses - Anti-epileptic drugs	
50 57 58 59 60	478	compared with Control	2

2
3
4
5
6
7
8
à
10
10
11
12
13
14
15
16
10
17
18
19
20
21
22
~~ 22
23
24
25
26
27
28
20
29
30
31
32
33
34
24
35
36
37
38
39
40
41
42
43
44
45
46
/7
41 40
48
49
50
51
52
52
50
04 55
55
56
57
58
50
60
())]

# 479**FIGURE LEGENDS**

# 480 **Figure 1. Study flow diagram**

# 481 Figure 2. Forest plots for cognitive developmental delay, autism/dyspraxia,

# 482 psychomotor developmental delay, language delay, and attention deficit

# 483 hyperactivity disorder outcome

# 484 Figure 3. Network diagrams for cognitive developmental delay, autism/dyspraxia,

# 485 **psychomotor developmental delay, language delay, and attention deficit**

# 486 hyperactivity disorder outcomes

# 487 Each treatment node is weighted according to the number of patients that have received the

# 488 particular treatment, and each edge is weighted according to the number of studies

# 489 *comparing the treatments it connects.*

# 490 <u>Abbreviations:</u> carbam - carbamazepine, clobaz - clobazam, clonaz - clonazepam, ethos -

# 491 ethosuximide, gabap - gabapentin, lamot - lamotrigine, levet - levetiracetam, oxcar -

# 492 oxcarbazepine, pheno - phenobarbital, pheny - phenytoin, primid - primidone, topir -

# 493 topiramate, valpro - valproate, vigab – vigabatrin

# **DECLARATIONS**

## **CONTRIBUTORS**

AAV analysed the data, interpreted the results, and drafted the manuscript. ACT and SES conceived and designed the study, helped obtain funding, interpreted the results, and helped write sections of the manuscript. PR and EC coordinated the review, screened citations and full-text articles, abstracted data, appraised quality, resolved discrepancies, contacted authors, and edited the manuscript. CS provided methodological support and screened citations and full-text articles and edited the manuscript. RK, ER, FY, JDS, KT, and HM screened citations and full-text articles, abstracted data, and/or appraised quality. BH, BRH and YF helped conceive the study and edited the manuscript. All authors read and approved the final manuscript.

# 30 505 ACKNOWLEDGEMENTS 31

We thank Dr. David Moher for providing his feedback on our protocol. We thank Dr. Laure Perrier for conducting the literature searches, Becky Skidmore for peer-reviewing the MEDLINE search, and Alissa Epworth for obtaining the full-text articles. We thank Alistair Scott, Wing Hui, and Geetha Sanmugalingham for screening some of the citations and/or abstracting some of the data for a few of the included studies, Misty Pratt and Mona Ghannad for helping scan reference lists, and Ana Guzman, Susan Le, and Inthuja Selvaratnam for contacting authors and formatting the manuscript. FUNDING 

516 Fellowship Program from the CIHR. SES is funded by a Tier 1 Canada Research Chair in

2		
3 4	517	Knowledge Translation. BH is funded by a CIHR/DSEN New Investigator Award in
5 6 7	518	Knowledge Synthesis. BRH receives funding from the Alberta Heritage Foundation for
7 8 9	519	Medical Research. ACT is funded by a Tier 2 Canada Research Chair in Knowledge
10 11	520	Synthesis. The funder had no role in the design and conduct of the study; collection,
12 13 14	521	management, analysis, and interpretation of the data; preparation, review, or approval of
15 16	522	the manuscript; or decision to submit the manuscript for publication.
17 18 19	523	COMPETING INTERESTS
20 21	524	None declared.
22 23	525	ETHICS APPROVAL
24 25 26	526	Not applicable.
27 28	527	PROVENANCE AND PEER REVIEW
29 30 31	528	Not commissioned; externally peer reviewed.
32 33	529	DATA SHARING STATEMENT
34 35 26	530	All datasets generated and/or analysed during the current study are available from the
36 37 38	531	corresponding author on reasonable request.
39 40	532	OPEN ACCESS
41 42 43	533	This is an Open Access article distributed in accordance with the Creative Commons
44 45	534	Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute,
46 47	535	remix, adapt, build upon this work non-commercially, and license their derivative works on
48 49 50	536	different terms, provided the original work is properly cited and the use is non-
51 52	537	commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.
53 54 55		
56 57		
58 59		77
60		27

## BMJ Open

#### 538 REFERENCES

7		
8	530	1 Sping F. Perugi C. Antiopilantic drugs: indications other than opilansy. <i>Epilantic Disord</i>
9	540	2004·6(2)·57-75
10	541	2 Harden CL Pennell PR Konnel RS et al Management issues for women with enilensyfocus
11	542	on pregnancy (an evidence-based review): III vitamin K folic acid blood levels and breast-feeding:
12 13	543	report of the quality standards subcommittee and therapeutics and technology assessment
14	544	subcommittee of the American Academy of Neurology and the American Enilensy Society <i>Enilensia</i>
15	545	2000-50(5)-1247-55
16	546	2 Samron FR yan Duijn CM Koch S at al Maternal use of antioniloptic drugs and the rick of
17	540	5. Saint en ED, van Duijn CM, Koch 5, et al. Maternal use of antiephephe ul us and the risk of
18	547	according with maternal englangy. Englancia, 1007,22(0),021,00
19	540 E40	Associated with inaternal epinepsy. Epinepsia. 1997;50(9):901-90.
20	549	4. Meduol K, Reynolus MW, Clean S, Fambach K, Probst C. Pregnancy outcomes in women
21	550 EE1	with epilepsy: a systematic review and meta-analysis of published pregnancy registries and
22	221	conorts. Epilepsy Res. 2008;81(1):1-13.
23	552	5. Bromley R, weston J, Adab N, et al. Treatment for epilepsy in pregnancy:
24 25	555	neurodevelopmental outcomes in the child. The Cochrane database of systematic reviews.
20 26	554	
20	555	6. Banach R, Boskovic R, Einarson T, Koren G. Long-term developmental outcome of children
28	556	of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of
29	55/	cohort studies. Drug Saf. 2010;33(1):73-9.
30	558	7. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive
31	559	outcomes at age 6 years (NEAD study): a prospective observational study. <i>Lancet Neurol</i> .
32	560	2013;12(3):244-52.
33	561	8. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of
34	562	autism spectrum disorders and childhood autism. <i>JAMA</i> . 2013;309(16):1696-703.
35	563	9. Wlodarczyk BJ, Palacios AM, George TM, Finnell RH. Antiepileptic drugs and pregnancy
36	564	outcomes. <i>Am J Med Genet A</i> . 2012;158a(8):2071-90.
37	565	10. Velez-Ruiz NJ, Meador KJ. Neurodevelopmental effects of fetal antiepileptic drug exposure.
30 30	566	Drug Saf. 2015;38(3):271-8.
40	567	11. Tricco AC, Cogo E, Angeliki VA, et al. Comparative safety of anti-epileptic drugs among
41	568	infants and children exposed in utero or during breastfeeding: protocol for a systematic review and
42	569	network meta-analysis. <i>Systematic reviews</i> . 2014;3:68.
43	570	12. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-
44	571	analysis study questionnaire to assess relevance and credibility to inform health care decision
45	572	making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014;17(2):157-73.
46	573	13. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of
47	574	systematic reviews incorporating network meta-analyses of health care interventions: checklist and
48	575	explanations. Ann Intern Med. 2015;162(11):777-84.
49 50	576	14. Veroniki AA, Cogo E, Rios P, et al. Comparative safety of anti-epileptic drugs during
50 51	577	pregnancy: a systematic review and network meta-analysis of congenital malformations and
52	578	prenatal outcomes. BMC Med. 2017;15(1):95.
53	579	15. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review
54	580	of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016;75:40-6.
55	581	16. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the
56	582	quality of nonrandomised studies in meta-analyses2000. Available from:
57	583	http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
58		
59		28
60		20

17. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One. 2013;8(10):e76654. Furukawa TA, Guyatt GH, Griffith LE. Can we individualize the 'number needed to treat'? An 18. empirical study of summary effect measures in meta-analyses. *Int J Epidemiol*. 2002;31(1):72-6. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment 19. comparisons. Stat Med. 2004;23(20):3105-24. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It 20. all depends on the distribution of effect modifiers. BMC Med. 2013;11:159. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-21. analysis: model estimation using multivariate meta-regression. Res Synth Methods. 2012;3(2):111-25. 22. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMI. 2003;326(7387):472. 23. Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. Int J Epidemiol. 2013;42(1):332-45. 24. Welton NJ, Sutton AJ, Cooper N, Abrams KR, Ades A. Evidence synthesis for decision making in healthcare. New York: Wiley; 2012. 25. Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Ser B Stat Methodol*. 2002;64(4):583-639. Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: Evolution, critique and future 26. directions. Stat Med. 2009;28(25):3049-67. Palmer T, Sterne J. Meta-Analysis in Stata: An Updated Collection from the Stata Journal. 27. White I, editor. Texas: Stata Press; 2016. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 28. 2011;342:d549. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. 29. *J R Stat Soc Ser A Stat Soc.* 2009;172(1):137-59. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for 30. presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin *Epidemiol.* 2011;64(2):163-71. Trinquart L, Attiche N, Bafeta A, Porcher R, Ravaud P. Uncertainty in Treatment Rankings: 31. Reanalysis of Network Meta-analyses of Randomized Trials. Ann Intern Med. 2016;164(10):666-73. 32. Bromley R, Baxter N, Calderbank R, Mawer G, Clayton-Smith J, Baker G. A comprehensive review of the language abilities of children exposed to valproate or carbamazepine in utero. American Epilepsy Society; Texas2010. Gogatishvili N, Ediberidze T, Lomidze G, Tatishvili N, Kasradze S. PO-0834 Long-term 33. Developmental Outcome Of Children Prenatally Exposed To Antiepileptic Drugs. Arch Dis Child. 2014;99(Suppl 2):A526. Gogatishvili N, Ediberidze T, Lomidze G, Tatishvili N, Kasradze S. Cognitive outcomes of 34. children with fetal antiepileptic drug exposure at the age of 3-6 years-preliminary data. 1st Congress of the European Academy of Neurology; Berlin: European Journal of Neurology; 2015. p. 329. 35. Miskov S, Juraski RG, Fucic A, et al. Croatian Pregnant Women with Epilepsy and Effects of Antiepileptic Drugs Exposure in their Offspring - seven years of prospective surveillance. American Epilepsy Society; Texas2010. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with 36. epilepsy. J Neurol Neurosurg Psychiatry. 2004;75(11):1575-83. 

1 2		
3	632	37 Dean ICS Hailey H. Moore SI Lloyd DI Turnnenny PD Little I Long term health and
4	633	neurodevelopment in children exposed to antiepileptic drugs before birth. <i>J Med Genet</i> .
5	634	2002;39(4):251-9.
7	635	38. Gaily E. Development and growth in children of epileptic mothers: a prospective controlled
8	636	study. Helsinki, Finland: University of Helsinki; 1990.
9	637	39. Katz JM, Pacia SV, Devinsky O. Current Management of Epilepsy and Pregnancy: Fetal
10	638	Outcome, Congenital Malformations, and Developmental Delay. <i>Epilepsy Behav</i> . 2001;2(2):119-23.
11	639	40. Veroniki AA, Straus SE, Fyraridis A, Tricco AC. The rank-heat plot is a novel way to present
12 13	640	the results from a network meta-analysis including multiple outcomes. <i>J Clin Epidemiol</i> . 2016.
14	641	41. Verby G, Engelsen BA, Gilnus NE. Early child development and exposure to antiepileptic
15	042 642	arugs prenatally and through breastreeding: a prospective conort study on children of women with
16	643 644	42 Shallcross R Bromley RI Irwin B Bonnett II Morrow I Baker GA Child development
1/ 10	645	following in utero exposure: levetiracetam vs sodium valproate. <i>Neurology</i> , 2011:76(4):383-9.
19	646	43. Zaccara G. Giovannelli F. Giorgi FS. Franco V. Gasparini S. Benedetto U. Tolerability of new
20	647	antiepileptic drugs: a network meta-analysis. <i>Eur J Clin Pharmacol</i> . 2017.
21	648	44. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions.
22	649	5.1.0 ed: The Cochrane Collaboration; 2009.
23	650	45. Kibret T, Richer D, Beyene J. Bias in identification of the best treatment in a Bayesian
24 25	651	network meta-analysis for binary outcome: a simulation study. <i>Clin Epidemiol</i> . 2014;6:451-60.
26	652	46. Dalessio DJ. Seizure Disorders and Pregnancy. <i>N Engl J Med</i> . 1985;312(9):559-63.
27	653	47. Effhimiou O, Mavridis D, Debray TP, et al. Combining randomized and non-randomized
28	654 (FF	evidence in network meta-analysis. <i>Stat Med.</i> 2017.
29	055 656	48. Schmitz S, Adams R, Walsh C. Incorporating data from various trial designs into a mixed
30 31	657	49 Cameron C Fireman B Hutton B et al Network meta-analysis incornorating randomized
32	658	controlled trials and non-randomized comparative cohort studies for assessing the safety and
33	659	effectiveness of medical treatments: challenges and opportunities. <i>Systematic reviews</i> . 2015:4:147.
34	660	50. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research.
35	661	Lancet. 1991;337(8746):867-72.
37	662	51. Veroniki AA, Straus SE, Soobiah C, Elliott MJ, Tricco AC. A scoping review of indirect
38	663	comparison methods and applications using individual patient data. BMC Med Res Methodol.
39	664	2016;16(1):47.
40	665	
41		
42 43		
44		
45		
46		
47 19		
40 49		
50		
51		
52		
53 54		
55		
56		
57		
58		
59 60		30
00		

% of Studies

3.45 20.69 17.24 58.62

68.97 17.24 3.45 6.90 3.45

100.00 0.00 0.00

37.93 62.07

62.07 31.03 3.45 0.00 0.00 3.45

13.79 17.24 27.59 27.59 6.90 6.90

> 58.62 17.24 17.24 17.24

Study/Patient Characteristic# of S (n=Year of publication1980-1989 1990-1999 2000-2009 2010-2015Continent (of country of study conduct)EuropeContinent (of country of study conduct)EuropeNorth America Asia Australia Trans-ContinentalAsia Australia Trans-ContinentalStudy designObservational cohort Case-control Randomized clinical trialRegistry studyYes NoSample size0-99 100-299 300-499 500-699 700-999 1000+Number of interventions2 3 4 4 5-7 8-10 11+Outcomes*.*7Cognitive Developmental Delay Autism/Dyspraxia Language Delay	Table 1. Summary Characteristics of in	cluded st
Year of publication         1980-1989         1990-1999         2000-2009         2010-2015         Continent (of country of study conduct)         Europe         North America         Asia         Australia         Trans-Continental         Study design         Observational cohort         Case-control         Randomized clinical trial         Registry study         Yes         0-99         100-299         300-499         500-699         700-999         1000+         Number of interventions         2         3         4         5-7         8-10         11+         Outcomes*.*         Cognitive Developmental Delay         Autism/Dyspraxia         Language Delay	Study/Patient Characteristic	# of S (n=
1980-1989           1990-1999           2000-2009           2010-2015           Continent (of country of study conduct)           Europe           North America           Asia           Australia           Trans-Continental           Study design           Observational cohort           Case-control           Randomized clinical trial           Registry study           Yes           No           Sample size           0-99           100-299           300-499           500-699           700-999           1000+           Number of interventions           2           3           4           5-7           8-10           11+           Outcomes*, <sup>†</sup> Cognitive Developmental Delay           Autism/Dyspraxia           Language Delay	Year of publication	
$\begin{array}{c} 1990-1999\\ 2000-2009\\ 2010-2015\\ \hline \hline \\ \hline \\$	1980-1989	-
$\begin{array}{c} 2000-2009\\ 2010-2015 \\ \hline \\ $	1990-1999	(
2010-2015Continent (of country of study conduct)EuropeNorth AmericaAsiaAustraliaTrans-ContinentalStudy designObservational cohortCase-controlRandomized clinical trialRegistry studyYesNoSample size0-99100-299300-499500-699700-9991000+Number of interventions2345-78-1011+Outcomes*, †Cognitive Developmental DelayAutism/DyspraxiaLanguage Delay	2000-2009	-
Continent (of country of study conduct)EuropeNorth AmericaAsiaAustraliaTrans-ContinentalStudy designObservational cohortCase-controlRandomized clinical trialRegistry studyYesNoSample size0-99100-299300-499500-699700-9991000+Number of interventions2345-78-1011+Outcomes*, †Cognitive Developmental DelayAutism/DyspraxiaLanguage Delay	2010-2015	1
Europe 2 North America Asia Australia Trans-Continental <u>Study design</u> Observational cohort Case-control Randomized clinical trial <u>Registry study</u> Yes No <u>Sample size</u> 0-99 100-299 300-499 500-699 700-999 1000+ <u>Number of interventions</u> 2 3 4 5-7 8-10 11+ <i>Outcomes*,<sup>†</sup></i> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	Continent (of country of study conduct)	
North America Asia Australia Trans-Continental Study design Observational cohort Case-control Randomized clinical trial Registry study Yes No Sample size 0-99 100-299 300-499 500-699 700-999 1000+ Number of interventions 2 3 4 5-7 8-10 11+ Outcomes <sup>*,†</sup> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	Europe	2
Asia Australia Trans-Continental Study design Observational cohort Case-control Randomized clinical trial Registry study Yes No Sample size 0-99 100-299 300-499 500-699 700-999 1000+ Number of interventions 2 3 4 5-7 8-10 11+ Outcomes <sup>*, †</sup> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	North America	
Australia Trans-Continental Study design Observational cohort Case-control Randomized clinical trial Registry study Yes No Sample size 0-99 100-299 300-499 500-699 700-999 1000+ Number of interventions 2 3 4 5-7 8-10 11+ Outcomes <sup>*,†</sup> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	Asia	
Trans-ContinentalStudy designObservational cohortCase-controlRandomized clinical trialRegistry studyYesNoSample size0-99100-299300-499500-699700-9991000+Number of interventions2345-78-1011+0utcomes* $^{\dagger}$ Cognitive Developmental DelayAutism/DyspraxiaLanguage Delay	Australia	
Study designObservational cohortCase-controlRandomized clinical trialRegistry studyYesNoSample size0-99100-299300-499500-699700-9991000+Number of interventions2345-78-1011+Outcomes*, †Cognitive Developmental DelayAutism/DyspraxiaLanguage Delay	Trans-Continental	
Observational cohort Case-control Randomized clinical trialRegistry studyYesNoSample size0-99100-299 300-499 500-699 700-999 1000+ $Number of interventions$ 2345-7 8-10 11+Outcomes*, †Cognitive Developmental Delay Autism/Dyspraxia Language Delay	Study design	
Case-control Randomized clinical trial Registry study Yes No Sample size 0-99 100-299 300-499 500-699 700-999 1000+ Number of interventions 2 3 4 5-7 8-10 11+ Outcomes <sup>*, †</sup> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	Observational cohort	2
Randomized clinical trial         Registry study         Yes         No         Sample size         0-99         100-299         300-499         500-699         700-999         1000+         Number of interventions         2         3         4         5-7         8-10         11+         Outcomes*, *         Cognitive Developmental Delay         Autism/Dyspraxia         Language Delay	Case-control	
Registry study         Yes           No         No           Sample size         0-99           100-299         300-499           300-499         500-699           700-999         1000+           Number of interventions         2           3         4           5-7         8-10           11+         Outcomes*, †           Cognitive Developmental Delay         2           Autism/Dyspraxia         Language Delay	Randomized clinical trial	
Yes         No           Sample size         0-99           100-299         300-499           300-499         500-699           700-999         1000+           Number of interventions         2           3         4           5-7         8-10           11+         0utcomes*, †           Cognitive Developmental Delay         2           Autism/Dyspraxia         2	Registry study	
No           Sample size           0-99           100-299           300-499           500-699           700-999           1000+           Number of interventions           2           3           4           5-7           8-10           11+           Outcomes*, <sup>†</sup> Cognitive Developmental Delay           Autism/Dyspraxia           Language Delay	Yes	1
Sample size         0-99         100-299         100-299         100-299         300-499         500-699         700-999         1000+         Number of interventions         2         3         4         5-7         8-10         11+         Outcomes*, †         8-10         11+         Outcomes*, †         Cognitive Developmental Delay         2         3         4         3         4         3         4         3         4         3         4         3         4         3         4         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         0         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         11+         1	N0	
0-99       100-299         300-499       500-699         500-999       1000+         Number of interventions       2         3       4         5-7       8-10         11+       0utcomes*, †         Cognitive Developmental Delay       2         Autism/Dyspraxia       1         Language Delay       2	Sample size	1
100-299         300-499         500-699         700-999         1000+         Number of interventions         2         3         4         5-7         8-10         11+         Outcomes*, †         Cognitive Developmental Delay         Autism/Dyspraxia         Language Delay	0-99	1
500-499 500-699 700-999 1000+ <u>Number of interventions</u> 2 3 4 5-7 8-10 11+ <u>Outcomes<sup>*, †</sup></u> Cognitive Developmental Delay <u>Autism/Dyspraxia</u> Language Delay	100-299	
300-099         700-999         1000+         Number of interventions         2         3         4         5-7         8-10         11+         Outcomes*, †         Cognitive Developmental Delay         Autism/Dyspraxia         Language Delay	500-499	
Number of interventions       2       3       4       5-7       8-10       11+       Outcomes*, †       Cognitive Developmental Delay       Autism/Dyspraxia       Language Delay	700-099	
Number of interventions         2         3         4         5-7         8-10         11+         Outcomes*, †         Cognitive Developmental Delay         Autism/Dyspraxia         Language Delay	700-399 1000±	
2 3 4 5-7 8-10 11+ Outcomes <sup>*,†</sup> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	Number of interventions	-
3 4 5-7 8-10 11+ Outcomes <sup>*,†</sup> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	2	4
4 5-7 8-10 <u>11+</u> <i>Outcomes</i> <sup>*,†</sup> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	3	ļ
5-7 8-10 11+ Outcomes <sup>*, †</sup> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	4	8
8-10 11+ Outcomes <sup>*, †</sup> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	5-7	8
11+ Outcomes <sup>*,†</sup> Cognitive Developmental Delay Autism/Dyspraxia Language Delay	8-10	-
Outcomes <sup>*,†</sup> Cognitive Developmental Delay Autism/Dyspraxia	11+	-
Cognitive Developmental Delay Autism/Dyspraxia	Outcomes <sup>*,†</sup>	
Autism/Dyspraxia	Cognitive Developmental Delav	1
Language Delay	Autism/Dyspraxia	Į
Dullguage Delay	Language Delay	Ţ

# studies

1

Study/Patient Characteristic	# of Studies (n=29)	% of Studies
Psychomotor Developmental Delay	11	37.93
Neonatal Seizures	2	6.90
Social Impairment	1	3.45
Funding		
Public	15	51.72
Private	0	0.00
Mixed public and private	4	13.79
NR/Unclear	10	34.48
Treatment indication		
Epilepsy	23	79.31
Mixed indications <sup>‡</sup>	0	0.00
Not reported	6	20.69
Epileptic control group <sup>§</sup>		
Yes	15	51.72
No/NR/NA	14	48.28
Mean maternal age		
24-26 y	2	6.90
27-29 y	5	17.24
30+ y	4	13.79
Not reported	18	62.07
AED exposure during pregnancy		
Reported as during 1 <sup>st</sup> trimester	6	20.69
Reported as any time during pregnancy	6	20.69
Not reported	17	58.62
Alcohol use during pregnancy		
Yes	5	17.24
NR	24	82.76
Tobacco use during pregnancy		
Yes	7	24.14
NR	22	75.86

<sup>‡</sup> Includes individuals taking AEDs for psychiatric disorders, migraine, and

neuropathic/neurological pain

<sup>§</sup> Consisted of women with Epilepsy who did not take AEDs during pregnancy

# 667 Table 2 Outcome measures and diagnostic scales used in analysis

Cognitive developmental delay	
Bayley Scales of Infant Development (children ≤42 mo.)	Score $\geq$ 2 standard deviations below the mean
Griffiths Scale of Infant Development (children >42 mo.)	Score $\geq$ 2 standard deviations below the mean
McCarthy Scales of Children's Abilities (children >30 mo.)	Score $\geq$ 1 standard deviations below the mean
Stanford-Binet IV Intelligence scale for children	Intelligence quotient <u>&lt;</u> 80
Touwen's Test	Above average number of items rated abnormal in one or more domains
Wechsler Scale of Preschool and Primary Intelligence	Intelligence quotient <90
Wechsler Intelligence Scale for Children - III	Intelligence quotient <80; verbal intelligence quotient <69
Developmental Assessment	Confirmed diagnosis by developmental pediatrician or pediatric neurologist
Autism/dyspraxia	
Developmental Assessment	Diagnosis confirmed by developmental specialists at 2 years of age
Medical Records	Confirmed diagnosis recorded in medical history; registry records (ICD-10 codes F84.0, F84.1, F84.5, F84.8, and F84.9)
Modified checklist for autism in toddlers	Scored positive for $\geq 2$ out of 6 critical items OR $\geq 3$ any items of the total scale
Psychomotor developmental delay	
Ages and Stages Questionnaire	>3 standard deviations from the test mean
Bayley Scales of Infant Development – Psychomotor Index	>2 standard deviations below the standardized mean for the test
Touwen's Test	Demonstrated dysfunctions in fine motor balance, fine motor functions, and coordination of extremities
Schedule of Growing Skills II	Scored as 'delayed' in $\geq 1$ domain of the test

3 4 5 6 7 8		Developmental Assessment	Infant scored >2 negative items (administered by general practitioner or pediatrician); diagnosis of neuromotor deficit confirmed by a trained nurse practitioner; infant failing to sit by 10 months or walk by 18 months
9 10		Health/Medical Records	Diagnosis of psychomotor delay recorded in medical records
11		Language Delay	
12		Ages and Stages Questionnaire	>3 standard deviations from the test mean
13 14 15		Clinical Evaluation of Language Fundamentals – 4 <sup>th</sup> Edition	Score <70 in core language domain; score <84 overall
16		Learning Accomplishment Profile	Below average performance in expressive speech (adjusted for age)
17 18 19 20 21 22		Comprehensive Language Assessment (Peabody Picture Vocabulary Test; Receptive Expressive Emergent Language Scale; Expressive One Word Picture Vocabulary Test, or Sequenced Inventory of Communication Development)	Scores/assessment indicate a >6 moth delay in age appropriate language development
23		ADHD	
24		Attention Problems and Hyperactivity Scales	Score >1 standard deviations from the test mean
25 26		Child Behaviour Checklist	≥6 positive items on checklist
27		Diagnostic and Statistical Manual – IV	≥5 positive items on checklist
28 29		Medical Records	Confirmed diagnosis in hospital/medical records made by a pediatrician or child psychiatrist
30 31		Neonatal Seizure	
32 33		Medical records	Record of seizures during 1 <sup>st</sup> year; confirmation of neonatal seizure by electroencephalography or diagnosis
34		Social Impairment	
35 36		Developmental Assessment	Scores dichotomized into 'normal' or 'adverse' range based on pre-
37 38		(Ages and Stages Questionnaire [6 and 18 months]; Child Behaviour Checklist [36 months])	defined values used by scale, for scales without pre-defined values cut- off was set at a score >2 standard deviations outside the test mean
39	668		





\*29 publications reporting 30 included studies.

TITLE: Study flow diagram

Active Treatment vs Contro	ol*		OR (95%Crl) (95%Prl)	SUCRA (95% Crl)
Carbam+Levet	•	t	0.52 (0.00,16.53) (0.00,19.20)	0.88 (0.06,1.00)
Carbam+Pheno	·	+	0.52 (0.00,15.20) (0.00,17.13)	0.88 (0.12,1.00)
Lamot	+	+	0.93 (0.09,5.10) (0.08,6.34)	0.76 (0.29,1.00)
Pheno+Pheny	·•	•	1.32 (0.00,33.67) (0.00,38.91)	0.71 (0.06,1.00]
Pheno	+ +		1.36 (0.18,7.02) (0.14,8.95)	0.71 (0.24,0.94)
Gabap	<b>⊢</b>	+	1.46 (0.04,13.48) (0.04,16.87)	0.65 (0.12,1.00)
Carbam			2.07 (0.82,5.48) (0.51,8.46)	0.53 (0.29,0.76)
Primid	+	+	2.15 (0.31,12.26) (0.24,16.25)	0.53 (0.12,0.94)
Pheny	-+	<b>♦</b> —- <b> -</b>	2.55 (0.72,8.55) (0.47,12.15)	0.47 (0.18,0.76)
Topir	-	<b>♦</b> +	3.14 (0.45,16.53) (0.35,20.69)	0.41 (0.06,0.88)
Levet	-+	<b>◆</b>	3.42 (0.65,16.40) (0.46,22.73)	0.41 (0.06,0.82)
Pheny+Valpro	·		3.99 (0.01,116.60) (0.01,136.30)	0.35 (0.00,1.00]
Carbam+Pheno+Pheny	· · · · ·	• •	4.83 (0.02,158.10) (0.02,187.50)	0.29 (0.00,1.00)
Ethos+Pheny	,	• •	6.24 (0.02,215.80) (0.02,243.80)	0.24 (0.00,1.00]
Valpro	-	• • •	7.40 (3.00,18.46) (1.81,27.63)	0.18 (0.06,0.41)
Carbam+Pheny		• •	10.88 (0.54,137.00) (0.43,159.20)	0.12 (0.00,0.82)
Carbam+Pheno+Valpro	+	•	44.96 (0.94,359.10) (0.80,421.70)	0.06 (0.00,0.71)
4.5e-05	0.007 1	148.4		

\* SUCRA (95%CrI): 0.76 (0.47,0.94)

# TITLE: Forest plots for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcome





\* SUCRA (95%CrI): 0.91 (0.55,1.00)

# TITLE: Forest plots for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcome

c. Psychomotor developmental delay			
Active Treatment vs Control*	OR (95%Crl) (95%Prl)	SUCRA (95% CrI)	
Levet + + +	0.27 (0.00,4.26) (0.00,4.65)	0.94 (0.29,1.00)	
Pheno+Pheny 🔶	→ 0.65 (0.00,13.32) (0.00,14.74)	0.82 (0.12,1.00)	
Carbam+Pheny 🛏 🔶		0.76 (0.06,1.00)	
Pheno +++	0.96 (0.39,2.29) (0.32,3.02)	0.76 (0.47,0.94)	
Carbam+Pheno + 🔶	+ 1.55 (0.31,6.92) (0.26,7.99)	0.59 (0.18,0.94)	
Carbam - + + +	1.68 (0.85,3.41) (0.59,4.61)	0.59 (0.35,0.82)	
Lamot ++++	1.86 (0.72,4.76) (0.57,6.07)	0.53 (0.24,0.82)	
Clonaz + +	→ 2.23 (0.47,9.62) (0.41,11.18)	0.47 (0.12,0.88)	
Pheny+Valpro 🛏 🔶	2.24 (0.01,46.45) (0.01,49.92)	0.47 (0.00,1.00)	
Carbam+Pheno+Pheny 🔶 🔶	→ 2.75 (0.01,63.24) (0.01,70.65)	0.41 (0.00,1.00)	
Clobaz	2.81 (0.21,22.20) (0.19,26.50)	0.41 (0.00,0.94)	
Pheny	+ 2.84 (0.97,7.93) (0.77,9.92)	0.41 (0.12,0.71)	
Ethos+Pheny 🔶	3.15 (0.00,84.86) (0.00,92.48)	0.35 (0.00,1.00)	
Topir + 🔶		0.29 (0.00,0.88))	
Valpro +•	+ 4.16 (2.04,8.75) (1.52,12.05)	0.24 (0.06,0.53)	
Gabap		0.12 (0.00,0.76)	
Carbam+Pheno+Valpro +		0.06 (0.00,0.59)	
4.5e-05 0.007 1	148.4		
Active treatment safer	Control safer		

\* SUCRA (95%CrI): 0.76 (0.53,0.94)

# TITLE: Forest plots for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcome



\* SUCRA (95%CrI): 0.75 (0.50,1.00)

# TITLE: Forest plots for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcome

0.67 (0.17,1.00)

0.67 (0.00,1.00)

0.50 (0.00,1.00)

0.33 (0.00,0.67)

0.17 (0.00,0.67)

0.50 (0.00,1.00)





TITLE: Network diagrams for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes.

CAPTION: Each treatment node is weighted according to the number of patients that have received the particular treatment, and each edge is weighted according to the number of studies comparing the treatments it connects.

Abbreviations: carbam - carbamazepine, clobaz - clobazam, clonaz - clonazepam, ethos - ethosuximide, gabap - gabapentin, lamot - lamotrigine, levet - levetiracetam, oxcar - oxcarbazepine, pheno phenobarbital, pheny - phenytoin, primid - primidone, topir - topiramate, valpro - valproate, vigab – vigabatrin

# PROTOCOL



**Open Access** 

# Comparative safety of anti-epileptic drugs among infants and children exposed *in utero* or during breastfeeding: protocol for a systematic review and network meta-analysis

Andrea C Tricco<sup>1</sup>, Elise Cogo<sup>1</sup>, Veroniki A Angeliki<sup>1</sup>, Charlene Soobiah<sup>1,2</sup>, Brian Hutton<sup>3</sup>, Brenda R Hemmelgarn<sup>4</sup>, David Moher<sup>3</sup>, Yaron Finkelstein<sup>5,6,7</sup> and Sharon E Straus<sup>1,8\*</sup>

### Abstract

**Background:** Epilepsy affects about 1% of the general population. Anti-epileptic drugs (AEDs) prevent or terminate seizures in individuals with epilepsy. Pregnant women with epilepsy may continue taking AEDs. Many of these agents cross the placenta and increase the risk of major congenital malformations, early cognitive and developmental delays, and infant mortality. We aim to evaluate the comparative safety of AEDs approved for chronic use in Canada when administered to pregnant and breastfeeding women and the effects on their infants and children through a systematic review and network meta-analysis.

**Methods:** Studies examining the effects of AEDs administered to pregnant and breastfeeding women regardless of indication (e.g., epilepsy, migraine, pain, psychiatric disorders) on their infants and children will be included. We will include randomized clinical trials (RCTs), quasi-RCTs, non-RCTs, controlled before-after, interrupted time series, cohort, registry, and case-control studies. The main literature search will be executed in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. We will seek unpublished literature through searches of trial protocol registries and conference abstracts. The literature search results screening, data abstraction, and risk of bias appraisal will be performed by two individuals, independently. Conflicts will be resolved through discussion. The risk of bias of experimental and quasi-experimental studies will be appraised using the Cochrane Effective Practice and Organization of Care Risk-of-Bias tool, methodological quality of observational studies will be appraised using the Newcastle-Ottawa Scale, and quality of reporting of safety outcomes will be conducted using the McMaster Quality Assessment Scale of Harms (McHarm) tool. If feasible and appropriate, we will conduct random effects meta-analysis. Network meta-analysis will be considered for outcomes that fulfill network meta-analysis assumptions.

The primary outcome is major congenital malformations (overall and by specific types), while secondary outcomes include fetal loss/miscarriage, minor congenital malformations (overall and by specific types), cognitive development, psychomotor development, small for gestational age, preterm delivery, and neonatal seizures. (Continued on next page)

Full list of author information is available at the end of the article



© 2014 Tricco et al.; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

<sup>\*</sup> Correspondence: sharon.straus@utoronto.ca

<sup>&</sup>lt;sup>1</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria Street,

East Building, Toronto, Ontario M5B 1 T8, Canada

<sup>&</sup>lt;sup>8</sup>Department of Geriatric Medicine, University of Toronto, 172 St. George Street,

Toronto, Ontario M5R 0A3, Canada

Page 44 of 90

### (Continued from previous page)

**Discussion:** Our systematic review will address safety concerns regarding the use of AEDs during pregnancy and breastfeeding. Our results will be useful to healthcare providers, policy-makers, and women of childbearing age who are taking anti-epileptic medications.

### Systematic review registration: PROSPERO CRD42014008925.

**Keywords:** Anti-epileptic drug, Breastfeeding, Comparative safety, Congenital malformation, Epilepsy, Fetus, Infant, Network meta-analysis, Pregnancy, Systematic review

### Background

Epilepsy is the most common chronic neurological condition, affecting 0.6 to 1% of the population [1,2]. Individuals with uncontrolled epilepsy experience recurrent seizures, which can have psychosocial and physical consequences, including a compromised life expectancy [3,4]. The goal of anti-epileptic treatment is to improve quality of life and health outcomes by reducing the frequency of seizures [4].

Anti-epileptic medications decrease seizures by reducing excitation and enhancing inhibition of neurons [5-7]. Many of these medications target different channels, including calcium, sodium, and glutamate, and are broadly classified as first generation agents (e.g., phenobarbitone, phenytoin, carbamazepine, sodium valproate, ethosuximide) and second generation agents (e.g., lamotrigine, levetiracetam, topiramate, gabapentin, vigabatrin, oxcarbazepine, clobazam, clonazepam, zonisamide, lacosamide, rufinamide, primidone) [8]. Due to the broad and varied mechanisms of action, the indications for some of these medications also include pain syndromes, psychiatric disorders, and migraine headaches [8].

Many clinical practice guidelines recommend that women of childbearing age continue to take their anti-epileptic medications; however, medications with lower risk of teratogenic events are advised [9,10] since anti-epileptic drugs (AEDs) cross the placenta or transfer through breast milk, posing risks to the fetus and infant [9,11,12].

Some AEDs have been associated with increased risk of harm to the fetus and infants. For example, exposure to valproate has led to increased risk of major congenital malformations [10], cognitive delay, and minor congenital abnormalities [13-16]. Phenobarbital has been associated with minor congenital abnormalities and developmental delay [17,18]. Carbamazepine and lamotrigine have been associated with minor congenital abnormalities [19-22]. However, other than studies of the use of valproate, many studies have produced inconsistent findings regarding harm to the fetus and infant with use of other agents [23]. As such, our objective is to evaluate the comparative safety of AEDs for infants and children who were exposed *in utero* or during breastfeeding through a systematic review and network meta-analysis.

