Medicines Adverse Reactions Committee

Meeting date	11/06/2020	Agenda item	3.2.1
Title	**Antiepileptic medicines and neurodevelopmental disorders**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**		**Sponsor**
Carbamazepine (CBZ)	**Tegretol Syrup, 100 mg/5mL** **Tegretol Tablet, 200 mg & 400 mg** **Tegretol CR Modified release tablet, 200 mg & 400 mg**		Novartis NZ Ltd
Lamotrigine (LTG)	**Arrow - Lamotrigine Chewable/dispersible tablet, 5 mg,** 25 mg, 50 mg & 100 mg		Teva Pharma (NZ) Ltd
	Lamictal Chewable/dispersible tablet, 2 mg, 5 mg, 25 mg, 50 mg & 100 mg		GSK (NZ) Ltd
	Logem Chewable/dispersible tablet, 25mg, 50 mg & 100 mg		Mylan NZ Ltd
Levetiracetam (LEV)	**Everet Film coated tablet, 250 mg, 500 mg, 750 mg & 1000 mg** Everet Oral solution, 100 mg/mL		REX Medical Ltd
	Levetiracetam-AFT Oral solution, 100 mg/mL Levetiracetam-AFT Solution for infusion, 100 mg/mL		AFT Pharmaceuticals Ltd
Phenobarbital (PB)	**Phenobarbitone (PSM) Tablet, 15 mg & 30 mg**		PSM Healthcare Ltd t/a API Consumer Brands
Phenytoin (PHT)	DBL™ Phenytoin Injection BP Solution for injection, 50 mg/mL **Dilantin Capsule, 30 mg, 100 mg** **Dilantin Infatabs Chewable tablet, 50 mg** **Dilantin Paediatric Oral suspension, 30 mg/5mL**		Pfizer NZ Ltd
Sodium valproate (VPA)	**Epilim Syrup, 200 mg/5mL** **Epilim 100 Crushable Tablet, 100 mg** **Epilim EC Modified release tablet, 200 mg & 500 mg** **Epilim IV Powder for injection with diluent, 100 mg/mL**		Sanofi-Aventis NZ Ltd
Topiramate (TPM)	**Topamax Film coated tablet, 25 mg, 50 mg, 100 mg & 200 mg** **Topamax Sprinkle Capsule, 15 mg, 25 mg** & 50 mg		Janssen-Cilag (NZ) Ltd
	Topiramate Actavis Film coated tablet, 25 mg, 50 mg, 100 mg & 200 mg		Teva Pharma (NZ) Ltd

PHARMAC funding	Funded products are highlighted in bold type above
Previous MARC meetings	Use of topiramate during pregnancy for migraine prevention 179th meeting Sept 2019 Use of sodium valproate in pregnancy 171st meeting Sept 2017 Safety of antiepileptic medicines in pregnancy 149th meeting March 2012 Valproate and fetal abnormalities 124th meeting Dec 2005
International action	Keppra (levetiracetam) SmPC updated in Nov 2018 with information from post-marketing experience on risk of neurodevelopmental disorders in infants exposed *in utero*: *Only limited evidence is available on the neurodevelopment of children exposed to Keppra monotherapy in utero. However, current epidemiological studies (on about 100 children) do not suggest an increased risk of neurodevelopmental disorders or delays.* https://www.ema.europa.eu/en/documents/procedural-steps-after/keppra-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf
Prescriber Update	Spotlight on topiramate December 2017 Spotlight on levetiracetam June 2017 Anticonvulsants and congenital malformations February 2009
Classification	Prescription medicine (Phenobarbital – Class C5 controlled drug)
Usage data	Ministry of Health National Collections data indicates the following pregnancy usage of AEDs in 2019: Lamotrigine (LTG) 123 Levetiracetam (LEV) 78 Carbamazapine (CBZ) 48 Topiramate (TOP) 25 Sodium valproate (VPA) 23 Phenobarbital (PB) 1 Phenytoin sodium (PHT) 0
Advice sought	**The Committee is asked to advise:** • Whether the current evidence supports an association between prenatal exposure to any of the antiepileptic medicines and adverse neurodevelopmental outcomes in the child? • Whether there is a need to update the data sheet for any of the antiepileptic medicines to reflect current knowledge on the risk of neurodevelopmental adverse effects associated with prenatal exposure?

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1 PURPOSE

The purpose of this report is to review the literature and other information on neurodevelopmental adverse effects in children exposed to approved first-line antiepileptic drugs (AEDs) *in utero*. The review will also compare the risk of neurodevelopmental adverse effects between different AEDs, and examine whether the current data sheets contain adequate information on these risks.

2 BACKGROUND

2.1 Epilepsy

Epilepsy is a common neurological disorder that affects 1-2% of the population [1], including women of childbearing age.

The International League Against Epilepsy (ILAE) uses the following practical definition of epilepsy [2]:

> *A disease of the brain defined by any of the following conditions:*
>
> *(1) At least two unprovoked (or reflex) seizures occurring >24 h apart;*
> *(2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;*
> *(3) Diagnosis of an epilepsy syndrome.*
>
> *Epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off antiseizure medicines for at least the last 5 years.*

Treatment of epilepsy should be individualised according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, and the individual's lifestyle and preferences [3].

The aim of treatment is to prevent the occurrence of seizures. A single antiepileptic drug (monotherapy) should be prescribed wherever possible. Careful dose titration is needed, starting with low doses and increasing gradually until seizures are controlled. When monotherapy with a first-line antiepileptic drug has failed, monotherapy with a second drug should be tried. Changing from one antiepileptic drug to another should be done with caution, slowly withdrawing the first drug only when the new regimen has been established. Combination therapy with two or more antiepileptic drugs may be necessary, but the concurrent use of antiepileptic drugs increases the risk of adverse effects and drug interactions. If combination therapy does not bring about worthwhile benefits, revert to the regimen (monotherapy or combination therapy) that provided the best balance between tolerability and efficacy. [3, 4]

2.2 Antiepileptic medicines in pregnancy

Maintaining seizure control throughout pregnancy is important for both maternal and fetal health. It is therefore usually necessary for women with epilepsy to continue treatment with an AED throughout her pregnancy.

AED exposure during pregnancy is associated with an increased risk of congenital malformations. A recent Cochrane Review [5] showed:

- Children exposed to CBZ, PHT or VPA have a higher risk of congenital malformation compared to children born to women without epilepsy and compared to children born to women with untreated epilepsy.
- Children exposed to PB or TPM are at increased risk of congenital malformation compared to children born to women without epilepsy.
- LTG was not associated with an increased risk of major congenital malformation

- LEV was not associated with an increased risk, but little data was available.
- Children exposed to VPA had the greatest risk of congenital malformation (10.93%, 95% CI 8.91 – 13.13).

Similarly, in a network meta-analysis of 96 studies involving 58,461 patients, a higher risk of major congenital malformations (compared to control) was associated with ethosuximide (OR 3.04; 95% CrI 1.23–7.07), VPA (OR 2.93; 95% CrI 2.36–3.69), TPM (OR 1.90; 95% CrI 1.17–2.97), PB (OR 1.83; 95% CrI 1.35–2.47), PHT (OR 1.67; 95% CrI 1.30–2.17) and CBZ (OR 1.37; 95% CrI 1.10–1.71) monotherapies. LTG (OR 0.96; 95% CrI 0.72–1.25) and LEV (OR 0.72; 95% CrI 0.43–1.16) were not associated with an increased risk compared to control. [6]

In addition to physical malformations, there is a growing body of evidence to suggest an association between prenatal exposure to AEDs and adverse neurodevelopmental outcomes in the child. AEDs readily cross the placenta, and animal models show that fetal exposure to certain AEDs is associated with altered neuronal development [7].

Early case reports and small observational studies suggested a link between maternal use of AEDs during pregnancy and cognitive impairment. Subsequent prospective studies reported a significant association between prenatal exposure to VPA and poorer cognitive functioning [8-11].

Concerns that other AEDs may be also associated with neurodevelopmental disorders has prompted further research in this area, including several systematic reviews of the literature, (discussed in section 3.1.1) [7, 12, 13].

Clear information on the potential risks associated with AEDs is necessary to maximise maternal health whilst minimising risk to the fetus, and to enable women to make informed decisions about treatment options during pregnancy.

2.3 New Zealand data sheets

Information in the New Zealand data sheets for approved first-line AEDs concerning their risk to the fetus is presented in Annex 1.

The data sheets for VPA, CBZ, PHT and PB include information on the risk of neurodevelopmental adverse effects.

VPA is associated with developmental disorders, described in the Epilim data sheet as follows [14]:

> *Developmental disorders*
>
> *Data has shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.*
>
> *Studies in preschool children exposed in utero to valproate show that some children may experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.*
>
> *Some data have suggested an association between in utero valproate exposure and the risk of impaired cognitive function, including developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ. IQ measured in school aged children with a history of valproate exposure in utero, was lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There is limited data on the long term outcomes.*

Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment.

Autism spectrum disorders have also been reported in children exposed to valproate in-utero (approximately three-fold increase compared with the general population). The risk of childhood autism is increased by approximately five-fold compared with the general population.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

The Tegretol (CBZ) data sheet notes that developmental disorders have been reported in association with the its use, but that conclusive evidence from controlled studies with CBZ monotherapy is lacking [15].

The Dilantin (PHT) data sheet states that there have been reports of 'fetal hydantoin syndrome', including microcephaly and mental deficiency, in children of women on treatment with phenytoin. [16]

The Phenobarbitone PSM (PB) data sheet notes that developmental disability has been associated with use in pregnancy [17].

There is no mention of neurodevelopmental adverse effects in the Lamictal (LTG), Everet (LEV) or Topamax (TPM) data sheets [18-20].

2.4 Usage

Ministry of Health National Collections data indicates that over the past 10 years (2010-2019) the numbers of women using VPA, CBZ and PHT have decreased, while the numbers using LTG and LEV in pregnancy have increased. (Figure 1)

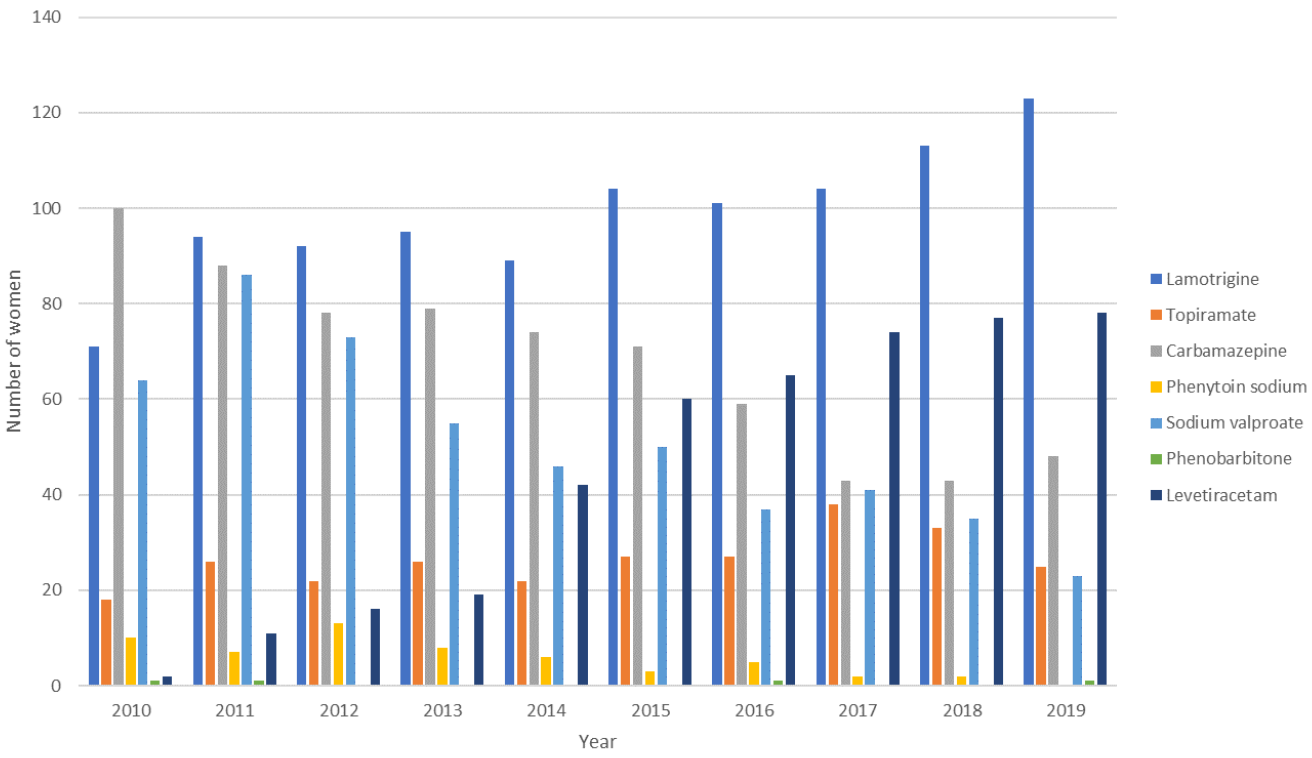


Figure 1. Women dispensed antiepileptic medicines in the 310 days preceding delivery, 2010-2019

Source: Ministry of Health, Collections. Women may be counted more than once, if more than one type of AED was dispensed during pregnancy.

Data for 2019 indicates that most women who were dispensed an AED during pregnancy were also dispensed a folic acid supplement (Table 1).

A breakdown of the AED dispensing data by trimester and the type of folic acid medicine (also displayed by trimester) is included in Annex 2. Use of dispensed folic acid during the pregnancy indicates engagement with a healthcare provider, suggesting that the woman is receiving antenatal care. Furthermore, use of dispensed folic acid in the 30 days prior to the start of the first trimester suggests that the pregnancy was planned.

Table 1. Folic acid dispensing for women who gave birth in 2019 who were also dispensed an antiepileptic drug (AED) in the 310 days preceding delivery.

Antiepileptic medicine	AED dispensed* (n)	Folic acid dispensed in 310 days before delivery # † (n)	Folic acid dispensed in 30 days before 1st trimester # (n)
Lamotrigine (LTG)	123	130	85
Topiramate (TPM)	25	22	18
Carbamazepine (CBZ)	48	43	12
Phenytoin (PHT)	0	0	0
Sodium valproate (VPA)	23	22	14
Phenobarbital (PB)	1	1	0
Levetiracetam (LEV)	78	84	35

* Women counted once for each type of AED dispensed during pregnancy.
# Includes prescriptions for: folic acid 5 mg tabs, folic acid 0.8 mg tabs, and ferrous fumarate 310 mg + 350 mcg folic acid tabs.
† Women dispensed more than one type of medicine during pregnancy are counted more than once.
Source: Ministry of Health, National Collections.

3 SCIENTIFIC INFORMATION

3.1 Published literature

A search of PubMed for studies about neurodevelopmental adverse effects associated with prenatal exposure to AEDs identified a large volume of literature. The scope was therefore narrowed to focus on studies concerning first-line AEDs that are approved for use in epilepsy in New Zealand. The AEDs included in the review are VPA, LTG, CBZ, PHT, PB, LEV and TPM. The review does not include unapproved AEDs (eg, retigabine, rufinamide), second-line AEDs (eg, vigabatrin, lacosamide), or AEDs that are not indicated for tonic-clonic seizures (ethosuximide, gabapentin, pregabalin).