## Methods/Design

### Protocol

A systematic review protocol was developed and registered with the PROSPERO database (CRD42014008925, available at: http://www.crd.york.ac.uk/PROSPERO/display\_record. asp?ID=CRD42014008925). It was revised with feedback from the decision-makers who posed the query within Health Canada, healthcare practitioners, content experts, and research methodologists. The reporting of our systematic review protocol was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols [24].

### Eligibility criteria

We will include studies examining the effects of AEDs on infants and children who were exposed in utero or during breastfeeding. We will include experimental studies (randomized clinical trials [RCTs], quasi-RCTs, non-RCTs), guasi-experimental studies (controlled before and after studies, interrupted time series), and observational studies (cohort, case-control, registry studies) of pregnant women at any stage of pregnancy and breastfeeding women and their infants/children. The rationale for including other study designs in addition to RCTs is that there are ethical issues in conducting RCTs of AEDs in pregnancy, so RCT evidence might not exist for some or all of these drugs. Given that our review includes rare outcomes, including observational evidence is crucial. In contrast to efficacy evaluation, safety assessment usually requires very large sample sizes to be able to detect adverse events. Therefore, while RCTs have lower risk of bias, they usually do not have the statistical power needed to adequately evaluate uncommon/rare safety outcomes due to Type II (i.e., false negative) error [25]. Given that our review includes rare outcomes, including observational evidence is crucial [26]. Additionally, observational studies can often provide more generalizable evidence due to the strict participant inclusion criteria in most RCTs [27]. Real-world safety evidence that has external validity is important for the assessment of the possible risks of AEDs in pregnant and breastfeeding women.

The diagnosis of neurodevelopmental delay related to *in utero* exposure is made before adolescence, and

57

58

59

hence, we will limit inclusion to children up to 12 years of age. AEDs that are approved for chronic use in Canada will be included. Drugs that are only used acutely or those that are not currently approved for use in Canada will be excluded, as the focus of this review is on the Canadian setting [28-32]. However, most of the medications we will examine are available in other countries as well. The relevant 16 medications and their synonyms are listed in Additional file 1, and the excluded drugs are listed in Additional file 2. Studies of all combinations and doses of these medications are eligible for inclusion. Since we are only interested in exposures that occur in *utero* or during breastfeeding, studies examining AEDs administered directly to infants or children will be excluded. All indications for AEDs will be included such as epilepsy, migraine, pain, and psychiatric disorders.

In order to be included, studies must compare an antiepileptic medication against another included anti-epileptic medication, placebo, a 'no intervention' control group, or combinations of two or more anti-epileptic medications. Only studies providing results for our outcomes of interest will be included. Our primary outcome is major congenital malformations (overall and by specific type, such as craniofacial defects and neural tube defects). Secondary outcomes include minor congenital malformations (overall and by specific type, such as epicanthal folds and microstomia), cognition (e.g., global cognitive functioning and specific cognitive domains such as attention), psychomotor development (e.g., autism, dyspraxia), small for gestational age, preterm delivery, neonatal seizures, and fetal loss/miscarriage. No other limitations will be imposed on the eligibility criteria, including published/unpublished material, language of dissemination, duration of follow-up, or year of publication. The draft eligibility criteria can be found in Additional file 3.

### Information sources and literature search

Our main literature search will be executed in the MED-LINE database. The search terms were drafted by an experienced librarian and can be found in Additional file 4. The search was peer reviewed by another librarian using the Peer Review of Electronic Search Strategies checklist [33].

In addition to MEDLINE, we will also search the EMBASE and the Cochrane Central Register of Controlled Trials databases. We will follow the MEDLINE search strategy for these databases, and the search terms will be adjusted accordingly. The electronic database search will be supplemented by searching for unpublished literature [34]. This will be accomplished through exploring conference abstracts, clinical trial registries, and contacting manufacturers of AEDs. We will also scan the reference lists of included studies and previous reviews in the area [23,35,36].

### Study selection process

**BMJ Open** 

The eligibility criteria screening form will be pilot-tested by the team and is presented in Additional file 3. We will calculate inter-rater reliability from the pilot-test and screening will only commence after high agreement (e.g., kappa statistic  $\geq$ 60%) is observed [37]. Subsequently, two reviewers will screen each title/abstract and potentially relevant full-text articles from the literature search results, independently. Conflicts will be resolved through discussion. All screening will occur using our online screening software (synthesi.SR) [38].

### Data items and data collection process

We will abstract data on the PICOS elements [39], including patient characteristics (e.g., age of the mother and infant/child, indication for anti-epileptic treatment, co-morbidities, concomitant medications), intervention details (e.g., type of anti-epileptic treatment, dose, route of administration, duration of treatment, timing [trimester] of treatment during pregnancy), comparator details (e.g., comparator agent, dose, route of administration), outcome results (e.g., major congenital abnormality, minor congenital abnormality, cognitive function, psychomotor development) at the longest duration of follow-up, and study characteristics (e.g., study design, country of conduct, year of conduct, sample size, setting). These characteristics will be abstracted using a data abstraction form created in Excel with an accompanying "cheat sheet" that will guide the reviewers with this process. The data abstraction form and cheat sheet will be pilot-tested and data abstraction will only commence when high agreement (e.g., kappa statistic ≥60%) [37] is observed. Each included study will be abstracted by two team members, independently, who will resolve disagreements through discussion.

### Methodological quality/risk of bias appraisal

We will use various tools to assess the methodological quality/risk of bias of each of the studies that fulfill our eligibility criteria. This will be conducted by two reviewers, independently, and conflicts will be resolved through discussion. First, we will appraise the risk of bias of experimental and quasi-experimental studies using the Cochrane Effective Practice and Organization of Care Risk-of-Bias tool [40]. Second, we will assess the methodological quality of observational studies using the Newcastle-Ottawa Scale [41]. Third, the quality of reporting of harms will be appraised using the McMaster Quality Assessment Scale of Harms (McHarm) tool [42].

### Synthesis of included studies

A narrative summary of study results will be presented along with evidence summary tables. When sufficient data are available, we will conduct random effects metaanalysis to calculate pooled odds ratios for dichotomous

data and pooled mean differences for continuous data

[43,44]. Direct (pairwise) meta-analysis will be per-

formed with RCTs alone in order to examine whether

the data are consistent between direct and indirect evi-

dence. If the large majority of included studies are obser-

vational, we will also conduct additional meta-analyses

including observational studies alone. Analyses will be

stratified by treatment indication (e.g., epilepsy, pain,

etc.) to reduce clinical heterogeneity between different

study populations whenever possible; for example, epilepsy itself in pregnant women is related to an increased

baseline risk of certain neonatal adverse outcomes. Stat-

istical, clinical, and methodological heterogeneity will be

examined prior to conducting the meta-analysis. Funnel

plots will be drawn for outcomes including at least 10

studies to explore asymmetry that might be explained by

clinical, statistical, and methodological heterogeneity.

The proportion of statistical heterogeneity will be exam-

ined using the  $I^2$  measure [45] and the magnitude of

statistical heterogeneity will be calculated using the re-

stricted maximum likelihood [46]. Meta-regression will

be conducted for clinically relevant subgroups or when

extensive statistical heterogeneity is observed (e.g.,  $I^2 \ge$ 

75%) [47]. This will allow the examination of the impact

of important factors on our results, such as maternal

age, dose, duration and timing (e.g., trimester) of anti-

epileptic treatment, co-morbidities, concomitant medi-

cations, risk of bias results, and sample size (due to Type

II statistical power errors with rare adverse events). To

ensure the meta-regression analysis is intuitive, the num-

i) transitivity (i.e., comparable distribution of effect modifiers across comparisons), which will be examined using boxplots or percentages to visually inspect potential effect modifiers of treatment effect [54]; ii) consistency between direct and indirect data, which will be examined locally (i.e., in certain paths of the network) using the loop-specific method [55,56] and the node-splitting method [57], and globally (i.e., evaluating the network as a whole), using the design-by-treatment interaction model [58]; and iii) we will quantify the amount of variability attributed to heterogeneity and inconsistency rather than sampling error, by calculating the  $I^2$  [59]. We will estimate the amount of heterogeneity using the restricted maximum likelihood method and assuming common within-network heterogeneity. We will compare the magnitude of heterogeneity between consistency and inconsistency models, as well as between meta-regression and network meta-analysis models to determine how much heterogeneity will be explained by inconsistency or the explanatory variable, respectively. We will first use the design-by-treatment model for the evaluation of inconsistency in a network as a whole and then, if inconsistency is detected, we will employ the loop-specific and node-splitting methods to identify which piece of evidence is responsible for inconsistency. As mentioned above, analyses will be stratified by treatment indication when clinically appropriate. Important heterogeneity and inconsistency will be explored using network metaregression using the same methods as described above,

Prior to conducting the network meta-analysis, we will hold a team meeting to finalize which treatment nodes will be included in the analysis since we are unclear about the indications, dosages, patient populations, and outcomes reported in all of the studies. We will discuss issues, including conducting a class versus independent drug analysis, inclusion of drug routes of administration and dosages, as well as timing of drug administration. These decisions will be examined through a sensitivity analysis in which we will classify treatment nodes using a different classification to see how stable our results are. The network meta-analysis results will be presented as summary treatment effects for each pair of treatments. Network meta-analysis will be conducted in Stata with the *mymeta* routine [60].

A sequential approach will be used for the network meta-analysis. We will first restrict our analysis to RCTs, which will be the primary analysis of interest. We will then include data from quasi-experimental studies, and finally, data from observational studies. This will provide an understanding of the contribution of each type of study design to our summary estimates, providing us with information on how these agents work above and beyond clinical trials.

ber of covariates examined will be less than 10% of the number of studies included in the meta-analysis for the particular outcome. We anticipate that many of these outcomes will be rare. To deal with studies reporting zero events in one treatment arm, 0.5 will be added to the numerator and 1 will be added to the denominator. We will exclude studies reporting zero events in all treatment arms for a particular outcome [48,49]. We also anticipate that we will encounter missing data in the included studies. We will contact the study authors for this data and if we are unable to receive the data, we will impute missing data (e.g., measures of variance) using established methods [50]. To ensure that our imputations do not bias our results, we will conduct a sensitivity analysis [51]. The meta-analysis and meta-regression will be analyzed in R using the *metafor* command [52]. A random-effects network meta-analysis will be con-

A random-effects network meta-analysis will be conducted to make inferences regarding the comparative safety of the various AEDs [15], as well as rank their safety using rankograms and the surface under the cumulative ranking curve [53]. We will ensure the following factors are present prior to conducting network meta-analysis: as necessary.

5

6

7

8

9

10

11

12

13 14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

### Discussion

Epilepsy is the most common chronic neurological condition, affecting 0.6 to 1% of the population [1,2]. Given that approximately a third of patients receiving AEDs are of reproductive age and almost half of pregnancies are unplanned [61], the fetus may be exposed to these in the first trimester of pregnancy, including during the critical stage of embryogenesis [62].

The comparative safety of these agents is currently unknown and our results will be important for policymakers, healthcare providers, and women of childbearing age. To ensure our results have wide dissemination and uptake, we will publish our results in open access journals, present our findings at scientific conferences, conduct dissemination meetings with key stakeholders (including policy-makers and healthcare providers), and produce policy briefs for Health Canada, the organization that posed this query.

### Additional files

Additional file 1: List of relevant medications. Additional file 2: Excluded drugs. Additional file 3: Draft eligibility criteria. Additional file 4: MEDLINE literature search.

### Abbreviations

AEDs: Anti-epileptic drugs; RCTs: Randomized clinical trials.

#### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

ACT conceived and designed the study, helped obtain funding for the study, and helped write the draft protocol. EC registered the protocol with the PROSPERO database and edited the draft protocol. AV helped write the draft protocol. CS edited the draft protocol. BH, BRH, DM, and YF provided input into the design, helped obtain funding for the study, and edited the draft protocol. SES conceived the study, designed the study, obtained the funding, and helped write the draft protocol. All authors read and approved the final protocol.

#### Acknowledgements

This systematic review was funded by the Canadian Institutes of Health Research/Drug Safety and Effectiveness Network (CIHR/DSEN). ACT and BH are funded by a CIHR/DSEN New Investigator Award in Knowledge Synthesis. BRH receives funding from the Alberta Heritage Foundation for Medical Research. DM is funded by a University of Ottawa Research Chair. SES is funded by a Tier 1 Canada Research Chair in Knowledge Translation. We thank Laure Perrier for conducting the literature searches and Becky Skidmore for peer reviewing the MEDLINE search strategy. We also thank Dr. Joseph Beyene for providing feedback on our original proposal and Wing Hui and Judy Tran for formatting the paper.

### Author details

<sup>1</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria Street, East Building, Toronto, Ontario M5B 1 T8, Canada. <sup>2</sup>Institute of Health Policy Management and Evaluation, University of Toronto, Health Sciences Building, 155 College Street, Suite 425, Toronto, Ontario M5T 3 M6, Canada. <sup>3</sup>Clinical Epidemiology Program, Centre for Practice-Changing Research, Ottawa Hospital Research Institute, The Ottawa Hospital – General Campus and University of Ottawa, 501 Smyth Road, Box 711, Ottawa, Ontario K1H 8 L6, Canada. <sup>4</sup>Departments of Medicine and Community Health Sciences, University of Calgary, TRW Building, 3rd Floor, 3280 Hospital Drive NW, Calgary, Alberta T2N 4Z6, Canada. <sup>5</sup>The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. <sup>6</sup>Department of Pediatrics, University of Toronto, 172 St. George Street, Toronto, Ontario M5R 0A3, Canada. <sup>7</sup>Department of Pharmacology and Toxicology, University of Toronto, Medical Sciences Building, 1 King's College Circle, Room 4207, Toronto, Ontario M5S 1A8, Canada. <sup>8</sup>Department of Geriatric Medicine, University of Toronto, 172 St. George Street, Toronto, Ontario M5R 0A3, Canada.

### Received: 9 April 2014 Accepted: 17 June 2014 Published: 25 June 2014

#### References

- Hauser WA, Hesdorffer D: Epilepsy, Frequency, Causes and Consequences. New York: Demos Publications; 1990.
- Wiebe S, Bellhouse DR, Fallahay C, Eliasziw M: Burden of epilepsy: the Ontario Health Survey. Can J Neurol Sci 1999, 26(4):263–270.
- Sperling MR: The consequences of uncontrolled epilepsy. CNS Spectr 2004, 9(2):98–101. 106–109.
- 4. Jones MW: Consequences of epilepsy: why do we treat seizures? Can J Neurol Sci 1998, 25(4):S24–S26.
- Dickenson AH, Ghandehari J: Anti-convulsants and anti-depressants. Handb Exp Pharmacol 2007, 177:145–177.
- Stefani A, Spadoni F, Bernardi G: Voltage-activated calcium channels: targets of antiepileptic drug therapy? Epilepsia 1997, 38(9):959–965.
- Snutch TP, Reiner PB: Ca<sup>2+</sup> channels: diversity of form and function. Curr Opin Neurobiol 1992, 2(3):247–253.
- Spina E, Perugi G: Antiepileptic drugs: indications other than epilepsy. Epileptic Disord 2004, 6(2):57–75.
- 9. Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, Hopp J, Ting TY, Hauser WA, Thurman D, Kaplan PW, Robinson JN, French JA, Wiebe S, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Shafer PO, Le Guen CL, American Academy of Neurology; American Epilepsy Society: Management issues for women with epilepsy–focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: report of the quality standards subcommittee and therapeutics and technology assessment subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009, 50(5):1247–1255.
- Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA, Wiebe S, Thurman D, Koppel BS, Kaplan PW, Robinson JN, Hopp J, Ting TY, Gidal B, Hovinga CA, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Hirtz D, Le Guen C, American Academy of Neurology; American Epilepsy Society: Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009, 50(5):1237–1246.
- Samren EB, van Duijn CM, Koch S, Hiilesmaa VK, Klepel H, Bardy AH, Mannagetta GB, Deichl AW, Gaily E, Granstrom ML, Meinardi H, Grobbee DE, Hofman A, Janz D, Lindhout D: Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 1997, 38(9):981–990.
- Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C: Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res* 2008, 81(1):1–13.
- Adab N, Jacoby A, Smith D, Chadwick D: Additional educational needs in children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2001, 70(1):15–21.
- Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, Coyle H, Fryer A, Gorry J, Gregg J, Mawer G, Nicolaides P, Pickering L, Tunnicliffe L, Chadwick DW: The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004, 75(11):1575–1583.
- Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M, Matila R, Kotila M, Nylund T, Bardy A, Kaaja E, Granstrom ML: Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology* 2004, 62(1):28–32.
- Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW, for the NEAD Study Group: Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 2009, 360(16):1597–1605.

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

- Holmes LB, Wyszynski DF, Lieberman E: The AED (antiepileptic drug) pregnancy registry: a 6-year experience. Arch Neurol 2004, 61(5):673–678.
- Reinisch JM, Sanders SA, Mortensen EL, Rubin DB: In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA 1995, 274(19):1518–1525.
- Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, Irwin B, McGivern RC, Morrison PJ, Craig J: Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2006, 77(2):193–198.
- Meador KJ, Baker GA, Finnell RH, Kalayjian LA, Liporace JD, Loring DW, Mawer G, Pennell PB, Smith JC, Wolff MC, NEAD Study Group: In utero antiepileptic drug exposure: fetal death and malformations. *Neurology* 2006, 67(3):407–412.
- Vajda FJ, Hitchcock A, Graham J, Solinas C, O'Brien TJ, Lander CM, Eadie MJ: Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur J Neurol* 2006, 13(6):645–654.
- Holmes LB, Baldwin EJ, Smith CR, Habecker E, Glassman L, Wong SL, Wyszynski DF: Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 2008, 70(22 Pt 2):2152–2158.
- Meador KJ, Penovich P, Baker GA, Pennell PB, Bromfield E, Pack A, Liporace JD, Sam M, Kalayjian LA, Thurman DJ, Moore E, Loring DW, NEAD Study Group: Antiepileptic drug use in women of childbearing age. *Epilepsy Behav* 2009, 15(3):339–343.
- 24. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L: Reporting Guidelines for Systematic Review Protocols. In 19th Cochrane Colloquium: 19–22 October 2011; Madrid, Spain.
- Ross CJ, Visscher H, Sistonen J, Brunham LR, Pussegoda K, Loo TT, Rieder MJ, Koren G, Carleton BC, Hayden MR, CPNDS Consortium: The Canadian Pharmacogenomics Network for Drug Safety: a model for safety pharmacology. *Thyroid* 2010, 20(7):681–687.
- Eypasch E, Lefering R, Kum CK, Troidl H: Probability of adverse events that have not yet occurred: a statistical reminder. *BMJ* 1995, 311(7005):619–620.
- 27. Atkins D: Creating and synthesizing evidence with decision makers in mind: integrating evidence from clinical trials and other study designs. *Med Care* 2007, **45**(10 Supl 2):S16–S22.
- Health Canada: Drug Product Database. http://www.hc-sc.gc.ca/dhp-mps/ prodpharma/databasdon/index-eng.php.
- 29. United States National Library of Medicine's ChemIDPlus Lite Database. http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp.
- 30. Canadian Pharmacists Association: E-CPS (Compendium of Pharmaceuticals and Specialties). http://www.e-therapeutics.ca/home.whatsnew.action.
- Epilepsy Canada: Anticonvulsant Medications. http://www.epilepsy.ca/en-CA/ Diagnosis-and-Treatment/Anticonvulsant-Medications.html.
- Epilepsy Ontario: Anticonvulsant/Anti-Seizure Medication from A to Z. http://epilepsyontario.org/anticonvulsantanti-seizure-medication-from-a-to-z/.
- Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C: An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol 2009, 62(9):944–952.
- Canadian Agency for Drugs and Technologies in Health: Grey Matters: A Practical Search Tool for Evidence-Based Medicine. http://www.cadth.ca/ resources/grey-matters.
- Adab N, Tudur SC, Vinten J, Williamson P, Winterbottom J: Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database Syst Rev 2004, 3:CD004848.
- Banach R, Boskovic R, Einarson T, Koren G: Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. Drug Saf 2010, 33(1):73–79.
- 37. Landis JR, Koch GG: The measurement of observer agreement for categorical data. *Biometrics* 1977, **33**(1):159–174.
- 38. Synthesi.SR. http://knowledgetranslation.ca/sysrev/login.php.
- Stone PW: Popping the (PICO) question in research and evidence-based practice. Appl Nurs Res 2002, 15(3):197–198.
- 40. Cochrane Effective Practice and Organization of Care Group Draft Risk of Bias Tool. http://epoc.cochrane.org/epoc-author-resources.
- The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. http://www.ohri.ca/programs/clinical\_epidemiology/ oxford.asp.

- Santaguida PL, Raina P, Ismaila A: The Development of the McHarm Quality Assessment Scale for Adverse Events. Hamilton, Ontario: McMaster University; 2008.
- Raudenbush SW: Analyzing Effect Sizes: Random Effects Models. In The Handbook of Research Synthesis and Meta-analysis. 2nd edition. Edited by Cooper H, Hedges LV, Valentine JC. New York: Russell Sage Foundation; 2009:295–315.
- 44. Viechtbauer W: Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat* 2005, **30**(3):261–293.
- 45. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002, **21**(11):1539–1558.
- 46. Viechtbauer W: Confidence intervals for the amount of heterogeneity in meta-analysis. *Stat Med* 2007, **26**(1):37–52.
- Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2009. http://www.cochrane.org/ handbook.
- Sweeting MJ, Sutton AJ, Lambert PC: What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004, 23(9):1351–1375.
- Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A: Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007, 26(1):53–77.
- 50. Littell JH, Corcoran J, Pillai V: Systematic Reviews and Meta-Analysis. New York: Oxford University Press; 2008.
- Carpenter J, Rucker G, Schwarzer G: Assessing the sensitivity of meta-analysis to selection bias: a multiple imputation approach. *Biometrics* 2011, 67(3):1066–1072.
- Conducting Meta-Analyses in R with the metafor Package. http://www.jstatsoft.org/v36/i03/.
- Salanti G, Ades AE, Ioannidis JP: Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011, 64(2):163–171.
- Salanti G: Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012, 3(2):80–97.
- Song F, Altman DG, Glenny AM, Deeks JJ: Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003, 326(7387):472.
- Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G: Evaluation of inconsistency in networks of interventions. Int J Epidemiol 2013, 42(1):332–345.
- 57. Dias S, Welton NJ, Caldwell DM, Ades AE: Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010, **29**(7–8):932–944.
- White IR, Barrett JK, Jackson D, Higgins JPT: Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012, 3(2):111–125.
- Jackson D, Barrett JK, Stephen R, White IR, Higgins JPT: A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. Stat Med 2014, In press.
- 60. White IR: Multivariate random-effects meta-regression: updates to mvmeta. *Stata J* 2011, 11(2):255–270.
- Centers for Disease Control and Prevention: Unintended Pregnancy Prevention. http://www.cdc.gov/reproductivehealth/unintendedpregnancy/.
- Yerby MS: Pregnancy, teratogenesis, and epilepsy. Neurol Clin 1994, 12(4):749–771.

### doi:10.1186/2046-4053-3-68

**Cite this article as:** Tricco *et al.*: Comparative safety of anti-epileptic drugs among infants and children exposed *in utero* or during breastfeeding: protocol for a systematic review and network meta-analysis. *Systematic Reviews* 2014 **3**:68.

1	
2	
3	
1	
4	
5	
6	
7	
8	
9	
10	
10	
11	
12	
13	
14	
15	
16	
17	
10	
10	
19	
20	
21	
22	
22	
23	
24	
25	
26	
27	
20	
20	
29	
30	
31	
32	
22	
33	
34	
35	
36	
37	
38	
20	
39	
40	
41	
42	
43	
11	
 / [	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
55	
90	
57	
58	
59	
60	
00	

PRISMA	NMA	Checklist
--------	-----	-----------

Section/Topic	Item #	Checklist Item <sup>*</sup>	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	1
ABSTRACT			
Structured summary	2	<ul> <li>Provide a structured summary including, as applicable:</li> <li>Background: main objectives</li> <li>Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis.</li> <li>Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed.</li> <li>Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</li> <li>Discussion/Conclusions: limitations; conclusions and implications of findings.</li> <li>Other: primary source of funding; systematic review registration number with registry name.</li> </ul>	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of</i> <i>why a network meta-analysis has been conducted</i> .	7
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	8

2
3
4
4
5
6
7
1
8
9
10
10
11
12
10
13
14
15
16
10
17
18
10
19
20
21
22
22
23
24
25
20
26
27
28
20
29
30
21
51
32
33
31
34
35
36
27
37
38
39
10
40
41
42
13
40
44
45
16
40
47
48
10
49
50
51
52
52
53
54
55
55
56
57
58
50
59
60

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly</i> <i>describe eligible treatments included in the</i> <i>treatment network, and note whether any have</i> <i>been clustered or merged into the same node (with</i> <i>justification).</i>	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Additional File 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Additional File 1
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	10-12
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9-10 (see also Appendix A)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	10-12

Planned methods of analysis	14	<ul> <li>Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to:</li> <li><i>Handling of multi-arm trials;</i></li> <li><i>Selection of variance structure;</i></li> <li><i>Selection of prior distributions in Bayesian analyses; and</i></li> <li><i>Assessment of model fit.</i></li> </ul>	10-12
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	10-11
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses <b>RESULTS</b> <sup>†</sup>	16	<ul> <li>Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul> <li>Sensitivity or subgroup analyses;</li> <li>Meta-regression analyses;</li> <li>Alternative formulations of the treatment network; and</li> <li>Use of alternative prior distributions for Bayesian analyses (if applicable).</li> </ul> </li> </ul>	11-12
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	13 and Figure 1
Presentation of network structure	<b>S</b> 3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	14-18
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, Appendices D and E
_			
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--		
3			
4			
5			
6			
7			
8			
9			
10			
11			
11			
12			
13			
14			
15			
16			
17			
10			
10			
19			
20			
21			
22			
23			
21			
24			
25			
26			
27			
28			
29			
30			
24			
31			
32			
~-			
33			
33 34			
33 34 35			
33 34 35 36			
33 34 35 36 27			
33 34 35 36 37			
33 34 35 36 37 38			
33 34 35 36 37 38 39			
33 34 35 36 37 38 39 40			
33 34 35 36 37 38 39 40 41			
33 34 35 36 37 38 39 40 41 42			
33 34 35 36 37 38 39 40 41 42 43			
33 34 35 36 37 38 39 40 41 42 43			
33 34 35 36 37 38 39 40 41 42 43 44			
33 34 35 36 37 38 39 40 41 42 43 44 45			
33 34 35 36 37 38 39 40 41 42 43 44 45 46			
33 34 35 36 37 38 39 40 41 42 43 44 45 46 47			
33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48			
33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49			
33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50			
33         34         35         36         37         38         39         40         41         42         43         44         45         46         47         48         50			
33         34           35         36           37         38           39         40           41         42           43         44           45         46           47         48           501         501			
33         34           35         36           37         38           30         40           42         43           44         45           46         47           48         99           50         51			
33         334         35         36         37         38         39         41         42         43         44         45         46         47         48         95         51         52         53			
$33 \\ 35 \\ 37 \\ 38 \\ 39 \\ 41 \\ 42 \\ 43 \\ 44 \\ 45 \\ 46 \\ 47 \\ 48 \\ 95 \\ 51 \\ 52 \\ 53 \\ 54 $			
33         334         35         36         37         38         39         41         42         43         445         46         47         48         50         52         53         55			
33         35         36           334         356         37         38         39         41         42         44         45         46         7         89         50         52         54         55         56         55         56			
$33 \\ 35 \\ 37 \\ 39 \\ 41 \\ 43 \\ 44 \\ 46 \\ 47 \\ 49 \\ 51 \\ 52 \\ 54 \\ 55 \\ 55 \\ 57 \\ 55 \\ 57 \\ 57 \\ 57$			
$33 \\ 35 \\ 37 \\ 39 \\ 41 \\ 42 \\ 44 \\ 45 \\ 46 \\ 47 \\ 49 \\ 51 \\ 52 \\ 54 \\ 55 \\ 57 \\ 55 \\ 57 \\ 20 \\ 57 \\ 57 \\ 57 \\ 57 \\ 57 \\ 57 \\ 57 \\ 5$			
$33 \\ 35 \\ 37 \\ 39 \\ 41 \\ 42 \\ 43 \\ 44 \\ 46 \\ 47 \\ 49 \\ 51 \\ 52 \\ 55 \\ 55 \\ 55 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 50$			
$33 \\ 35 \\ 37 \\ 39 \\ 41 \\ 42 \\ 44 \\ 45 \\ 46 \\ 47 \\ 49 \\ 51 \\ 52 \\ 53 \\ 55 \\ 57 \\ 59 \\ 59 \\ 51 \\ 51 \\ 51 \\ 51 \\ 51 \\ 51$			

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Appendix F
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches</i> <i>may be needed to deal with information from</i> <i>larger networks</i> .	N/A (data can be provided by the corresponding author)
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger</i> <i>networks, authors may focus on comparisons</i> <i>versus a particular comparator (e.g. placebo or</i> <i>standard care), with full findings presented in an</i> <i>appendix. League tables and forest plots may be</i> <i>considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	15-18, Figure 3, Appendices H, I, J
Exploration for inconsistency	<b>S</b> 5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	14 (see also Appendix H)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	14 (see also Appendix G)
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied</i> , <i>alternative choice of prior distributions for</i> <i>Bayesian analyses</i> , and so forth).	Appendix K
Summary of	24	Summarize the main findings, including the	19-21
evidence		strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the</i> <i>assumptions, such as transitivity and consistency.</i> <i>Comment on any concerns regarding network</i> <i>geometry (e.g., avoidance of certain comparisons).</i>	21-23

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	26-27

**Abbreviations:** PICOS - population, intervention, comparators, outcomes, study design \* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

<sup>†</sup> Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.



### **Supplementary Online Content**

Appendix A. Newcastle-Ottawa Scale scoring guide	2
Appendix B. List of included studies	11
Appendix C. Key excluded studies	14
Appendix D. Table of Individual Study characteristics	16
Appendix E. Table of Patient characteristics	21
Appendix F. Methodological quality of observational studies – Newcastle Ottawa Scale results	23
Appendix G. Comparison-adjusted funnel plots <sup>*</sup>	25
Appendix H. Statistically significant network meta-analysis results along with meta-analysis results, transitivity, and inconsistency assessments	26
Appendix I. Rank-heat plot of cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes*	30
Appendix J. Number of studies and treatments per outcome	32
Appendix K. Sensitivity and network meta-regression analyses - Anti-epileptic drugs compared	d
with Control	33



<sup>1</sup> For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

#### Appendix A. Newcastle-Ottawa Scale scoring guide

#### **COHORT Studies**

Excel Column	NOS* Answer Options**	NOS Coding Manual*
RefID	Enter the report's RefID.	
DA	Enter your initials.	
First author	Enter the first author's last name.	
Year of publication	Enter the year of the publication.	
SELECTION:	-	
1) Representative-	a) truly representative of the	Item is assessing the representativeness of exposed individuals in the
ness of the exposed	average pregnant woman	community, not the representativeness of the sample of women from
cohort	taking AEDs in the	some general population.
	community	
	b) somewhat representative of the average pregnant woman taking AEDs in the	For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (a.g. members of a health maintenance organisation (HMO) will
	<ul><li>c) selected group of users e.g., nurses, volunteers</li></ul>	be a representative sample of estrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated,
	d) no description of the derivation of the cohort	these excluded groups are not the predominant users of estrogen).
		Note:
		Truly representative (A) is a population-based cohort at the provincial or
		national levels (e.g., a sample from 2 cities is not enough). We need very
		'broad' sample of the population.
		Somewhat representative (D) includes minute clinics, how it is how it as
		community-based.
2) Selection of the	a) drawn from the same	Note:
non-exposed cohort	community as the exposed	In our review of mostly multi-arm studies, this question pertains to the

1	
2	
2	
3	
4	
5	
6	
7	
Q	
0	
9	
10	
11	
12	
13	
14	
15	
10	
10	
17	
18	
19	
20	
21	
2 I 22	
22	
23	
24	
25	
26	
27	
28	
20	
29	
30	
31	
32	
33	
31	
25	
30	
36	
37	
38	
39	
40	
/1	
41	
42	
43	
44	
45	
46	
/7	
41	
48	
10	

	<ul> <li>cohort</li> <li>b) drawn from a different source</li> <li>c) no description of the derivation of the non-exposed cohort</li> </ul>	study's comparator group(s) – including "active" controls (for example, a less teratogenic AED). Therefore, this will often be 'A' for our studies.
3) Ascertainment of exposure	<ul> <li>a) secure record (e.g., surgical records)</li> <li>b) structured interview</li> <li>c) written self-report</li> <li>d) no description</li> </ul>	Note: Option 'A' includes patient hospital records, prescription drug database, or hospital/clinic visits (e.g., patient is asked about "current" AED use during a visit with their doctor).Option 'B' includes a hospital/clinic visit, but the patients are asked to remember their AED use during pregnancy (e.g., retrospectively ascertained exposure).If a study used both medical records and interviews for everyone, select 'A'.
4) Demonstration that outcome of interest was not present at start of study	a) yes b) no	In the case of mortality studies, outcome of interest is still the presence of a disease/incident, rather than death. That is to say that a statement of 'no history of disease or incident' earns a star (i.e. option 'A'). <u>Note:</u> Since our review is on pregnant women, this question is 'A' for all. <b>Please email us if a study involves breastfeeding women.</b>
COMPARABILITY	:	
1) Comparability of cohorts on the basis of the design or analysis	<ul> <li>a) answer is BOTH B &amp; C (i.e. study controls for age and one other important factor)</li> <li>b) study controls for age of the women</li> <li>c) study controls for any other important factor</li> <li>d) study does not control for any</li> </ul>	Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

important factor or it is not described	There may be multiple ratings for this item for different categories of exposure (e.g., ever vs. never, current vs. previous or never). [A maximum of 2 stars can be allotted in this category].
	Note: The study should have initially matched the groups or presented adjuster odds ratios, AND in addition, since in our review we are analyzing each AED arm separately (instead of the whole exposed cohort), the study must also report the factor of interest <b>for 'each AED arm'</b> (or state that <b>'each AED arm'</b> is matched).
09	Thus, there are 2 parts to this question:
	1) The study should have matched/adjusted for age at whatever level of groups they were focused on (even if they aren't our abstracted AED arms); AND
	2) Then the study should also have reported the age for each AED ar
	If they haven't done both of these 2 things, it's a 'D' here (unless they happen to combine these by reporting adjusted ORs for each of our AEI arms).
	For our review, this generally pertains to <b>the comparability of the MOTHERS</b> .
	The exception here is in studies of cognitive/psychomotor development disorders in children - when age of the children should be comparable.
	The "other important factors" here are any one of these.
	<ul> <li>history of congenital malformations (CMs), fetal losses, preterm deliveries or small babies.</li> </ul>
	• family history of genetic problems or CMs.