Neurodevelopmental adverse effects of interest included autistic spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), developmental delay and cognitive impairment.

Two studies, a Cochrane review published in 2014 [7] and a network meta-analysis (NMA) [21] published in 2017, had examined the literature on neurodevelopmental adverse effects associated with prenatal exposure to AEDs (see 3.1.1) Using these studies as a starting point, this review focuses on the literature that has been published subsequently. No new prospective observational cohort

studies were identified. Five recent register-based data-linkage studies have been published since 2017, including three Danish population-based studies. A further Danish register study that was published in 2013 and included in the NMA, is also described here due to its size and robust methodology (section 3.1.2). Finally, one recent retrospective cohort study was identified for the review (section 3.1.3).

3.1.1 Systematic Review and Meta-analyses

3.1.1.1 Veroniki et al, 2017 (BMJ Open)

Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis [21] (Annexes 3a & 3b)

Objective

To compare the safety of AEDs and assess their impact on development in infants and children exposed *in utero* or during breast feeding, using a systematic review and network meta-analysis (NMA)[1].

Methods

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched up to 27 April 2017 for randomised clinical trials (RCTs) and observational studies that assessed infants or children aged ≤ 12 years whose mothers had taken AEDs (monotherapy or polytherapy) during pregnancy and/or breast feeding. All randomised controlled trials (RCTs), quasi-RCTs and observational studies were eligible.

Screening, data abstraction and quality appraisal were completed in duplicate by independent reviewers.

Exposures: AEDs of interest were carbamazepine, clobazam, clonazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate, valproate, and vigabatrin. Comparators included placebo, no AED, or other AEDs alone or in combination.

Primary outcomes: cognitive developmental delay and autism/dyspraxia.

Secondary outcomes: ADHD, language delay, neonatal seizures, psychomotor developmental delay and social impairment.

Analyses: Methodological quality was appraised with the Newcastle-Ottawa Scale (NOS) [22].

The odds ratio (OR) was used for each dichotomous outcome. To account for anticipated methodological and clinical heterogeneity across studies, and to achieve the highest generalisability in the meta-analytical treatment effects, a random-effects model was applied.

An NMA was applied for connected evidence networks and prespecified treatment nodes. Effect modifiers used to test the transitivity assumption for each outcome were: 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 was presented in tables for each outcome. The consistency assumption was evaluated for the entire network of each outcome.

For cognitive developmental delay and autism/dyspraxia outcomes, network meta-regression analyses for maternal age and baseline risk (ie, using the control group) were conducted, when ≥10 studies provided relevant information. Sensitivity analyses for cognitive developmental delay and autism/dyspraxia outcomes were performed for treatment indication of epilepsy, large study size (ie, >300), maternal alcohol intake, maternal tobacco use, only first-generation AEDs and

[1] A short video on network meta-analysis is available at https://training.cochrane.org/resource/key-concepts-network-meta-analysis-nma.

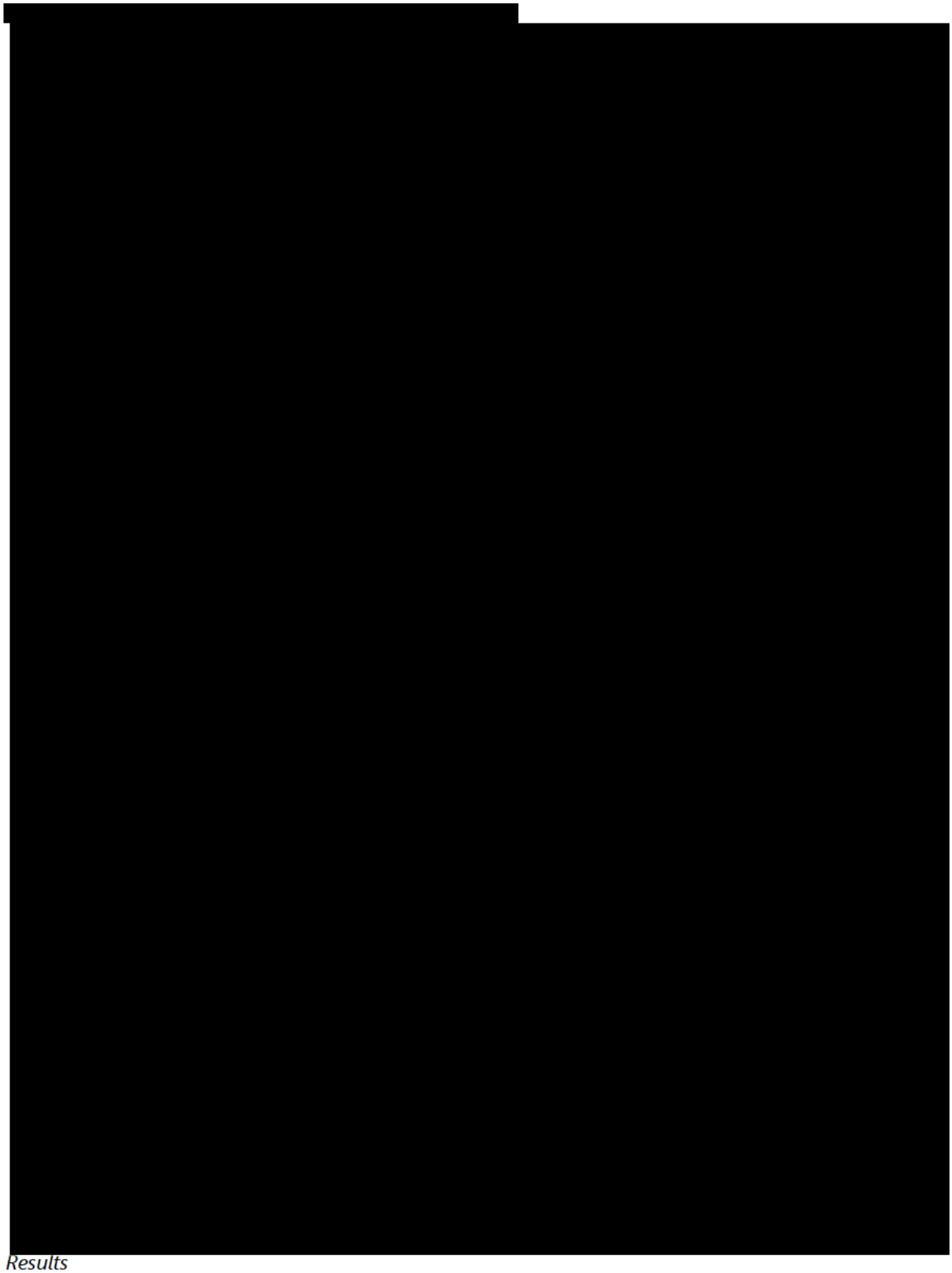
methodological quality. For autism/dyspraxia, a sensitivity analysis on maternal IQ/psychiatric history was also conducted.

The median and 95% credible intervals (CrIs) were calculated for each parameter value.

The estimated safety of the included AEDs was ranked using the surface under the cumulative ranking (SUCRA) curve. The larger the SUCRA for a treatment, the higher its safety rank among all the available treatment options. SUCRA values are presented along with 95% CrIs to capture the uncertainty in the parameter values.

The analysis included 29 cohort studies involving 5100 children of women who took AEDs (Figure 2).

Table 2 shows an overview of the included studies.



Results

Cognitive developmental delay: 11 cohort studies included a total of 933 children and examined 18 treatments (τ2=0.12, 95% CrI 0.00 to 1.15; Figure 3a). One study included children exposed to AEDs both *in utero* and through breast feeding, and 10 included children exposed to AEDs *in utero*. Across all AEDs, only valproate was associated with significantly increased odds of cognitive developmental delay compared with control (OR 7.40, 95% CrI 3.00 to 18.46; Figure 4a). Sensitivity analyses restricted

to studies that only included women receiving AEDs to treat epilepsy, studies comparing only first-generation AEDs, studies that reported maternal alcohol or tobacco use, and studies with high methodological quality on the NOS item 'comparability of cohorts' were consistent with the NMA results. Sensitivity analysis with studies of high methodological quality on the NOS item 'adequacy of follow-up' found no statistically significant results.

Autism/dyspraxia: 5 cohort studies, 2551 children exposed *in utero* and examined 12 treatments (τ2=0.16, 95% CrI 0.00 to 1.95; Figure 3b). Compared with control, valproate (OR 17.29, 95% CrI 2.40 to 217.60), oxcarbazepine (OR 13.51, 95% CrI 1.28 to 221.40), lamotrigine (OR 8.88, 95% CrI 1.28 to 112.00) and lamotrigine+valproate (OR 132.70, 95% CrI 7.41 to 3851.00) were significantly associated with increased occurrence of autism/dyspraxia (Figure 4b). Restricting the NMA to studies that only included women receiving AEDs to treat epilepsy produced results that were generally in agreement with the NMA results, except that oxcarbazepine was no longer in the network. Two cohort studies of 404 offspring of women with a history of tobacco use compared four treatments and found similar results except that oxcarbazepine and lamotrigine+valproate were no longer in the network. The results were in agreement in sensitivity analyses including only higher methodological quality studies in the 'comparability of cohorts' item on the NOS and the 'adequacy of follow-up of cohorts', except that lamotrigine was no longer statistically significant.

Psychomotor developmental delay: 11 cohort studies, 1145 children exposed *in utero* and examined 18 treatments (τ2=0.06, 95% CrI 0.00 to 0.63; Figure 3c). Valproate (OR 4.16, 95% CrI 2.04 to 8.75) and carbamazepine+phenobarbital+valproate (OR 19.12, 95% CrI 1.49 to 337.50) were significantly more harmful than control (Figure 4c).

Language delay: 5 cohort studies, 509 children and examined 5 treatments (τ2=0.16, 95% CrI 0.00 to 2.15; Figure 3d). One study included children exposed to AEDs *in utero* and through breast feeding, and four included children exposed to AEDs *in utero*. Compared with control, valproate was the only treatment significantly associated with increased odds of language delay (OR 7.95, 95% CrI 1.50 to 49.13; Figure 4d).

ADHD: 5 cohort studies included a total of 816 children and examined 7 treatments (τ^2=0.11, 95% CrI 0.00 to 1.29; Figure 3e). One study included children exposed to AEDs *in utero* and through breast feeding, and four studies included children exposed to AEDs *in utero*. None of the treatment comparisons reached statistical significance (Figure 4e).

Social impairment: One cohort study included 422 children exposed to AEDs *in utero* and through breast feeding. The children were exposed to carbamazepine (n=48), lamotrigine (n=71), valproate (n=27) and control (n=278). No significant differences in social impairment were identified.

Strengths and limitations

The systematic review followed the Cochrane Handbook [23] and ISPOR guidelines [24], and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for NMA [25]. The study compared and ranked the safety of AEDs and calculated predictive intervals, which account for between-study variation and provide a predicted range for the treatment effect estimate.

The authors reported the following limitations:

1. Differences in drug dosages could not be accounted for, and it was assumed that different dosages of the same AED were equally effective. Multiple dosages for the same treatment were combined for the analysis.
2. Several poly-therapies 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. Ranking the probabilities may be biased towards the treatments with the smallest number of studies, which may have influenced the SUCRA results. Effect sizes need to be taken into account when considering the SUCRA values.
3. Conclusions were based on evidence from observational studies only, as no RCTs were found in the systematic literature search. The results may have been affected by inherent biases due

to confounding and shortcomings of these studies. For example, many of the included studies did not report important treatment effect modifiers such as family history of autism, ADHD and maternal IQ, and severity of epilepsy. Exploration of the impact of these factors through subgroup analysis and meta-regression was not possible.

4. There was an imbalance in the methodological study quality appraisal across treatment comparisons and most outcomes, which may affect the results. Residual confounding may exist due to unknown factors or factors that could not be assessed due to a lack of data. However, the assessment of consistency suggested no disagreement between the different sources of evidence in the network.
5. The tendency towards small-study effects is greater with observational studies than with randomised trials. However, the assessment of small-study effects using adjusted funnel plots suggested no evidence for their prevalence. Also, most of the included studies compared multiple treatments inducing correlations in each funnel plot, which may mask asymmetry. Although data points were plotted corresponding to the study-specific basic parameters to reduce correlations, this issue may still exist.
6. Subgroup analysis by type of exposure (breast feeding vs *in utero*) was not conducted due to the small number of studies included in the NMA and due to the poor reporting (22 studies did not report whether AED exposure also occurred during breast feeding). All studies were included in the analysis irrespective of the type of exposure.

Conclusion

Across all outcomes and treatments compared with control, valproate alone or combined with another AED was associated with the greatest odds, whereas oxcarbazepine and lamotrigine were associated with increased occurrence of autism. Counselling is advised for women considering pregnancy to tailor the safest regimen.

Comments:

Study method:

A network meta-analysis (NMA) is a method for comparing three or more interventions for the same health condition, some of which may not have been compared directly (head-to-head) in the same study.

For example, if a study compares treatment A with treatment B, and another study compares treatment B with treatment C, then treatment A and treatment C can be compared indirectly using network meta-analysis. provided that the studies measure the same endpoints, and effect modifiers are equally distributed.

The analysis assumes (i) exchangeability (similarity), (ii) homogeneity, and (iii) transitivity (consistency) of the studies. [26-28]. Transitivity means both direct (A-B and B-C) and indirect (A-C) comparisons should be consistent.

Although the method normally requires RCTs, techniques have been developed to enable non-randomised studies to be included in NMAs [27].

A detailed study protocol for the systematic review and Bayesian random-effects network meta-analysis was published separately [29].

Study findings:

VPA was associated with significantly increased odds of cognitive developmental delay compared with control (OR 7.40, 95% CrI 3.00 to 18.46), although this association was lost when the analysis was restricted to studies of high methodological quality on the NOS item 'adequacy of follow-up'.

VPA (OR 17.29, 95% CrI 2.40 to 217.60) and LTG (OR 8.88, 95% CrI 1.28 to 112.00) were significantly associated with autism/dyspraxia, and the association remained when the analysis was restricted to use in epilepsy. Statistical significance was lost for LTG in the sensitivity analyses using only higher quality studies.

VPA was significantly more harmful than control (OR 4.16, 95% CrI 2.04 to 8.75) in the analysis for psychomotor developmental delay.

VPA was associated with an increased odds of language delay (OR 7.95, 95% CrI 1.50 to 49.13).

None of the treatment comparisons reached statistical significance for ADHD.

Only one study examined social impairment, and no difference was identified between CBZ, LTG, VPA and control.

In summary, VPA was associated with cognitive developmental delay, autism/dyspraxia, psychomotor developmental delay and language delay. LTG was associated with an increased occurrence of autism overall, but not when the analysis was restricted to the higher quality studies.