		<ul> <li>alcohol use.</li> <li>nutritional deficiencies (e.g., lack of folic acid).</li> <li><u>Example:</u> <ul> <li>Option 'B' indicates that the study initially matched groups based on the women's age (or reported adjusted ORs) AND they report the mean women's age for EACH of our arms (e.g., for Tx1, Tx2, etc.).</li> </ul> </li> </ul>
OUTCOME: 1) Assessment of	a) independent OR blind	For some outcomes (e.g. fractured hip) reference to the medical record is
1) Assessment of outcome	<ul> <li>a) Independent OK bind assessment</li> <li>b) record linkage</li> <li>c) self-report</li> <li>d) no description</li> </ul>	<ul> <li>For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.</li> <li>a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.)</li> <li>b) Record linkage (e.g. identified through ICD codes on database records)</li> <li>c) Self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)</li> <li>d) No description.</li> </ul> Note: Blind (A) is if they tell us that the outcome assessors were blinded to exposures; or if the outcome is objective. For our purposes, we will focus on the primary outcome of interest of our systematic review, which is <u>major malformations (an objective outcome)</u> . So most of ours will be A, unless the study is only on a secondary outcome (e.g., cognitive development) and is based on the mother's self-report of their child (e.g., not a clinical examination).
2) Was follow-up	a) yes	An acceptable length of time should be decided before quality assessment

long enough for outcomes to occur	b) no	begins (e.g. 5 yrs. for exposure to breast implants)
		Note:For this component, focus only on the outcomes that are reported in the results.For our purposes, we will focus on the primary outcome of interest of our systematic review, which is major malformations.
	0,00	<ul> <li>For studies focusing on 'birth' outcomes (i.e. malformations, preterm, fetal losses, born small), the answer is 'A' if they follow the groups until birth.</li> <li>For studies focusing on cognitive developmental disorders, an</li> </ul>
	6	<ul> <li>adequate follow-up period (i.e. child's age) is 4 years.</li> <li>For studies focusing on psychomotor delays, an adequate follow-up period is the earliest point of detection of the disorder.</li> <li>For studies focusing on neonatal seizures, an adequate follow-up period (i.e. infant's age) is 6 months.</li> </ul>
3) Adequacy of	a) complete follow up - all	This item assesses the follow-up of the exposed and non-exposed cohorts
follow up of	subjects accounted for	to ensure that losses are not related to either the exposure or the outcome.
cohorts	<ul> <li>b) subjects lost to follow up unlikely to introduce bias - small number lost (see 'Note'), or description provided of those lost</li> <li>c) follow up rate is inadequate (see 'Note') and no description of those lost</li> </ul>	<ul> <li><u>Note:</u></li> <li><u>Especially check ones that start their total sample size (or figure diagram) with only the ones who had "complete" data (or only those who they had "successfully" recruited), as these are often a 'D' (since they don't report on the ones NOT followed up).</u></li> <li>For a prospective study. &gt;90% follow-up rate per year is adequate</li> </ul>
	d) no statement	<ul> <li>(e.g., 10% dropout or less for 1 year, 20% for 2 years of follow-up, etc.). This includes missing or incomplete data, etc.</li> <li>For a retrospective cohort study, ≥80% follow-up rate is adequate; including the ones that they could NOT recruit or who would NOT participate.</li> <li>For a survey/mail questionnaire, ≥75% response rate is adequate. (For</li> </ul>

	a survey, a dropout rate is congruent to a survey response rate).
--	-------------------------------------------------------------------

#### **CASE-CONTROL Studies**

Excel Column	NOS* Answer Options**	NOS Coding Manual*
RefID	Enter the report's RefID.	
DA	Enter your initials.	
First author	Enter the first author's last name.	
Year of publication	Enter the year of the publication.	
SELECTION:		
1) Is the case definition adequate?	<ul> <li>a) yes, with independent validation</li> <li>b) yes, e.g., record linkage or based on self-reports</li> <li>c) no description</li> </ul>	<ul> <li>a) Requires some independent validation (e.g. &gt;1 person/record/time/ process to extract information, or reference to primary record source such as x-rays or medical/hospital records)</li> <li>b) Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record</li> <li>c) No description</li> </ul> Note: This question is assessing the group of infants that have the outcome of interest (a.g., CMs), i.e. the "cases" in a case control study design.
2) Representative- ness of the cases	<ul> <li>a) consecutive or obviously representative series of cases</li> <li>b) potential for selection biases, or not stated</li> </ul>	<ul> <li>a) All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample)</li> <li>b) Not satisfying requirements in part (a), or not stated.</li> <li><u>Note:</u> Option 'A' is a population-based sample.</li> </ul>
3) Selection of controls	<ul><li>a) community controls</li><li>b) hospital controls</li><li>c) no description</li></ul>	This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

4) Definition of controls	<ul> <li>a) no history of disease (endpoint)</li> <li>b) no description of source</li> </ul>	<ul> <li>a) Community controls (i.e. same community as cases and would be cases if had outcome)</li> <li>b) Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population</li> <li>c) No description</li> <li><u>Note:</u> This question is assessing the group of infants that don't have the outcome (e.g., CMs) – i.e. the "controls" in a case-control study design.</li> <li><u>Community controls (A) includes a population-based sample.</u></li> <li>a) If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded.</li> <li>b) No mention of history of outcome</li> </ul>
		Note: Since our review is on fetal effects, this question is 'A' for all studies. Please email us if a study involves exposure during breastfeeding.
COMPARABILITY	:	
1) Comparability of cases and controls on the basis of the design or analysis	<ul> <li>a) answer is BOTH B &amp; C (i.e. study controls for age and one other important factor)</li> <li>b) study controls for age of the women</li> </ul>	Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.
or anary 515	<ul> <li>c) study controls for any other important factor</li> <li>d) study does not control for any important factor or it is not described</li> </ul>	Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never). [A maximum

		of 2 stars can be allotted in this category].
		<ul> <li><u>Note:</u> The study should have initially matched the groups, AND in addition, since in our review we are analyzing each AED arm separately (instead of the whole cases group), the study must also report the factor of interest for 'each AED arm' (or state that 'each AED arm' is matched).</li> <li>For our review, this generally pertains to the comparability of the MOTHERS of the cases and controls. The exception here is in studies of cognitive/psychomotor development disorders in children - when age of the children should be comparable.</li> <li>The "other important factors" here are any one of these:</li> <li>history of congenital malformations (CMs), fetal losses, preterm deliveries or small babies.</li> <li>family history of genetic problems or CMs.</li> <li>alcohol use.</li> <li>nutritional deficiencies (e.g., lack of folic acid).</li> <li>For example, Option 'B' indicates that the study initially matched groups based on the women's age AND they report the mean women's age for EACH arm (e.g., for Tx1, Tx2, etc.).</li> </ul>
EXPOSURE:		
1) Assessment of exposure	<ul> <li>a) secure record (e.g., surgical records)</li> <li>b) structured interview where blind to case/control status</li> <li>c) interview not blinded to</li> </ul>	Note: Option 'A' includes patient hospital records, prescription drug database, or hospital/clinic visits (e.g., patient is asked about "current" AED use during a visit with their doctor).
	<ul><li>case/control status</li><li>d) written self-report or medical</li></ul>	"Interview" here includes a hospital/clinic visit, but the patients are asked to remember their AED use during pregnancy (e.g., retrospectively

Page 63 of 90

**BMJ** Open

	record only	ascertained exposure).
	e) no description	
2) Same method of	a) yes	Note:
ascertainment for	b) no	This question is asking whether the method of <u>ascertainment of exposure</u>
cases and controls		was the same for 'cases' (with the outcome) and 'controls' (without the
		outcome; in this case-control study design).
3) Non-response	a) same rate for both groups	Note:
rate	b) non-respondents described	For our review, this pertains to either the infants or the mothers of the
	c) rate different and no	case and control groups.
	designation	
		We're allowing 10% dropout per year for a prospective study – e.g., 10%
		for 1 year, 20% for 2 years of follow-up, etc.
		For a survey, we allow for a 75% response rate in order for it be adequate.
		For a survey, a dropout rate is congruent to a survey response rate.

\*Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Available at: <u>http://www.ohri.ca/programs/clinical\_epidemiology/oxford.asp</u>

\*\*In the **"NOS Coding Manual" column**, the first section for each item is copied straight from the NOS documentation while the lower portions in each item are our "Notes" tailored for the AED review.

#### Appendix B. List of included studies

A total of 29 cohort studies  $^{1-29}$  with 9 companion reports  $^{30-38}$  were included:

1. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry*. 2004;75(11):1575-83.

2. Arkilo D, Hanna J, Dickens D, et al. Pregnancy and neurodevelopmental outcomes with in-utero antiepileptic agent exposure. A pilot study. *Eur J Paediatr Neurol*. 2015;19(1):37-40.

3. Bromley R, Baxter N, Calderbank R, Mawer G, Clayton-Smith J, Baker G. A comprehensive review of the language abilities of children exposed to valproate or carbamazepine in utero. American Epilepsy Society; Texas2010.

4. Bromley RL, Mawer GE, Briggs M, et al. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry*. 2013;84(6):637-43.

5. Bromley RL, Calderbank R, Cheyne CP, et al. Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate. *Neurology*. 2016;87(18):1943-53.

6. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA*. 2013;309(16):1696-703.

7. Cohen MJ, Meador KJ, Browning N, et al. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6years. *Epilepsy Behav.* 2013;29(2):308-15.

8. Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child*. 2011;96(7):643-7.

9. Dean JCS, Hailey H, Moore SJ, Lloyd DJ, Turnpenny PD, Little J. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. *J Med Genet*. 2002;39(4):251-9.

10. D'Souza SW, Robertson IG, Donnai D, Mawer G. Fetal phenytoin exposure, hypoplastic nails, and jitteriness. *Arch Dis Child*. 1991;66(3):320-4.

11. Eriksson K, Viinikainen K, Mönkkönen A, et al. Children exposed to valproate in utero—Population based evaluation of risks and confounding factors for long-term neurocognitive development. *Epilepsy Res.* 2005;65(3):189-200.

12. Gaily E. Development and growth in children of epileptic mothers: a prospective controlled study. Helsinki, Finland: University of Helsinki; 1990.

13. Gogatishvili N, Ediberidze T, Lomidze G, Tatishvili N, Kasradze S. PO-0834 Long-term Developmental Outcome Of Children Prenatally Exposed To Antiepileptic Drugs. *Arch Dis Child*. 2014;99(Suppl 2):A526.

14. Gogatishvili N, Ediberidze T, Lomidze G, Tatishvili N, Kasradze S. Cognitive outcomes of children with fetal antiepileptic drug exposure at the age of 3-6 years-preliminary data. 1st Congress of the European Academy of Neurology; Berlin: European Journal of Neurology; 2015. p. 329.

15. Hurault-Delarue C, Damase-Michel C, Finotto L, et al. Psychomotor developmental effects of prenatal exposure to psychotropic drugs: a study in EFEMERIS database. *Fundam Clin Pharmacol*. 2016;30(5):476-82.

16. Jones KL, Lacro RV, Johnson KA, Adams J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med.* 1989;320(25):1661-6.

17. Katz JM, Pacia SV, Devinsky O. Current Management of Epilepsy and Pregnancy: Fetal Outcome, Congenital Malformations, and Developmental Delay. Epilepsy Behav. 2001;2(2):119-23.

18. Koch S, Jager-Roman E, Losche G, Nau H, Rating D, Helge H. Antiepileptic drug treatment in pregnancy: drug side effects in the neonate and neurological outcome. Acta Paediatr. 1996:85(6):739-46.

Mawer G, Clayton-Smith J, Coyle H, Kini U. Outcome of pregnancy in women attending 19. an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. Seizure. 2002;11(8):512-8.

Miskov S, Juraski RG, Fucic A, et al. Croatian Pregnant Women with Epilepsy and 20. Effects of Antiepileptic Drugs Exposure in their Offspring - seven years of prospective surveillance. American Epilepsy Society; Texas2010.

Miskov S, Juraski RG, Mikula I, et al. The Croatian model of integrative prospective 21. management of epilepsy and pregnancy. Acta Clin Croat. 2016;55(4):535-48.

Nadebaum C, Anderson VA, Vajda F, Reutens DC, Barton S, Wood AG. Language skills 22. of school-aged children prenatally exposed to antiepileptic drugs. *Neurology*. 2011;76(8):719-26.

23. Rihtman T, Parush S, Ornoy A. Developmental outcomes at preschool age after fetal exposure to valproic acid and lamotrigine: cognitive, motor, sensory and behavioral function. Reprod Toxicol. 2013;41:115-25.

24. Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. JAMA. 1994;271(10):767-70.

Shankaran S, Woldt E, Nelson J, Bedard M, Delaney-Black V. Antenatal phenobarbital 25. therapy and neonatal outcome. II: Neurodevelopmental outcome at 36 months. *Pediatrics*. 1996;97(5):649-52.

van der Pol MC, Hadders-Algra M, Huisjes HJ, Touwen BC. Antiepileptic medication in 26. pregnancy: late effects on the children's central nervous system development. Am J Obstet Gynecol. 1991;164(1 Pt 1):121-8.

Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to 27. antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. JAMA Neurol. 2013;70(11):1367-74.

Veiby G, Daltveit AK, Schjolberg S, et al. Exposure to antiepileptic drugs in utero and 28. child development: a prospective population-based study. *Epilepsia*. 2013;54(8):1462-72.

Wood AG, Nadebaum C, Anderson V, et al. Prospective assessment of autism traits in 29. children exposed to antiepileptic drugs during pregnancy. *Epilepsia*. 2015;56(7):1047-55.

Bromley RL, Mawer G, Clayton-Smith J, Baker GA. Autism spectrum disorders 30. following in utero exposure to antiepileptic drugs. Neurology. 2008;71(23):1923-4.

Gaily EK, Granstrom ML, Hillesmaa VK, Bardy AH. Head circumference in children of 31. epileptic mothers: contributions of drug exposure and genetic background. *Epilepsy Res.* 1990;5(3):217-22.

Hillesmaa V. A prospective study on maternal and fetal outcome in 139 women with 32. epilepsy. Helsinki: University of Helsinki; 1982.

Hiilesmaa VK, Bardy A, Teramo K. Obstetric outcome in women with epilepsy. Am J 33. Obstet Gynecol. 1985;152(5):499-504.

Rasalam AD, Hailey H, Williams JH, et al. Characteristics of fetal anticonvulsant 34. syndrome associated autistic disorder. Dev Med Child Neurol. 2005;47(8):551-5.

35. Tomson T, Battino D, Bonizzoni E, et al. Antiepileptic drugs and intrauterine death: A prospective observational study from EURAP. *Neurology*. 2015;85(7):580-8.

36. Viinikainen K, Eriksson K, Monkkonen A, et al. The effects of valproate exposure in utero on behavior and the need for educational support in school-aged children. *Epilepsy Behav*. 2006;9(4):636-40.

37. Vinten J, Adab N, Kini U, Gorry J, Gregg J, Baker GA. Neuropsychological effects of exposure to anticonvulsant medication in utero. *Neurology*. 2005;64(6):949-54.

38. Vinten J, Bromley RL, Taylor J, Adab N, Kini U, Baker GA. The behavioral consequences of exposure to antiepileptic drugs in utero. Epilepsy Behav. 2009;14(1):197-201. 

### Appendix C. Key excluded studies

Author, Year	Research Group	Title	Reason for Exclusion
Meador, 2009 <sup>39</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs	Outcomes only reported as continuous variables
Meador, 2010 <sup>40</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Effects of breastfeeding in children of women taking antiepileptic drugs	Outcomes only reported as continuous variables
Meador, 2011 <sup>41</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age	Outcomes only reported as continuous variables
Meador, 2012 <sup>42</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Effects of fetal antiepileptic drug exposure: Outcomes at age 4.5 years	Outcomes only reported as continuous variables
Meador, 2013 <sup>43</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study	Outcomes only reported as continuous variables
Shallcross, 2011 <sup>44</sup>	Liverpool and Manchester Neurodevelopment Group and The UK Epilepsy and Pregnancy Register	Child development following in utero exposure: Levetiracetam vs. sodium valproate	Outcomes only reported as continuous variables
Shallcross, 2014 <sup>45</sup>	Liverpool and Manchester	In utero exposure to levetiracetam vs. valproate: Development and language at 3 years of age	Outcomes only reported as continuous variables

Neurodevelopment	
Group and The UK	
Epilepsy and Pregnancy	
Register	

#### References

39. Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med.* 2009;360(16):1597-605.

40. Meador KJ, Baker GA, Browning N, et al. Effects of breastfeeding in children of women taking antiepileptic drugs. *Neurology*. 2010;75(22):1954-60.

41. Meador KJ, Baker GA, Browning N, et al. Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. *Brain*. 2011;134(Pt 2):396-404.

42. Meador KJ, Baker GA, Browning N, et al. Effects of fetal antiepileptic drug exposure: outcomes at age 4.5 years. *Neurology*. 2012;78(16):1207-14.

43. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013;12(3):244-52.

44. Shallcross R, Bromley RL, Irwin B, Bonnett LJ, Morrow J, Baker GA. Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology*. 2011;76(4):383-9.

45. Shallcross R, Bromley RL, Cheyne CP, et al. In utero exposure to levetiracetam vs valproate: development and language at 3 years of age. *Neurology*. 2014;82(3):213-21.

Author, Year	Country of conduct	Registry or Setting	Study period	Interventions	Outcomes	Funding
Adab, 2004 <sup>*1</sup> [CR: Vinten 2005 <sup>37</sup> Vinten, 2009 <sup>38</sup> ]	UK	Mersey Regional Epilepsy Clinic; Epilepsy Clinic at the Manchester Royal Infirmary; Antenatal clinic at St Mary's Hospital, Manchester	2000- 2001	Carbam, Control, Valpro	Cognitive Developmental Delay, Psychomotor Developmental Delay	NR
Arkilo, 2015 <sup>2</sup>	USA	Minnesota Epilepsy Group	2006- 2011	Carbam, Lamot, Levet, Pheny, Valpro	Autism/Dyspraxia, Psychomotor Developmental Delay	NR
Bromley, 2010 <sup>3</sup>	UK	Liverpool and Manchester Neurodevelopment Group	NR	Carbam, Valpro	Language Delay	NR
Bromley, 2013 <sup>4</sup> [CR: Bromley, 2008 <sup>30</sup> ]	UK	Liverpool and Manchester Neurodevelopment group	2000- 2004	Carbam, Control, Lamot, Valpro	Autism/Dyspraxia, ADHD	mixed public & private
Bromley, 2016 <sup>5</sup> †	UK	UK Epilepsy and Pregnancy Register	2004- 2007	Control, Gabap, Levet, Topir, Valpro	Cognitive Developmental Delay	public
Christensen, 2013 <sup>6</sup> †	Denmark	Danish Civil Registration System; Danish Prescription Register; Danish Psychiatric Central Register; Danish Birth Register; Danish	1996- 2006	Carbam, Clonaz, Lamot, Oxcar, Valpro	Autism/Dyspraxia	public

		National Hospital Register				
Cohen, 2013 <sup>7</sup>	USA;UK	Neurodevelopmental Effects of Antiepileptic Drugs Study Group	1999- 2004	Carbam, Lamot, Pheny, Valpro,	ADHD	public
Cummings, 2011 <sup>8</sup> † [CR: Tomson, 2015 <sup>35</sup> ]	Northern Ireland	UK Epilepsy and Pregnancy Register (Northern Ireland); Northern Ireland Child Health System	1996- 2005	Carbam, Lamot, Valpro,	Cognitive Developmental Delay	public
Dean, 2002 <sup>9</sup> [CR: Rasalam, 2005 <sup>34</sup> ]	Scotland	Aberdeen Maternity Hospital	1976- 2000	Carbam, Carbam+Pheno, Carbam+Pheny, Carbam+Valpro, Control, Ethos, Pheno, Pheno+Pheny, Pheno+Valpro, Pheny, Primid, Valpro	Psychomotor Developmental Delay, ADHD	NR
D'Souza, 1991 <sup>10</sup>	United Kingdom	St Mary's Hospital	1980- 1982	Carbam, Control, Pheno, Pheny, Valpro	Cognitive Developmental Delay	public
Eriksson, 2005 <sup>11</sup> † [CR: Viinikainen, 2006 <sup>36</sup> ]	Finland	Kuopio University Hospital	1989- 2000	Carbam, Control, Valpro	Cognitive Developmental Delay, Psychomotor Developmental Delay	public

Page	71	of	90	
------	----	----	----	--

Gaily, 1990 <sup>12</sup> [CR: Gaily, 1990 <sup>31</sup> ; Hiilesmaa, 1982 <sup>32</sup> ; Hiilesmaa, 1985 <sup>33</sup> ]	Finland	Helsinki University Central Hospital	1975- 1979	Carbam, Carbam+Pheno+Pheny, Carbam+Pheny, Carbam+Valpro, Control, Ethos+Pheny, Pheno+Pheny, Pheny, Pheny+Primid, Pheny+Valpro	Cognitive Developmental Delay , Psychomotor Developmental Delay	mixe publ priva
Gogatishvili, 2014 <sup>13</sup>	Georgia	Georgian National AED- Pregnancy Registry	NR	Carbam, Lamot, Valpro	Cognitive Developmental Delay	publ
Gogatishvili, 2015 <sup>14</sup>	Georgia	Georgian National AED- Pregnancy Registry	NR	Carbam, Carbam+Levet, Lamot, Pheno, Valpro	Language Delay	publi
Hurault- Delarue, 2012 <sup>15</sup>	France	EFEMERIS database - Caisse Primaire d'Assurance Maladie of Haute-Garonne and Maternal and Infant Protection Service; Antenatal Diagnostic Centre	2004- 2008	Carbam, Clobaz, Clonaz, Gabap, Lamot, Pheno, Topir, Valpro	Psychomotor Developmental Delay	NR
Jones, 1989 <sup>16</sup> †	US	California Teratogen Registry	1979- 1988	Carbam, Carbam+Pheno, Carbam+Pheno+Valpro, Carbam+Primid	Cognitive Developmental Delay , Psychomotor Developmental Delay	publi
Katz, 2001 <sup>17</sup>	USA	Mount Sinai Comprehensive Epilepsy Center	1990- 2000	Carbam, Control, Lamot, Pheno, Pheny, Primid, Valpro	Cognitive Developmental Delay	NR

Koch, 1996 <sup>18</sup>	Germany	NR	1976- 1983	Pheno, Pheny, Primid, Valpro	Cognitive Developmental Delay	public
Mawer, 2002 <sup>19</sup>	England	Manchester Royal Infirmary	1990- 1999	Carbam, Lamot, Pheny, Valpro	Cognitive Developmental Delay	NR
Miskov, 2010 <sup>20</sup>	Croatia	NR	2003- 2010	Carbam, Control, Gabap, Lamot, Valpro	Psychomotor Developmental Delay, Neonatal Seizures	NR
Miskov, 2016 <sup>21</sup>	Croatia	Sestre milosrdnice University Hospital Center	2003- 2013	Carbam, Carbam+Lamot, Carbam+Pheno, Carbam+Pheny+Topir, Control, Clonaz+Valpro, Gabap, Lamot, Oxcar, Pheno, Pheny, Topir+Valpro, Valpro	Attention Deficit Hyperactivity Disorder	NR
Nadebaum, 2011 <sup>22</sup> ;†	Australia	Australian Registry of Antiepileptic Drug Use in Pregnancy	2007- 2009	Carbam, Lamot, Valpro	Language Delay	mixed public & private
Rihtman, 2013 <sup>23</sup>	Israel	Israeli Teratogen Information Service	NR	Lamot, Valpro	Neonatal Seizure	mixed public & private
Scolnik, 1994 <sup>24</sup>	Canada	Hospital for Sick Children - Motherisk Program; North York General Hospital; Toronto Hospital; Oshawa General Hospital	1987- 1992	Carbam, Pheny	Cognitive Developmental Delay	public

Page	73	of	90
1			

Shankaran, 1996 <sup>25</sup>	USA	Children's Hospital of Michigan	NR	Control, Pheno	Psychomotor Developmental Delay, Language Delay	public
Van der Pol, 1991 <sup>26</sup>	Netherlands	Groningen University Hospital	1973- 1981	Carbam, Carbam+Pheno, Control, Pheno	Psychomotor Developmental Delay	public
Veiby, 2013a <sup>27</sup> †	Norway	Norwegian Institute of Public Health- Mother and Child Cohort Study	1999- 2009	Carbam, Control, Lamot, Valpro	Social Impairment	public
Veiby, 2013b <sup>28</sup> †	Norway	Medical Birth Registry of Norway	1999- 2008	Carbam, Control, Lamot, Valpro	Psychomotor Developmental Delay, Autism/Dyspraxia, Language Delay, ADHD	public
Wood, 2015 <sup>29</sup> †	Australia	Australian Registry of Antiepileptic Drug Use in Pregnancy	2007- 2010	Carbam, Carbam+Clonaz, Carbam+Lamot, Carbam+Pheny, Lamot+Valpro, Valpro	Autism/Dyspraxia	public

Carbam = Carbamazepine; Clobaz = Clobazam; Clonaz = Clonazepam; Ethos = Ethosuximide; Gabap = Gabapentin; Lamot = Lamotrigine; Levet = Levetiracetam; Oxcar = Oxcarbazepine; Pheno = Phenobarbital; Pheny = Phenytoin; Primid = Primidone; Topir = Topiramate; Valpro = Valproate; Vigab = Viagabatrin

\*Single publication reporting on two separate cohorts †Registry Studies

Author, Year	Indication	Sample Size*	Mean Age (Women)	Mean Age (Children)/ Follow-up period†	AED Exposure Timing	Maternal Alcohol Use n/N‡	Maternal Tobacco Use n/N‡
Adab, 2004a <sup>1</sup> § [CR: Vinten 2005 <sup>37</sup> ; Vinten, 2009 <sup>38</sup> ]	Epilepsy	177	26.1	9-10.5	NR	24/279‡	68/249‡
Adab, 2004b <sup>1</sup> § [CR: Vinten 2005 <sup>37</sup> ; Vinten, 2009 <sup>38</sup> ]	Epilepsy	81	26.1	3-3.33	NR	24/279‡	68/249‡
Arkilo, $2015^2$	Epilepsy	59	NR	NA	First trimester	NR	NR
Bromley, 2010 <sup>3</sup>	NR	60	NR	6-7	Whole pregnancy	NR	NR
Bromley, 2013 <sup>4</sup> [CR: Bromley, 2008 <sup>30</sup> ]	Epilepsy	156	28	6	NR	28/156	42/156
Bromley, 2016 <sup>5</sup>	Epilepsy	185	NR	NR	NR	31/185	35/185
Christensen, 2013 <sup>6</sup>	NR	2011	NR	NR	Whole pregnancy	NR	NR
Cohen, 2013 <sup>7</sup>	Epilepsy	108	30	6	NR	12/192‡	NR
Cummings, 2011 <sup>8</sup> [CR: Tomson, 2015 <sup>35</sup> ]	Epilepsy	142	NR	2-3	Whole pregnancy	32/108‡	19/108‡
Dean, 2002 <sup>9</sup> [CR: Rasalam, 2005 <sup>34</sup> ]	Epilepsy	287	27	3.75-15.5	First trimester	NR	NR
D'Souza, 1991 <sup>10</sup>	Epilepsy	42	26.5	2.5-3.5	Whole pregnancy	NR	NR
Eriksson, 2005 <sup>11</sup> [CR: Viinikainen, 2006 <sup>36</sup> ]	Epilepsy	39	28.2	NR	NR	NR	NR

Gaily, 1990 <sup>12</sup>							
[CR: Gaily, 1990 <sup>31</sup> ; Hiilesmaa, 1982 <sup>32</sup> ;	Epilepsy	134	27.8	5.5	First trimester	NR	NR
Hiilesmaa, 1985 <sup>33</sup>							
Gogatishvili, 2014 <sup>13</sup>	NR	39	NR	2 to 4	NR	NR	NR
Gogatishvili, 2015 <sup>14</sup>	NR	23	NR	3 to 6	NR	NR	NR
Hurault-Delarue, 2012 <sup>15</sup>	NR	109	NR	0.75	NR	NR	NR
Jones, 1989 <sup>16</sup>	Epilepsy	63	NR	NR	Whole pregnancy	NR	NR
Katz, 2001 <sup>17</sup>	Epilepsy	51	31	NR	NR	NR	NR
Koch, 1996 <sup>18</sup>	Epilepsy	40	NR	6	First trimester	NR	NR
Mawer, 2002 <sup>19</sup>	Epilepsy	52	NR	NR	NR	NR	NR
Miskov, 2010 <sup>20</sup>	Epilepsy	55	NR	NR	NR	NR	NR
Miskov, 2016 <sup>21</sup>	Epilepsy	74	34	NR	NR	NR	6/74
Nadebaum, 2011 <sup>22</sup>	Epilepsy	66	31.6	7.4	First trimester	NR	5/66
Rihtman, 2013 <sup>23</sup>	Epilepsy	72	NR C	NR	Whole pregnancy	NR	NR
Scolnik, 1994 <sup>24</sup>	Epilepsy	75	NR	1.5-3	1st trimester	NR	NR
Shankaran, 1996 <sup>25</sup>	NR	96	NR	NR	NR	NR	NR
Van der Pol, 1991 <sup>26</sup>	Epilepsy	57	NR	6-13	NR	NR	NR
Veiby, 2013a <sup>27</sup>	Epilepsy	422	NR	0.5	NR	NR	NR
Veiby, 2013b <sup>28</sup>	Epilepsy	248	28.9	3	NR	NR	68/726‡
Wood, 2015 <sup>29</sup>	Epilepsy	77	NR	6-8	NR	NR	NR

\* Sample size used for analysis; ineligible treatment arms (i.e. treatment arms with excluded drugs or unspecified polytherapy) are not included in the count

<sup>†</sup> The mean age for children/follow-up period data were only collected for outcomes related to cognitive and/or psychomotor development

‡ Total sample size is based on the number of women enrolled in the study; may differ from the sample size used for analysis

§ Single publication reporting on two separate cohorts

Appendix F. Methodological quality of observational studies – Newcastle Ottawa Scale results

First Author, Year	Representativen ess of the exposed cohort	Selection of the non- exposed cohort	Ascertainme nt of exposure	Demonstratio n that outcome of interest was not present at start of study	Comparabili ty of cohorts on the basis of the design or analysis	Assessmen t of outcome	Was follow-up long enough for outcomes to occur	Adequac y of follow up of cohorts
Adab, 2004 <sup>1</sup>	В	А	А	А	С	А	А	С
Arkilo, 2015 <sup>2</sup>	В	A	В	А	D	А	А	С
Bromley, $2010^3$	D	А	D	А	D	D	В	D
Bromley, 2013 <sup>4</sup>	А	А	A	А	А	А	А	С
Bromley, 2016 <sup>5</sup>	А	А	A	А	А	А	А	С
Christensen, 2013 <sup>6</sup>	А	А	А	А	А	В	А	В
Cohen, 2013 <sup>7</sup>	А	А	D	A	А	А	А	С
Cummings, 2011 <sup>8</sup>	А	А	А	А	А	А	А	С
Dean, 2002 <sup>9</sup>	В	А	А	А	D	Α	А	С
D'Souza, 1991 <sup>10</sup>	В	А	А	А	D	А	А	А
Eriksson, 2005 <sup>11</sup>	В	А	А	А	В	А	А	D
Gaily, 1990 <sup>12</sup>	В	А	А	А	D	А	А	А
Gogatishvili, 2014 <sup>13</sup>	А	А	D	А	D	А	А	D
Gogatishvili, 2015 <sup>14</sup>	А	А	D	А	D	А	А	D

Page	77	of	90	
------	----	----	----	--

Hurault-								
Delarue, 2012 <sup>15</sup>	А	А	А	А	А	А	А	
Jones, 1989 <sup>16</sup>	А	А	В	А	D	А	А	
Katz, 2001 <sup>17</sup>	В	А	А	А	D	А	А	
Koch, 1996 <sup>18</sup>	В	А	В	А	D	А	А	
Mawer, 2002 <sup>19</sup>	В	А	А	А	D	А	А	
Miskov, 2010 <sup>20</sup>	D	А	D	А	D	D	А	
Miskov, 2016 <sup>21</sup>	С	A	А	А	D	А	А	
Nadebaum, 2011 <sup>22</sup>	А	А	A	А	А	А	А	
Rihtman, 2013 <sup>23</sup>	А	В	А	А	А	А	А	
Scolnik, 1994 <sup>24</sup>	В	А	А	А	D	А	А	
Shankaran, 1996 <sup>25</sup>	В	А	А	A	D	А	А	
Van der Pol, 1991 <sup>26</sup>	В	А	D	А	А	А	А	
Veiby, 2013a <sup>27</sup>	А	А	А	А	A	Α	А	
Veiby, 2013b <sup>28</sup>	А	А	А	А	А	А	А	
Wood. 2015 <sup>29</sup>	А	А	А	А	D	A	А	

BMJ Open



Log-odds ratio centered at comparison-specific pooled effect

\* Funnel plots have been produced only for outcomes with  $\geq 10$  studies. For multi-arm studies we plot data points from each study-specific basic parameter (treatment comparisons with a study-specific common comparator)

BMJ Open

# Appendix H. Statistically significant network meta-analysis results along with meta-analysis results, transitivity, and inconsistency assessments

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatment Indication	Timing	Comparability of cohorts	Adequacy of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
	Cogn	itive Develop	mental Dela	y (10 studi	ies, 748 patients	s, 14 treatme	nts)	
Lamot vs Valpro	4 (NA)	140 (31.00)	Epilepsy	NR	Н	Н	0.17 (0.02-0.87)	0.13 (0.01-0.57) (0.01-0.75)
Valpro vs Control	4 (0.06)	267 (28.80)	Epilepsy	1st trimester	Н	Н	8.15 (3.19-22.33)	7.40 (3.00-18.46) (1.81-27.63)
Valpro vs Carbam	6 (NA)	310 (27.80)	Epilepsy	NR	Н	L	3.32 (1.56-7.04)	3.54 (1.69-7.26) (0.95-12.32)
Valpro vs Pheno	3 (NA)	36 (27.80)	Epilepsy	1st trimester	Н	L	4.25 (0.82-34.07)	5.59 (1.21-35.07) (0.93-45.99)
Valpro vs Pheny	3 (NA)	58 (31.00)	Epilepsy	1st trimester	Н	L	3.12 (0.75-14.12)	2.88 (1.04-8.49) (0.69-12.62)
Common between-st	udy variance acro	ess treatment co	omparisons			-7/	0.13	0.12 (0.00-1.15)
Residual deviance: 4	4.72 Data p	points: 47	DIC: 78.7				(0.00 0.97)	(NA)
Evaluation of consist	tency using the de	sign-by-treatm	ent interaction	n model	Chi-square test: 1 Degrees of Freed	4.15 om: 17	P- value: 0.66 Heterogeneity: 0	

1	
2	
2	
3	
4	
5	
6	
7	
8	
0	
9	
10	
11	
12	
13	
14	
15	
10	
16	
17	
18	
19	
20	
21	
21	
22	
23	
24	
25	
26	
27	
20	
20	
29	
30	
31	
32	
33	
24	
25	
35	
36	
37	
38	
39	
40	
10	
41	
42	
43	
44	
45	
46	
-10 //7	
47	
48	
10	

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatment Indication	Timing	Comparability of cohorts	Adequacy of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
		Autism Dys	praxia (5 st	udies, 2551	l patients, 12 tr	eatments)		
Lamot vs Control	2 (0.00)	254 (27.75)	Epilepsy	1st trimester	Н	Н	13.77 (2.06-188.00)	8.88 (1.29-112.00) (0.94-146.80)
Lamot+Valpro vs Carbam	1 (NA)	40 (NR)	Epilepsy	NR	L	L	15.02 (2.04-171.90)	22.89 (2.58-219.00) (1.90-282.20)
Lamot+Valpro vs Clonaz	NA	NR	NR	NR	NR	NR	NA	20.21 (1.48-351.30) (1.15-455.00)
Lamot+Valpro vs Control	NA	NR	NR	NR	NR	NR	NA	$ \begin{array}{r} 132.70 \\ (7.41-3.9 \times 10^3) \\ (5.82-4.6 \times 10^3) \end{array} $
Lamot+Valpro vs Lamot	NA	NR	NR	NR	NR	NR	NA	14.61 (1.51-149.10) (1.14-196.80)
Oxcar vs Control	NA	NR	NR	NR	NR	NR	NA	$ \begin{array}{r}     13.51 \\     (1.28-221.40) \\     (0.86-267.40) \end{array} $
Valpro vs Carbam	5 (NA)	1003 (27.83)	Epilepsy	1st trimester	L	L	3.20 (1.20-8.68)	3.02 (1.09-8.40) (0.57-14.31)
Valpro vs Control	2 (0.00)	249 (27.75)	Epilepsy	1st trimester	Н	Н	9.19 (1.14-132.10)	17.29 (2.40-217.60) (1.61-274.90)
Common between-stud	ly variance acro	oss treatment co	omparisons				0.12	0.16
Residual deviance: 24	Data points	s: 24 DIC: 4	44				(0.00-1.37)	(0.00-1.95) (NA)
Evaluation of consistent interaction model	ncy using the de	esign-by-treatm	ent	Chi-square Degrees of	test: 3.79 Freedom: 5		P- value: 0.57 Heterogeneity: 0	

Page	81	of	90
------	----	----	----

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatment Indication	Timing	Comparability of cohorts	Adequacy of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
	Psycho	omotor Devel	opmental De	lay (11 stu	idies, 1145 patie	nts, 18 treatm	ents)	
Carbam+Pheno+Valpr vs Control	<sup>o</sup> NA	NR	NR	NR	NR	NR	NA	19.12 (1.49-337.50) (1.34-370.40)
Carbam+Pheno+Valpr vs Pheno	<sup>o</sup> NA	NR	NR	NR	NR	NR	NA	19.86 (1.38-393.60) (1.26-423.30
Levet vs Carbam+Pheno+Valpr	o NA	NR	NR	NR	NR	NR	NA	0.01 (0.00-0.58) (0.00-0.62)
Valpro vs Carbam	7 (NA)	331 (27.80)	Epilepsy	1st trimester	Н	Н	2.72 (1.39-5.67)	2.45 (1.27-4.88) (0.95-6.77)
Valpro vs Control	5 (0.07)	331 (28.38)	Epilepsy	1st trimester	Н	Н	3.53 (1.60-8.64)	4.16 (2.04-8.75) (1.52-12.05)
Valpro vs Pheno	2 (NA)	141 (NR)	Epilepsy	1st trimester	Н	Н	3.68 (1.17-12.30)	4.32 (1.72-11.20) (1.34-14.51)
Common between-stud	y variance act	ross treatment o	comparisons			J	0.05	0.06
Residual deviance: 45	Data poin	ts: 51 DIC:	: 78				(0.00-0.49)	(0.00-0.63) (NA)
Evaluation of consister interaction model	ncy using the d	design-by-treatr	nent	Chi-square Degrees of	test: 13.46 Freedom: 21		P- value: 0.89 Heterogeneity: 0	

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatment Indication	Timing	Comparability of cohorts	Adequacy of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
		Languag	e Delay (5 st	udies, 509	patients, 5 trea	tments)		
Valpro vs Control	1 (0.03)	173 (28.90) Ep	pilepsy	NR	L	Н	6.96 (1.14-37.03)	7.95 (1.50-49.13) (0.96-74.52)
Common between-stu	dy variance acro	oss treatment c	omparisons					0.16
Residual deviance: 12	2 Data points	s: 14 DIC:	23				0.15 (0.00-1.85)	(0.00-2.15) (NA)
Evaluation of consist interaction model	ency using the de	esign-by-treatm	nent	Chi-square Degrees of	test: 2.33 Freedom: 3		P- value: 0.50 Heterogeneity: 0	
		ADI	HD (4 studies	s, 750 pati	ents, 6 treatmen	its)		
			No statisti	cally signif	ficant results			
Residual deviance: 12	2 Data points	s: 17 DIC:	22					
Abbreviations: ADHD risk of bias; MA - Meta Carbam = Carbamazepi Levetiracetam; Oxcar = Viagabatrin	- Attention Defic -analysis; NA - No ne; Clobaz = Clob Oxcarbazepine; F	it Hyperactivity ot applicable; NI pazam; Clonaz = Pheno = Phenoba	Disorder; CrI - 0 MA - Network M Clonazepam; E rrbital; Pheny =	Credible Inte Meta-analysi thos = Ethos Phenytoin; I	erval; DIC - Devianc s; NR- Not Reported suximide; Gabap = C Pridmid = Primidone	ce Information C l; PrI - Predictive Gabapentin; Lam ; Topir = Topira	riterion; H- high risk e Interval ot = Lamotrigine; Lev mate; Valpro = Valpr	of bias; L - low vet = roate; Vigab =
				29				
	For	peer review o	nly - http://bm	njopen.bm	j.com/site/about/g	guidelines.xht	ml	

## Appendix I. Rank-heat plot of cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes\*



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abbreviations: carbam - carbamazepine, clobaz - clobazam, clonaz - clonazepam, ethos - ethosuximide, gabap - gabapentin, lamot - lamotrigine, levet - levetiracetam, oxcar - oxcarbazepine, pheno - phenobarbital, pheny - phenytoin, primid - primidone, topir - topiramate, valpro - valproate, vigab - vigabatrin

\*Rank-heat plot of cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes (5 circles) and 25 treatments (25 radii). Each sector is coloured according to the surface under the cumulative ranking curve value of the corresponding treatment and outcome using the transformation of three colours red (0%), yellow (50%), and green (100%).

Total studies	Range of study arms	# of treatments	# of patients	# of direct treatment comparisons	# of NMA treatment comparisons	Statistically significant NMA treatment effects	# of studies with zero events in all arms	# of studies with ineligible outcome definition*
<b>Cognitive Dev</b>	elopmental	l Delay	-	-	-			
11	(2,8)	18	933	62	153	5	1	5
Autism/Dyspr	axia							
5	(4,6)	12	2551	34	66	8	0	4
Neonatal Seize	ıre							
1	(2,2)	2	69	1	0	0	1	1
Psychomotor 3	Developme	ental Delay						
11	(2,8)	18	1145	74	153	6	0	5
Language Del	ay							
5	(2,4)	5	509	7	10	1	0	3
ADHD								
5	(4,6)	7	816	20	21	0	0	0
Social Impair	ment							
1	(4,4)	4	422	1	0	0	0	0
Abbreviations	: ADHD - A	Attention Defic	it Hyperact	ivity Disorder; N	MA - Network M	Meta-analysis		

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI
Cognitive Developmental Delay – Sensitivity	Analysis - Epilepsy o	nly (10 studies, 910 patien	ts, 17 treatments)
Carbamazepine vs Control	2.08	(0.79 - 5.82)	(0.47 - 9.34)
Carbamazepine+Phenobarbital vs Control	0.62	(0.00 - 15.31)	(0.00 - 19.29)
Carbamazepine+Phenobarbital+Phenytoin vs Control	4.75	(0.01 - 164.80)	(0.01 - 192.50)
Carbamazepine+Phenobarbital+Valproate vs Control	15.00	(1.00 - 367.10)	(0.82 - 426.90)
Carbamazepine+Phenytoin vs Control	9.84	(0.60 - 136.30)	(0.49 - 164.50)
Ethosuximide+Phenytoin vs Control	6.53	(0.02 - 216.00)	(0.02 - 251.30)
Gabapentin vs Control	1.43	(0.05 - 14.28)	(0.04 - 18.20)
Lamotrigine vs Control	0.79	(0.05 - 5.12)	(0.05 - 6.66)
Levetiracetam vs Control	3.46	(0.65 - 17.14)	(0.47 - 23.57)
Phenobarbital vs Control	0.55	(0.01 - 5.38)	(0.01 - 6.85)
Phenobarbital+Phenytoin vs Control	1.28	(0.00 - 36.18)	(0.00 - 44.03)
Phenytoin vs Control	2.47	(0.65 - 8.25)	(0.41 - 12.47)
Phenytoin+Valproate vs Control	3.68	(0.01 - 121.00)	(0.01 - 135.00)
Primidone vs Control	1.97	(0.25 - 12.16)	(0.19 - 16.25)
Topiramate vs Control	3.06	(0.42 - 17.51)	(0.32 - 23.57)
Valproate vs Control	7.48	(2.99 - 19.04)	(1.67 - 31.21)
Common within-network between-study variance	0.16	(0.00 - 1.36)	
Evaluation of inconsistency using the design-by-treatmen	t interaction model	Chi-square test: 12.98 Degrees of Freedom: 14	P-value: 0.53 Heterogeneity: 0.00
Cognitive Developmental Delay - Sensitivity Analys	sis - First generation A	AEDs only (6 studies, 480	patients, 13 treatments)
Carbamazepine vs Control	1.68	(0.37 - 7.82)	(0.19 - 14.98)
Carbamazepine+Phenytoin vs Control	8.98	(0.36 - 169.90)	(0.26 - 243.60)
Carbamazepine+Phenobarbital vs Control	0.46	(0.00 - 21.02)	(0.00 - 28.01)
Carbamazepine+Phenobarbital+Phenytoin vs Control	4.12	(0.01 - 180.10)	(0.00 - 236.30)
Carbamazepine+Phenobarbital+Valproate vs Control	12.84	(0.50 - 435.70)	(0.35 - 604.30)
Ethosuximide+Phenytoin vs Control	5.65	(0.01 - 219.00)	(0.01 - 291.50)

#### Appendix K. Sensitivity and network meta-regression analyses - Anti-epileptic drugs compared with Control

 BMJ Open

<b>Treatment Comparison</b>	NMA Odds Ratio	95% CrI	95% PrI
Phenobarbital vs Control	0.64	(0.00 - 26.02)	(0.00 - 35.36)
Phenobarbital+Phenytoin vs Control	1.06	(0.00 - 37.64)	(0.00 - 50.85)
Phenytoin vs Control	2.08	(0.26 - 12.50)	(0.13 - 22.02)
Phenytoin+Valproate vs Control	3.14	(0.00 - 135.80)	(0.00 - 178.90)
Primidone vs Control	3.30	(0.18 - 43.76)	(0.12 - 68.72)
Valproate vs Control	13.22	(3.20 - 64.06)	(1.50 - 128.40)
Common within-network between-study variance	0.27	(0.00 - 2.97)	
Evaluation of inconsistency using the design-by-treatme	nt interaction model	Chi-square test: 3.31 Degrees of Freedom: 3	P-value: 0.35 Heterogeneity: 0.00
Cognitive Developmental Delay - Sensitivity Analysis	s - Maternal Alcohol or	r Tobacco use (3 studies, a	504 patients, 7 treatme
Carbamazepine vs Control	1.97	(0.40 - 10.01)	(0.19 - 21.27)
Gabapentin vs Control	1.47	(0.04 - 19.01)	(0.02 - 27.11)
Lamotrigine vs Control	0.41	(0.00 - 10.09)	(0.00 - 13.61)
Levetiracetam vs Control	3.55	(0.43 - 24.13)	(0.23 - 42.39)
Topiramate vs Control	3.17	(0.30 - 24.07)	(0.18 - 44.87)
Valproate vs Control	7.79	(1.84 - 29.60)	(0.84 - 62.77)
Common within-network between-study variance	0.27	(0.00 - 3.29)	
Evaluation of inconsistency using the design-by-treatme	nt interaction model	Chi-square test: 2.69 Degrees of Freedom: 2	P-value: 0.26 Heterogeneity: NA
Cognitive Developmental Delay - Sensi	tivity Analysis - Low <b>R</b>	Risk of Bias: "Adequacy of the second s	of follow-up''
(4 studie	s, 283 patients, 12 trea	tments)	2
Carbamazepine vs Control	2.68	$(0.05 - 2.9 \times 10^3)$	$(0.03 - 4.3 \times 10^{3})$
Carbamazepine+Phenobarbital vs Control	0.67	$(0.00 - 2.2 \times 10^3)$	$(0.00 - 2.9 \times 10^3)$
Carbamazepine+Phenobarbital+Phenytoin vs Control	5.23	$(0.01 - 7.2 \times 10^3)$	$(0.00 - 1.1 \times 10^4)$
Carbamazepine+Phenobarbital+Valproate vs Control	22.18	$(0.10 - 4.8 \times 10^4)$	$(0.06 - 7.7 \times 10^4)$
		$(0.12 \ 1.2 \ 1.0^{4})$	$(0.07 \ 1.9 \ 1.0^4)$
Carbamazepine+Phenytoin vs Control	11.45	$(0.13 - 1.2 \times 10)$	$(0.07 - 1.8 \times 10)$
Carbamazepine+Phenytoin vs Control         Ethosuximide+Phenytoin vs Control	<u> </u>	$\frac{(0.13 - 1.2 \times 10^{3})}{(0.01 - 8.3 \times 10^{3})}$	$\frac{(0.07 - 1.8 \times 10^{4})}{(0.00 - 1.4 \times 10^{4})}$
Carbamazepine+Phenytoin vs Control Ethosuximide+Phenytoin vs Control Lamotrigine vs Control	<u>11.45</u> <u>6.45</u> 0.52	$\begin{array}{r} (0.13 - 1.2 \times 10^{-3}) \\ \hline (0.01 - 8.3 \times 10^{3}) \\ \hline (0.00 - 1.2 \times 10^{3}) \end{array}$	$\frac{(0.07 - 1.8 \times 10^{7})}{(0.00 - 1.4 \times 10^{4})}$ (0.00 - 1.9 x 10 <sup>3</sup> )
Carbamazepine+Phenytoin vs Control Ethosuximide+Phenytoin vs Control Lamotrigine vs Control Phenobarbital+Phenytoin vs Control	11.45 6.45 0.52 1.33	$(0.13 - 1.2 \times 10^{3})$ $(0.01 - 8.3 \times 10^{3})$ $(0.00 - 1.2 \times 10^{3})$ $(0.00 - 1.8 \times 10^{3})$	$   \begin{array}{r}     (0.07 - 1.8 \times 10^{7}) \\     (0.00 - 1.4 \times 10^{4}) \\     (0.00 - 1.9 \times 10^{3}) \\     (0.00 - 2.7 \times 10^{3})   \end{array} $

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
1	
2	
3	
4	
5	
6	
7	
0	
0	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI
Phenytoin+Valproate vs Control	3.94	$(0.00 - 6.7 \times 10^3)$	$(0.00 - 8.8 \times 10^3)$
Valproate vs Control	5.9	$(0.06 - 9.7 \times 10^3)$	$(0.03 - 1.5 \times 10^4)$
Common within-network between-study variance	1.01	(0.01 - 5.85)	
Evaluation of inconsistency using the design-by-treatment	nt interaction model	Chi-square test: 5.07 Degrees of Freedom: 2	P-value: 0.08 Heterogeneity: 0.00
Cognitive Developmental Delay - Sensitive	vity Analysis - Low Ri	isk of Bias: ''Comparabili	ty of cohorts''
(3 studie	s, 366 patients, 7 treat	tments)	
Carbamazepine vs Control	1.46	(0.11 - 19.59)	(0.06 - 38.10)
Gabapentin vs Control	1.19	(0.03 - 22.80)	(0.02 - 39.35)
Lamotrigine vs Control	0.27	(0.00 - 11.80)	(0.00 - 19.37)
Levetiracetam vs Control	2.90	(0.30 - 32.81)	(0.15 - 62.97)
Topiramate vs Control	2.55	(0.22 - 29.21)	(0.11 - 64.23)
Valproate vs Control	5.79	(1.05 - 47.35)	(0.47 - 102.90)
Common within-network between-study variance	0.38	(0.00 - 4.14)	
Evaluation of inconsistency using the design-by-treatment	nt interaction model	Chi-square test: 1.47 Degrees of Freedom: 2	P-value: 0.48 Heterogeneity: NA
Cognitive Developmenta	l Delay – Network M	eta-regression Analysis	
(11 studie	s, 933 patients, 18 trea	atments)	
Carbamazepine vs Control	1.99	(0.64 - 6.18)	(0.40 - 9.77)
Carbamazepine+Levetiracetam vs Control	0.54	(0.00 - 16.36)	(0.00 - 19.87)
Carbamazepine+Phenobarbital vs Control	0.50	(0.00 - 16.10)	(0.00 - 19.36)
Carbamazepine+Phenobarbital+Phenytoin vs Control	4.36	(0.01 - 171.20)	(0.01 - 194.60)
Carbamazepine+Phenobarbital+Valproate vs Control	14.58	(0.90 - 413.20)	(0.74 - 488.90)
Carbamazepine+Phenytoin vs Control	9.44	(0.50 - 130.50)	(0.39 - 162.40)
Ethosuximide+Phenytoin vs Control	5.77	(0.01 - 234.70)	(0.01 - 268.10)
Gabapentin vs Control	1.37	(0.04 - 15.51)	(0.03 - 19.10)
Lamotrigine vs Control	0.87	(0.07 - 5.14)	(0.06 - 6.76)
Levetiracetam vs Control	3.43	(0.57 - 18.78)	(0.42 - 24.85)
Phenobarbital vs Control	1.16	(0.13 - 8.59)	(0.10 - 11.43)
Phenobarbital+Phenytoin vs Control	1.34	(0.00 - 39.21)	(0.00 - 49.39)

 **BMJ Open** 

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI
Phenytoin vs Control	2.43	(0.55 - 9.14)	(0.36 - 13.45
Phenytoin+Valproate vs Control	3.58	(0.01 - 134.20)	(0.01 - 161.7
Primidone vs Control	2.03	(0.21 - 16.49)	(0.16 - 21.39
Topiramate vs Control	2.93	(0.41 - 16.34)	(0.31 - 22.9
Valproate vs Control	7.03	(2.26 - 20.02)	(1.41 - 30.92
Common within-network between-study variance	0.16	(0.00 - 1.27)	
Regression Coefficient	1.01	(0.76 - 1.56)	
Evaluation of inconsistency using the design-by-treatm	ent interaction model	Chi-square test: 14.15 Degrees of Freedom: 17	P-value: 0.6 Heterogeneity:
Autism/Dyspraxia - Sensitivity Analysis - La	rge cohort (>300 patient	ts) - (1 study, 2,551 patien	ts, 5 treatments)**
Clonazepam vs Carbamazepine	1.08	(0.24 - 4.85)	_
Lamotrigine vs Carbamazepine	1.20	(0.36 - 4.00)	-
Oxcarbazepine vs Carbamazepine	2.13	(0.62 - 7.35)	-
Valproate vs Carbamazepine	3.05	(0.97 - 9.52)	-
Common within-network between-study variance	NA	NA	
Evaluation of inconsistency using the design-by-treatm	ent interaction model	NA	NA
Autism/Dyspraxia - Sensitivity Ana	lysis - Epilepsy only (4 s	tudies, 540 patients, 10 tro	eatments)
Carbamazepine vs Control	5.20	(0.54 - 90.53)	(0.33 - 133.0
Carbamazepine+Clonazepam vs Control	7.90	(0.01 - 653.30)	(0.01 - 881.0
Carbamazepine+Lamotrigine vs Control	4.25	(0.01 - 333.60)	(0.01 - 446.9
Carbamazepine+Phenytoin vs Control	9.03	(0.01 - 666.30)	(0.01 - 893.0
Lamotrigine vs Control	10.24	(1.25 - 171.40)	(0.67 - 248.5
Lamotrigine+Valproate vs Control	120.20	$(5.25 - 4.5 \times 10^3)$	(3.51 - 6.0 x 1
Levetiracetam vs Control	3.52	(0.00 - 272.20)	(0.00 - 364.3
Phenytoin vs Control	8.10	(0.01 - 577.50)	(0.01 - 754.6
Valproate vs Control	14.41	(1.66 - 252.10)	(0.88 - 378.0
Common within-network between-study variance	0.31	(0.00 - 3.04)	
Evaluation of inconsistency using the design-by-treatm	ent interaction model	Chi-square test: 2.9 Degrees of Freedom: 3	P-value: 0.41 Heterogeneity: 0.06

2	
3	
1	
4	
5	
6	
7	
8	
0	
9	
10	
11	
12	
13	
10	
14	
15	
16	
17	
18	
10	
19	
20	
21	
22	
23	
24	
24	
25	
26	
27	
28	
20	
29	
30	
31	
32	
33	
3/	
0 <del>4</del>	
35	
36	
37	
38	
30	
40	
40	
41	
42	
43	
11	
44	
45	
46	
47	
48	

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI
Autism/Dyspraxia - Sensitivity Analysis	- Maternal Tobacco Us	se (4 studies, 540 patients,	10 treatments)
Carbamazepine vs Control	2.51	(0.05 - 154.30)	(0.04 - 254.50)
Lamotrigine vs Control	24.84	$(2.14 - 1.2 \times 10^3)$	$(1.23 - 2.2 \times 10^3)$
Valproate vs Control	33.40	$(2.60 - 1.7 \times 10^3)$	$(1.45 - 2.9 \times 10^3)$
Common within-network between-study variance	0.39	(0.00 - 4.47)	
Evaluation of inconsistency using the design-by-treatme	ent interaction model	NA - all closed loops are fo	rmed from a multi-arm study
Autism/Dyspraxia - Sensitivity Analysi	s - Maternal Alcohol U	se (1 study, 156 patients, 4	4 treatments)
	Excluded due to	_	_
Carbamazepine vs Control	zero events		
Lamotrigine vs Control	4.65	(0.21 - 100.00)	-
Valproate vs Control	7.75	(0.42 - 142.86)	-
Common within-network between-study variance	1.91	(0.36 - 10.13)	
Evaluation of inconsistency using the design-by-treatme	ent interaction model	NA	NA
Autism/Dyspraxia - Sensitivity	Analysis - Low Risk of	Bias: "Adequacy of Follow	w-up''
(3 studie	s, 2,244 patients, 10 tre	atments)	3
Carbamazepine vs Control	3.97	$(0.17 - 2.4 \times 10^3)$	$(0.11 - 3.0 \times 10^3)$
Carbamazepine+Clonazepam vs Control	7.48	$(0.01 - 7.8 \times 10^3)$	$(0.01 - 9.0 \times 10^3)$
Carbamazepine+Lamotrigine vs Control	4.47	$(0.00 - 5.0 \times 10^3)$	$(0.00 - 5.7 \times 10^3)$
Carbamazepine+Phenytoin vs Control	7.23	$(0.01 - 6.6 \times 10^3)$	$(0.01 - 8.2 \times 10^3)$
Clonazepam vs Control	4.88	$(0.12 - 3.2 \times 10^3)$	$(0.09 - 3.8 \times 10^3)$
Lamotrigine vs Control	6.55	$(0.30 - 4.4 \times 10^3)$	$(0.21 - 4.7 \times 10^3)$
Lamotrigine+Valproate vs Control	113.50	$(2.33 - 7.8 \times 10^4)$	$(1.62 - 8.9 \times 10^4)$
Oxcarbazepine vs Control	10.23	$(0.36 - 6.8 \times 10^3)$	$(0.26 - 7.5 \times 10^3)$
Valproate vs Control	13.97	$(0.68 - 8.4 \times 10^3)$	$(0.47 - 1.0 \times 10^4)$
Common within-network between-study variance	0.23	(0.00 - 2.88)	
Evaluation of inconsistency using the design-by-treatme	ent interaction model	Chi-square test: 2.17 Degrees of Freedom: 3	P-value: 0.54 Heterogeneity: 0.00
Autism/Dyspraxia - Sensitivity A	nalysis - Low Risk of B	ias: "Comparability of Co	ohorts''
(4 studie	s, 2,395 patients, 12 tre	atments)	
Carbamazepine vs Control	9.55	(0.90 - 246.20)	(0.61 - 329.40)

### **BMJ Open**

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI
Carbamazepine+Clonazepam vs Control	13.58	$(0.01 - 1.3 \times 10^3)$	(0.01 - 1.6 x 10
Carbamazepine+Lamotrigine vs Control	7.11	(0.01 - 614.20)	(0.01 - 717.60)
Carbamazepine+Phenytoin vs Control	10.97	$(0.01 - 1.1 \times 10^3)$	(0.01 - 1.4 x 10
Clonazepam vs Control	8.33	(0.45 - 263.10)	(0.33 - 353.70)
Lamotrigine vs Control	10.98	(1.07 - 283.50)	(0.71 - 358.20)
Lamotrigine+Valproate vs Control	194.10	$(8.06 - 8.4 \times 10^3)$	(6.28 - 1.0 x 10 <sup>°</sup>
Levetiracetam vs Control	4.25	(0.00 - 390.90)	(0.00 - 485.30)
Oxcarbazepine vs Control	17.60	(1.22 - 552.20)	(0.86 - 727.40)
Phenytoin vs Control	9.76	(0.01 - 861.60)	(0.01 - 1.0 x 10
Valproate vs Control	21.06	(1.86 - 525.40)	(1.25 - 681.90)
Common within-network between-study variance	0.19	(0.00 - 2.43)	
Evaluation of inconsistency using the design-by-treatment	t interaction model	Chi-square test: 3.36 Degrees of Freedom: 5	P-value: 0.64 Heterogeneity: 0.00
Autism/Dyspraxia - Sensitivity Analy	sis - Maternal IQ (1	study, 77 patients, 6 treat	ments)**
Carbamazepine+Clonazepam vs Carbamazepine	1.86	(0.07 - 47.62)	-
Carbamazepine+Lamotrigine vs Carbamazepine	1.18	(0.05 - 27.78)	-
Carbamazepine+Phenytoin vs Carbamazepine	1.86	(0.07 - 47.62)	-
Lamotrigine+Valproate vs Carbamazepine	15.87	(1.87 - 142.86)	-
Valproate vs Carbamazepine	1.33	(0.18 - 10.20)	-
Common within-network between-study variance	NA	NA	
Evaluation of inconsistency using the design-by-treatment	t interaction model	NA	NA

Abbreviations: NMA – Network Meta-analysis; OR – odds ratio; CrI – Credible Interval; PrI – Predictive Interval

\*\* Network did not include a control arm, comparison with Carbamazepine is reported instead

# **BMJ Open**

### Comparative safety of anti-epileptic drugs for neurological development in children exposed during pregnancy and breastfeeding: a systematic review and network metaanalysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2017-017248.R2
Article Type:	Research
Date Submitted by the Author:	01-Jun-2017
Complete List of Authors:	Veroniki, Areti Angeliki; Li Ka Shing Knowledge Institute, St. Michael's Hospital Rios, Patricia; Li Ka Shing Knowledge Institute, St. Michael's Hospital Cogo, Elise; Li Ka Shing Knowledge Institute, St. Michael's Hospital Straus, Sharon; Li Ka Shing Knowledge Institute, St. Michael's Hospital; University of Toronto, Department of Medicine Finkelstein, Yaron; The Hospital for Sick Children; University of Toronto, Department of Paediatrics Kealey, M.; Li Ka Shing Knowledge Institute, St. Michael's Hospital Reynen, Emily; Li Ka Shing Knowledge Institute, St. Michael's Hospital Soobiah, Charlene; Li Ka Shing Knowledge Institute, St. Michael's Hospital; University of Toronto, Institute for Health Policy Management & Evaluation Thavorn, Kednapa; University of Ottawa, School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine; The Ottawa Hospital Research Institute, Clinical Epidemiology Program Hutton, Brian; University of Ottawa, School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine; Ottawa Hospital Research Institute, Center for Practice Changing Research Hemmelgarn, BR; University of Calgary, Departments of Medicine and Community Health Sciences Yazdi, Fatemeh; Li Ka Shing Knowledge Institute, St. Michael's Hospital D'Souza, Jennifer; Li Ka Shing Knowledge Institute, St. Michael's Hospital MacDonald, Heather; Li Ka Shing Knowledge Institute, St. Michael's Hospital Tricco, Andrea; Li Ka Shing Knowledge Institute, St. Michael's Hospital University of Toronto, Epidemiology Division, Dalla Lana School of Public Health
<b>Primary Subject Heading</b> :	Neurology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	multiple treatment meta-analysis, knowledge synthesis, Epilepsy < NEUROLOGY, pregnancy, infants, developmental delay



2
2
3
4
5
6
7
0
8
9
10
11
40
12
13
14
15
16
10
17
18
19
20
20
21
22
23
2/
24 05
25
26
27
28
20
29
30
31
32
02
33
34
35
36
07
37
38
39
40
11
41
42
43
44
15
40
46
47
48
10
73
50
51
52
52
55
54
55
56
57
50
20
59
60

1

2

3

# Comparative safety of anti-epileptic drugs for neurological development in children exposed during pregnancy and breastfeeding: a systematic review and network meta-analysis Areti Angeliki Veroniki, PhD, MSc<sup>1</sup> Email: VeronikiA@smh.ca

4	Areti Angeliki Veroniki, PhD, MSc <sup>1</sup>	Email: <u>VeronikiA@smh.ca</u>
5	Patricia Rios, MSc <sup>1</sup>	Email: <u>RiosP@smh.ca</u>
6	Elise Cogo, ND, MLIS <sup>1</sup>	Email: <u>CogoE@smh.ca</u>
7	Sharon E. Straus, MD, MSc <sup>1,2</sup>	Email: <u>Sharon.straus@utoronto.ca</u>
8	Yaron Finkelstein, MD <sup>3,4,5</sup>	Email: <u>Yaron.Finkelstein@sickkids.ca</u>
9	Ryan Kealey, PhD <sup>1</sup>	Email: <u>ryan.kealey@utoronto.ca</u>
10	Emily Reynen, MD, CM, PharmD <sup>1</sup>	Email: <u>ereynen@gmail.com</u>
11	Charlene Soobiah, PhD (Cand.) <sup>1,6</sup>	Email: <u>SoobiahC@smh.ca</u>
12	Kednapa Thavorn, PhD <sup>7,8,9</sup>	Email: <u>kthavorn@ohri.ca</u>
13	Brian Hutton, PhD, MSc <sup>7,10</sup>	Email: <u>bhutton@ohri.ca</u>
14	Brenda R. Hemmelgarn, MD, PhD <sup>11</sup>	Email: <u>Bhemmelg@ucalgary.ca</u>
15	Fatemeh Yazdi, MSc <sup>1</sup>	Email: <u>SabaghYazdiF@smh.ca</u>
16	Jennifer D'Souza, HBSc <sup>1</sup>	Email: jennifer.dsouza@mail.utoronto.ca
17	Heather MacDonald, MSc <sup>1</sup>	Email: <u>hrmacdonald@gmail.com</u>
18	Andrea C. Tricco, PhD, MSc <sup>1,12,*</sup>	Email: <u>TriccoA@smh.ca</u>
19	AUTHOR DETAILS	

- 20 <sup>1</sup> Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria Street, East Building,
- 21 Toronto, Ontario, M5B 1W8, Canada

### BMJ Open

2		
3 4	22	<sup>2</sup> Department of Medicine, University of Toronto, 27 King's College Circle, Toronto, Ontario
5 6 7	23	M5S 1A1, Canada
7 8 9	24	<sup>3</sup> The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canad
10 11	25	<sup>4</sup> Department of Paediatrics, University of Toronto, 172 St. George Street, Toronto, Ontario,
12 13 14	26	M5R 0A3, Canada
15 16	27	<sup>5</sup> Department of Pharmacology and Toxicology, University of Toronto, Medical Sciences
17 18 10	28	Building, Room 4207, 1 King's College Circle, Toronto, Ontario, M5S 1A8, Canada
20 21	29	<sup>6</sup> Institute for Health Policy Management & Evaluation, University of Toronto, 4th Floor,
22 23	30	155 College Street, Toronto, Ontario, M5T 3M6, Canada
24 25 26	31	<sup>7</sup> School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine,
27 28	32	University of Ottawa, Roger-Guindon Building, 451 Smyth Road, Ottawa, Ontario, K1H 8M5
29 30 21	33	Canada
32 33	34	<sup>8</sup> Clinical Epidemiology Program, Ottawa Hospital Research Institute, The Ottawa Hospital,
34 35	35	501 Smyth Road, Ottawa, Ontario, K1H 8L6, Canada
36 37 38	36	<sup>9</sup> Institute of Clinical and Evaluative Sciences (ICES uOttawa), 1053 Carling Avenue, Ottawa
39 40	37	Ontario, K1Y 4E9, Canada
41 42 43	38	<sup>10</sup> Ottawa Hospital Research Institute, Center for Practice Changing Research, The Ottawa
43 44 45	39	Hospital–General Campus, 501 Smyth Road, PO Box 201B, Ottawa, Ontario, K1H 8L6,
46 47	40	Canada.
48 49 50	41	<sup>11</sup> Departments of Medicine and Community Health Sciences, University of Calgary, TRW
51 52	42	Building, 3rd Floor, 3280 Hospital Drive NW, Calgary, Alberta, T2N 4Z6, Canada
53 54 55	43	<sup>12</sup> Epidemiology Division, Dalla Lana School of Public Health, University of Toronto, 6th
56 57	44	Floor, 155 College Street, Toronto, Ontario, M5T 3M7, Canada
58 59		
60		

# **\*Corresponding author**

- 46 Prof. Andrea C. Tricco, PhD
- 47 Scientist, Knowledge Translation Program,
- 48 Li Ka Shing Knowledge Institute, St. Michael's Hospital,
- 49 209 Victoria Street, East Building, Toronto, Ontario, M5B 1W8, Canada
  - 50 Phone: 416-864-6060, Fax: 416-864-5805, Email: <u>TriccoA@smh.ca</u>

- **Keywords:** multiple treatment meta-analysis, knowledge synthesis, epilepsy, pregnancy,
- 53 infants, developmental delay.
- **Word count**: abstract (300 words); main text (4,000 words); 2 tables; 3 figures; 3
- 55 additional files; 51 references

Page 5 of 90

**BMJ Open** 

1		
2 3 4	56	ABSTRACT
5 6 7	57	Objectives: Compare the safety of anti-epileptic drugs (AEDs) on neurodevelopment of
8 9	58	infants/children exposed in-utero or during breastfeeding.
10 11 12	59	Design and Setting: Systematic review and Bayesian random-effects network meta-
13 14	60	analysis (NMA). Medline, EMBASE, and the Cochrane Central Register of Controlled Trials
15 16 17	61	were searched until April 27 <sup>th</sup> , 2017. Screening, data abstraction, and quality appraisal
18 19	62	were completed in duplicate by independent reviewers.
20 21 22	63	<b>Participants</b> : 29 cohort studies including 5,100 infants/children.
22 23 24	64	Interventions: Mono- and poly-therapy AEDs including first-generation (carbamazepine,
25 26	65	clobazam, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproate) and
27 28 29	66	newer-generation (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate,
30 31	67	vigabatrin) AEDs. Epileptic women who did not receive AEDs during pregnancy or
32 33 34	68	breastfeeding served as the control group.
35 36	69	Primary and secondary Outcome measures: Cognitive developmental delay and
37 38 20	70	autism/dyspraxia were primary outcomes. Attention deficit hyperactivity disorder,
39 40 41	71	language delay, neonatal seizures, psychomotor developmental delay, and social
42 43	72	impairment were secondary outcomes.
44 45 46	73	Results: The NMA on cognitive developmental delay (11 cohort studies, 933 children, 18
47 48	74	treatments) suggested among all AEDs only valproate was statistically significantly
49 50	75	associated with more children experiencing cognitive developmental delay when compared
52 53	76	with control (odds ratio (OR)=7.40, 95% credible interval (CrI): 3.00-18.46). The NMA on
54 55	77	autism (5 cohort studies, 2,551 children, 12 treatments), suggested that oxcarbazepine
56 57 58	78	(OR=13.51, CrI: 1.28-221.40), valproate (N=485, OR=17.29, 95% CrI: 2.40-217.60),
59 60		4

lamotrigine (OR=8.88, CrI: 1.28-112.00), and lamotrigine+valproate (OR=132.70, CrI:
7.41-3,851.00) were associated with significantly greater odds of developing autism
compared with control. The NMA on Psychomotor developmental delay (11 cohort studies,
1,145 children, 18 treatments) found that valproate (OR=4.16, CrI: 2.04-8.75) and
carbamazepine+phenobarbital+valproate (OR=19.12, CrI: 1.49-337.50) were associated
with significantly greater odds of psychomotor delay compared with control.
Conclusions: Valproate alone or combined with another AED is associated with the
greatest odds of adverse neurodevelopmental outcomes compared with control.
Oxcarbazepine and lamotrigine were associated with increased occurrence of autism.
Counselling is advised for women considering pregnancy to tailor the safest regimen.
Registration: PROSPERO database (CRD42014008925).
Keywords: multiple treatment meta-analysis, knowledge synthesis, epilepsy, pregnancy,
infants, developmental delay.
ARTICLE SUMMARY
Strengths and limitations of this study
Strengths and minutions of this study
• 29 cohort studies involving 5,100 children of women who took AEDs were included
in this systematic review. More evidence from long-term follow-up studies is
required.
• This study was the first that compared and ranked the safety of AEDs, including
comparative safety of treatments that have not been directly compared.

1 2			
2 3 4	100	٠	Across all neurological outcomes and treatments compared with control, valproate
5 6 7	101		alone or combined with another AED is associated with the greatest odds of adverse
7 8 9	102		development.
10 11	103	•	Oxcarbazepine and lamotrigine were associated with increased occurrence of
$\begin{array}{c} 12\\ 13\\ 14\\ 56\\ 17\\ 89\\ 02\\ 12\\ 23\\ 45\\ 26\\ 7\\ 89\\ 03\\ 33\\ 33\\ 33\\ 33\\ 33\\ 30\\ 41\\ 23\\ 44\\ 56\\ 7\\ 89\\ 01\\ 22\\ 35\\ 55\\ 56\\ \end{array}$	104		autism.

**INTRODUCTION** 

Anti-epileptic drugs (AEDs) are used by pregnant women for various conditions, such as epilepsy, pain syndromes, psychiatric disorders, and chronic migraine.<sup>1</sup> AED use during pregnancy is associated with risks to the fetus, as these drugs can cross the placenta or may be transferred to the infant through breastfeeding and may be associated with adverse neurodevelopment outcomes.<sup>2-4</sup> Two systematic reviews examined the association between AED exposure and neurodevelopment *in utero*, and reported that exposure to valproate was linked to significantly lower IQ scores and poorer overall neurodevelopmental outcomes in the children of women who used these medications.<sup>56</sup> No significant associations were found between neurodevelopment and exposure to other AEDs such as carbamazepine, lamotrigine, or phenytoin.<sup>5-8</sup> However, there is a lack of sufficiently powered studies to assess the impact of AEDs on neurodevelopment in children of women exposed to these agents, especially for newer generation drugs, thus highlighting the need for a systematic review.910 The aim of this study was to compare the safety of AEDs and assess their impact on neurodevelopment in infants and children exposed *in-utero* or during breastfeeding, employing a systematic review and network meta-analysis (NMA). 

# METHODS The methods are briefly described here; details can be found in the published protocol (Additional File 1).<sup>11</sup> This study was registered with PROSPERO (CRD42014008925). We followed the ISPOR<sup>12</sup> guidelines for our NMA, and reported our findings using the PRISMA extension for NMA (Additional File 2).<sup>13</sup> Eligibility criteria All randomized clinical trials (RCTs), quasi-RCTs, and observational studies were eligible.

Included studies assessed infants or children  $\leq 12$  years of age whose mothers consumed AEDs during pregnancy and/or while breastfeeding. Both mono- and poly-therapy AEDs were eligible, including first-generation (i.e., carbamazepine, clobazam, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproate) and newer-generation (i.e., marketed >1990: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin), with no restrictions on AED dosage. Placebo, no AED, other AEDs alone or in combination, were considered as comparators. Duplicate studies that used the same registry or population sample (i.e., companion studies) were used for supplementary information only. No language or other restrictions were imposed. The primary neurological outcomes were cognitive developmental delay and autism/dyspraxia, and the secondary outcomes included attention deficit hyperactivity disorder (ADHD), language delay, neonatal seizures, psychomotor developmental delay, and social impairment. Table 1 shows the outcome measures and diagnostic scales used. We initially intended to evaluate all safety outcomes in infants/ children exposed to AEDs *in-utero* or during breastfeeding in one publication, but given the breadth of evidence we

1 2			
2 3 4	144	identified, we report results related to risk of major congenital malformations, birth, and	
5 6 7	145	prenatal outcomes in a companion paper. <sup>14</sup>	
7 8 9	146	Information sources	
10 11	147	An experienced librarian executed search strategies for MEDLINE, EMBASE, and the	
12 13 14	148	Cochrane Central Register of Controlled Trials up to March 18, 2014, and then updated the	ì
15 16	149	search in April 27 <sup>th</sup> 2017. The search strategy for MEDLINE was peer-reviewed by another	ſ
17 18 19	150	librarian using the PRESS checklist, <sup>15</sup> and is available in the protocol. <sup>11</sup> Additional studies	
20 21	151	were identified by scanning references and contacting authors. Unpublished studies were	
22 23 24	152	sought by searching clinical trial registries and conference abstracts.	
24 25 26	153	Study selection and data collection	
27 28	154	After a calibration exercise, titles/abstracts (level 1) and full-text papers (level 2) were	
29 30 31	155	screened by two reviewers independently. Upon completion of level 1, 6% of citations wer	e
32 33	156	discrepant between reviewer pairs, whereas at the conclusion of level 2, 16% of articles	
34 35 36	157	were discrepant. Conflicts were resolved through discussion or by a third reviewer. The	
37 38	158	same approach was used for data abstraction and appraisal of methodological quality.	
39 40	159	Three rounds of pilot testing were conducted prior to data abstraction to train reviewers	
41 42 43	160	and refine the data abstraction form. For studies published in the last 10 years, authors	
44 45	161	were contacted to request clarification or additional data.	
46 47 48	162	Appraisal of methodological quality	
49 50	163	Only observational studies were identified and included for analysis, and their	
51 52 53	164	methodological quality was appraised with the Newcastle-Ottawa Scale (NOS) (Additional	
54 55	165	File 3: Appendix A). <sup>16</sup> For each outcome with $\geq$ 10 studies, the comparison-adjusted funnel	
56 57	166	plot was used to assess small-study effects, <sup>17</sup> where the overall treatment effect for each	
50 59 60			9

1 2		
3 4	167	comparison was estimated under the fixed-effect meta-analysis model. All eligible
5 6 7	168	medications were ordered from oldest to newest using their international market approval
8 9	169	dates. Hence, the comparison-adjusted funnel plot additionally assesses the hypothesis that
10 11	170	newer AEDs are favoured over older ones. To overcome some of the correlations induced
12 13 14	171	by multi-arm studies, which may cause overestimation and mask funnel plot asymmetry,
15 16	172	we plotted data points corresponding to the study-specific basic parameters (treatment
17 18 10	173	comparisons with common comparator). In each study, we used the control group as the
20 21	174	common comparator or if this was missing, we used the oldest treatment comparator
22 23	175	against the remaining AEDs.
24 25 26 27 28 29	176	Synthesis of included studies
	177	We used the odds ratio (OR) for each dichotomous outcome, and outcome data were
29 30 31	178	pooled using hierarchical meta-analysis and NMA models and the Markov Chain Monte
32 33	179	Carlo sampling method in a Bayesian framework. To account for anticipated
34 35 26	180	methodological and clinical heterogeneity across studies, and to achieve the highest
36 37 38	181	generalizability in the meta-analytical treatment effects, we applied a random-effects
39 40	182	model. <sup>18</sup>
41 42 43	183	A NMA was applied for connected evidence networks and pre-specified treatment nodes. <sup>19</sup>
44 45	184	We assessed the transitivity assumption for each outcome <i>a priori</i> using the effect
46 47 48	185	modifiers: age, baseline risk, treatment indication, timing, and methodological quality. The
49 50	186	mean of each continuous effect modifier and the mode of each categorical effect modifier
51 52	187	for each pairwise comparison were presented in tables for each outcome. <sup>20</sup> The consistency
53 54 55	188	assumption was evaluated for the entire network of each outcome using the random-
56 57	189	effects design-by-treatment interaction model when multiple studies were available in
ວຽ 59 60		10

1
2
3
4
5
5
6
7
8
à
10
10
11
12
13
14
14
15
16
17
18
10
19
20
21
22
23
23
24
25
26
27
21
28
29
30
31
20
32
33
34
35
26
30
37
38
39
40
40
41
42
43
44
45
46
47
48
40
49
50
51
52
52
55
54
55
56
57
57
58
59
60

1

190 each network design or the fixed-effect design-by-treatment interaction model when a 191 single study informed each network design.<sup>21</sup> If inconsistency was identified, further 192 examination for local inconsistency in parts of the network was completed using the loopspecific method.<sup>22 23</sup> Common within-network between-study variance ( $\tau^2$ ) across 193 194 treatment comparisons was assumed in the meta-analysis, NMA, and design-by-treatment 195 interaction model, so that treatment comparisons including a single study can borrow 196 strength from the remaining network. This assumption was clinically reasonable, as the 197 treatments included were of the same nature. In the loop-specific approach, common 198 within-loop  $\tau^2$  was assumed. 199 For cognitive developmental delay and autism/dyspraxia outcomes, network meta-200 regression analyses for maternal age and baseline risk (i.e., using the control group) were 201 conducted, when  $\geq 10$  studies provided relevant information, assuming a common fixed 202 coefficient across treatment comparisons for AEDs vs. control. Sensitivity analyses for 203 cognitive developmental delay and autism/dyspraxia outcomes were performed for 204 treatment indication of epilepsy, large study size (i.e., >300), maternal alcohol intake, 205 maternal tobacco use, only first-generation AEDs, and methodological quality. The 206 sensitivity analysis for methodological quality was restricted to studies with low risk of 207 bias for the two items on the NOS where the greatest proportion of studies received a low-208 quality score: adequacy of follow-up of cohorts and comparability of cohorts. For 209 autism/dyspraxia, a sensitivity analysis on maternal IQ/psychiatric history was 210 additionally conducted. We measured the goodness of fit using the posterior mean of the 211 residual deviance, the degree of  $\tau^2$ , and the deviance information criterion (DIC). In a well-212 fitting model the posterior mean residual deviance should be close to the number of data

Page 13 of 90

1

 $\begin{array}{r} 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 55\\ 56\\ 57\\ 58\\ 59\\ \end{array}$ 

60

### **BMJ Open**

2		
3 4 5 6 7	213	points. <sup>24 25</sup> A difference of 3 units in the DIC between a NMA and a network meta-
	214	regression model was considered important and the lowest value of the DIC corresponded
8 9	215	to the model with the best fit. <sup>24 25</sup>
10 11	216	All analyses were conducted in OpenBUGS <sup>26</sup> assuming non-informative priors for all model
12 13 14	217	parameters, and $\tau \sim N(0,1)$ , $\tau > 0$ . The first 10,000 iterations were discarded and then
15 16	218	100,000 simulations were run with thinning of 10 values. Convergence was checked by
17 18 10	219	visual inspection of the evaluation of the mixing of two chains. The median and 95% CrI
20 21	220	were calculated for each parameter value. The <i>network</i> command <sup>27</sup> was used to apply the
22 23	221	design-by-treatment interaction model.
24 25 26 27 28 29 30 31 32 33	222	For NMA estimates, a 95% predictive interval (PrI) is also reported to capture the
	223	magnitude of $ au^2$ and present the interval within which the treatment effect of a future
	224	study is expected to lie. <sup>28 29</sup> The estimated safety of the included AEDs was ranked using the
	225	surface under the cumulative ranking (SUCRA) curve. <sup>30</sup> The larger the SUCRA for a
34 35	226	treatment, the higher its safety rank among all the available treatment options. SUCRA
36 37 38	227	values are presented along with 95% CrIs to capture the uncertainty in the parameter
39 40	228	values. <sup>31</sup>
41 42		
43 44		

### RESULTS

### Literature search and included studies

Our literature search identified 5,707 titles and abstracts, which after the screening process yielded 681 articles potentially relevant for inclusion (Figure 1). After full-text review, 95 studies fulfilled eligibility criteria along with 17 studies identified through supplemental methods. Of the 112 total eligible studies in the complete review,<sup>14</sup> 29 articles with seven companion reports and two potentially overlapping registry studies included one or more relevant neurological outcomes (Additional File 3: Appendix B). Four of the studies included in this analysis were conference abstracts with usable data.<sup>32-35</sup> and four studies,<sup>36-39</sup> not captured in the original literature search, were identified through reference scanning. A table with the key excluded studies and a rationale for their exclusion is presented in Additional File 3: Appendix C. Study and patient characteristics We included 29 cohort studies (5,100 patients) published between 1989 and 2016 (Table 2; Additional File 3: Appendix D, E). The number of patients included in each study ranged from 23 to 2,011 (median 74.5). Most studies (76%) were published after 2000, 62% of the studies included fewer than 100 patients, and the 52% of the studies included a control group of pregnant/breastfeeding women with epilepsy who did not receive AEDs. The mean maternal age ranged from 24 to 34 years. About half of the studies (52%) were funded through government/public research funding. 