3.1.1.2 Haskey and Galbally, 2017 (Aust NZ J Psych)

Mood stabilizers in pregnancy and child developmental outcomes: A systematic review [13] (Annex 4)

Objective

To examine strengths and limitations of current research on child developmental outcomes following prenatal exposure to mood stabilizers, and to explore whether there are any differences between agents for detrimental effects on child development following exposure *in utero*.

Methods

Systematic search of MEDLINE, PubMed, EMBASE, and PsychINFO databases for studies that examined the effects of mood stabilizers including sodium valproate, carbamazepine, lamotrigine, lithium and second-generation antipsychotics on child developmental outcomes. For AEDs, the review only covered the period June 2014 to September 2016, as a Cochrane Review (see 3.1.1.3) had recently studied child neurodevelopmental outcomes following *in utero* exposure to AEDs in studies published from 1946 to May 2014.

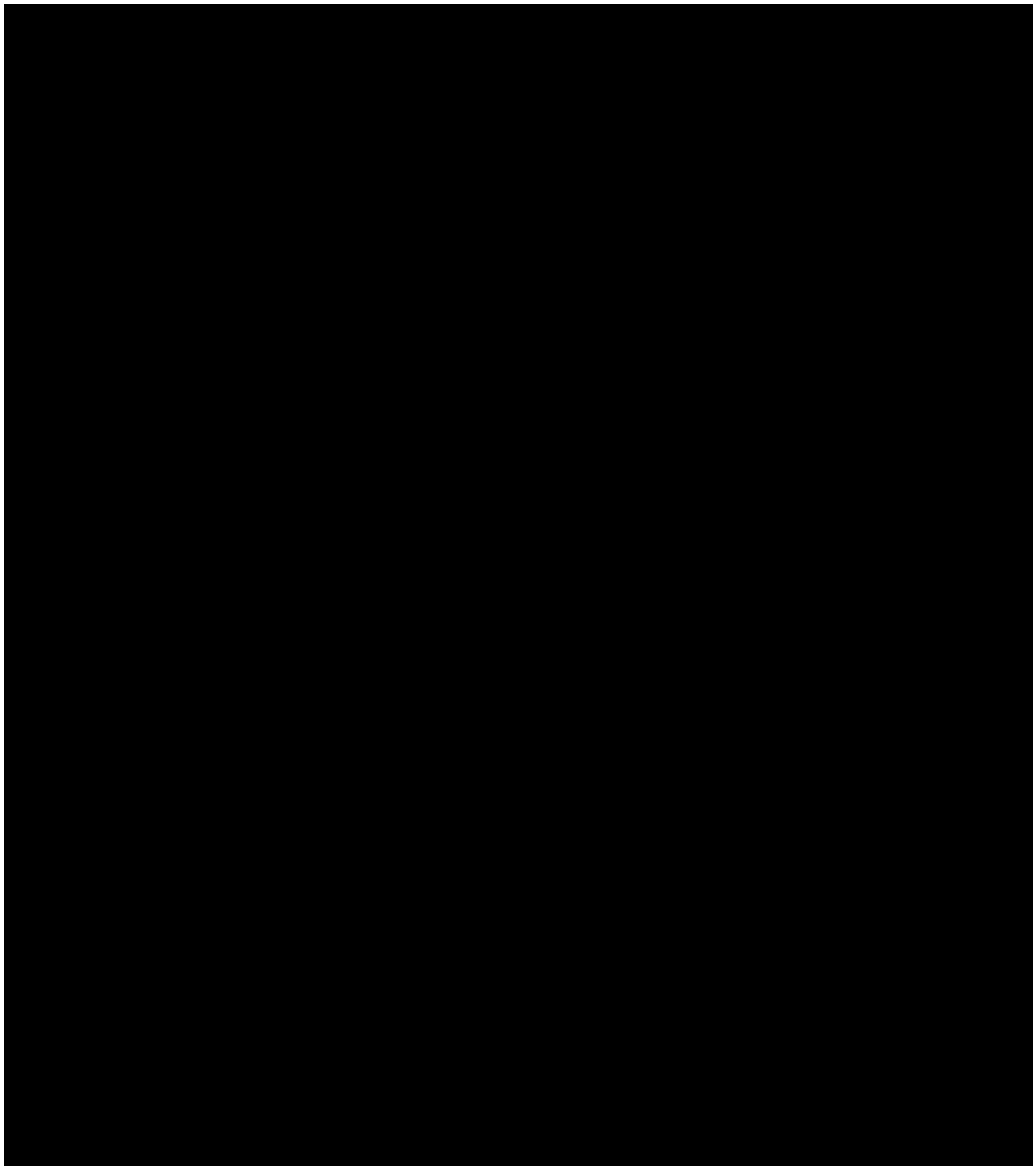
Inclusion criteria: original research, English language, prospective and retrospective data, human studies, any exposure during pregnancy to medicines of interest, and measured child neurodevelopmental outcomes using standardised neuropsychological methods, clinical examination or academic assessments at 6 months of age and older.

Exclusion criteria: use of AEDs for indications other than mood stabilisation or mood disorders in Australia, review articles, theoretical discussions, case studies, and studies in non-pregnant women.

PRISMA guidelines for reporting of systematic reviews and meta-analyses were followed.

Fifteen articles were included in the critical review. A flow chart of the included studies is shown in Figure 5.

Controlled cohort studies were the highest level of evidence available. The studies were rated according to the Newcastle-Ottawa Quality Assessment Scale (NOS).



Results

Of the 15 studies identified, 10 examined AEDs, including three prospective cohorts with controls, two prospective cohorts without controls, one retrospective cohort and four registry-based retrospective cohorts (Table 3). All studies were in women with epilepsy and included sodium valproate. Nine studies included carbamazepine and eight included lamotrigine.

Four studies examined dose-response relationships (Baker *et al.*, 2015; Bromley *et al.*, 2016; Deshmukh *et al.*, 2016; Wood *et al.*, 2015) [30-33].

Four studies examined AED monotherapy alone (Arkilo *et al.*, 2015; Bromley *et al.*, 2016; Deshmukh *et al.*, 2016; Marcon *et al.*, 2015) [31, 32, 34]

Four studies compared monotherapy and polytherapy (Baker *et al.*, 2015; Gopinath *et al.*, 2015; Guveli *et al.*, 2015; Wood *et al.*, 2015) [30, 33, 35, 36].

Two studies did not specify the use of monotherapy or polytherapy (Elkjaer *et al.*, 2016; Gogatishvili *et al.*, 2015).

The most consistent finding was a dose-response relationship with VPA, with doses above 800-1000 mg associated with poorer neurodevelopmental outcomes. CBZ was not found to be associated with lower IQ in any of the studies, but one study [30] found an association with lower verbal ability. LTG was not associated with adverse effects on IQ or specific cognitive skills, compared to other AEDs or controls. AED polytherapy was found to carry an increased risk [30, 35, 36].

Full Scale Intellectual Quotient (FSIQ) was measured in five studies, using Differential Ability Scales, Wechsler Preschool and Primary Scale of Intelligence-IV (WPPSI-IV) or Wechsler Intelligence Scale for Children-IV (WISC-IV). Other studies used a range of methods to examine adaptive behaviour, socialization, motor skills, neurological function, autism traits and academic grades (Table 3). In one study, developmental specialists performed clinical assessments, but the method used was not specified [34].

Baker *et al* [30] reported that children exposed prenatally to >800 mg/day of VPA had an IQ score that was 9.7 points lower than unexposed children derived from the general population. Additionally, the risk of IQ < 85 was eight times higher in children born to women treated with high doses of VPA (>800 mg/day) than in those born to control women (adjusted relative risk (RR) = 8.6, 95% CI 3.1 to 18.8, $p < 0.001$). There was no significant increase in risk of IQ < 85 for low-dose VPA (<800 mg/day). However, verbal abilities were lower and educational interventions were required more frequently compared to unexposed children. This study used multiple regression analysis to adjust for confounders including maternal IQ and maternal seizures.