Methodological quality results 

Twenty-nine observational studies were appraised using the NOS (Additional File 3:

Appendix F). Overall, the studies were of good methodological quality and were rated as

### **BMJ Open**

3 4	252	high quality across most items: 28 studies (97%) selected the non-exposed cohort from	the
5 6 7	253	same community as the exposed cohort, 26 (90%) included a representative or somewhat	at
7 8 9	254	representative sample, 27 (93%) assessed outcomes independently, with blinding, or via	a
10 11	255	record linkage (e.g., identified through database records), and 23 (79%) ascertained	
12 13 14	256	exposure via secured records (e.g., database records) or structured interviews. The	
15 16	257	comparability of cohorts and adequacy of follow-up were the lowest scoring items acros	S
17 18	258	the studies with only 12 (41%) and 10 (34%) studies rated as high quality on these item	s.
19 20 21	259	No evidence for small-study effects was identified by the visual inspection of the	
22 23	260	comparison-adjusted funnel plots (Additional File 3: Appendix G).	
24 25 26	261	Statistical analysis results	
20 27 28	262	No important concerns were raised regarding the violation of the transitivity assumption	n
29 30	263	when maternal age, baseline risk, treatment indication, and timing were assessed	
31 32 33	264	(Additional File 3: Appendix H). However, the average methodological quality appraisal	
34 35	265	across treatment comparisons varied across treatment comparisons. The evaluation of the	he
36 37 38	266	consistency assumption using the design-by-treatment interaction model suggested that	-
39 40	267	there was no evidence of significant inconsistency across all outcomes (Additional File 3	:
41 42 42	268	Appendix H).	
43 44 45	269	In the following sections, we present the significant NMA results by outcome for AEDs	
46 47	270	compared with control (i.e., no exposure to AEDs), while the SUCRA values from all	
48 49 50	271	outcomes are presented in Figure 2 and depicted in a rank-heat plot ( <u>http://rh.ktss.ca/</u> ) <sup>4</sup>	40
50 51 52	272	in Additional File 3: Appendix I.	
53 54	273	Cognitive developmental delay	
55 56 57			
58 59			1 /
60			14

2	
3	
4	1
5	
6	4
7	
8	2
9 10	
10	
12	
12	
14	4
15	
16	4
17	
18	2
19	
20	
21	4
22	
23	4
24	
25	2
26	
27	;
28	-
29	
30 31	4
32	
33	4
34	
35	2
36	
37	
38	•
39	
40	4
41	
42	2
43	
44 45	2
45 46	
40 17	
47 78	4
40 40	
50	4
51	
52	2
53	
54	:
55	•
56	
57	
58	
59	
60	

1

274	The NMA for cognitive developmental delay (definitions in Table 1) included 11 cohort
275	studies, 933 children, and examined 18 treatments (Figure 3a; Additional File 3: Appendix
276	J; $\tau^2$ =0.12, 95% CrI: 0.00-1.15). One study included children exposed to AEDs both <i>in-utero</i>
277	and through breastfeeding, and ten included children exposed to AEDs in-utero. Across all
278	AEDs, only valproate was associated with significantly increased odds of cognitive
279	developmental delay when compared with control (odds ratio (OR)=7.40, 95% credible
280	interval (CrI): 3.00-18.46; Figure 2a; Additional File 3: Appendix H).
281	The same results were observed in a network meta-regression of baseline risk for offspring
282	of women with epilepsy who were not exposed to AEDs (estimated regression coefficient
283	on OR scale: 1.01, 95% CrI: 0.76-1.56; τ²=0.16, 95% CrI: 0.00-1.24; residual deviance=
284	45.27, data points= 47, DIC= 80.17). Similarly, the sensitivity analyses restricted to: a)
285	studies that only included women receiving AEDs to treat epilepsy (10 studies, 910
286	children, 17 treatments; $\tau^2$ =0.16, 95% CrI: 0.00-1.36), b) studies comparing only first-
287	generation AEDs (6 studies, 480 children, 13 treatments; $\tau^2$ =0.28, 95% CrI: 0.00-2.97), c)
288	studies that reported maternal alcohol or tobacco use (3 studies, 504 children, 7
289	treatments; $\tau^2$ =0.27, 95% CrI: 0.00-3.29), and d) studies with high methodological quality
290	on NOS item 'comparability of cohorts' (3 studies, 366 children, 7 treatments; $\tau^2$ =0.38, 95%
291	CrI: 0.00-4.14), were consistent with the NMA results (Additional File 3: Appendix K). The
292	sensitivity analysis with studies of high methodological quality on the NOS item 'adequacy
293	of follow-up' found no statistically significant results (4 studies, 283 patients, 12
294	treatments; $\tau^2$ =1.01, 95% CrI: 0.01-5.85; Additional File 3: Appendix K).
295	Autism/dyspraxia

Page 17 of 90

1

### **BMJ Open**

2	
3 ₄	2
4 5	
6	2
7 8	2
9	2
10 11	2
12	
13 14	3
15	2
16 17	5
18	3
19	
20 21	3
22	3
23 24	0
25	3
26 27	2
28	3
29 30	3
31	
32 33	3
34	2
35 36	З
37	3
38 39	
40	3
41 42	3
43	0
44 45	3
46	0
47 48	3
49	3
50 51	-
52	3
53 54	n
55	3
56	
ว/ 58	
59	
60	

296	The NMA on autism/dyspraxia (definitions in Table 1) included five cohort studies, 2,551
297	children exposed <i>in utero</i> , and examined 12 treatments ( $\tau^2$ =0.16, 95% CrI: 0.00-1.95;
298	Figure 3b; Additional File 3: Appendix H). Compared with control, only valproate
299	(OR=17.29, 95% CrI: 2.40-217.60), oxcarbazepine (OR= 13.51, 95% CrI: 1.28-221.40),
300	lamotrigine (OR= 8.88, 95% CrI: 1.28-112.00), and lamotrigine+valproate (OR=132.70,
301	95% CrI: 7.41-3851.00) were significantly associated with increased occurrence of
302	autism/dyspraxia (Figure 2b).
303	Restricting the NMA to studies including only women with epilepsy as their treatment
304	indication produced results that were generally in agreement with the NMA results, except
305	that oxcarbazepine was no longer in the network (4 cohort studies, 540 children, 10
306	treatments; $\tau^2$ =0.31, 95% CrI: 0.00-304). Two cohort studies of 404 offspring of women
307	with a history of tobacco use compared 4 treatments and found similar results except that
308	oxcarbazepine and lamotrigine+valproate were no longer in the network ( $ au^2$ =0.39, 95%
309	CrI: 0.00-4.47). The results were in agreement in sensitivity analyses including only higher
310	methodological quality studies in the 'comparability of cohorts' item on the NOS (4 studies,
311	2,395 children, 12 treatments; $\tau^2$ =0.19, 95% CrI: 0.00-2.43) and the 'adequacy of follow-up
312	of cohorts' (3 studies, 2244 children, 10 treatments; $\tau^2$ =0.23, 95% CrI: 0.00-2.88), except
313	that lamotrigine was no longer statistically significant than control for the latter
314	(Additional File 3: Appendix K).
315	Neonatal Seizure
316	One cohort study included 72 children who were exposed to AEDs in-utero as well as
317	through breastfeeding reported on the incidence of neonatal seizures. The study compared

2		
3 4	318	valproate against lamotrigine and found no significant difference in neonatal seizures
5 6 7	319	between the two drugs (OR=0.18, 95% CI: 0.01-3.70).
7 8 9	320	Psychomotor developmental delay
10 11	321	The NMA on psychomotor developmental delay (definitions in Table 1) included 11 cohort
12 13 14	322	studies, 1,145 children exposed <i>in utero</i> , and examined 18 treatments ( $\tau^2$ =0.06, 95% CrI:
15 16	323	0.00-0.63; Figure 3c; Additional File 3: Appendices H, J). Valproate (OR=4.16, 95% CrI:
17 18 10	324	2.04-8.75) and carbamazepine+phenobarbital+valproate (OR=19.12, 95% CrI: 1.49-
20 21	325	337.50) were significantly more harmful than control (Figure 2c).
22 23	326	Language delay
24 25 26	327	The NMA on language delay (definitions in Table 1) included five cohort studies, 509
20 27 28	328	children, and examined five treatments ( $\tau^2$ =0.16, 95% CrI: 0.00-2.15; Figure 3d; Additional
29 30	329	File 3: Appendices H, J). One study included children exposed to AEDs <i>in-utero</i> and through
31 32 33	330	breastfeeding, and four included children exposed to AEDs in-utero. Compared with
34 35	331	control, valproate was the only treatment significantly associated with increased odds of
36 37 38	332	language delay (OR=7.95, 95% CrI: 1.50-49.13; Figure 2d).
39 40	333	Attention deficit hyperactivity disorder
41 42 43	334	The NMA on ADHD (definitions in Table 1) included five cohort studies, 816 children, and
44 45	335	examined seven treatments ( $\tau^2$ =0.11, 95% CrI: 0.00-1.29). One study included children
46 47	336	exposed to AEDs in-utero and through breastfeeding, while four studies included children
48 49 50	337	exposed to AEDs in-utero. None of the treatment comparisons reached statistical
51 52	338	significance (Figure 3e; Figure 2e; Additional File 3: Appendices H, J).
53 54 55	339	Social Impairment
56 57 58		
59 60		17

1

Page 19 of 90

### **BMJ Open**

2		
3 4	340	One cohort study included 422 children exposed to AEDs in-utero as well as through
5 6 7	341	breastfeeding. The children were exposed to carbamazepine (n=48), lamotrigine (n=71),
7 8 9	342	valproate (n=27) and control (n=278). No significant differences in social impairment were
10 11	343	identified. <sup>41</sup>
$\begin{array}{c}12\\13\\14\\56\\78\\90\\12\\22\\22\\22\\22\\22\\22\\22\\22\\22\\22\\22\\22\\$	344	

### **DISCUSSION**

Our results suggest that AEDs generally pose a risk for infants and children exposed *in*-*utero* or during breastfeeding. Valproate was significantly associated with more children experiencing autism/dyspraxia, language, cognitive and psychomotor developmental delays versus children who were not exposed to AEDs. Oxcarbazepine, lamotrigine and lamotrigine+valproate were associated with increased occurrence of autism/dyspraxia, whereas for the cognitive developmental delay and psychomotor developmental delay outcomes, children exposed to the combination of carbamazepine, phenobarbital, and valproate were at greater odds of harm than those who were not exposed to AEDs. However, these results should be interpreted with caution, as a number of factors (e.g., anticonvulsant dosing, severity of epilepsy, duration of exposure, serum concentrations of exposure, mother's IQ/education) that may all influence outcomes were not identified in these studies. Also, our subsequent analyses may be underpowered due to missing data (e.g., 17 of the 27 studies did not report maternal age, 23 of 27 studies did not report alcohol use, 22 of 27 studies did not report tobacco use, and 14 of 27 studies did not include control group). NMA is a particularly useful tool for decision-makers because it allows the ranking of

361 NMA is a particularly useful tool for decision-makers because it allows the ranking of
362 treatments for each outcome. However, the results of our SUCRA curves should be
363 interpreted with caution, especially due to the small number of studies and children
364 included in each NMA, which is also reflected in the high uncertainty around the SUCRA
365 values (Figure 2).<sup>31</sup>

366 Our results are consistent with a longitudinal study of 311 children that found exposure to
367 lamotrigine was associated with significantly higher IQ scores and verbal function at six

Page 21 of 90

### **BMJ Open**

years of age compared to children exposed to valproate (Additional File 3: Appendix C).<sup>7</sup> As indicated in Additional File 3: Appendix C, we were unable to include this study because the outcome was reported as a continuous measure, where we focused on dichotomous outcomes to facilitate interpretation. Our results are supported by findings from a cohort study, which found that children exposed to levetiracetam were not at increased risk for delayed development compared to unexposed children (Additional File 3: Appendix C).<sup>42</sup> As indicated in Additional File 3: Appendix C, we were unable to include this study due to the same reason as above. A NMA of 195 RCTs (including 28,013 both male and female patients) showed that gabapentin and levetiracetam showed the best tolerability profile compared with other AEDs, whereas oxcarbazepine and topiramate had a higher withdrawal rate, and lamotrigine an intermediate withdrawal rate.<sup>43</sup> Across all outcomes, valproate alone or combined with another AED (even with a newer-generation agent, e.g., lamotrigine) was associated with the greatest odds. Similarly, two previous systematic reviews that did not conduct a NMA found valproate was associated with significantly lower IQ scores and poorer overall neurodevelopmental outcomes when compared to an unexposed control group.<sup>56</sup> Also consistent with our results, a 2014 Cochrane review including 28 studies (10 of these studies were included in the meta-analyses; with a maximum number of five studies per meta-analysis) concluded that AED polytherapy led to poorer developmental outcomes and IO compared to healthy controls, epileptic controls, and unspecified monotherapy.<sup>5</sup> This Cochrane review also concluded that insufficient data exist for newer AEDs. However, unlike our review, it included and analysed fewer studies, and did not differentiate between specific polytherapy regimens, and thus did not compare these regimens versus each other or specific monotherapy AEDs.

These risks must be balanced with the need to control seizure activity in pregnancy and 6 thus informed decision-making by patients and clinicians is critical. Strengths of our study include a comprehensive systematic review methodology that followed the Cochrane Handbook<sup>44</sup> and ISPOR<sup>12</sup> guidelines, and reported using the PRISMA extension for NMA.<sup>13</sup> To the best of our knowledge, our study was the first that compared and ranked the safety of AEDs. We evaluated the comparative safety of treatments that have not been directly compared head-to-head before. In addition, we calculated predictive intervals, which account for between-study variation and provide a predicted range for the treatment effect estimate, should a future study be conducted. On average, the predictive intervals suggested that our results are robust. Our systematic review has a few limitations worth noting. First, due to the complexity of the data and the studies' underreporting, differences in drug dosages could not be accounted for, and it was assumed that different dosages of the same AED were equally effective. When a study reported multiple dosages for the same treatment, we combined the data for this treatment. This is common for cohort studies, which report on a number of different types of exposures amongst patients. Second, several polytherapies had high SUCRA estimates but very wide CrIs, which is due to the small number of studies included for each drug combination with underpowered sample sizes. Evidence suggests that ranking probabilities for a treatment of being the best may be biased toward the treatments with the smallest number of studies, which may have influenced our SUCRA results.<sup>31 45</sup> As such, the effect sizes need to be taken into account when considering the SUCRA values. Third, due to the absence of evidence from RCTs, our conclusions were based on evidence from observational studies only, and inherent biases because of 

Page 23 of 90

### **BMJ Open**

confounding and shortcomings of these studies may have impacted our findings. For example, the included studies often failed to report important treatment effect modifiers,<sup>46</sup> such as family history of autism, ADHD, and maternal IQ, severity of epilepsy making it impossible for us to explore their impact through subgroup analysis and meta-regression. Recent research has explored methods to incorporate non-randomized with randomized evidence in a NMA and have highlighted the need to carefully explore the level of confidence in the non-randomized evidence.<sup>47 48</sup> The use of observational studies allows the assessment of the safety profile of AED treatments and offers the opportunity to evaluate effects in pregnancy.<sup>49</sup> Future large-scale observational studies are needed to allow the evaluation of rare adverse events that otherwise cannot be adequately evaluated in RCTs, especially during pregnancy. Fourth, although no intransitivity for most effect modifiers assessed was evident, there was an imbalance in the methodological study quality appraisal across treatment comparisons and most outcomes, which may impact our results. Unknown factors or factors that could not be assessed due to dearth of data may pose the risk of residual confounding bias, and hence risk the validity of the transitivity assumption. However, the assessment of consistency suggested no disagreement between the different sources of evidence in the network. Fifth, although the tendency towards small-study effects is greater with observational studies than with randomized trials,<sup>50</sup> the assessment of small-study effects using adjusted funnel plots suggested no evidence for their prevalence. Also, the majority of the included studies in this review compared multiple treatments inducing correlations in each funnel plot, which may mask asymmetry. Although we plotted data points corresponding to the study-specific basic parameters to reduce correlations, this issue may still exist. Sixth, we were unable to conduct subgroup

1 2		
3 4	437	analysis by type of exposure (breastfeeding versus <i>in utero</i> ) due to the small number of
5 6 7	438	studies included in the NMA and due to the poor reporting; 22 studies did not report
7 8 9	439	whether exposure was also in breastfeeding (additional to <i>in utero</i> ). Hence, we included all
10 11	440	studies in the analysis irrespective of the type of exposure.
12 13 14	441	More evidence from long-term follow-up studies is required to further delineate
15 16	442	neurodevelopmental risks in children. Future studies should assess the genetic
17 18 10	443	contribution from the biological father, maternal seizures during pregnancy, exposure
20 21	444	through breastfeeding only, types of epilepsy, and maternal family history. Registries
22 23	445	should aim to include a suitable control group and collect information on potential
24 25 26	446	confounders, such as alcohol and tobacco use, allowing researchers to identify the safest
27 28	447	agents for different patient-level covariates, and enhance decision-making for healthcare
29 30 31	448	providers and patients. A critical evaluation of the validity of the control group is also
32 33	449	necessary, in order to examine potential differences between the treated and the not
34 35 26	450	treated populations. An individual patient data NMA would likely provide further clarity to
36 37 38	451	the field, which allows the tailoring of management to specific patient characteristics. <sup>51</sup>
39 40	452	CONCLUSION
41 42 43	453	Across all outcomes and treatments compared with control, valproate alone or combined
44 45	454	with another AED was associated with the greatest odds, whereas oxcarbazepine and
46 47 48	455	lamotrigine were associated with increased occurrence of autism. Counselling is advised
49 50	456	for women considering pregnancy to tailor the safest regimen.
51 52 53		
53 54 55		
56		
57 58		

59

1 2 3 4	457	LIST OF ABBREVIATIONS	
5 6 7	458	AEDs: Anti-epileptic drugs; CrI: Credible interval; NMA: Network Meta-analysis; OR: Od	ds
7 8 9	459	ratio; PrI: Predictive interval; SUCRA curve: Surface under the cumulative ranking curve	Э
10 11 12	460	ADDITIONAL FILES	
13 14	461	Additional File 1: Protocol	
15 16 17 18 19	462	Additional File 2: PRISMA NMA Checklist	
20 21	463	Additional File 3: Supplementary Online Content (Appendices A-O)	
22 23 24	464	Appendix A. Newcastle-Ottawa Scale scoring guide	
25 26	465	Appendix B. List of included studies	
27 28 29	466	Appendix C. Key Excluded Studies	
30 31	467	Appendix D. Table of Individual Study Characteristics	
32 33 34	468	Appendix E. Table of Patient Characteristics	
35 36	469	Appendix F. Methodological quality of observational studies – Newcastle Ottawa Scale	
37 38 20	470	Appendix G. Comparison-adjusted funnel plots	
39 40 41	471	Appendix H. Statistically significant network meta-analysis results along with meta-	
42 43	472	analysis results, transitivity, and inconsistency assessments	
44 45 46	473	Appendix I. Rank-heat plot of cognitive developmental delay, autism/dyspraxia,	
47 48	474	psychomotor developmental delay, language delay, and attention deficit hyperactivity	
49 50 51	475	disorder outcomes	
52 53	476	Appendix J. Number of studies and treatments per outcome	
54 55	477	Appendix K. Sensitivity and network meta-regression analyses - Anti-epileptic drugs	
50 57 58 59 60	478	compared with Control	2

2
3
4
5
6
7
1
8
9
10
10
11
12
13
14
15
10
16
17
18
19
20
20
21
22
23
21
24
25
26
27
28
20
29
30
31
32
33
33
34
35
36
37
20
30
39
40
41
42
10
40
44
45
46
47
10
4ð
49
50
51
52
52
53
54
55
56
57
51
58
59
60

# 479**FIGURE LEGENDS**

### 480 **Figure 1. Study flow diagram**

481 Figure 2. Forest plots for cognitive developmental delay, autism/dyspraxia,

482 psychomotor developmental delay, language delay, and attention deficit

483 hyperactivity disorder outcome

484 Figure 3. Network diagrams for cognitive developmental delay, autism/dyspraxia,

485 **psychomotor developmental delay, language delay, and attention deficit** 

### 486 hyperactivity disorder outcomes

487 Each treatment node is weighted according to the number of patients that have received the

488 particular treatment, and each edge is weighted according to the number of studies

489 *comparing the treatments it connects.* 

490 <u>Abbreviations:</u> carbam - carbamazepine, clobaz - clobazam, clonaz - clonazepam, ethos -

491 ethosuximide, gabap - gabapentin, lamot - lamotrigine, levet - levetiracetam, oxcar -

492 oxcarbazepine, pheno - phenobarbital, pheny - phenytoin, primid - primidone, topir -

493 topiramate, valpro - valproate, vigab – vigabatrin

## **DECLARATIONS**

### **CONTRIBUTORS**

AAV analysed the data, interpreted the results, and drafted the manuscript. ACT and SES conceived and designed the study, helped obtain funding, interpreted the results, and helped write sections of the manuscript. PR and EC coordinated the review, screened citations and full-text articles, abstracted data, appraised quality, resolved discrepancies, contacted authors, and edited the manuscript. CS provided methodological support and screened citations and full-text articles and edited the manuscript. RK, ER, FY, JDS, KT, and HM screened citations and full-text articles, abstracted data, and/or appraised quality. BH, BRH and YF helped conceive the study and edited the manuscript. All authors read and approved the final manuscript.

# 30 505 ACKNOWLEDGEMENTS 31

We thank Dr. David Moher for providing his feedback on our protocol. We thank Dr. Laure Perrier for conducting the literature searches, Becky Skidmore for peer-reviewing the MEDLINE search, and Alissa Epworth for obtaining the full-text articles. We thank Alistair Scott, Wing Hui, and Geetha Sanmugalingham for screening some of the citations and/or abstracting some of the data for a few of the included studies, Misty Pratt and Mona Ghannad for helping scan reference lists, and Ana Guzman, Susan Le, and Inthuja Selvaratnam for contacting authors and formatting the manuscript. FUNDING 

516 Fellowship Program from the CIHR. SES is funded by a Tier 1 Canada Research Chair in

2		
3 4	517	Knowledge Translation. BH is funded by a CIHR/DSEN New Investigator Award in
5 6 7	518	Knowledge Synthesis. BRH receives funding from the Alberta Heritage Foundation for
7 8 9	519	Medical Research. ACT is funded by a Tier 2 Canada Research Chair in Knowledge
10 11	520	Synthesis. The funder had no role in the design and conduct of the study; collection,
12 13 14	521	management, analysis, and interpretation of the data; preparation, review, or approval of
15 16	522	the manuscript; or decision to submit the manuscript for publication.
17 18 19	523	COMPETING INTERESTS
20 21	524	None declared.
22 23	525	ETHICS APPROVAL
24 25 26	526	Not applicable.
27 28	527	PROVENANCE AND PEER REVIEW
29 30 31	528	Not commissioned; externally peer reviewed.
32 33	529	DATA SHARING STATEMENT
34 35	530	All datasets generated and/or analysed during the current study are available from the
30 37 38	531	corresponding author on reasonable request.
39 40	532	OPEN ACCESS
41 42 43	533	This is an Open Access article distributed in accordance with the Creative Commons
44 45	534	Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute,
46 47	535	remix, adapt, build upon this work non-commercially, and license their derivative works on
48 49 50	536	different terms, provided the original work is properly cited and the use is non-
51 52	537	commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.
53 54 55		
56 57		
58 59		27
bU		27

### BMJ Open

### 538 REFERENCES

7		
8	530	1 Sping F. Perugi C. Antiopilantic drugs: indications other than opilansy. <i>Epilantic Disord</i>
9	540	2004·6(2)·57-75
10	541	2 Harden CL Pennell PR Konnel RS et al Management issues for women with enilensyfocus
11	542	on pregnancy (an evidence-based review): III vitamin K folic acid blood levels and breast-feeding:
12 13	543	report of the quality standards subcommittee and therapeutics and technology assessment
14	544	subcommittee of the American Academy of Neurology and the American Enilensy Society <i>Enilensia</i>
15	545	2000-50(5)-1247-55
16	546	2 Samron FR yan Duijn CM Koch S at al Maternal use of antioniloptic drugs and the rick of
17	540	s. Same in ED, van Duijn CM, Koch S, et al. Maternal use of antiephephe ut us sand the fisk of
18	547	according with maternal onlongy <i>Enilongia</i> 1007.29(0).091.00
19	540	Associated with indicidial epilepsy. Epilepsia. 1997,50(9):901-90.
20	549	4. Meduol K, Reynolus MW, Clean S, Fambach K, Probst C. Pregnancy outcomes in women
21	550 EE1	schorte, Enilenzy Des 2000-01(1):1.12
22	221	Conorts. Epilepsy Res. 2008;81(1):1-13.
23	552	5. Bromley R, weston J, Adab N, et al. I reatment for epilepsy in pregnancy:
24 25	555	neurodevelopmental outcomes in the child. The Cochrane database of systematic reviews.
20 26	554	
20	555	6. Banach R, Boskovic R, Einarson T, Koren G. Long-term developmental outcome of children
28	556	of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of
29	55/	cohort studies. Drug Saf. 2010;33(1):73-9.
30	558	7. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive
31	559	outcomes at age 6 years (NEAD study): a prospective observational study. <i>Lancet Neurol</i> .
32	560	2013;12(3):244-52.
33	561	8. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of
34	562	autism spectrum disorders and childhood autism. <i>JAMA</i> . 2013;309(16):1696-703.
35	563	9. Wlodarczyk BJ, Palacios AM, George TM, Finnell RH. Antiepileptic drugs and pregnancy
36	564	outcomes. <i>Am J Med Genet A</i> . 2012;158a(8):2071-90.
37	565	10. Velez-Ruiz NJ, Meador KJ. Neurodevelopmental effects of fetal antiepileptic drug exposure.
30 30	566	Drug Saf. 2015;38(3):271-8.
40	567	11. Tricco AC, Cogo E, Angeliki VA, et al. Comparative safety of anti-epileptic drugs among
41	568	infants and children exposed in utero or during breastfeeding: protocol for a systematic review and
42	569	network meta-analysis. <i>Systematic reviews</i> . 2014;3:68.
43	570	12. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-
44	571	analysis study questionnaire to assess relevance and credibility to inform health care decision
45	572	making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014;17(2):157-73.
46	573	13. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of
47	574	systematic reviews incorporating network meta-analyses of health care interventions: checklist and
48	575	explanations. Ann Intern Med. 2015;162(11):777-84.
49 50	576	14. Veroniki AA, Cogo E, Rios P, et al. Comparative safety of anti-epileptic drugs during
50 51	577	pregnancy: a systematic review and network meta-analysis of congenital malformations and
52	578	prenatal outcomes. BMC Med. 2017;15(1):95.
53	579	15. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review
54	580	of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016;75:40-6.
55	581	16. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the
56	582	quality of nonrandomised studies in meta-analyses2000. Available from:
57	583	http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
58		
59		28
60		20

17. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One. 2013;8(10):e76654. Furukawa TA, Guyatt GH, Griffith LE. Can we individualize the 'number needed to treat'? An 18. empirical study of summary effect measures in meta-analyses. *Int J Epidemiol*. 2002;31(1):72-6. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment 19. comparisons. Stat Med. 2004;23(20):3105-24. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It 20. all depends on the distribution of effect modifiers. BMC Med. 2013;11:159. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-21. analysis: model estimation using multivariate meta-regression. Res Synth Methods. 2012;3(2):111-25. 22. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMI. 2003;326(7387):472. 23. Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. Int J Epidemiol. 2013;42(1):332-45. 24. Welton NJ, Sutton AJ, Cooper N, Abrams KR, Ades A. Evidence synthesis for decision making in healthcare. New York: Wiley; 2012. 25. Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Ser B Stat Methodol*. 2002;64(4):583-639. Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: Evolution, critique and future 26. directions. Stat Med. 2009;28(25):3049-67. Palmer T, Sterne J. Meta-Analysis in Stata: An Updated Collection from the Stata Journal. 27. White I, editor. Texas: Stata Press; 2016. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 28. 2011;342:d549. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. 29. *J R Stat Soc Ser A Stat Soc.* 2009;172(1):137-59. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for 30. presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin *Epidemiol.* 2011;64(2):163-71. Trinquart L, Attiche N, Bafeta A, Porcher R, Ravaud P. Uncertainty in Treatment Rankings: 31. Reanalysis of Network Meta-analyses of Randomized Trials. Ann Intern Med. 2016;164(10):666-73. 32. Bromley R, Baxter N, Calderbank R, Mawer G, Clayton-Smith J, Baker G. A comprehensive review of the language abilities of children exposed to valproate or carbamazepine in utero. American Epilepsy Society; Texas2010. Gogatishvili N, Ediberidze T, Lomidze G, Tatishvili N, Kasradze S. PO-0834 Long-term 33. Developmental Outcome Of Children Prenatally Exposed To Antiepileptic Drugs. Arch Dis Child. 2014;99(Suppl 2):A526. Gogatishvili N, Ediberidze T, Lomidze G, Tatishvili N, Kasradze S. Cognitive outcomes of 34. children with fetal antiepileptic drug exposure at the age of 3-6 years-preliminary data. 1st Congress of the European Academy of Neurology; Berlin: European Journal of Neurology; 2015. p. 329. 35. Miskov S, Juraski RG, Fucic A, et al. Croatian Pregnant Women with Epilepsy and Effects of Antiepileptic Drugs Exposure in their Offspring - seven years of prospective surveillance. American Epilepsy Society; Texas2010. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with 36. epilepsy. J Neurol Neurosurg Psychiatry. 2004;75(11):1575-83. 