Similarly, Bromley *et al* [31] found that increasing dose of VPA was associated with poorer FSIQ after adjustment for confounders, with FSIQ score = –10.6 (95% CI –16.3 to –5, $p < 0.001$) compared to other AEDs.

In contrast, Gopinath *et al* [35] found comparable FSIQ in the VPA group compared to lamotrigine and CBZ. However, lower doses of VPA (<800 mg) were used.

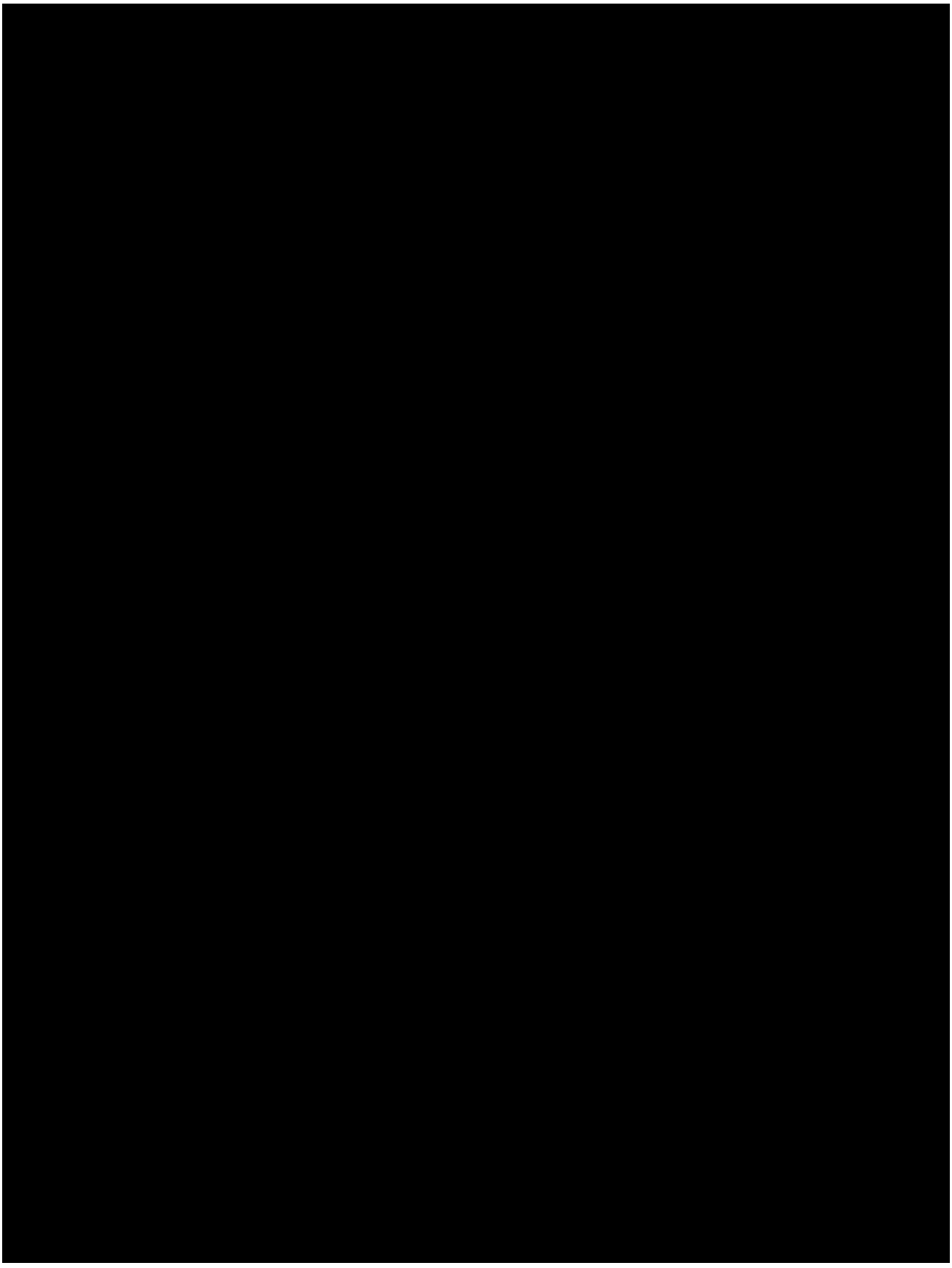
Bromley *et al* [31] found decreased verbal, non-verbal and expressive language abilities with increasing doses of VPA.

Deshmukh *et al* [32] found specific deficits in motor skills and socialization for VPA compared to lamotrigine and CBZ.

In an Australian study, Wood *et al* [33] found exposure to high VPA dose *in utero* was a significant predictor of increased rates of autistic traits after controlling for several confounders, including polytherapy and maternal IQ.

Conclusions

This review found higher neurodevelopmental risk with VPA, which is consistent with previous research. Follow-up into adulthood is needed to determine whether the impact on children is persistent or transient.



[redacted]

Comments:

This review focused on neurodevelopmental effects of prenatal exposure to mood stabilisers, including AEDs (sodium valproate, lamotrigine and carbamazepine).

Studies were excluded if the AED was used for an indication other than mood stabilisation or mood disorders. Studies that included the use of AEDs for epilepsy were therefore excluded.

An earlier Cochrane Review of neurodevelopmental adverse effects associated with *in utero* exposure to AEDs for epilepsy had covered studies of AEDs prior to May 2014, so this review only included studies of AEDs for the period June 2014 to September 2016.

The quality of the studies was assessed on the 9-point NOS scale, and scores ranged from 3-8 (median 6). NOS rates the studies based on the selection of the study groups, comparability of the groups, and the ascertainment of either the exposure (case-control studies) or outcome of interest (cohort studies) www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

The results of the individual studies were not combined in a meta-analysis.

As the studies in this review only included outcomes in children of women who use AEDs for mood stabilisation, the findings may not be generalisable to children of women who use AEDs for epilepsy. There may be underlying baseline risk differences between these populations.

3.1.1.3 Bromley et al, 2014 (Cochrane Database of Systematic Reviews)

Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child [7] (Annex 5)

Objective

To assess the effects of prenatal exposure to commonly prescribed AEDs on neurodevelopmental outcomes in the child, and to assess the methodological quality of the evidence.

Methods

The review examined neurodevelopmental outcomes following exposure to AEDs during pregnancy compared to (1) unexposed pregnancies in women representative of the general population or (2) unexposed pregnancies in women with epilepsy.

Databases searched: Cochrane Epilepsy Group Specialized Register (May 2014), Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2014, Issue 4), MEDLINE (via Ovid) (1946 to May 2014), EMBASE (May 2014), Pharmline (May 2014) and Reprotox (May 2014). No language restrictions were applied. Conference abstracts from the preceding five years and reference lists from the included studies were also reviewed.

Inclusion/exclusion criteria: Studies considered for the review were randomised controlled trials (RCTs), prospective observational cohort studies, and cohort studies set within pregnancy registers. Data linkage studies and retrospective cohort studies were excluded.

Participants eligible for the treatment group were:

- Pregnant women with epilepsy taking a single AED of interest

Participants eligible for the control groups were:

- Pregnant women with epilepsy taking an AED (to enable AED treatment comparisons), or
- Pregnant women with epilepsy not taking an AED, or
- Pregnant women who did not have epilepsy

Exposures: The treatment group included women with epilepsy receiving any AED, including: phenobarbitone, phenytoin (PHT), carbamazepine (CBZ), oxcarbazepine (OXC), sodium valproate (VPA), lamotrigine (LTG), topiramate (TPM), gabapentin, vigabatrin, tiagabine, zonisamide, levetiracetam (LEV), ethosuximide, clobazam, clonazepam, zonisamide, pregabalin, lacosamide, retigabine, rufinamide, and sulthiame.

Control groups were (1) women with a diagnosis of epilepsy who were not taking AEDs and (2) women without epilepsy who were not taking medication for a chronic condition during pregnancy. Women with epilepsy taking monotherapy treatment were employed as a 'comparator' group in analyses to enable AED treatment comparisons.

Studies reporting AED use solely in pregnant women with conditions other than epilepsy (eg, mood disorders, pain) were excluded.

Primary outcome measure: Global cognitive ability, represented by a summary score of key cognitive processes such as reasoning, processing speed, mental flexibility and knowledge. The most frequently-reported measure of global cognitive functioning is the intelligence quotient (IQ). Typically, in younger children global ability assessments also include assessment of motor and social skills, due to their

importance at this age, producing an outcome reported as the development quotient (DQ). Typically, standardised measures of IQ and DQ have a mean of 100 and a standard deviation of 15, meaning that scores under 85 would be below the average range.

Secondary outcome measures:

- Neurodevelopmental disorders including:
  - autistic spectrum disorders
  - attention deficit-hyperactivity disorder (ADHD)
  - dyspraxia.

  Diagnoses were author-defined, but consistent with the Diagnostic and Statistical Manual (DSM-IV) criteria for these conditions.
- Cognitive domain scores including:
  - attention
  - executive function
  - language
  - memory
  - visuospatial

Measurement of treatment effect: The primary outcome of global cognitive ability (DQ and IQ) and secondary outcomes relating to cognitive domains were measured on a continuous scale, and the measure of treatment effect was the mean difference (MD). Secondary outcomes relating to the presence of a neurodevelopmental disorder or an IQ below a specified range were categorical data, and the measure of treatment effect was the risk ratio (RR). As data were sparse, with some studies reporting zero events in one or both groups, the risk difference (RD) was also calculated.

Data synthesis: For each comparison with data available for at least two studies, a meta-analysis was performed to provide overall estimates of treatment effect. A fixed-effect model was utilised for the primary data analyses, with exploration of potential explanations for heterogeneity. Secondary analyses, adopting a random-effects model to incorporate the assumption that the different studies were estimating different yet related treatment effects, was undertaken. Sources of variability between the studies were also investigated. For continuous outcomes the pooled MD was calculated with the 95% CI. For categorical outcomes the pooled RR was calculated with the 95% CI. As data were sparse for many studies a further analysis was undertaken to calculate the RD and 95% CI. Sensitivity analysis was undertaken to explore the robustness of the results with different assumptions regarding the method of analysis.

Studies were not included in a meta-analysis if there was only one study contributing to a comparison, the measure used was not a standardised measure, or the assessment used to measure the outcome was fundamentally different to others (that is overall data from Griffiths Mental Development Scales assessment and data from assessments conducted with the Bayley Scales of Infant and Toddler Development). These studies were discussed narratively within the results and discussion sections.

Comparisons included:

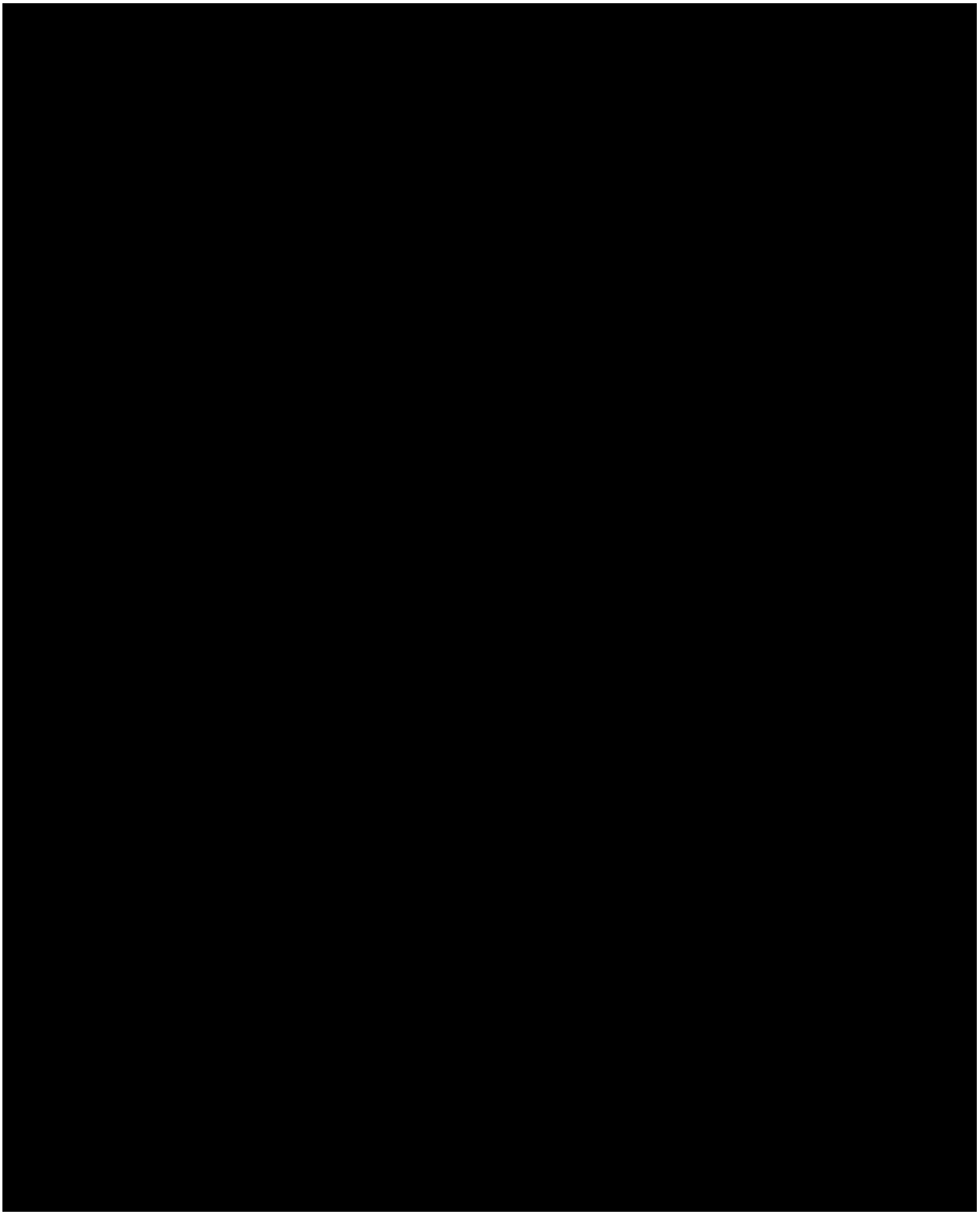
1. specific monotherapy group versus controls on global cognitive functioning;
2. specific monotherapy group versus controls on neurodevelopmental disorders;
3. specific monotherapy group versus controls on specific cognitive domains;
4. specific monotherapy group versus specific monotherapy group on all above outcomes.

Each comparison was stratified by control group, study design and measurement characteristics to ensure appropriate combination of study data.

Study selection

The study selection flow diagram is shown in Figure 6. There were 57 eligible full texts, from which 28 independent studies were included in the review (22 prospective cohort studies and six registry-based studies). The remaining 29 papers presented additional information on the same cohort as an included study.