1 2		
3	632	37 Dean ICS Hailey H. Moore SI Lloyd DI Turnnenny PD Little I Long term health and
4	633	neurodevelopment in children exposed to antiepileptic drugs before birth. <i>J Med Genet</i> .
5	634	2002;39(4):251-9.
7	635	38. Gaily E. Development and growth in children of epileptic mothers: a prospective controlled
8	636	study. Helsinki, Finland: University of Helsinki; 1990.
9	637	39. Katz JM, Pacia SV, Devinsky O. Current Management of Epilepsy and Pregnancy: Fetal
10	638	Outcome, Congenital Malformations, and Developmental Delay. <i>Epilepsy Behav</i> . 2001;2(2):119-23.
11	639	40. Veroniki AA, Straus SE, Fyraridis A, Tricco AC. The rank-heat plot is a novel way to present
12	640	the results from a network meta-analysis including multiple outcomes. <i>J Clin Epidemiol</i> . 2016.
14	641	41. Verby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic
15	64Z	drugs prenatally and through breastfeeding: a prospective cohort study on children of women with
16	043 644	42 Shalleross P. Bromley DI. Junin P. Bonnett II. Morrow I. Baker CA. Child development
17	645	following in utero exposure: levetiracetam vs sodium valproate. <i>Neurology</i> 2011:76(4):383-9
18	646	43 Zaccara G Giovannelli F Giorgi FS Franco V Gasparini S Benedetto II Tolerability of new
20	647	antiepileptic drugs: a network meta-analysis. <i>Eur I Clin Pharmacol.</i> 2017.
21	648	44. Higgins IPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions.
22	649	5.1.0 ed: The Cochrane Collaboration; 2009.
23	650	45. Kibret T, Richer D, Beyene J. Bias in identification of the best treatment in a Bayesian
24	651	network meta-analysis for binary outcome: a simulation study. <i>Clin Epidemiol</i> . 2014;6:451-60.
25	652	46. Dalessio DJ. Seizure Disorders and Pregnancy. <i>N Engl J Med</i> . 1985;312(9):559-63.
27	653	47. Efthimiou O, Mavridis D, Debray TP, et al. Combining randomized and non-randomized
28	654	evidence in network meta-analysis. <i>Stat Med</i> . 2017.
29	655	48. Schmitz S, Adams R, Walsh C. Incorporating data from various trial designs into a mixed
30	656	treatment comparison model. <i>Stat Med.</i> 2013;32(17):2935-49.
31	657 650	49. Cameron C, Fireman B, Hutton B, et al. Network meta-analysis incorporating randomized
33	050 659	effectiveness of medical treatments: challenges and opportunities. Sustematic reviews, 2015;4:147
34	660	50 Fasterbrook PI Berlin IA Conalan R Matthews DR Publication hias in clinical research
35	661	Lancet, 1991:337(8746):867-72.
36	662	51. Veroniki AA, Straus SE, Soobiah C, Elliott MI, Tricco AC, A scoping review of indirect
<i>31</i> ২৪	663	comparison methods and applications using individual patient data. BMC Med Res Methodol.
39	664	2016;16(1):47.
40	665	
41		
42		
43 11		
44		
46		
47		
48		
49 50		
50		
52		
53		
54		
55		
50 57		
58		
59		
60		30
# **Table 1. Outcome measures and diagnostic scales used in analysis**

Cognitive developmental delay			
Bayley Scales of Infant Development	Score $\geq$ 2 standard deviations below the mean		
(children <u>&lt;</u> 42 mo.)			
Griffiths Scale of Infant Development	Score >2 standard deviations below the mean		
(children >42 mo.)	Score <u>-</u> 2 standard deviations below the mean		
McCarthy Scales of Children's Abilities	Score >1 standard deviations below the mean		
(children >30 mo.)	Score -1 Standard deviations below the mean		
Stanford-Binet IV Intelligence scale for children	Intelligence quotient <u>&lt;</u> 80		
Touwen's Test	Above average number of items rated abnormal in one or more		
Touwen's rest	domains		
Wechsler Scale of Preschool and Primary	Intelligence quotient <90		
Intelligence			
Wechsler Intelligence Scale for Children - III	Intelligence quotient <80; verbal intelligence quotient <69		
Developmental Assessment	Confirmed diagnosis by developmental pediatrician or pediatric		
	neurologist Notes and the second s		
Autism/dyspraxia			
Developmental Assessment	Diagnosis confirmed by developmental specialists at 2 years of age		
Medical Records	Confirmed diagnosis recorded in medical history; registry records		
	(ICD-10 codes F84.0, F84.1, F84.5, F84.8, and F84.9)		
Modified checklist for autism in toddlers	Scored positive for $\geq 2$ out of 6 critical items OR $\geq 3$ any items of the total		
	scale		
Psychomotor developmental delay			
Ages and Stages Questionnaire	>3 standard deviations from the test mean		
Bayley Scales of Infant Development – Psychomotor	>2 standard doviations below the standardized mean for the test		
Index	~2 Standard deviations below the Standardized mean for the test		
Touwan's Test	Demonstrated dysfunctions in fine motor balance, fine motor functions,		
100/00113 1630	and coordination of extremities		
Schedule of Growing Skills II	Scored as 'delayed' in $\geq 1$ domain of the test		

3 4 5 6 7 8		Developmental Assessment	Infant scored >2 negative items (administered by general practitioner or pediatrician); diagnosis of neuromotor deficit confirmed by a trained nurse practitioner; infant failing to sit by 10 months or walk by 18 months
9 10		Health/Medical Records	Diagnosis of psychomotor delay recorded in medical records
11		Language Delay	
12		Ages and Stages Questionnaire	>3 standard deviations from the test mean
13 14 15		Clinical Evaluation of Language Fundamentals – 4 <sup>th</sup> Edition	Score <70 in core language domain; score <84 overall
16		Learning Accomplishment Profile	Below average performance in expressive speech (adjusted for age)
17 18 19 20 21 22		Comprehensive Language Assessment (Peabody Picture Vocabulary Test; Receptive Expressive Emergent Language Scale; Expressive One Word Picture Vocabulary Test, or Sequenced Inventory of Communication Development)	Scores/assessment indicate a >6 moth delay in age appropriate language development
23		ADHD	
24		Attention Problems and Hyperactivity Scales	Score >1 standard deviations from the test mean
25 26		Child Behaviour Checklist	≥6 positive items on checklist
27		Diagnostic and Statistical Manual – IV	≥5 positive items on checklist
28 29		Medical Records	Confirmed diagnosis in hospital/medical records made by a pediatrician or child psychiatrist
30 31		Neonatal Seizure	
32 33		Medical records	Record of seizures during 1 <sup>st</sup> year; confirmation of neonatal seizure by electroencephalography or diagnosis
34		Social Impairment	
35		Developmental Assessment	Scores dichotomized into 'normal' or 'adverse' range based on pre-
30 37 38		(Ages and Stages Questionnaire [6 and 18 months]; Child Behaviour Checklist [36 months])	defined values used by scale, for scales without pre-defined values cut- off was set at a score >2 standard deviations outside the test mean
39	667	<b>b</b> #2	

Study/Patient Characteristic	# of Studies (n=29)	% of Studies
Year of publication		
1980-1989	1	3.45
1990-1999	6	20.69
2000-2009	5	17.24
2010-2015	17	58.62
Continent (of country of study conduct)		
Europe	20	68.97
North America	5	17.24
Asia	1	3.45
Australia	2	6.90
Trans-Continental	1	3.45
Study design		
Observational cohort	29	100.00
Case-control	0	0.00
Randomized clinical trial	0	0.00
Registry study	A	
Yes	11	37.93
No	18	62.07
Sample size		
0-99	18	62.07
100-299	9	31.03
300-499	1	3.45
500-699	0	0.00
700-999	0	0.00
1000+	1	3.45
Number of interventions		~
2	4	13.79
3	5	17.24
4	8	27.59
5-7	8	27.59
8-10	2	6.90
11+	2	6.90
Outcomes <sup>*,†</sup>		
Cognitive Developmental Delay	12	58.62
Autism/Dyspraxia	5	17.24
Language Delay	5	17.24
ADHD	5	17.24
Psychomotor Developmental Delay	11	37.93
i sychomotor Developmental Delay	11	57.75

# 668Table 2. Summary characteristics of included studies

Study/Pat	ient Characteristic	# of Studies (n=29)	% of Studies
	Neonatal Seizures	2	6.90
	Social Impairment	1	3.45
Funding			
	Public	15	51.72
	Private	0	0.00
	Mixed public and private	4	13.79
	NR/Unclear	10	34.48
Treatment	indication		
	Epilepsy	23	79.31
	Mixed indications <sup>‡</sup>	0	0.00
	Not reported	6	20.69
Epileptic co	ntrol group <sup>§</sup>		
	Yes	15	51.72
	No/NR/NA	14	48.28
Mean mate	rnal age		
	24-26 y	2	6.90
	27-29 y	5	17.24
	30+ y	4	13.79
	Not reported	18	62.07
AED exposu	re during pregnancy		
Rep	ported as during 1 <sup>st</sup> trimester	5	17.24
Reported a	is any time during pregnancy	4	13.79
During	pregnancy and breastfeeding	5	17.24
	Not reported	15	51.72
Alcohol use	during pregnancy		
	Yes	5	17.24
	NR	24	82.76
Tobacco us	e during pregnancy		
	Yes	7	24.14
	NR	22	75.86
Abbreviation NA - Not appl *Values in thi † Percentage of ‡ Includes ind neuropathic/	<b>ns:</b> ADHD - Attention Deficit Hyperact icable; NR - Not reported s category do not match totals as som of total number of included studies (n ividuals taking AEDs for psychiatric d neurological pain	ivity Disorder; AED - a e studies report more =29) lisorders, migraine, ar	anti-epileptic drug(s); than one outcome id

**BMJ Open** 





\*29 publications reporting 30 included studies.

TITLE: Study flow diagram

Active Treatment vs Contro	ol*		OR (95%Crl) (95%Prl)	SUCRA (95% Crl)
Carbam+Levet	•	<del>,</del>	0.52 (0.00,16.53) (0.00,19.20)	0.88 (0.06,1.00)
Carbam+Pheno	·	+	0.52 (0.00,15.20) (0.00,17.13)	0.88 (0.12,1.00)
Lamot	+	+	0.93 (0.09,5.10) (0.08,6.34)	0.76 (0.29,1.00)
Pheno+Pheny	·•	•	1.32 (0.00,33.67) (0.00,38.91)	0.71 (0.06,1.00]
Pheno	+ +		1.36 (0.18,7.02) (0.14,8.95)	0.71 (0.24,0.94)
Gabap	<b>⊢</b>	+	1.46 (0.04,13.48) (0.04,16.87)	0.65 (0.12,1.00)
Carbam			2.07 (0.82,5.48) (0.51,8.46)	0.53 (0.29,0.76)
Primid	+	+	2.15 (0.31,12.26) (0.24,16.25)	0.53 (0.12,0.94)
Pheny	-+	<b>♦</b> —- <b> -</b>	2.55 (0.72,8.55) (0.47,12.15)	0.47 (0.18,0.76)
Topir	-	<b>♦</b> +	3.14 (0.45,16.53) (0.35,20.69)	0.41 (0.06,0.88)
Levet	-+	<b>◆</b>	3.42 (0.65,16.40) (0.46,22.73)	0.41 (0.06,0.82)
Pheny+Valpro	· · · · ·		3.99 (0.01,116.60) (0.01,136.30)	0.35 (0.00,1.00]
Carbam+Pheno+Pheny	· · · · ·	• •	4.83 (0.02,158.10) (0.02,187.50)	0.29 (0.00,1.00)
Ethos+Pheny	,	• •	6.24 (0.02,215.80) (0.02,243.80)	0.24 (0.00,1.00]
Valpro	-	• • •	7.40 (3.00,18.46) (1.81,27.63)	0.18 (0.06,0.41)
Carbam+Pheny		• •	10.88 (0.54,137.00) (0.43,159.20)	0.12 (0.00,0.82)
Carbam+Pheno+Valpro	+	•	44.96 (0.94,359.10) (0.80,421.70)	0.06 (0.00,0.71)
4.5e-05	0.007 1	148.4		

\* SUCRA (95%CrI): 0.76 (0.47,0.94)

# TITLE: Forest plots for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcome





\* SUCRA (95%CrI): 0.91 (0.55,1.00)

# TITLE: Forest plots for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcome

c. Psychomotor developmental delay				
Active Treatment vs Control*	OR (95%Crl) (95%Prl)	SUCRA (95% CrI)		
Levet + + +	0.27 (0.00,4.26) (0.00,4.65)	0.94 (0.29,1.00)		
Pheno+Pheny 🔶	→ 0.65 (0.00,13.32) (0.00,14.74)	0.82 (0.12,1.00)		
Carbam+Pheny 🛏 🔶		0.76 (0.06,1.00)		
Pheno ++++	0.96 (0.39,2.29) (0.32,3.02)	0.76 (0.47,0.94)		
Carbam+Pheno + 🔶	+ 1.55 (0.31,6.92) (0.26,7.99)	0.59 (0.18,0.94)		
Carbam - + + +	1.68 (0.85,3.41) (0.59,4.61)	0.59 (0.35,0.82)		
Lamot ++++	1.86 (0.72,4.76) (0.57,6.07)	0.53 (0.24,0.82)		
Clonaz + +	→ 2.23 (0.47,9.62) (0.41,11.18)	0.47 (0.12,0.88)		
Pheny+Valpro 🛏 🔶	2.24 (0.01,46.45) (0.01,49.92)	0.47 (0.00,1.00)		
Carbam+Pheno+Pheny 🔶 🔶	→ 2.75 (0.01,63.24) (0.01,70.65)	0.41 (0.00,1.00)		
Clobaz	2.81 (0.21,22.20) (0.19,26.50)	0.41 (0.00,0.94)		
Pheny	+ 2.84 (0.97,7.93) (0.77,9.92)	0.41 (0.12,0.71)		
Ethos+Pheny 🔶	3.15 (0.00,84.86) (0.00,92.48)	0.35 (0.00,1.00)		
Topir + 🔶		0.29 (0.00,0.88))		
Valpro +•	+ 4.16 (2.04,8.75) (1.52,12.05)	0.24 (0.06,0.53)		
Gabap		0.12 (0.00,0.76)		
Carbam+Pheno+Valpro +		0.06 (0.00,0.59)		
4.5e-05 0.007 1	148.4			
Active treatment safer	Control safer			

\* SUCRA (95%CrI): 0.76 (0.53,0.94)

# TITLE: Forest plots for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcome



\* SUCRA (95%CrI): 0.75 (0.50,1.00)

# TITLE: Forest plots for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcome

0.67 (0.17,1.00)

0.67 (0.00,1.00)

0.50 (0.00,1.00)

0.33 (0.00,0.67)

0.17 (0.00,0.67)

0.50 (0.00,1.00)





TITLE: Network diagrams for cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes.

CAPTION: Each treatment node is weighted according to the number of patients that have received the particular treatment, and each edge is weighted according to the number of studies comparing the treatments it connects.

Abbreviations: carbam - carbamazepine, clobaz - clobazam, clonaz - clonazepam, ethos - ethosuximide, gabap - gabapentin, lamot - lamotrigine, levet - levetiracetam, oxcar - oxcarbazepine, pheno phenobarbital, pheny - phenytoin, primid - primidone, topir - topiramate, valpro - valproate, vigab – vigabatrin

## PROTOCOL



**Open Access** 

# Comparative safety of anti-epileptic drugs among infants and children exposed *in utero* or during breastfeeding: protocol for a systematic review and network meta-analysis

Andrea C Tricco<sup>1</sup>, Elise Cogo<sup>1</sup>, Veroniki A Angeliki<sup>1</sup>, Charlene Soobiah<sup>1,2</sup>, Brian Hutton<sup>3</sup>, Brenda R Hemmelgarn<sup>4</sup>, David Moher<sup>3</sup>, Yaron Finkelstein<sup>5,6,7</sup> and Sharon E Straus<sup>1,8\*</sup>

#### Abstract

**Background:** Epilepsy affects about 1% of the general population. Anti-epileptic drugs (AEDs) prevent or terminate seizures in individuals with epilepsy. Pregnant women with epilepsy may continue taking AEDs. Many of these agents cross the placenta and increase the risk of major congenital malformations, early cognitive and developmental delays, and infant mortality. We aim to evaluate the comparative safety of AEDs approved for chronic use in Canada when administered to pregnant and breastfeeding women and the effects on their infants and children through a systematic review and network meta-analysis.

**Methods:** Studies examining the effects of AEDs administered to pregnant and breastfeeding women regardless of indication (e.g., epilepsy, migraine, pain, psychiatric disorders) on their infants and children will be included. We will include randomized clinical trials (RCTs), quasi-RCTs, non-RCTs, controlled before-after, interrupted time series, cohort, registry, and case-control studies. The main literature search will be executed in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. We will seek unpublished literature through searches of trial protocol registries and conference abstracts. The literature search results screening, data abstraction, and risk of bias appraisal will be performed by two individuals, independently. Conflicts will be resolved through discussion. The risk of bias of experimental and quasi-experimental studies will be appraised using the Cochrane Effective Practice and Organization of Care Risk-of-Bias tool, methodological quality of observational studies will be appraised using the Newcastle-Ottawa Scale, and quality of reporting of safety outcomes will be conducted using the McMaster Quality Assessment Scale of Harms (McHarm) tool. If feasible and appropriate, we will conduct random effects meta-analysis. Network meta-analysis will be considered for outcomes that fulfill network meta-analysis assumptions.

The primary outcome is major congenital malformations (overall and by specific types), while secondary outcomes include fetal loss/miscarriage, minor congenital malformations (overall and by specific types), cognitive development, psychomotor development, small for gestational age, preterm delivery, and neonatal seizures. (Continued on next page)

Full list of author information is available at the end of the article



© 2014 Tricco et al.; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

<sup>\*</sup> Correspondence: sharon.straus@utoronto.ca

<sup>&</sup>lt;sup>1</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria Street,

East Building, Toronto, Ontario M5B 1 T8, Canada

<sup>&</sup>lt;sup>8</sup>Department of Geriatric Medicine, University of Toronto, 172 St. George Street,

Toronto, Ontario M5R 0A3, Canada

Page 44 of 90

#### (Continued from previous page)

**Discussion:** Our systematic review will address safety concerns regarding the use of AEDs during pregnancy and breastfeeding. Our results will be useful to healthcare providers, policy-makers, and women of childbearing age who are taking anti-epileptic medications.

#### Systematic review registration: PROSPERO CRD42014008925.

**Keywords:** Anti-epileptic drug, Breastfeeding, Comparative safety, Congenital malformation, Epilepsy, Fetus, Infant, Network meta-analysis, Pregnancy, Systematic review

#### Background

Epilepsy is the most common chronic neurological condition, affecting 0.6 to 1% of the population [1,2]. Individuals with uncontrolled epilepsy experience recurrent seizures, which can have psychosocial and physical consequences, including a compromised life expectancy [3,4]. The goal of anti-epileptic treatment is to improve quality of life and health outcomes by reducing the frequency of seizures [4].

Anti-epileptic medications decrease seizures by reducing excitation and enhancing inhibition of neurons [5-7]. Many of these medications target different channels, including calcium, sodium, and glutamate, and are broadly classified as first generation agents (e.g., phenobarbitone, phenytoin, carbamazepine, sodium valproate, ethosuximide) and second generation agents (e.g., lamotrigine, levetiracetam, topiramate, gabapentin, vigabatrin, oxcarbazepine, clobazam, clonazepam, zonisamide, lacosamide, rufinamide, primidone) [8]. Due to the broad and varied mechanisms of action, the indications for some of these medications also include pain syndromes, psychiatric disorders, and migraine headaches [8].

Many clinical practice guidelines recommend that women of childbearing age continue to take their anti-epileptic medications; however, medications with lower risk of teratogenic events are advised [9,10] since anti-epileptic drugs (AEDs) cross the placenta or transfer through breast milk, posing risks to the fetus and infant [9,11,12].

Some AEDs have been associated with increased risk of harm to the fetus and infants. For example, exposure to valproate has led to increased risk of major congenital malformations [10], cognitive delay, and minor congenital abnormalities [13-16]. Phenobarbital has been associated with minor congenital abnormalities and developmental delay [17,18]. Carbamazepine and lamotrigine have been associated with minor congenital abnormalities [19-22]. However, other than studies of the use of valproate, many studies have produced inconsistent findings regarding harm to the fetus and infant with use of other agents [23]. As such, our objective is to evaluate the comparative safety of AEDs for infants and children who were exposed *in utero* or during breastfeeding through a systematic review and network meta-analysis.

## Methods/Design

#### Protocol

A systematic review protocol was developed and registered with the PROSPERO database (CRD42014008925, available at: http://www.crd.york.ac.uk/PROSPERO/display\_record. asp?ID=CRD42014008925). It was revised with feedback from the decision-makers who posed the query within Health Canada, healthcare practitioners, content experts, and research methodologists. The reporting of our systematic review protocol was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols [24].

#### Eligibility criteria

We will include studies examining the effects of AEDs on infants and children who were exposed in utero or during breastfeeding. We will include experimental studies (randomized clinical trials [RCTs], quasi-RCTs, non-RCTs), guasi-experimental studies (controlled before and after studies, interrupted time series), and observational studies (cohort, case-control, registry studies) of pregnant women at any stage of pregnancy and breastfeeding women and their infants/children. The rationale for including other study designs in addition to RCTs is that there are ethical issues in conducting RCTs of AEDs in pregnancy, so RCT evidence might not exist for some or all of these drugs. Given that our review includes rare outcomes, including observational evidence is crucial. In contrast to efficacy evaluation, safety assessment usually requires very large sample sizes to be able to detect adverse events. Therefore, while RCTs have lower risk of bias, they usually do not have the statistical power needed to adequately evaluate uncommon/rare safety outcomes due to Type II (i.e., false negative) error [25]. Given that our review includes rare outcomes, including observational evidence is crucial [26]. Additionally, observational studies can often provide more generalizable evidence due to the strict participant inclusion criteria in most RCTs [27]. Real-world safety evidence that has external validity is important for the assessment of the possible risks of AEDs in pregnant and breastfeeding women.

The diagnosis of neurodevelopmental delay related to *in utero* exposure is made before adolescence, and

57

58

59

hence, we will limit inclusion to children up to 12 years of age. AEDs that are approved for chronic use in Canada will be included. Drugs that are only used acutely or those that are not currently approved for use in Canada will be excluded, as the focus of this review is on the Canadian setting [28-32]. However, most of the medications we will examine are available in other countries as well. The relevant 16 medications and their synonyms are listed in Additional file 1, and the excluded drugs are listed in Additional file 2. Studies of all combinations and doses of these medications are eligible for inclusion. Since we are only interested in exposures that occur in *utero* or during breastfeeding, studies examining AEDs administered directly to infants or children will be excluded. All indications for AEDs will be included such as epilepsy, migraine, pain, and psychiatric disorders.

In order to be included, studies must compare an antiepileptic medication against another included anti-epileptic medication, placebo, a 'no intervention' control group, or combinations of two or more anti-epileptic medications. Only studies providing results for our outcomes of interest will be included. Our primary outcome is major congenital malformations (overall and by specific type, such as craniofacial defects and neural tube defects). Secondary outcomes include minor congenital malformations (overall and by specific type, such as epicanthal folds and microstomia), cognition (e.g., global cognitive functioning and specific cognitive domains such as attention), psychomotor development (e.g., autism, dyspraxia), small for gestational age, preterm delivery, neonatal seizures, and fetal loss/miscarriage. No other limitations will be imposed on the eligibility criteria, including published/unpublished material, language of dissemination, duration of follow-up, or year of publication. The draft eligibility criteria can be found in Additional file 3.

#### Information sources and literature search

Our main literature search will be executed in the MED-LINE database. The search terms were drafted by an experienced librarian and can be found in Additional file 4. The search was peer reviewed by another librarian using the Peer Review of Electronic Search Strategies checklist [33].

In addition to MEDLINE, we will also search the EMBASE and the Cochrane Central Register of Controlled Trials databases. We will follow the MEDLINE search strategy for these databases, and the search terms will be adjusted accordingly. The electronic database search will be supplemented by searching for unpublished literature [34]. This will be accomplished through exploring conference abstracts, clinical trial registries, and contacting manufacturers of AEDs. We will also scan the reference lists of included studies and previous reviews in the area [23,35,36].

#### Study selection process

**BMJ Open** 

The eligibility criteria screening form will be pilot-tested by the team and is presented in Additional file 3. We will calculate inter-rater reliability from the pilot-test and screening will only commence after high agreement (e.g., kappa statistic  $\geq$ 60%) is observed [37]. Subsequently, two reviewers will screen each title/abstract and potentially relevant full-text articles from the literature search results, independently. Conflicts will be resolved through discussion. All screening will occur using our online screening software (synthesi.SR) [38].

#### Data items and data collection process

We will abstract data on the PICOS elements [39], including patient characteristics (e.g., age of the mother and infant/child, indication for anti-epileptic treatment, co-morbidities, concomitant medications), intervention details (e.g., type of anti-epileptic treatment, dose, route of administration, duration of treatment, timing [trimester] of treatment during pregnancy), comparator details (e.g., comparator agent, dose, route of administration), outcome results (e.g., major congenital abnormality, minor congenital abnormality, cognitive function, psychomotor development) at the longest duration of follow-up, and study characteristics (e.g., study design, country of conduct, year of conduct, sample size, setting). These characteristics will be abstracted using a data abstraction form created in Excel with an accompanying "cheat sheet" that will guide the reviewers with this process. The data abstraction form and cheat sheet will be pilot-tested and data abstraction will only commence when high agreement (e.g., kappa statistic ≥60%) [37] is observed. Each included study will be abstracted by two team members, independently, who will resolve disagreements through discussion.

#### Methodological quality/risk of bias appraisal

We will use various tools to assess the methodological quality/risk of bias of each of the studies that fulfill our eligibility criteria. This will be conducted by two reviewers, independently, and conflicts will be resolved through discussion. First, we will appraise the risk of bias of experimental and quasi-experimental studies using the Cochrane Effective Practice and Organization of Care Risk-of-Bias tool [40]. Second, we will assess the methodological quality of observational studies using the Newcastle-Ottawa Scale [41]. Third, the quality of reporting of harms will be appraised using the McMaster Quality Assessment Scale of Harms (McHarm) tool [42].

#### Synthesis of included studies

A narrative summary of study results will be presented along with evidence summary tables. When sufficient data are available, we will conduct random effects metaanalysis to calculate pooled odds ratios for dichotomous

data and pooled mean differences for continuous data

[43,44]. Direct (pairwise) meta-analysis will be per-

formed with RCTs alone in order to examine whether

the data are consistent between direct and indirect evi-

dence. If the large majority of included studies are obser-

vational, we will also conduct additional meta-analyses

including observational studies alone. Analyses will be

stratified by treatment indication (e.g., epilepsy, pain,

etc.) to reduce clinical heterogeneity between different

study populations whenever possible; for example, epilepsy itself in pregnant women is related to an increased

baseline risk of certain neonatal adverse outcomes. Stat-

istical, clinical, and methodological heterogeneity will be

examined prior to conducting the meta-analysis. Funnel

plots will be drawn for outcomes including at least 10

studies to explore asymmetry that might be explained by

clinical, statistical, and methodological heterogeneity.

The proportion of statistical heterogeneity will be exam-

ined using the  $I^2$  measure [45] and the magnitude of

statistical heterogeneity will be calculated using the re-

stricted maximum likelihood [46]. Meta-regression will

be conducted for clinically relevant subgroups or when

extensive statistical heterogeneity is observed (e.g.,  $I^2 \ge$ 

75%) [47]. This will allow the examination of the impact

of important factors on our results, such as maternal

age, dose, duration and timing (e.g., trimester) of anti-

epileptic treatment, co-morbidities, concomitant medi-

cations, risk of bias results, and sample size (due to Type

II statistical power errors with rare adverse events). To

ensure the meta-regression analysis is intuitive, the num-

i) transitivity (i.e., comparable distribution of effect modifiers across comparisons), which will be examined using boxplots or percentages to visually inspect potential effect modifiers of treatment effect [54]; ii) consistency between direct and indirect data, which will be examined locally (i.e., in certain paths of the network) using the loop-specific method [55,56] and the node-splitting method [57], and globally (i.e., evaluating the network as a whole), using the design-by-treatment interaction model [58]; and iii) we will quantify the amount of variability attributed to heterogeneity and inconsistency rather than sampling error, by calculating the  $I^2$  [59]. We will estimate the amount of heterogeneity using the restricted maximum likelihood method and assuming common within-network heterogeneity. We will compare the magnitude of heterogeneity between consistency and inconsistency models, as well as between meta-regression and network meta-analysis models to determine how much heterogeneity will be explained by inconsistency or the explanatory variable, respectively. We will first use the design-by-treatment model for the evaluation of inconsistency in a network as a whole and then, if inconsistency is detected, we will employ the loop-specific and node-splitting methods to identify which piece of evidence is responsible for inconsistency. As mentioned above, analyses will be stratified by treatment indication when clinically appropriate. Important heterogeneity and inconsistency will be explored using network metaregression using the same methods as described above,

Prior to conducting the network meta-analysis, we will hold a team meeting to finalize which treatment nodes will be included in the analysis since we are unclear about the indications, dosages, patient populations, and outcomes reported in all of the studies. We will discuss issues, including conducting a class versus independent drug analysis, inclusion of drug routes of administration and dosages, as well as timing of drug administration. These decisions will be examined through a sensitivity analysis in which we will classify treatment nodes using a different classification to see how stable our results are. The network meta-analysis results will be presented as summary treatment effects for each pair of treatments. Network meta-analysis will be conducted in Stata with the *mymeta* routine [60].

A sequential approach will be used for the network meta-analysis. We will first restrict our analysis to RCTs, which will be the primary analysis of interest. We will then include data from quasi-experimental studies, and finally, data from observational studies. This will provide an understanding of the contribution of each type of study design to our summary estimates, providing us with information on how these agents work above and beyond clinical trials.

ber of covariates examined will be less than 10% of the number of studies included in the meta-analysis for the particular outcome. We anticipate that many of these outcomes will be rare. To deal with studies reporting zero events in one treatment arm, 0.5 will be added to the numerator and 1 will be added to the denominator. We will exclude studies reporting zero events in all treatment arms for a particular outcome [48,49]. We also anticipate that we will encounter missing data in the included studies. We will contact the study authors for this data and if we are unable to receive the data, we will impute missing data (e.g., measures of variance) using established methods [50]. To ensure that our imputations do not bias our results, we will conduct a sensitivity analysis [51]. The meta-analysis and meta-regression will be analyzed in R using the *metafor* command [52]. A random-effects network meta-analysis will be con-

A random-effects network meta-analysis will be conducted to make inferences regarding the comparative safety of the various AEDs [15], as well as rank their safety using rankograms and the surface under the cumulative ranking curve [53]. We will ensure the following factors are present prior to conducting network meta-analysis: as necessary.

5

6

7

8

9

10

11

12

13 14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

#### Discussion

Epilepsy is the most common chronic neurological condition, affecting 0.6 to 1% of the population [1,2]. Given that approximately a third of patients receiving AEDs are of reproductive age and almost half of pregnancies are unplanned [61], the fetus may be exposed to these in the first trimester of pregnancy, including during the critical stage of embryogenesis [62].

The comparative safety of these agents is currently unknown and our results will be important for policymakers, healthcare providers, and women of childbearing age. To ensure our results have wide dissemination and uptake, we will publish our results in open access journals, present our findings at scientific conferences, conduct dissemination meetings with key stakeholders (including policy-makers and healthcare providers), and produce policy briefs for Health Canada, the organization that posed this query.

#### Additional files

Additional file 1: List of relevant medications. Additional file 2: Excluded drugs. Additional file 3: Draft eligibility criteria. Additional file 4: MEDLINE literature search.

#### Abbreviations

AEDs: Anti-epileptic drugs; RCTs: Randomized clinical trials.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

ACT conceived and designed the study, helped obtain funding for the study, and helped write the draft protocol. EC registered the protocol with the PROSPERO database and edited the draft protocol. AV helped write the draft protocol. CS edited the draft protocol. BH, BRH, DM, and YF provided input into the design, helped obtain funding for the study, and edited the draft protocol. SES conceived the study, designed the study, obtained the funding, and helped write the draft protocol. All authors read and approved the final protocol.

#### Acknowledgements

This systematic review was funded by the Canadian Institutes of Health Research/Drug Safety and Effectiveness Network (CIHR/DSEN). ACT and BH are funded by a CIHR/DSEN New Investigator Award in Knowledge Synthesis. BRH receives funding from the Alberta Heritage Foundation for Medical Research. DM is funded by a University of Ottawa Research Chair. SES is funded by a Tier 1 Canada Research Chair in Knowledge Translation. We thank Laure Perrier for conducting the literature searches and Becky Skidmore for peer reviewing the MEDLINE search strategy. We also thank Dr. Joseph Beyene for providing feedback on our original proposal and Wing Hui and Judy Tran for formatting the paper.

#### Author details

<sup>1</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria Street, East Building, Toronto, Ontario M5B 1 T8, Canada. <sup>2</sup>Institute of Health Policy Management and Evaluation, University of Toronto, Health Sciences Building, 155 College Street, Suite 425, Toronto, Ontario M5T 3 M6, Canada. <sup>3</sup>Clinical Epidemiology Program, Centre for Practice-Changing Research, Ottawa Hospital Research Institute, The Ottawa Hospital – General Campus and University of Ottawa, 501 Smyth Road, Box 711, Ottawa, Ontario K1H 8 L6, Canada. <sup>4</sup>Departments of Medicine and Community Health Sciences, University of Calgary, TRW Building, 3rd Floor, 3280 Hospital Drive NW, Calgary, Alberta T2N 4Z6, Canada. <sup>5</sup>The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. <sup>6</sup>Department of Pediatrics, University of Toronto, 172 St. George Street, Toronto, Ontario M5R 0A3, Canada. <sup>7</sup>Department of Pharmacology and Toxicology, University of Toronto, Medical Sciences Building, 1 King's College Circle, Room 4207, Toronto, Ontario M5S 1A8, Canada. <sup>8</sup>Department of Geriatric Medicine, University of Toronto, 172 St. George Street, Toronto, Ontario M5R 0A3, Canada.

#### Received: 9 April 2014 Accepted: 17 June 2014 Published: 25 June 2014

#### References

- Hauser WA, Hesdorffer D: Epilepsy, Frequency, Causes and Consequences. New York: Demos Publications; 1990.
- Wiebe S, Bellhouse DR, Fallahay C, Eliasziw M: Burden of epilepsy: the Ontario Health Survey. Can J Neurol Sci 1999, 26(4):263–270.
- Sperling MR: The consequences of uncontrolled epilepsy. CNS Spectr 2004, 9(2):98–101. 106–109.
- 4. Jones MW: Consequences of epilepsy: why do we treat seizures? Can J Neurol Sci 1998, 25(4):S24–S26.
- Dickenson AH, Ghandehari J: Anti-convulsants and anti-depressants. Handb Exp Pharmacol 2007, 177:145–177.
- Stefani A, Spadoni F, Bernardi G: Voltage-activated calcium channels: targets of antiepileptic drug therapy? *Epilepsia* 1997, 38(9):959–965.
- Snutch TP, Reiner PB: Ca<sup>2+</sup> channels: diversity of form and function. Curr Opin Neurobiol 1992, 2(3):247–253.
- Spina E, Perugi G: Antiepileptic drugs: indications other than epilepsy. Epileptic Disord 2004, 6(2):57–75.
- 9. Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, Hopp J, Ting TY, Hauser WA, Thurman D, Kaplan PW, Robinson JN, French JA, Wiebe S, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Shafer PO, Le Guen CL, American Academy of Neurology; American Epilepsy Society: Management issues for women with epilepsy–focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: report of the quality standards subcommittee and therapeutics and technology assessment subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009, 50(5):1247–1255.
- Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA, Wiebe S, Thurman D, Koppel BS, Kaplan PW, Robinson JN, Hopp J, Ting TY, Gidal B, Hovinga CA, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Hirtz D, Le Guen C, American Academy of Neurology; American Epilepsy Society: Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009, 50(5):1237–1246.
- Samren EB, van Duijn CM, Koch S, Hiilesmaa VK, Klepel H, Bardy AH, Mannagetta GB, Deichl AW, Gaily E, Granstrom ML, Meinardi H, Grobbee DE, Hofman A, Janz D, Lindhout D: Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 1997, 38(9):981–990.
- Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C: Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res* 2008, 81(1):1–13.
- Adab N, Jacoby A, Smith D, Chadwick D: Additional educational needs in children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2001, 70(1):15–21.
- Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, Coyle H, Fryer A, Gorry J, Gregg J, Mawer G, Nicolaides P, Pickering L, Tunnicliffe L, Chadwick DW: The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004, 75(11):1575–1583.
- Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M, Matila R, Kotila M, Nylund T, Bardy A, Kaaja E, Granstrom ML: Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology* 2004, 62(1):28–32.
- Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW, for the NEAD Study Group: Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 2009, 360(16):1597–1605.

#### **BMJ Open**

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

- Holmes LB, Wyszynski DF, Lieberman E: The AED (antiepileptic drug) pregnancy registry: a 6-year experience. Arch Neurol 2004, 61(5):673–678.
- Reinisch JM, Sanders SA, Mortensen EL, Rubin DB: In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA 1995, 274(19):1518–1525.
- Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, Irwin B, McGivern RC, Morrison PJ, Craig J: Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2006, 77(2):193–198.
- Meador KJ, Baker GA, Finnell RH, Kalayjian LA, Liporace JD, Loring DW, Mawer G, Pennell PB, Smith JC, Wolff MC, NEAD Study Group: In utero antiepileptic drug exposure: fetal death and malformations. *Neurology* 2006, 67(3):407–412.
- Vajda FJ, Hitchcock A, Graham J, Solinas C, O'Brien TJ, Lander CM, Eadie MJ: Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur J Neurol* 2006, 13(6):645–654.
- Holmes LB, Baldwin EJ, Smith CR, Habecker E, Glassman L, Wong SL, Wyszynski DF: Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 2008, 70(22 Pt 2):2152–2158.
- Meador KJ, Penovich P, Baker GA, Pennell PB, Bromfield E, Pack A, Liporace JD, Sam M, Kalayjian LA, Thurman DJ, Moore E, Loring DW, NEAD Study Group: Antiepileptic drug use in women of childbearing age. *Epilepsy Behav* 2009, 15(3):339–343.
- 24. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L: Reporting Guidelines for Systematic Review Protocols. In 19th Cochrane Colloquium: 19–22 October 2011; Madrid, Spain.
- Ross CJ, Visscher H, Sistonen J, Brunham LR, Pussegoda K, Loo TT, Rieder MJ, Koren G, Carleton BC, Hayden MR, CPNDS Consortium: The Canadian Pharmacogenomics Network for Drug Safety: a model for safety pharmacology. *Thyroid* 2010, 20(7):681–687.
- Eypasch E, Lefering R, Kum CK, Troidl H: Probability of adverse events that have not yet occurred: a statistical reminder. *BMJ* 1995, 311(7005):619–620.
- 27. Atkins D: Creating and synthesizing evidence with decision makers in mind: integrating evidence from clinical trials and other study designs. *Med Care* 2007, **45**(10 Supl 2):S16–S22.
- Health Canada: Drug Product Database. http://www.hc-sc.gc.ca/dhp-mps/ prodpharma/databasdon/index-eng.php.
- 29. United States National Library of Medicine's ChemIDPlus Lite Database. http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp.
- 30. Canadian Pharmacists Association: E-CPS (Compendium of Pharmaceuticals and Specialties). http://www.e-therapeutics.ca/home.whatsnew.action.
- Epilepsy Canada: Anticonvulsant Medications. http://www.epilepsy.ca/en-CA/ Diagnosis-and-Treatment/Anticonvulsant-Medications.html.
- Epilepsy Ontario: Anticonvulsant/Anti-Seizure Medication from A to Z. http://epilepsyontario.org/anticonvulsantanti-seizure-medication-from-a-to-z/.
- Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C: An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol 2009, 62(9):944–952.
- Canadian Agency for Drugs and Technologies in Health: Grey Matters: A Practical Search Tool for Evidence-Based Medicine. http://www.cadth.ca/ resources/grey-matters.
- Adab N, Tudur SC, Vinten J, Williamson P, Winterbottom J: Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database Syst Rev 2004, 3:CD004848.
- Banach R, Boskovic R, Einarson T, Koren G: Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. Drug Saf 2010, 33(1):73–79.
- 37. Landis JR, Koch GG: The measurement of observer agreement for categorical data. *Biometrics* 1977, **33**(1):159–174.
- 38. Synthesi.SR. http://knowledgetranslation.ca/sysrev/login.php.
- Stone PW: Popping the (PICO) question in research and evidence-based practice. Appl Nurs Res 2002, 15(3):197–198.
- 40. Cochrane Effective Practice and Organization of Care Group Draft Risk of Bias Tool. http://epoc.cochrane.org/epoc-author-resources.
- The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. http://www.ohri.ca/programs/clinical\_epidemiology/ oxford.asp.

- Santaguida PL, Raina P, Ismaila A: The Development of the McHarm Quality Assessment Scale for Adverse Events. Hamilton, Ontario: McMaster University; 2008.
- Raudenbush SW: Analyzing Effect Sizes: Random Effects Models. In The Handbook of Research Synthesis and Meta-analysis. 2nd edition. Edited by Cooper H, Hedges LV, Valentine JC. New York: Russell Sage Foundation; 2009:295–315.
- 44. Viechtbauer W: Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat* 2005, **30**(3):261–293.
- 45. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002, **21**(11):1539–1558.
- 46. Viechtbauer W: Confidence intervals for the amount of heterogeneity in meta-analysis. *Stat Med* 2007, **26**(1):37–52.
- Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2009. http://www.cochrane.org/ handbook.
- Sweeting MJ, Sutton AJ, Lambert PC: What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004, 23(9):1351–1375.
- Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A: Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007, 26(1):53–77.
- 50. Littell JH, Corcoran J, Pillai V: *Systematic Reviews and Meta-Analysis*. New York: Oxford University Press; 2008.
- Carpenter J, Rucker G, Schwarzer G: Assessing the sensitivity of meta-analysis to selection bias: a multiple imputation approach. *Biometrics* 2011, 67(3):1066–1072.
- Conducting Meta-Analyses in R with the metafor Package. http://www.jstatsoft.org/v36/i03/.
- Salanti G, Ades AE, Ioannidis JP: Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011, 64(2):163–171.
- Salanti G: Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012, 3(2):80–97.
- Song F, Altman DG, Glenny AM, Deeks JJ: Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003, 326(7387):472.
- Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G: Evaluation of inconsistency in networks of interventions. Int J Epidemiol 2013, 42(1):332–345.
- 57. Dias S, Welton NJ, Caldwell DM, Ades AE: Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010, **29**(7–8):932–944.
- White IR, Barrett JK, Jackson D, Higgins JPT: Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012, 3(2):111–125.
- Jackson D, Barrett JK, Stephen R, White IR, Higgins JPT: A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. Stat Med 2014, In press.
- 60. White IR: Multivariate random-effects meta-regression: updates to mvmeta. *Stata J* 2011, 11(2):255–270.
- Centers for Disease Control and Prevention: Unintended Pregnancy Prevention. http://www.cdc.gov/reproductivehealth/unintendedpregnancy/.
- Yerby MS: Pregnancy, teratogenesis, and epilepsy. Neurol Clin 1994, 12(4):749–771.

#### doi:10.1186/2046-4053-3-68

**Cite this article as:** Tricco *et al.*: Comparative safety of anti-epileptic drugs among infants and children exposed *in utero* or during breastfeeding: protocol for a systematic review and network meta-analysis. *Systematic Reviews* 2014 **3**:68.

1	
2	
3	
1	
4	
5	
6	
7	
8	
9	
10	
10	
11	
12	
13	
14	
15	
16	
17	
10	
10	
19	
20	
21	
22	
22	
23	
24	
25	
26	
27	
20	
20	
29	
30	
31	
32	
22	
33	
34	
35	
36	
37	
38	
20	
39	
40	
41	
42	
43	
11	
 / [	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
55	
90	
57	
58	
59	
60	
00	

PRISMA	NMA	Checklist
--------	-----	-----------

Section/Topic	Item #	Checklist Item <sup>*</sup>	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	1
ABSTRACT			
Structured summary	2	<ul> <li>Provide a structured summary including, as applicable:</li> <li>Background: main objectives</li> <li>Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis.</li> <li>Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed.</li> <li>Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</li> <li>Discussion/Conclusions: limitations; conclusions and implications of findings.</li> <li>Other: primary source of funding; systematic review registration number with registry name.</li> </ul>	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of</i> <i>why a network meta-analysis has been conducted</i> .	7
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	8

2
3
4
4
5
6
7
1
8
9
10
10
11
12
10
13
14
15
16
10
17
18
10
19
20
21
22
22
23
24
25
20
26
27
28
20
29
30
21
51
32
33
31
34
35
36
27
37
38
39
10
40
41
42
13
40
44
45
16
40
47
48
10
49
50
51
52
52
53
54
55
55
56
57
58
50
59
60

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly</i> <i>describe eligible treatments included in the</i> <i>treatment network, and note whether any have</i> <i>been clustered or merged into the same node (with</i> <i>justification).</i>	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Additional File 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Additional File 1
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	10-12
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9-10 (see also Appendix A)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	10-12

Planned methods of analysis	14	<ul> <li>Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to:</li> <li><i>Handling of multi-arm trials;</i></li> <li><i>Selection of variance structure;</i></li> <li><i>Selection of prior distributions in Bayesian analyses; and</i></li> <li><i>Assessment of model fit.</i></li> </ul>	10-12
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	10-11
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses <b>RESULTS</b> <sup>†</sup>	16	<ul> <li>Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul> <li>Sensitivity or subgroup analyses;</li> <li>Meta-regression analyses;</li> <li>Alternative formulations of the treatment network; and</li> <li>Use of alternative prior distributions for Bayesian analyses (if applicable).</li> </ul> </li> </ul>	11-12
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	13 and Figure 1
Presentation of network structure	<b>S</b> 3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	14-18
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, Appendices D and E

_	
3	
4	
5	
6	
7	
8	
9	
10	
11	
11	
12	
13	
14	
15	
16	
17	
10	
10	
19	
20	
21	
22	
23	
21	
24	
25	
26	
27	
28	
29	
30	
24	
31	
32	
~-	
33	
33 34	
33 34 35	
33 34 35 36	
33 34 35 36 27	
33 34 35 36 37	
33 34 35 36 37 38	
33 34 35 36 37 38 39	
33 34 35 36 37 38 39 40	
33 34 35 36 37 38 39 40 41	
33 34 35 36 37 38 39 40 41 42	
33 34 35 36 37 38 39 40 41 42 43	
33 34 35 36 37 38 39 40 41 42 43	
33 34 35 36 37 38 39 40 41 42 43 44	
33 34 35 36 37 38 39 40 41 42 43 44 45	
33 34 35 36 37 38 39 40 41 42 43 44 45 46	
33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	
33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48	
33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49	
33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50	
33         34         35         36         37         38         39         40         41         42         43         44         45         46         47         48         50	
33         34           35         36           37         38           39         40           41         42           43         44           45         46           47         48           501         501	
33         334         35         36         37         38         39         40         42         43         44         45         46         47         48         950         51         52	
33         334         35         36         37         38         39         41         42         43         44         45         46         47         48         95         51         52         53	
$33 \\ 35 \\ 36 \\ 37 \\ 38 \\ 39 \\ 41 \\ 42 \\ 43 \\ 44 \\ 45 \\ 46 \\ 47 \\ 48 \\ 95 \\ 51 \\ 52 \\ 53 \\ 54 $	
33       35       36         334       35       36         37       38       39       41         42       43       445       46         47       48       90       51       52         53       54       55       55	
33         35         36           334         356         37         38         39         41         42         44         45         46         50         51         52         54         55         56	
$33 \\ 35 \\ 37 \\ 39 \\ 41 \\ 43 \\ 44 \\ 46 \\ 47 \\ 49 \\ 51 \\ 52 \\ 54 \\ 55 \\ 55 \\ 57 \\ 55 \\ 57 \\ 57 \\ 57$	
$33 \\ 35 \\ 37 \\ 39 \\ 41 \\ 43 \\ 44 \\ 46 \\ 47 \\ 49 \\ 51 \\ 52 \\ 54 \\ 55 \\ 57 \\ 55 \\ 57 \\ 20 \\ 57 \\ 57 \\ 57 \\ 57 \\ 57 \\ 57 \\ 57 \\ 5$	
$33 \\ 35 \\ 37 \\ 39 \\ 41 \\ 42 \\ 43 \\ 44 \\ 46 \\ 47 \\ 49 \\ 51 \\ 52 \\ 55 \\ 55 \\ 55 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 57 \\ 50 \\ 50$	
$33 \\ 35 \\ 37 \\ 39 \\ 41 \\ 42 \\ 44 \\ 45 \\ 46 \\ 47 \\ 49 \\ 51 \\ 52 \\ 53 \\ 55 \\ 57 \\ 59 \\ 59 \\ 51 \\ 51 \\ 51 \\ 55 \\ 57 \\ 59 \\ 51 \\ 51 \\ 51 \\ 51 \\ 51 \\ 51 \\ 51$	

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Appendix F
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches</i> <i>may be needed to deal with information from</i> <i>larger networks</i> .	N/A (data can be provided by the corresponding author)
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger</i> <i>networks, authors may focus on comparisons</i> <i>versus a particular comparator (e.g. placebo or</i> <i>standard care), with full findings presented in an</i> <i>appendix. League tables and forest plots may be</i> <i>considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	15-18, Figure 3, Appendices H, I, J
Exploration for inconsistency	<b>S</b> 5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	14 (see also Appendix H)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	14 (see also Appendix G)
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied</i> , <i>alternative choice of prior distributions for</i> <i>Bayesian analyses</i> , and so forth).	Appendix K
Summary of	24	Summarize the main findings, including the	19-21
evidence		strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the</i> <i>assumptions, such as transitivity and consistency.</i> <i>Comment on any concerns regarding network</i> <i>geometry (e.g., avoidance of certain comparisons).</i>	21-23

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	26-27

**Abbreviations:** PICOS - population, intervention, comparators, outcomes, study design \* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

<sup>†</sup> Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.



# **Supplementary Online Content**

Appendix A. Newcastle-Ottawa Scale scoring guide	2
Appendix B. List of included studies	11
Appendix C. Key excluded studies	14
Appendix D. Table of Individual Study characteristics	16
Appendix E. Table of Patient characteristics	21
Appendix F. Methodological quality of observational studies – Newcastle Ottawa Scale results	\$23
Appendix G. Comparison-adjusted funnel plots <sup>*</sup>	25
Appendix H. Statistically significant network meta-analysis results along with meta-analysis results, transitivity, and inconsistency assessments	26
Appendix I. Rank-heat plot of cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes*	30
Appendix J. Number of studies and treatments per outcome	32
Appendix K. Sensitivity and network meta-regression analyses - Anti-epileptic drugs compared	d
with Control	33



<sup>1</sup> For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

## Appendix A. Newcastle-Ottawa Scale scoring guide

## **COHORT Studies**

Excel Column	NOS* Answer Options**	NOS Coding Manual*
RefID	Enter the report's RefID.	
DA	Enter your initials.	
First author	Enter the first author's last name.	
Year of publication	Enter the year of the publication.	
SELECTION:		
1) Representative-	a) truly representative of the	Item is assessing the representativeness of exposed individuals in the
ness of the exposed	average pregnant woman	community, not the representativeness of the sample of women from
cohort	taking AEDs in the community	some general population.
	<ul> <li>b) somewhat representative of the average pregnant woman taking AEDs in the community</li> <li>c) selected group of users e.g., nurses, volunteers</li> <li>d) no description of the</li> </ul>	For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of estrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of estrogen).
	derivation of the cohort	Note:         Truly representative (A) is a population-based cohort at the provincial or national levels (e.g., a sample from 2 cities is not enough). We need very 'broad' sample of the population.         Somewhat representative (B) includes private clinics, hospital-based, or

		community-based
2) Selection of the	a) drawn from the same	Note:
2) Selection of the non-exposed cohort	<ul> <li>a) drawn from the same community as the exposed cohort</li> <li>b) drawn from a different source</li> <li>c) no description of the derivation of the non-exposed cohort</li> </ul>	In our review of mostly multi-arm studies, this question pertains to the study's comparator group(s) – including "active" controls (for example, a less teratogenic AED). Therefore, this will often be 'A' for our studies.
3) Ascertainment of exposure	<ul> <li>a) secure record (e.g., surgical records)</li> <li>b) structured interview</li> <li>c) written self-report</li> <li>d) no description</li> </ul>	Note:         Option 'A' includes patient hospital records, prescription drug database, or hospital/clinic visits (e.g., patient is asked about "current" AED use during a visit with their doctor).         Option 'B' includes a hospital/clinic visit, but the patients are asked to remember their AED use during pregnancy (e.g., retrospectively ascertained exposure).         If a study used both medical records and interviews for everyone select
		'A'.
4) Demonstration that outcome of interest was not present at start of study	a) yes b) no	In the case of mortality studies, outcome of interest is still the presence of a disease/incident, rather than death. That is to say that a statement of 'no history of disease or incident' earns a star (i.e. option 'A'). <u>Note:</u> Since our review is on pregnant women, this question is 'A' for all.
		Please email us if a study involves breastfeeding women.
COMPARABILITY	•	
1) Comparability of cohorts on the basis of the design or analysis	<ul> <li>a) answer is BOTH B &amp; C (i.e. study controls for age and one other important factor)</li> <li>b) study controls for age of the women</li> </ul>	Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

c) study contro	s for any other Note: If the relative risk for the exposure of interest is adjusted for the confounders listed then the groups will be considered to be comparable
d) study does r	on each variable used in the adjustment.
important fa	ctor or it is not
described	There may be multiple ratings for this item for different categories of
	exposure (e.g., ever vs. never, current vs. previous or never). [A
	maximum of 2 stars can be allotted in this category].
	Note:
	I he study should have initially matched the groups or presented adjusted
	AFD arm separately (instead of the whole exposed cohort), the study
	must also report the factor of interest for 'each AED arm' (or state the
	'each AED arm' is matched).
	Thus, there are 2 parts to this question:
	1) The study should have matched/adjusted for age at whatever level of groups they ware focused on (over if they grow't our shotrested AFI
	arms). AND
	2) Then the study should also have reported the age for each AED a
	If they haven't done both of these 2 things, it's a 'D' here (unless they
	happen to combine these by reporting adjusted ORs for each of our AE
	For our review, this generally pertains to <b>the comparability of the</b>
	MOTHERS.
	The exception here is in studies of cognitive/psychomotor developmen
	disorders in children - when age of the children should be comparable.
	The "other important factors" here are any one of these

		<ul> <li>history of congenital malformations (CMs), fetal losses, preterm deliveries or small babies.</li> <li>family history of genetic problems or CMs.</li> <li>alcohol use.</li> <li>nutritional deficiencies (e.g., lack of folic acid).</li> </ul> Example: <ul> <li>Option 'B' indicates that the study initially matched groups based on the women's acce (or expected a diverted OB c) AND there expect the constraints of the study initially divergence of the study initially divergence of the study initially divergence of the study initial divergence of the study ini</li></ul>
	í A	women's age for EACH of our arms (e.g., for Tx1, Tx2, etc.).
OUTCOME:		
1) Assessment of outcome	<ul> <li>a) independent OR blind assessment</li> <li>b) record linkage</li> <li>c) self-report</li> <li>d) no description</li> </ul>	<ul> <li>For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.</li> <li>a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.)</li> <li>b) Record linkage (e.g. identified through ICD codes on database records)</li> <li>c) Self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)</li> <li>d) No description.</li> </ul> Note: Blind (A) is if they tell us that the outcome assessors were blinded to exposures; or if the outcome is objective.
		For our purposes, we will focus on the primary outcome of interest of our systematic review, which is <u>major malformations (an objective outcome)</u> .

	So most of ours will be A, unless the study is only on a secondary
	outcome (e.g., cognitive development) and is based on the mother's self-
	report of their child (e.g., not a clinical examination).
a) yes	An acceptable length of time should be decided before quality assessment
b) no	begins (e.g. 5 yrs. for exposure to breast implants)
	Note:
	For this component, focus only on the outcomes that are reported in the
	results.
	For our purposes, we will focus on the primary outcome of interest of our
	systematic review, which is major malformations.
	• For studies focusing on 'birth' outcomes (i.e. malformations, preterm,
	fetal losses, born small), the answer is 'A' if they follow the groups
	until birth.
	• For studies focusing on cognitive developmental disorders, an
	adequate follow-up period (i.e. child's age) is 4 years.
	• For studies focusing on psychomotor delays, an adequate follow-up
	period is the earliest point of detection of the disorder.
	• For studies focusing on neonatal seizures, an adequate follow-up
	period (i.e. infant's age) is 6 months.
a) complete follow up - all	This item assesses the follow-up of the exposed and non-exposed cohorts
subjects accounted for	to ensure that losses are not related to either the exposure or the outcome.
b) subjects lost to follow up	
unlikely to introduce bias -	Note:
small number lost (see	Especially check ones that start their total sample size (or figure
'Note'), or description	diagram) with only the ones who had "complete" data (or only those
provided of those lost	who they had "successfully" recruited), as these are often a 'D' (since
c) follow up rate is inadequate	they don't report on the ones NOT followed up).
(see 'Note') and no	
description of those lost	• For a prospective study, $\geq 90\%$ follow-up rate per year is adequate
<ul><li>description of those lost</li><li>d) no statement</li></ul>	<ul> <li>For a prospective study, ≥90% follow-up rate per year is adequate (e.g., 10% dropout or less for 1 year, 20% for 2 years of follow-up,</li> </ul>
	<ul> <li>a) yes</li> <li>b) no</li> <li>a) complete follow up - all subjects accounted for</li> <li>b) subjects lost to follow up unlikely to introduce bias - small number lost (see 'Note'), or description provided of those lost</li> <li>c) follow up rate is inadequate (see 'Note') and no</li> </ul>

<ul> <li>For a retrospective cohort study, ≥80% follow-up rate is adequate; including the ones that they could NOT recruit or who would NOT participate.</li> <li>For a survey/mail questionnaire, ≥75% response rate is adequate. (For a survey, a dropout rate is congruent to a survey response rate).</li> </ul>
_

# **CASE-CONTROL Studies**

Evol Column	NOS* Answer Ontions**	NOS Coding Monuel*
Exter Column	NOS Answer Options	NOS Counig Manual
RefID	Enter the report's RefID.	
DA	Enter your initials.	
First author	Enter the first author's last name.	
Year of publication	Enter the year of the publication.	
SELECTION:		
1) Is the case	a) yes, with independent	a) Requires some independent validation (e.g. >1 person/record/time/
definition	validation	process to extract information, or reference to primary record source
adequate?	b) yes, e.g., record linkage or	such as x-rays or medical/hospital records)
-	based on self-reports	b) Record linkage (e.g. ICD codes in database) or self-report with no
	c) no description	reference to primary record
	i, i i i i i	c) No description
		Note:
		This question is assessing the group of infants that have the outcome of
		interest (e.g., $CMs$ ) – i.e. the "cases" in a case-control study design.
2) Representative-	a) consecutive or obviously	a) All eligible cases with outcome of interest over a defined period of
ness of the cases	representative series of cases	time, all cases in a defined catchment area, all cases in a defined
	b) potential for selection biases,	hospital or clinic, group of hospitals, health maintenance organisation,
	or not stated	or an appropriate sample of those cases (e.g. random sample)
		b) Not satisfying requirements in part (a), or not stated.

		Note:
		Option 'A' is a population-based sample.
3) Selection of	a) community controls	This item assesses whether the control series used in the study is derived
controls	<ul><li>b) hospital controls</li><li>c) no description</li></ul>	from the same population as the cases and essentially would have been cases had the outcome been present.
	<b>O</b>	a) Community controls (i.e. same community as cases and would be cases if had outcome)
	De	<ul><li>b) Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population</li><li>c) No description</li></ul>
		Note
		This question is assessing the group of infants that don't have the
	·	outcome (e.g. $CM_s$ ) – i.e. the "controls" in a case-control study design
		outcome (e.g., ettis) i.e. the controls in a cuse control study design.
		Community controls (A) includes a population-based sample.
4) Definition of controls	<ul><li>a) no history of disease (endpoint)</li><li>b) no description of source</li></ul>	a) If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded.
		b) No mention of history of outcome
		Note:
		Since our review is on fetal effects, this question is 'A' for all studies.
		Please email us if a study involves exposure during breastfeeding.
COMPARABILIT	Y:	
1) Comparability	a) answer is BOTH B & C (i.e.	Either cases and controls must be matched in the design and/or
of cases and	study controls for age and one	confounders must be adjusted for in the analysis. Statements of no
controls on the	other important factor)	differences between groups or that differences were not statistically
basis of the design	b) study controls for age of the	significant are not sufficient for establishing comparability.

or analysis	women c) study controls for any other Note: If the odds ratio for the exposure of interest is adjusted for the
	important factor increase is adjusted for the considered to be comparable
	d) study does not control for any on each variable used in the adjustment.
	important factor or it is not
	described There may be multiple ratings for this item for different categories of
	exposure (e.g. ever vs. never, current vs. previous or never). [A maximu
	of 2 stars can be allotted in this category].
	Note:
	The study should have initially matched the groups, AND in addition,
	since in our review we are analyzing each AED arm separately (instead
	the whole cases group), the study must also report the factor of interest
	for 'each AED arm' (or state that 'each AED arm' is matched).
	For our review, this generally pertains to the comparability of the
	MOTHERS of the cases and controls.
	The exception here is in studies of cognitive/psychomotor development
	disorders in children - when age of the children should be comparable.
	The "other important factors" here are any one of these:
	<ul> <li>history of congenital malformations (CMs), fetal losses, preterm</li> </ul>
	deliveries or small babies.
	• family history of genetic problems or CMs.
	• alcohol use.
	• nutritional deficiencies (e.g., lack of folic acid).
	For example, Option 'B' indicates that the study initially matched group
	based on the women's age AND they report the mean women's age for
	EACH arm (e.g., for Tx1, Tx2, etc.).
<b>EXPOSURE:</b>	

1) Assessment of	a) secure record (e.g., surgical	Note:	
exposure	records)	Option 'A' includes patient hospital records, prescription drug database,	
•	b) structured interview where	or hospital/clinic visits (e.g., patient is asked about "current" AED use	
	blind to case/control status	during a visit with their doctor).	
	c) interview not blinded to		
	case/control status	"Interview" here includes a hospital/clinic visit, but the patients are asked	
	d) written self-report or medical	to remember their AED use during pregnancy (e.g., retrospectively	
	record only	ascertained exposure).	
	e) no description		
2) Same method of	a) yes	Note:	
ascertainment for	b) no	This question is asking whether the method of ascertainment of exposure	
cases and controls		was the same for 'cases' (with the outcome) and 'controls' (without the	
		outcome; in this case-control study design).	
3) Non-response	a) same rate for both groups	Note:	
rate	b) non-respondents described	For our review, this pertains to either the infants or the mothers of the	
	c) rate different and no	case and control groups.	
	designation		
		We're allowing 10% dropout per year for a prospective study – e.g., 10%	
		for 1 year, 20% for 2 years of follow-up, etc.	
		For a survey, we allow for a 75% response rate in order for it be adequate.	
		For a survey, a dropout rate is congruent to a survey response rate.	

\*Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Available at: <u>http://www.ohri.ca/programs/clinical\_epidemiology/oxford.asp</u>

\*\*In the **"NOS Coding Manual" column**, the first section for each item is copied straight from the NOS documentation while the lower portions in each item are our "Notes" tailored for the AED review.

## Appendix B. List of included studies

A total of 29 cohort studies<sup>1-29</sup> with 9 companion reports<sup>30-38</sup> were included

1. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry*. 2004;75(11):1575-83.

2. Arkilo D, Hanna J, Dickens D, et al. Pregnancy and neurodevelopmental outcomes with in-utero antiepileptic agent exposure. A pilot study. *Eur J Paediatr Neurol*. 2015;19(1):37-40.

3. Bromley R, Baxter N, Calderbank R, Mawer G, Clayton-Smith J, Baker G. A comprehensive review of the language abilities of children exposed to valproate or carbamazepine in utero. American Epilepsy Society; Texas2010.

4. Bromley RL, Calderbank R, Cheyne CP, et al. Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate. *Neurology*. 2016;87(18):1943-53.

5. Bromley RL, Mawer GE, Briggs M, et al. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry*. 2013;84(6):637-43.

6. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA*. 2013;309(16):1696-703.

7. Cohen MJ, Meador KJ, Browning N, et al. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6years. *Epilepsy Behav*. 2013;29(2):308-15.

8. Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child*. 2011;96(7):643-7.

9. Dean JCS, Hailey H, Moore SJ, Lloyd DJ, Turnpenny PD, Little J. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. *J Med Genet*. 2002;39(4):251-9.

10. D'Souza SW, Robertson IG, Donnai D, Mawer G. Fetal phenytoin exposure, hypoplastic nails, and jitteriness. *Arch Dis Child*. 1991;66(3):320-4.

11. Eriksson K, Viinikainen K, Mönkkönen A, et al. Children exposed to valproate in utero—Population based evaluation of risks and confounding factors for long-term neurocognitive development. *Epilepsy Res.* 2005;65(3):189-200.

12. Gaily E. Development and growth in children of epileptic mothers: a prospective controlled study. Helsinki, Finland: University of Helsinki; 1990.

13. Gogatishvili N, Ediberidze T, Lomidze G, Tatishvili N, Kasradze S. PO-0834 Long-term Developmental Outcome Of Children Prenatally Exposed To Antiepileptic Drugs. *Arch Dis Child*. 2014;99(Suppl 2):A526.

14. Gogatishvili N, Ediberidze T, Lomidze G, Tatishvili N, Kasradze S. Cognitive outcomes of children with fetal antiepileptic drug exposure at the age of 3-6 years-preliminary data. 1st Congress of the European Academy of Neurology; Berlin: European Journal of Neurology; 2015. p. 329.

15. Hurault-Delarue C, Damase-Michel C, Finotto L, et al. Psychomotor developmental effects of prenatal exposure to psychotropic drugs: a study in EFEMERIS database. *Fundam Clin Pharmacol*. 2016;30(5):476-82.

16. Jones KL, Lacro RV, Johnson KA, Adams J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med.* 1989;320(25):1661-6.

### **BMJ Open**

17. Katz JM, Pacia SV, Devinsky O. Current Management of Epilepsy and Pregnancy: Fetal Outcome, Congenital Malformations, and Developmental Delay. Epilepsy Behav. 2001;2(2):119-23.

18. Koch S, Jager-Roman E, Losche G, Nau H, Rating D, Helge H. Antiepileptic drug treatment in pregnancy: drug side effects in the neonate and neurological outcome. Acta Paediatr. 1996:85(6):739-46.

Mawer G, Clayton-Smith J, Coyle H, Kini U. Outcome of pregnancy in women attending 19. an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. Seizure. 2002;11(8):512-8.

Miskov S, Juraski RG, Fucic A, et al. Croatian Pregnant Women with Epilepsy and 20. Effects of Antiepileptic Drugs Exposure in their Offspring - seven years of prospective surveillance. American Epilepsy Society; Texas2010.

Miskov S, Juraski RG, Mikula I, et al. The Croatian model of integrative prospective 21. management of epilepsy and pregnancy. Acta Clin Croat. 2016;55(4):535-48.

Nadebaum C, Anderson VA, Vajda F, Reutens DC, Barton S, Wood AG. Language skills 22. of school-aged children prenatally exposed to antiepileptic drugs. *Neurology*. 2011;76(8):719-26.

23. Rihtman T, Parush S, Ornoy A. Developmental outcomes at preschool age after fetal exposure to valproic acid and lamotrigine: cognitive, motor, sensory and behavioral function. Reprod Toxicol. 2013;41:115-25.

24. Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. JAMA. 1994;271(10):767-70.

Shankaran S, Woldt E, Nelson J, Bedard M, Delaney-Black V. Antenatal phenobarbital 25. therapy and neonatal outcome. II: Neurodevelopmental outcome at 36 months. *Pediatrics*. 1996;97(5):649-52.

van der Pol MC, Hadders-Algra M, Huisjes HJ, Touwen BC. Antiepileptic medication in 26. pregnancy: late effects on the children's central nervous system development. Am J Obstet Gynecol. 1991;164(1 Pt 1):121-8.

Veiby G, Daltveit AK, Schjolberg S, et al. Exposure to antiepileptic drugs in utero and 27. child development: a prospective population-based study. *Epilepsia*. 2013;54(8):1462-72.

Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to 28. antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. JAMA Neurol. 2013;70(11):1367-74.

Wood AG, Nadebaum C, Anderson V, et al. Prospective assessment of autism traits in 29. children exposed to antiepileptic drugs during pregnancy. *Epilepsia*. 2015;56(7):1047-55.

Bromley RL, Mawer G, Clayton-Smith J, Baker GA. Autism spectrum disorders 30. following in utero exposure to antiepileptic drugs. Neurology. 2008;71(23):1923-4.

Gaily EK, Granstrom ML, Hillesmaa VK, Bardy AH. Head circumference in children of 31. epileptic mothers: contributions of drug exposure and genetic background. *Epilepsy Res.* 1990;5(3):217-22.

Hillesmaa V. A prospective study on maternal and fetal outcome in 139 women with 32. epilepsy. Helsinki: University of Helsinki; 1982.

Hiilesmaa VK, Bardy A, Teramo K. Obstetric outcome in women with epilepsy. Am J 33. Obstet Gynecol. 1985;152(5):499-504.

Rasalam AD, Hailey H, Williams JH, et al. Characteristics of fetal anticonvulsant 34. syndrome associated autistic disorder. Dev Med Child Neurol. 2005;47(8):551-5.

35. Tomson T, Battino D, Bonizzoni E, et al. Antiepileptic drugs and intrauterine death: A prospective observational study from EURAP. *Neurology*. 2015;85(7):580-8.

36. Viinikainen K, Eriksson K, Monkkonen A, et al. The effects of valproate exposure in utero on behavior and the need for educational support in school-aged children. *Epilepsy Behav*. 2006;9(4):636-40.

37. Vinten J, Adab N, Kini U, Gorry J, Gregg J, Baker GA. Neuropsychological effects of exposure to anticonvulsant medication in utero. *Neurology*. 2005;64(6):949-54.

38. Vinten J, Bromley RL, Taylor J, Adab N, Kini U, Baker GA. The behavioral consequences of exposure to antiepileptic drugs in utero. Epilepsy Behav. 2009;14(1):197-201. 

## Appendix C. Key excluded studies

Author, Year	Research Group	Title	Reason for Exclusion
Meador, 2009 <sup>39</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs	Outcomes only reported as continuous variables
Meador, 2010 <sup>40</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Effects of breastfeeding in children of women taking antiepileptic drugs	Outcomes only reported as continuous variables
Meador, 2011 <sup>41</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age	Outcomes only reported as continuous variables
Meador, 2012 <sup>42</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Effects of fetal antiepileptic drug exposure: Outcomes at age 4.5 years	Outcomes only reported as continuous variables
Meador, 2013 <sup>43</sup>	Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study Group	Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study	Outcomes only reported as continuous variables
Shallcross, 2011 <sup>44</sup>	Liverpool and Manchester Neurodevelopment Group and The UK Epilepsy and Pregnancy Register	Child development following in utero exposure: Levetiracetam vs. sodium valproate	Outcomes only reported as continuous variables
Shallcross, 2014 <sup>45</sup>	Liverpool and Manchester	In utero exposure to levetiracetam vs. valproate: Development and language at 3 years of age	Outcomes only reported as continuous variables
Neurodevelopment			
------------------------	--		
Group and The UK			
Epilepsy and Pregnancy			
Register			

#### References

39. Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med.* 2009;360(16):1597-605.

40. Meador KJ, Baker GA, Browning N, et al. Effects of breastfeeding in children of women taking antiepileptic drugs. *Neurology*. 2010;75(22):1954-60.

41. Meador KJ, Baker GA, Browning N, et al. Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. *Brain*. 2011;134(Pt 2):396-404.

42. Meador KJ, Baker GA, Browning N, et al. Effects of fetal antiepileptic drug exposure: outcomes at age 4.5 years. *Neurology*. 2012;78(16):1207-14.

43. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013;12(3):244-52.

44. Shallcross R, Bromley RL, Irwin B, Bonnett LJ, Morrow J, Baker GA. Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology*. 2011;76(4):383-9.

45. Shallcross R, Bromley RL, Cheyne CP, et al. In utero exposure to levetiracetam vs valproate: development and language at 3 years of age. *Neurology*. 2014;82(3):213-21.

46. Cohen MJ, Meador KJ, Browning N, et al. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6 years. *Epilepsy Behav*. 2013;29(2):308-15.

10

### Appendix D. Table of Individual Study characteristics

Author, Year	Country of conduct	Registry or Setting	Registry or Setting Study period Interventions		Outcomes	Funding
Adab, 2004 <sup>*1</sup> [CR: Vinten 2005 <sup>37</sup> Vinten, 2009 <sup>38</sup> ]	UK	Mersey Regional Epilepsy Clinic; Epilepsy Clinic at the Manchester Royal Infirmary; Antenatal clinic at St Mary's Hospital, Manchester	2000- 2001	Carbam, Control, Valpro	Cognitive Developmental Delay, Psychomotor Developmental Delay	NR
Arkilo, 2015 <sup>2</sup>	USA	Minnesota Epilepsy Group	2006- 2011	Carbam, Lamot, Levet, Pheny, Valpro	Autism/Dyspraxia, Psychomotor Developmental Delay	NR
Bromley, 2010 <sup>3</sup>	UK	Liverpool and Manchester Neurodevelopment Group	NR	Carbam, Valpro	Language Delay	NR
Bromley, 2013 <sup>5</sup> [CR: Bromley, 2008 <sup>30</sup> ]	UK	Liverpool and Manchester Neurodevelopment group	2000- 2004	Carbam, Control, Lamot, Valpro	Autism/Dyspraxia, ADHD	mixed public & private
Bromley, 2016 <sup>4</sup> †	UK	UK Epilepsy and Pregnancy Register	2004- 2007	Control, Gabap, Levet, Topir, Valpro	Cognitive Developmental Delay	public
Christensen, 2013 <sup>6</sup> †	Denmark	Danish Civil Registration System; Danish Prescription Register; Danish Psychiatric Central Register; Danish	1996- 2006	Carbam, Clonaz, Lamot, Oxcar, Valpro	Autism/Dyspraxia	public

**BMJ Open** 

		Birth Register; Danish National Hospital Register				
Cohen, 2013 <sup>46</sup>	USA;UK	Neurodevelopmental Effects of Antiepileptic Drugs Study Group	1999- 2004	Carbam, Lamot, Pheny, Valpro,	ADHD	public
Cummings, 2011 <sup>8</sup> † [CR: Tomson, 2015 <sup>35</sup> ]	Northern Ireland	UK Epilepsy and Pregnancy Register (Northern Ireland); Northern Ireland Child Health System	1996- 2005	Carbam, Lamot, Valpro,	Cognitive Developmental Delay	public
Dean, 2002 <sup>9</sup> [CR: Rasalam, 2005 <sup>34</sup> ]	Scotland	Aberdeen Maternity Hospital	1976- 2000	Carbam, Carbam+Pheno, Carbam+Pheny, Carbam+Valpro, Control, Ethos, Pheno, Pheno+Pheny, Pheno+Valpro, Pheny, Primid, Valpro	Psychomotor Developmental Delay, ADHD	NR
D'Souza, 1991 <sup>10</sup>	United Kingdom	St Mary's Hospital	1980- 1982	Carbam, Control, Pheno, Pheny, Valpro	Cognitive Developmental Delay	public
Eriksson, 2005 <sup>11</sup> † [CR: Viinikainen, 2006 <sup>36</sup> ]	Finland	Kuopio University Hospital	1989- 2000	Carbam, Control, Valpro	Cognitive Developmental Delay, Psychomotor Developmental Delay	public

Page	71	of	90	
------	----	----	----	--

Gaily, $1990^{12}$ [CR: Gaily, $1990^{31}$ ; Helsin Hiilesmaa, Finland Centra $1982^{32}$ ; Hiilesmaa, $1985^{33}$ ]		Helsinki University Central Hospital	1975- 1979	Carbam, Carbam+Pheno+Pheny, Carbam+Pheny, Carbam+Valpro, Control, Ethos+Pheny, Pheno+Pheny, Pheny, Pheny+Primid, Pheny+Valpro	Cognitive Developmental Delay , Psychomotor Developmental Delay	mixe publ priva	
Gogatishvili, 2014 <sup>13</sup>	Georgia	Georgian National AED- Pregnancy Registry	NR	Carbam, Lamot, Valpro	Cognitive Developmental Delay	publ	
Gogatishvili, 2015 <sup>14</sup>	Georgia	Georgian National AED- Pregnancy Registry	NR	Carbam, Carbam+Levet, Lamot, Pheno, Valpro	Language Delay	publi	
Hurault- Delarue, 2012 <sup>15</sup> France France Delarue, 2012 <sup>15</sup> France EFEMERIS data Caisse Primaire d'Assurance Ma Haute-Garonne a Maternal and Inf Protection Servio Antenatal Diagno Centre		EFEMERIS database - Caisse Primaire d'Assurance Maladie of Haute-Garonne and Maternal and Infant Protection Service; Antenatal Diagnostic Centre	2004- 2008	Carbam, Clobaz, Clonaz, Gabap, Lamot, Pheno, Topir, Valpro	Psychomotor Developmental Delay	NR	
Jones, 1989 <sup>16</sup> †	US	California Teratogen Registry	1979- 1988	Carbam, Carbam+Pheno, Carbam+Pheno+Valpro, Carbam+Primid	Cognitive Developmental Delay , Psychomotor Developmental Delay	publi	
Katz, 2001 <sup>17</sup>	USA	Mount Sinai Comprehensive Epilepsy Center	1990- 2000	Carbam, Control, Lamot, Pheno, Pheny, Primid, Valpro	Cognitive Developmental Delay	NR	

BMJ Open

Koch, 1996 <sup>18</sup>	Germany	ıy NR		Pheno, Pheny, Primid, Valpro	Cognitive Developmental Delay	public
Mawer, 2002 <sup>19</sup>	England	Manchester Royal Infirmary	1990- 1999	Carbam, Lamot, Pheny, Valpro	Cognitive Developmental Delay	NR
Miskov, 2010 <sup>20</sup>	Croatia	NR	2003- 2010	Carbam, Control, Gabap, Lamot, Valpro	Psychomotor Developmental Delay, Neonatal Seizures	NR
Miskov, 2016 <sup>21</sup>	Croatia	Sestre milosrdnice University Hospital Center	2003- 2013	Carbam, Carbam+Lamot, Carbam+Pheno, Carbam+Pheny+Topir, Control, Clonaz+Valpro, Gabap, Lamot, Oxcar, Pheno, Pheny, Topir+Valpro, Valpro	Attention Deficit Hyperactivity Disorder	NR
Nadebaum, 2011 <sup>22</sup> †	Australia	Australian Registry of Antiepileptic Drug Use in Pregnancy	2007- 2009	Carbam, Lamot, Valpro	Language Delay	mixed public & private
Rihtman, 2013 <sup>23</sup>	Israel	Israeli Teratogen Information Service	NR	Lamot, Valpro	Neonatal Seizure	mixed public & private
Scolnik, 1994 <sup>24</sup>	Canada	Hospital for Sick Children - Motherisk Program; North York General Hospital; Toronto Hospital; Oshawa General Hospital	1987- 1992	Carbam, Pheny	Cognitive Developmental Delay	public

Page	73	of	90
1			

Shankaran, 1996 <sup>25</sup>	USA	Children's Hospital of Michigan	NR	Control, Pheno	Psychomotor Developmental Delay, Language Delay	public
Van der Pol, 1991 <sup>26</sup>	Netherlands	Groningen University Hospital	1973- 1981	Carbam, Carbam+Pheno, Control, Pheno	Psychomotor Developmental Delay	public
Veiby, 2013a <sup>27</sup> †	Norway	Norwegian Institute of Public Health- Mother and Child Cohort Study	1999- 2009	Carbam, Control, Lamot, Valpro	Social Impairment	public
Veiby, 2013b <sup>28</sup> †	Norway	Medical Birth Registry of Norway	1999- 2008	Carbam, Control, Lamot, Valpro	Psychomotor Developmental Delay, Autism/Dyspraxia, Language Delay, ADHD	public
Wood, 2015 <sup>29</sup> †	Australia	Australian Registry of Antiepileptic Drug Use in Pregnancy	2007- 2010	Carbam, Carbam+Clonaz, Carbam+Lamot, Carbam+Pheny, Lamot+Valpro, Valpro	Autism/Dyspraxia	public

Carbam = Carbamazepine; Clobaz = Clobazam; Clonaz = Clonazepam; Ethos = Ethosuximide; Gabap = Gabapentin; Lamot = Lamotrigine; Levet = Levetiracetam; Oxcar = Oxcarbazepine; Pheno = Phenobarbital; Pheny = Phenytoin; Primid = Primidone; Topir = Topiramate; Valpro = Valproate; Vigab = Viagabatrin

\*Single publication reporting on two separate cohorts †Registry Studies

### **Appendix E. Table of Patient characteristics**

Author, Year	Indication	Sample Size*	Mean Age (Women)	Mean Age (Children)/ Follow-up period†	AED Exposure Timing	Maternal Alcohol Use n/N‡	Maternal Tobacco Use n/N‡
Adab, 2004a <sup>1</sup> § [CR: Vinten 2005 <sup>37</sup> ; Vinten, 2009 <sup>38</sup> ]	Epilepsy	177	26.1	9-10.5	NR	24/279‡	68/249‡
Adab, 2004b <sup>1</sup> § [CR: Vinten 2005 <sup>37</sup> ; Vinten, 2009 <sup>38</sup> ]	Epilepsy	81	26.1	3-3.33	NR	24/279‡	68/249‡
Arkilo, $2015^2$	Epilepsy	59	NR	NA	First trimester	NR	NR
Bromley, $2010^3$	NR	60	NR	6-7	Whole pregnancy	NR	NR
Bromley, 2013 <sup>5</sup> [CR: Bromley, 2008 <sup>30</sup> ]	Epilepsy	156	28	6	NR	28/156	42/156
Bromley, 2016 <sup>4</sup>	Epilepsy	185	NR	NR	NR	31/185	35/185
Christensen, 2013 <sup>6</sup>	NR	2011	NR	NR	Whole pregnancy	NR	NR
Cohen, 2013 <sup>46</sup>	Epilepsy	108	30	6	During pregnancy and breastfeeding	12/192‡	NR
Cummings, 2011 <sup>8</sup> [CR: Tomson, 2015 <sup>35</sup> ]	Epilepsy	142	NR	2-3	During pregnancy and breastfeeding	32/108‡	19/108‡
Dean, 2002 <sup>9</sup> [CR: Rasalam, 2005 <sup>34</sup> ]	Epilepsy	287	27	3.75-15.5	First trimester	NR	NR
D'Souza, 1991 <sup>10</sup>	Epilepsy	42	26.5	2.5-3.5	Whole pregnancy	NR	NR
Eriksson, 2005 <sup>11</sup> [CR: Viinikainen, 2006 <sup>36</sup> ]	Epilepsy	39	28.2	NR	NR	NR	NR

Gaily, 1990 <sup>12</sup> [CR: Gaily, 1990 <sup>31</sup> ; Hiilesmaa, 1982 <sup>32</sup> ; Hiilesmaa, 1985 <sup>33</sup>	Epilepsy	134	27.8	5.5	First trimester	NR	NR
Gogatishvili, 2014 <sup>13</sup>	NR	39	NR	2 to 4	NR	NR	NR
Gogatishvili, 2015 <sup>14</sup>	NR	23	NR	3 to 6	NR	NR	NR
Hurault-Delarue, 2012 <sup>15</sup>	NR	109	NR	0.75	NR	NR	NR
Jones, 1989 <sup>16</sup>	Epilepsy	63	NR	NR	Whole pregnancy	NR	NR
Katz, 2001 <sup>17</sup>	Epilepsy	51	31	NR	NR	NR	NR
Koch, 1996 <sup>18</sup>	Epilepsy	40	NR	6	First trimester	NR	NR
Mawer, 2002 <sup>19</sup>	Epilepsy	52	NR	NR	NR	NR	NR
Miskov, 2010 <sup>20</sup>	Epilepsy	55	NR	NR	NR	NR	NR
Miskov, 2016 <sup>21</sup>	Epilepsy	74	34	NR	NR	NR	6/74
Nadebaum, 2011 <sup>22</sup>	Epilepsy	66	31.6	7.4	During pregnancy and breastfeeding	NR	5/66
Rihtman, 2013 <sup>23</sup>	Epilepsy	72	NR C	NR	During pregnancy and breastfeeding	NR	NR
Scolnik, 1994 <sup>24</sup>	Epilepsy	75	NR	1.5-3	1st trimester	NR	NR
Shankaran, 1996 <sup>25</sup>	NR	96	NR	NR	NR	NR	NR
Van der Pol, 1991 <sup>26</sup>	Epilepsy	57	NR	6-13	NR	NR	NR
Veiby, 2013a <sup>27</sup>	Epilepsy	422	NR	0.5	During pregnancy and breastfeeding	NR	NR
Veiby, 2013b <sup>28</sup>	Epilepsy	248	28.9	3	NR	NR	68/726
Wood, 2015 <sup>29</sup>	Epilepsy	77	NR	6-8	NR	NR	NR

**Abbreviations:** NA – Not applicable; NR – Not reported

\* Sample size used for analysis; ineligible treatment arms (i.e. treatment arms with excluded drugs or unspecified polytherapy) are not included in the count

† The mean age for children/follow-up period data were only collected for outcomes related to cognitive and/or psychomotor development

‡ Total sample size is based on the number of women enrolled in the study; may differ from the sample size used for analysis

§ Single publication reporting on two separate cohorts

BMJ Open

Appendix F. Methodological quality of observational studies – Newcastle Ottawa Scale results

First Author, Year	Representativen ess of the exposed cohort	Selection of the non- exposed cohort	Ascertainme nt of exposure	Demonstratio n that outcome of interest was not present at start of study	Comparabili ty of cohorts on the basis of the design or analysis	Assessmen t of outcome	Was follow-up long enough for outcomes to occur	Adequac y of follow up of cohorts
Adab, 2004 <sup>1</sup>	В	А	Α	А	С	А	А	С
Arkilo, 2015 <sup>2</sup>	В	A	В	А	D	А	А	С
Bromley, $2010^3$	D	А	D	А	D	D	В	D
Bromley, 2013 <sup>5</sup>	А	А	A	А	А	А	А	С
Bromley, 2016 <sup>4</sup>	А	А	А	А	А	А	А	С
Christensen, 2013 <sup>6</sup>	А	А	А	А	А	В	А	В
Cohen, 2013 <sup>46</sup>	А	А	D	A	А	А	А	С
Cummings, 2011 <sup>8</sup>	А	А	А	А	А	А	А	С
Dean, 2002 <sup>9</sup>	В	А	А	А	D	Α	А	С
D'Souza, 1991 <sup>10</sup>	В	А	А	А	D	А	А	А
Eriksson, 2005 <sup>11</sup>	В	A	A	А	В	A	A	D
Gaily, 1990 <sup>12</sup>	В	А	А	А	D	А	А	А
Gogatishvili, 2014 <sup>13</sup>	А	А	D	А	D	А	А	D
Gogatishvili, 2015 <sup>14</sup>	A	А	D	А	D	A	А	D

Page	77	of	90	
------	----	----	----	--

Hurault-								
Delarue, 2012 <sup>15</sup>	А	А	А	А	А	А	А	
Jones, 1989 <sup>16</sup>	А	А	В	А	D	А	А	
Katz, 2001 <sup>17</sup>	В	А	А	А	D	А	А	
Koch, 1996 <sup>18</sup>	В	А	В	А	D	А	А	
Mawer, 2002 <sup>19</sup>	В	А	А	А	D	А	А	
Miskov, 2010 <sup>20</sup>	D	А	D	А	D	D	А	
Miskov, 2016 <sup>21</sup>	С	A	А	А	D	А	А	
Nadebaum, 2011 <sup>22</sup>	А	А	A	А	А	А	А	
Rihtman, 2013 <sup>23</sup>	А	В	А	А	А	А	А	
Scolnik, 1994 <sup>24</sup>	В	А	А	А	D	А	А	
Shankaran, 1996 <sup>25</sup>	В	А	А	A	D	А	А	
Van der Pol, 1991 <sup>26</sup>	В	А	D	А	А	А	А	
Veiby, 2013a <sup>27</sup>	А	А	А	А	A	Α	А	
Veiby, 2013b <sup>28</sup>	А	А	А	А	А	А	А	
Wood. 2015 <sup>29</sup>	А	А	А	А	D	A	А	

BMJ Open



Log-odds ratio centered at comparison-specific pooled effect

\* Funnel plots have been produced only for outcomes with  $\geq 10$  studies. For multi-arm studies we plot data points from each study-specific basic parameter (treatment comparisons with a study-specific common comparator)

**BMJ Open** 

# Appendix H. Statistically significant network meta-analysis results along with meta-analysis results, transitivity, and inconsistency assessments

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatment Indication	Timing	Comparability of cohorts	Adequacy of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
	Cogn	itive Develop	omental Dela	y (10 studi	ies, 748 patients	, 14 treatme	ents)	
Lamot vs Valpro	4 (NA)	140 (31.00)	Epilepsy	NR	Н	Н	0.17 (0.02-0.87)	0.13 (0.01-0.57) (0.01-0.75)
Valpro vs Control	4 (0.06)	267 (28.80)	Epilepsy	1st trimester	Н	Н	8.15 (3.19-22.33)	7.40 (3.00-18.46) (1.81-27.63)
Valpro vs Carbam	6 (NA)	310 (27.80)	Epilepsy	NR	Н	L	3.32 (1.56-7.04)	3.54 (1.69-7.26) (0.95-12.32)
Valpro vs Pheno	3 (NA)	36 (27.80)	Epilepsy	1st trimester	Н	L	4.25 (0.82-34.07)	5.59 (1.21-35.07) (0.93-45.99)
Valpro vs Pheny	3 (NA)	58 (31.00)	Epilepsy	1st trimester	Н	L	3.12 (0.75-14.12)	2.88 (1.04-8.49) (0.69-12.62)
Common between-s	tudy variance a	cross treatme	ent compariso	ons			0.13	0.12
Residual deviance:	44.72 Data	points: 47	DIC: 78.7				(0.00-0.97)	(0.00-1.15) (NA)
Evaluation of consi. model	stency using the	e design-by-tr	eatment inter	action	Chi-square test: Degrees of Free	14.15 dom: 17	P- value: 0.66 Heterogeneity: 0	
	For	peer review o	nly - http://bm	26 J <b>jopen.bmj.</b>	com/site/about/g	uidelines.xh	tml	

2
3
3
4
5
6
7
1
8
9
10
10
11
12
13
10
14
15
16
17
40
18
19
20
24
21
22
23
24
24
25
26
27
20
20
29
30
31
22
32
33
34
25
55
36
37
38
00
39
40
41
12
42
43
44
45
16
40
47
48
10

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatment Indication	Timing	Comparability of cohorts	Adequacy of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
		Autism Dys	praxia (5 st	udies, 2551	l patients, 12 tr	eatments)		
Lamot vs Control	2 (0.00)	254 (27.75)	Epilepsy	1st trimester	Н	Н	13.77 (2.06-188.00)	8.88 (1.29-112.00) (0.94-146.80)
Lamot+Valpro vs Carbam	1 (NA)	40 (NR)	Epilepsy	NR	L	L	15.02 (2.04-171.90)	22.89 (2.58-219.00) (1.90-282.20)
Lamot+Valpro vs Clonaz	NA	NR	NR	NR	NR	NR	NA	20.21 (1.48-351.30) (1.15-455.00)
Lamot+Valpro vs Control	NA	NR	NR	NR	NR	NR	NA	132.70 (7.41-3.9 x 10 <sup>3</sup> ) (5.82-4.6 x 10 <sup>3</sup> )
Lamot+Valpro vs Lamot	NA	NR	NR	NR	NR	NR	NA	14.61 (1.51-149.10) (1.14-196.80)
Oxcar vs Control	NA	NR	NR	NR	NR	NR	NA	13.51 (1.28-221.40) (0.86-267.40)
Valpro vs Carbam	5 (NA)	1003 (27.83)	Epilepsy	1st trimester	L L	O <sub>L</sub>	3.20 (1.20-8.68)	3.02 (1.09-8.40) (0.57-14.31)
Valpro vs Control	2 (0.00)	249 (27.75)	Epilepsy	1st trimester	Н	Н	9.19 (1.14-132.10)	17.29 (2.40-217.60) (1.61-274.90)
Common between-st	tudy variance o	across treatme	nt comparise	ons			0.12	0.16 (0.00-1.95)
Residual deviance:	24 Data poin	ts: 24 DIC:	44					(NA)
Evaluation of consist interaction model	stency using th	e design-by-tre	eatment	Chi-square Degrees of	test: 3.79 Freedom: 5		P- value: 0.57 Heterogeneity:	0

Page	81	of	90
------	----	----	----

No Treatment S Comparison Bas	umber of Studies (Mean seline Risk	Number of patients (Mean Age)	Treatment Indication	Timing	Comparability of cohorts	Adequacy of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
	Psych	omotor Develo	opmental De	lay (11 stu	dies, 1145 patier	nts, 18 treatr	nents)	
Carbam+Pheno+Valpro vs Control	NA	NR	NR	NR	NR	NR	NA	19.12 (1.49-337.50) (1.34-370.40)
Carbam+Pheno+Valpro vs Pheno	NA	NR	NR	NR	NR	NR	NA	19.86 (1.38-393.60) (1.26-423.30)
Levet vs Carbam+Pheno+Valpro	NA	NR	NR	NR	NR	NR	NA	0.01 (0.00-0.58) (0.00-0.62)
Valpro vs Carbam	7 (NA)	331 (27.80)	Epilepsy	1st trimester	Н	Н	2.72 (1.39-5.67)	2.45 (1.27-4.88) (0.95-6.77)
Valpro vs Control	5 (0.07)	331 (28.38)	Epilepsy	1st trimester	Н	Н	3.53 (1.60-8.64)	4.16 (2.04-8.75) (1.52-12.05)
Valpro vs Pheno	2 (NA)	141 (NR)	Epilepsy	1st trimester	Н	Н	3.68 (1.17-12.30)	4.32 (1.72-11.20) (1.34-14.51)
Common between-study	variance	e across treatm	ent comparis	ons			0.05	0.06
Residual deviance: 45	Data poi	ints: 51 DIC	: 78				0.05 (0.00-0.49)	(0.00-0.63) (NA)
Evaluation of consistend interaction model	cy using t	the design-by-tr	reatment	Chi-square Degrees of	e test: 13.46 Freedom: 21		P- value: 0.89 Heterogeneity: 0	
	Fo	or peer review o	only - http://br	28 njopen.bmj	.com/site/about/g	uidelines.xht	ml	

2
3
4
4
5
6
7
1
8
9
10
10
11
12
12
13
14
15
16
10
17
18
19
10
20
21
22
~~
23
24
25
20
26
27
28
20
29
30
31
00
32
33
34
25
30
36
37
20
38
39
40
11
41
42
43
11
44
45
46
47
41
48
10

Treatment Comparison	Number of Studies (Mean Baseline Risk)	Number of patients (Mean Age)	Treatment Indication	Timing	Comparability of cohorts	Adequacy of follow up of cohorts	MA Odds Ratio (95% CrI)	NMA Odds Ratio (95% CrI) (95% PrI)
		Languag	e Delay (5 stu	udies, 509	patients, 5 treat	tments)		
Valpro vs Control	1 (0.03)	173 (28.90) E <sub>F</sub>	pilepsy	NR	L	Н	6.96 (1.14-37.03)	7.95 (1.50-49.13) (0.96-74.52)
Common between-s	tudy variance d	across treatme	ent compariso	ons			0.15	0.16
Residual deviance:	12 Data poin	ts: 14 DIC:	: 23				(0.00-1.85)	(0.00-2.15) (NA)
Evaluation of consi interaction model	stency using th	e design-by-tr	reatment	Chi-square Degrees of	e test: 2.33 f Freedom: 3		P- value: 0.50 Heterogeneity: 0	)
		ADI	HD (4 studies	s, 750 pati	ents, 6 treatmen	ts)		
			No statistic	cally signij	ficant results			
Residual deviance:	12 Data poin	ts: 17 DIC:	: 22		181			
Abbreviations: ADHD risk of bias; MA - Meta Carbam = Carbamazepi Levetiracetam; Oxcar = Viagabatrin	) - Attention Defic -analysis; NA - N ne; Clobaz = Clol Oxcarbazepine; I	it Hyperactivity ot applicable; Nl oazam; Clonaz = Pheno = Phenoba	Disorder; CrI - ( MA - Network M Clonazepam; En arbital; Pheny = 1	Credible Inte Meta-analysi thos = Ethos Phenytoin; F	erval; DIC - Devianc s; NR- Not Reported uximide; Gabap = G Pridmid = Primidone	e Information ( l; PrI - Predictiv abapentin; Lan ; Topir = Topir	Criterion; H- high risk ve Interval not = Lamotrigine; Le amate; Valpro = Valp	t of bias; L - low evet = proate; Vigab =
	For	neer review o	nlv - http://bm	29 Niopen hmi	com/site/about/o	uidelines vh	tml	



## Appendix I. Rank-heat plot of cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abbreviations: carbam - carbamazepine, clobaz - clobazam, clonaz - clonazepam, ethos - ethosuximide, gabap - gabapentin, lamot - lamotrigine, levet - levetiracetam, oxcar - oxcarbazepine, pheno - phenobarbital, pheny - phenytoin, primid - primidone, topir - topiramate, valpro - valproate, vigab - vigabatrin

\*Rank-heat plot of cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay, language delay, and attention deficit hyperactivity disorder outcomes (5 circles) and 25 treatments (25 radii). Each sector is coloured according to the surface under the cumulative ranking curve value of the corresponding treatment and outcome using the transformation of three colours red (0%), yellow (50%), and green (100%).

BMJ Open

Total studies	Range of study arms	# of treatments	# of patients	# of direct treatment comparisons	# of NMA treatment comparisons	Statistically significant NMA treatment effects	# of studies with zero events in all arms	# of studies with ineligible outcome definition*
<b>Cognitive Dev</b>	elopmental	Delay						
11	(2,8)	18	933	62	153	5	1	5
Autism/Dyspr	axia							
5	(4,6)	12	2551	34	66	8	0	4
Neonatal Seizi	ure							
1	(2,2)	2	69	1	0	0	1	1
Psychomotor ]	Developme	ntal Delay						
11	(2,8)	18	1145	74	153	6	0	5
Language Dela	ay							
5	(2,4)	5	509	7	10	1	0	3
ADHD								
5	(4,6)	7	816	20	21	0	0	0
Social Impair	ment							
1	(4,4)	4	422	1	0	0	0	0

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI
Cognitive Developmental Delay – Sensitivity	Analysis - Epilepsy or	nly (10 studies, 910 patien	ts, 17 treatments)
Carbamazepine vs Control	2.08	(0.79 - 5.82)	(0.47 - 9.34)
Carbamazepine+Phenobarbital vs Control	0.62	(0.00 - 15.31)	(0.00 - 19.29)
Carbamazepine+Phenobarbital+Phenytoin vs Control	4.75	(0.01 - 164.80)	(0.01 - 192.50)
Carbamazepine+Phenobarbital+Valproate vs Control	15.00	(1.00 - 367.10)	(0.82 - 426.90)
Carbamazepine+Phenytoin vs Control	9.84	(0.60 - 136.30)	(0.49 - 164.50)
Ethosuximide+Phenytoin vs Control	6.53	(0.02 - 216.00)	(0.02 - 251.30)
Gabapentin vs Control	1.43	(0.05 - 14.28)	(0.04 - 18.20)
Lamotrigine vs Control	0.79	(0.05 - 5.12)	(0.05 - 6.66)
Levetiracetam vs Control	3.46	(0.65 - 17.14)	(0.47 - 23.57)
Phenobarbital vs Control	0.55	(0.01 - 5.38)	(0.01 - 6.85)
Phenobarbital+Phenytoin vs Control	1.28	(0.00 - 36.18)	(0.00 - 44.03)
Phenytoin vs Control	2.47	(0.65 - 8.25)	(0.41 - 12.47)
Phenytoin+Valproate vs Control	3.68	(0.01 - 121.00)	(0.01 - 135.00)
Primidone vs Control	1.97	(0.25 - 12.16)	(0.19 - 16.25)
Topiramate vs Control	3.06	(0.42 - 17.51)	(0.32 - 23.57)
Valproate vs Control	7.48	(2.99 - 19.04)	(1.67 - 31.21)
Common within-network between-study variance	0.16	(0.00 - 1.36)	
Evaluation of inconsistency using the design-by-treatmen	t interaction model	Chi-square test: 12.98 Degrees of Freedom: 14	P-value: 0.53 Heterogeneity: 0.00
Cognitive Developmental Delay - Sensitivity Analys	is - First generation A	AEDs only (6 studies, 480	patients, 13 treatments)
Carbamazepine vs Control	1.68	(0.37 - 7.82)	(0.19 - 14.98)
Carbamazepine+Phenytoin vs Control	8.98	(0.36 - 169.90)	(0.26 - 243.60)
Carbamazepine+Phenobarbital vs Control	0.46	(0.00 - 21.02)	(0.00 - 28.01)
Carbamazepine+Phenobarbital+Phenytoin vs Control	4.12	(0.01 - 180.10)	(0.00 - 236.30)
Carbamazepine+Phenobarbital+Valproate vs Control	12.84	(0.50 - 435.70)	(0.35 - 604.30)
Ethosuximide+Phenytoin vs Control	5.65	(0.01 - 219.00)	(0.01 - 291.50)

### Appendix K. Sensitivity and network meta-regression analyses - Anti-epileptic drugs compared with Control

 BMJ Open

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI
Phenobarbital vs Control	0.64	(0.00 - 26.02)	(0.00 - 35.36)
Phenobarbital+Phenytoin vs Control	1.06	(0.00 - 37.64)	(0.00 - 50.85)
Phenytoin vs Control	2.08	(0.26 - 12.50)	(0.13 - 22.02)
Phenytoin+Valproate vs Control	3.14	(0.00 - 135.80)	(0.00 - 178.90)
Primidone vs Control	3.30	(0.18 - 43.76)	(0.12 - 68.72)
Valproate vs Control	13.22	(3.20 - 64.06)	(1.50 - 128.40)
Common within-network between-study variance	0.27	(0.00 - 2.97)	
Evaluation of inconsistency using the design-by-treatment	nt interaction model	Chi-square test: 3.31 Degrees of Freedom: 3	P-value: 0.35 Heterogeneity: 0.00
<b>Cognitive Developmental Delay - Sensitivity Analysis</b>	- Maternal Alcohol or	r Tobacco use (3 studies,	504 patients, 7 treatmen
Carbamazepine vs Control	1.97	(0.40 - 10.01)	(0.19 - 21.27)
Gabapentin vs Control	1.47	(0.04 - 19.01)	(0.02 - 27.11)
Lamotrigine vs Control	0.41	(0.00 - 10.09)	(0.00 - 13.61)
Levetiracetam vs Control	3.55	(0.43 - 24.13)	(0.23 - 42.39)
Topiramate vs Control	3.17	(0.30 - 24.07)	(0.18 - 44.87)
Valproate vs Control	7.79	(1.84 - 29.60)	(0.84 - 62.77)
Common within-network between-study variance	0.27	(0.00 - 3.29)	
Evaluation of inconsistency using the design-by-treatment	nt interaction model	Chi-square test: 2.69 Degrees of Freedom: 2	P-value: 0.26 Heterogeneity: NA
<b>Cognitive Developmental Delay - Sensit</b>	tivity Analysis - Low <b>F</b>	Risk of Bias: "Adequacy of the second s	of follow-up''
(4 studies	s, 283 patients, 12 trea	tments)	2
Carbamazepine vs Control	2.68	$(0.05 - 2.9 \times 10^3)$	$(0.03 - 4.3 \times 10^{3})$
Carbamazepine+Phenobarbital vs Control	0.67	$(0.00 - 2.2 \times 10^3)$	$(0.00 - 2.9 \times 10^3)$
Carbamazepine+Phenobarbital+Phenytoin vs Control	5.23	$(0.01 - 7.2 \times 10^3)$	$(0.00 - 1.1 \times 10^4)$
Carbamazepine+Phenobarbital+Valproate vs Control	22.18	$(0.10 - 4.8 \times 10^4)$	$(0.06 - 7.7 \times 10^4)$
Carbamazepine+Phenytoin vs Control	11.45	$(0.13 - 1.2 \times 10^4)$	$(0.07 - 1.8 \times 10^4)$
Ethosuximide+Phenytoin vs Control	6.45	$(0.01 - 8.3 \times 10^3)$	$(0.00 - 1.4 \text{ x} 10^4)$
Lamotrigine vs Control	0.52	$(0.00 - 1.2 \times 10^3)$	$(0.00 - 1.9 \times 10^3)$
Phenobarbital+Phenytoin vs Control	1.33	$(0.00 - 1.8 \times 10^3)$	$(0.00 - 2.7 \times 10^3)$
Phenytoin vs Control	1.67	$(0.03 - 1.8 \times 10^3)$	$(0.01 - 2.5 \times 10^3)$
-		. ,	•

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2	
3	т
4	 Phenytoin⊥Valnr
5 6	Velproste ve Con
7	Common within a
8	Common within-
9 10	Evaluation of inc
11	Cog
12	
13	Carbamazepine v
14	Gabapentin vs Co
16	Lamotrigine vs C
17	Levetiracetam vs
18 10	Topiramate vs Co
20	Valproate vs Con
21	Common within-r
22	
23 24	Evaluation of inco
25	
26	
27	Carbamazepine
20 29	Carbamazepine+
30	Carbamazepine+
31	Carbamazepine+
32 33	Carbamazepine+
34	Carbamazepine+
35	Ethosuximide+P
36 27	Gabapentin vs C
37 38	Lamotrigine vs (
39	Levetiracetam v
40	Phenobarbital vs
41 42	Phenobarbital (B
42	
44	
45	
46 47	
48	

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI		
enytoin+Valproate vs Control	3.94	$(0.00 - 6.7 \times 10^3)$	$(0.00 - 8.8 \times 10^3)$		
lproate vs Control	5.9	$(0.06 - 9.7 \times 10^3)$	$(0.03 - 1.5 \times 10^4)$		
mmon within-network between-study variance	1.01	(0.01 - 5.85)			
aluation of inconsistency using the design-by-treatmen	t interaction model	Chi-square test: 5.07	P-value: 0.08		
		Degrees of Freedom: 2	Heterogeneity: 0.00		
Cognitive Developmental Delay - Sensitiv	ity Analysis - Low Ri	sk of Bias: "Comparabili	ty of cohorts''		
(3 studies, 366 patients, 7 treatments)					
rbamazepine vs Control	1.46	(0.11 - 19.59)	(0.06 - 38.10)		
bapentin vs Control	1.19	(0.03 - 22.80)	(0.02 - 39.35)		
motrigine vs Control	0.27	(0.00 - 11.80)	(0.00 - 19.37)		
vetiracetam vs Control	2.90	(0.30 - 32.81)	(0.15 - 62.97)		
piramate vs Control	2.55	(0.22 - 29.21)	(0.11 - 64.23)		
lproate vs Control	5.79	(1.05 - 47.35)	(0.47 - 102.90)		
mmon within-network between-study variance	0.38	(0.00 - 4.14)			
aluation of inconsistency using the design-by-treatmen	t interaction model	Chi-square test: 1.47	P-value: 0.48		
		Degrees of Freedom: 2	Heterogeneity: NA		
Cognitive Developmental Delay – Network Meta-regression Analysis					
(11 studies	<u>, 933 patients, 18 trea</u>	itments)	(0.400.77)		
arbamazepine vs Control	1.99	(0.64 - 6.18)	(0.40 - 9.77)		
arbamazepine+Levetiracetam vs Control	0.54	(0.00 - 16.36)	(0.00 - 19.87)		
arbamazepine+Phenobarbital vs Control	0.50	(0.00 - 16.10)	(0.00 - 19.36)		
arbamazepine+Phenobarbital+Phenytoin vs Control	4.36	(0.01 - 171.20)	(0.01 - 194.60)		
arbamazepine+Phenobarbital+Valproate vs Control	14.58	(0.90 - 413.20)	(0.74 - 488.90)		
arbamazepine+Phenytoin vs Control	9.44	(0.50 - 130.50)	(0.39 - 162.40)		
thosuximide+Phenytoin vs Control	5.77	(0.01 - 234.70)	(0.01 - 268.10)		
abapentin vs Control	1.37	(0.04 - 15.51)	(0.03 - 19.10)		
amotrigine vs Control	0.87	(0.07 - 5.14)	(0.06 - 6.76)		
evetiracetam vs Control	3.43	(0.57 - 18.78)	(0.42 - 24.85)		
henobarbital vs Control	1.16	(0.13 - 8.59)	(0.10 - 11.43)		
henobarbital+Phenytoin vs Control	1.34	(0.00 - 39.21)	(0.00 - 49.39)		

 **BMJ Open** 

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI
Phenytoin vs Control	2.43	(0.55 - 9.14)	(0.36 - 13.45)
Phenytoin+Valproate vs Control	3.58	(0.01 - 134.20)	(0.01 - 161.70
Primidone vs Control	2.03	(0.21 - 16.49)	(0.16 - 21.39)
Topiramate vs Control	2.93	(0.41 - 16.34)	(0.31 - 22.91)
Valproate vs Control	7.03	(2.26 - 20.02)	(1.41 - 30.92)
Common within-network between-study variance	0.16	(0.00 - 1.27)	
Regression Coefficient	1.01	(0.76 - 1.56)	
Evaluation of inconsistency using the design-by-treatment	nent interaction model	Chi-square test: 14.15 Degrees of Freedom: 17	P-value: 0.66 Heterogeneity: 0.
Autism/Dyspraxia - Sensitivity Analysis - La	rge cohort (>300 patien	ts) - (1 study, 2,551 patien	ts, 5 treatments)**
Clonazepam vs Carbamazepine	1.08	(0.24 - 4.85)	-
Lamotrigine vs Carbamazepine	1.20	(0.36 - 4.00)	-
Oxcarbazepine vs Carbamazepine	2.13	(0.62 - 7.35)	-
Valproate vs Carbamazepine	3.05	(0.97 - 9.52)	-
Common within-network between-study variance	NA	NA	
Evaluation of inconsistency using the design-by-treatm	ent interaction model	NA	NA
Autism/Dyspraxia - Sensitivity Ana	lysis - Epilepsy only (4 s	tudies, 540 patients, 10 tr	eatments)
Carbamazepine vs Control	5.20	(0.54 - 90.53)	(0.33 - 133.0
Carbamazepine+Clonazepam vs Control	7.90	(0.01 - 653.30)	(0.01 - 881.0
Carbamazepine+Lamotrigine vs Control	4.25	(0.01 - 333.60)	(0.01 - 446.9
Carbamazepine+Phenytoin vs Control	9.03	(0.01 - 666.30)	(0.01 - 893.0
Lamotrigine vs Control	10.24	(1.25 - 171.40)	(0.67 - 248.5
Lamotrigine+Valproate vs Control	120.20	$(5.25 - 4.5 \times 10^3)$	(3.51 - 6.0 x 1
Levetiracetam vs Control	3.52	(0.00 - 272.20)	(0.00 - 364.3
Phenytoin vs Control	8.10	(0.01 - 577.50)	(0.01 - 754.6
Valproate vs Control	14.41	(1.66 - 252.10)	(0.88 - 378.0
Common within-network between-study variance	0.31	(0.00 - 3.04)	
Evaluation of inconsistency using the design-by-treatm	ent interaction model	Chi-square test: 2.9 Degrees of Freedom: 3	P-value: 0.41 Heterogeneity: 0.00

2 3	
4 5	
6	
7 8	
9 10	
11 12	
13	
14 15	
16 17	
18	
20	
21 22	
23 24	
25 26	
27	
28 29	
30 31	
32 33	
34	
36	
37 38	
39 40	
41	
43	
44 45	
46 47	
48	

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI	
Autism/Dyspraxia - Sensitivity Analysis - Maternal Tobacco Use (4 studies, 540 patients, 10 treatments)				
Carbamazepine vs Control	2.51	(0.05 - 154.30)	(0.04 - 254.50)	
Lamotrigine vs Control	24.84	$(2.14 - 1.2 \times 10^3)$	$(1.23 - 2.2 \times 10^3)$	
Valproate vs Control	33.40	$(2.60 - 1.7 \times 10^3)$	$(1.45 - 2.9 \times 10^3)$	
Common within-network between-study variance	0.39	(0.00 - 4.47)		
Evaluation of inconsistency using the design-by-treatment	t interaction model	NA - all closed loops are for	ormed from a multi-arm study	
Autism/Dyspraxia - Sensitivity Analysis	- Maternal Alcohol U	se (1 study, 156 patients, 4	4 treatments)	
Carbamazepine vs Control	Excluded due to	-	-	
	zero events	(0.21 100.00)		
Lamotrigine vs Control	4.65	(0.21 - 100.00)	-	
Valproate vs Control	1.15	(0.42 - 142.86)	-	
<i>Common within-network between-study variance</i>	1.91	(0.36 - 10.13)		
Evaluation of inconsistency using the design-by-treatment interaction model NA NA				
Autism/Dyspraxia - Sensitivity Analysis - Low Risk of Bias: "Adequacy of Follow-up" (3 studies 2 244 patients 10 treatments)				
Carbamazepine vs Control	3.97	$(0.17 - 2.4 \times 10^3)$	$(0.11 - 3.0 \times 10^3)$	
Carbamazepine+Clonazepam vs Control	7.48	$(0.01 - 7.8 \times 10^3)$	$(0.01 - 9.0 \times 10^3)$	
Carbamazepine+Lamotrigine vs Control	4.47	$(0.00 - 5.0 \times 10^3)$	$(0.00 - 5.7 \times 10^3)$	
Carbamazepine+Phenytoin vs Control	7.23	$(0.01 - 6.6 \times 10^3)$	$(0.01 - 8.2 \times 10^3)$	
Clonazepam vs Control	4.88	$(0.12 - 3.2 \times 10^3)$	$(0.09 - 3.8 \times 10^3)$	
Lamotrigine vs Control	6.55	$(0.30 - 4.4 \times 10^3)$	$(0.21 - 4.7 \times 10^3)$	
Lamotrigine+Valproate vs Control	113.50	$(2.33 - 7.8 \times 10^4)$	$(1.62 - 8.9 \times 10^4)$	
Oxcarbazepine vs Control	10.23	$(0.36 - 6.8 \times 10^3)$	$(0.26 - 7.5 \times 10^3)$	
Valproate vs Control	13.97	$(0.68 - 8.4 \times 10^3)$	$(0.47 - 1.0 \times 10^4)$	
Common within-network between-study variance	0.23	(0.00 - 2.88)		
Evaluation of inconsistency using the design-by-treatment	t interaction model	Chi-square test: 2.17 Degrees of Freedom: 3	P-value: 0.54 Heterogeneity: 0.00	

Treatment Comparison	NMA Odds Ratio	95% CrI	95% PrI
Autism/Dyspraxia - Sensitivity A	Analysis - Low Risk of B	Bias: "Comparability of C	ohorts''
(4 studie	es, 2,395 patients, 12 tre	atments)	
Carbamazepine vs Control	9.55	(0.90 - 246.20)	(0.61 - 329.40)
Carbamazepine+Clonazepam vs Control	13.58	$(0.01 - 1.3 \times 10^3)$	$(0.01 - 1.6 \times 10^3)$
Carbamazepine+Lamotrigine vs Control	7.11	(0.01 - 614.20)	(0.01 - 717.60)
Carbamazepine+Phenytoin vs Control	10.97	$(0.01 - 1.1 \times 10^3)$	$(0.01 - 1.4 \times 10^3)$
Clonazepam vs Control	8.33	(0.45 - 263.10)	(0.33 - 353.70)
Lamotrigine vs Control	10.98	(1.07 - 283.50)	(0.71 - 358.20)
Lamotrigine+Valproate vs Control	194.10	$(8.06 - 8.4 \times 10^3)$	$(6.28 - 1.0 \times 10^4)$
Levetiracetam vs Control	4.25	(0.00 - 390.90)	(0.00 - 485.30)
Oxcarbazepine vs Control	17.60	(1.22 - 552.20)	(0.86 - 727.40)
Phenytoin vs Control	9.76	(0.01 - 861.60)	$(0.01 - 1.0 \times 10^3)$
Valproate vs Control	21.06	(1.86 - 525.40)	(1.25 - 681.90)
Common within-network between-study variance	0.19	(0.00 - 2.43)	
Evaluation of inconsistency using the design-by-treatment	ent interaction model	Chi-square test: 3.36 Degrees of Freedom: 5	P-value: 0.64 Heterogeneity: 0.00
Autism/Dyspraxia - Sensitivity An	alysis - Maternal IQ (1	study, 77 patients, 6 treat	ments)**
Carbamazepine+Clonazepam vs Carbamazepine	1.86	(0.07 - 47.62)	-
Carbamazepine+Lamotrigine vs Carbamazepine	1.18	(0.05 - 27.78)	-
Carbamazepine+Phenytoin vs Carbamazepine	1.86	(0.07 - 47.62)	-
Lamotrigine+Valproate vs Carbamazepine	15.87	(1.87 - 142.86)	-
Valproate vs Carbamazepine	1.33	(0.18 - 10.20)	-
Common within-network between-study variance	NA	NA	
Evaluation of inconsistency using the design-by-treatm	ent interaction model	NA	NA
Abbreviations: NMA – Network Meta-analysis; OR – odds ratio;	CrI – Credible Interval; PrI –	Predictive Interval	

Abbreviations: NMA - Network Meta-analysis; OR - odds ratio; CrI - Credible Interval; PrI - Predictive Interval

\*\* Network did not include a control arm, comparison with Carbamazepine is reported instead