Ten of the 28 studies were included in the meta-analysis. The 18 remaining studies could not be pooled due to differences in the methodology or completeness of reporting, so were discussed in narrative form only.



Study quality

Study quality varied. More recent studies tended to be larger and to report individual AED outcomes from blinded assessments, which indicate improved methodological quality.

Bias was assessed based on confounding, blinding, incomplete outcome data, selective outcome reporting, and other bias. For the blinding domains of 'sequence generation' and 'allocation concealment', all studies were rated as high risk of bias, but the low score related to the type of study design (none were randomised controlled trials). Important potential confounders included: maternal IQ, socio-economic status, epilepsy type, seizure exposure, child age at assessment, child gender, child gestational age at birth or birth weight, polytherapy.

Results

Neurodevelopmental outcomes of children exposed to each medicine were reported under the following headings:

- Neurodevelopmental outcomes of children exposed to AED compared to control children
    - Developmental quotient (DQ)
        - AED vs controls (women without epilepsy)
        - AED vs controls (women with epilepsy not taking AEDs
    - Intellectual quotient (IQ)
        - AED vs controls (women without epilepsy)
        - AED vs controls (women with epilepsy not taking AEDs
    - Autistic spectrum disorder
    - Specific cognitive abilities
    - AED vs controls: prevalence of below average performance
    - Dose of AED

The key results are summarised below.

<u>Carbamazepine</u>

The DQ was lower in children exposed to CBZ (n = 50) than in children born to women without epilepsy (n = 79); mean difference (MD) of -5.58 (95% CI -10.83 to -0.34, P = 0.04).

The DQ of children exposed to CBZ (n = 163) was also lower compared to children of women with untreated epilepsy (n = 58) (MD -7.22, 95% CI -12.76 to - 1.67, P = 0.01).

Further analysis using a random-effects model indicated that these results were due to variability within the studies and that there was no significant association with CBZ.

The IQ of older children exposed to CBZ (n = 150) was not lower than that of children born to women without epilepsy (n = 552) (MD -0.03, 95% CI -3.08 to 3.01, P = 0.98).

Similarly, the IQ of children exposed to CBZ (n = 163) was not lower to the children of women with untreated epilepsy (n = 87) (MD 1.84, 95% CI -2.13 to 5.80, P = 0.36).

<u>Sodium valproate</u>

The DQ in children exposed to VPA (n = 123) was lower than the DQ in children of women with untreated epilepsy (n = 58) (MD -8.72, 95% CI -14.31 to -3.14, P = 0.002).

The IQ of children exposed to VPA (n = 76) was lower than for children born to women without epilepsy (n = 552) (MD -8.94, 95% CI -11.96 to -5.92, P < 0.00001).

Children exposed to VPA (n = 89) also had lower IQ than children born to women with untreated epilepsy (n = 87) (MD -8.17, 95% CI -12.80 to -3.55, P = 0.0005).

Drug comparisons

In younger children there was no significant difference in the DQ of children exposed to CBZ (n = 210) vs VPA (n=160) (MD 4.16, 95% CI -0.21 to 8.54, P = 0.06). However, the IQ of children exposed to VPA (n = 112) was significantly lower than for those exposed to CBZ (n = 191) (MD 8.69, 95% CI 5.51 to 11.87, P < 0.00001).

The IQ of children exposed to CBZ (n = 78) versus LTG (n = 84) was not significantly different (MD -1.62, 95% CI -5.44 to 2.21, P = 0.41).

There was no significant difference in the DQ of children exposed to CBZ (n = 172) vs PHT (n = 87) (MD 3.02, 95% CI -2.41 to 8.46, P = 0.28). The IQ abilities of children exposed to CBZ (n = 75) were not different from the abilities of children exposed to PHT (n = 45) (MD -3.30, 95% CI -7.91 to 1.30, P = 0.16).

IQ was significantly lower for children exposed to VPA (n = 74) vs LTG (n = 84) (MD -10.80, 95% CI -14.42 to -7.17, P < 0.00001).

DQ was higher in children exposed to PHT (n = 80) vs VPA (n = 108) (MD 7.04, 95% CI 0.44 to 13.65, P = 0.04). Similarly, IQ was higher in children exposed to PHT (n = 45) vs VPA (n = 61) (MD 9.25, 95% CI 4.78 to 13.72, P < 0.0001).

Dose effect

A dose effect for VPA was reported in six studies, with higher doses (800 to 1000 mg daily or above) associated with a poorer cognitive outcome in the child.

There was no convincing evidence of a dose effect for CBZ, PHT or LTG.

Studies not included in the meta-analysis mostly supported the findings of the meta-analyses.

Conclusion

Pre-natal exposure to VPA is associated with a reduction in IQ, which may affect education and occupational outcomes in later life. However, for some women VPA is the most effective drug at controlling seizures. Informed treatment decisions require detailed counselling about these risks at treatment initiation and at pre-conceptual counselling.

There was insufficient data about newer AEDs, and further research is needed. Most women with epilepsy should continue their medication during pregnancy as uncontrolled seizures also carries a maternal risk.

Comments:
The results for CBZ illustrate the need for careful investigation and analysis of results so that spurious positive associations are not mistakenly reported. The numbers of children examined in these studies is small so some smaller effects on cognitive abilities may have been missed. Overall the results support an effect for valproate only.

3.1.2 Data-linkage studies

3.1.2.1 Christensen et al, 2019 (JAMA Netw Open)

Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention-deficit/hyperactivity disorder in offspring [12]

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2720066

Objective

To determine whether prenatal exposure to valproate and other AEDs is associated with an increased risk of **ADHD** in the offspring.

Methods

Population-based prospective cohort study of all singleton children born alive in Denmark between 1 January 1997 and 31 December 2011 (n=913 302) using data provided by Statistics Denmark. The cohort was followed up from birth until the day of the ADHD diagnosis (ICD-10-DCR diagnosis and/or use of ADHD medication), death, emigration, or 31 December 2015; whichever came first.

The Danish Civil Registration System assigns a unique personal identification number to all individuals at birth or on immigration, which enables complete linkage of individual information in national registries. The Danish National Prescription Registry holds unique information on all redeemed prescriptions purchased by patients (excluding treatments given only in hospitals) since 1 January 2016. AED exposure window was defined as 30 days before estimated day of conception (EDC) to day of birth (DOB). Exposure to AEDs was defined as any redeemed prescriptions with Anatomical Therapeutic Chemical (ATC) code N03A (antiepileptic drugs) or N05BA09 (clobazam) within the exposure window. Monotherapy and polytherapy were defined as redemption of prescriptions for only one type of AED and more than one type of AED, respectively, during exposure window. Mothers may also have redeemed prescriptions for other types of medicines in the exposure window.

Risk of ADHD was estimated for the most commonly used AEDs in Denmark at the time: VPA, CBZ, clonazepam, LTG and OXC. The mean daily dose of AED was estimated from the total amount of AED redeemed from 30 days before pregnancy to birth, divided by the number of days in the same period.

Children with new diagnoses of ADHD were identified in the Danish Psychiatric Central Research Register, based on ICD-10-DCR codes F90 and F98.8. The Danish National Prescription Registry was also used to identify children in the cohort prescribed medicines used to treat ADHD (N06BA01, amphetamine; N06BA02, dexamphetamine; N06BA04, methylphenidate; N06BA09, atomoxetine; N06BA11, dexmethylphenidate; and N06BA12, lisdexamfetamine).

Information on parity was obtained from the Danish Medical Birth Registry. The Danish National Patient Register was used to identify children diagnosed with congenital malformations, and mothers diagnosed with epilepsy before the birth of the child. The Danish Psychiatric Central Research Register was used to identify mothers diagnosed with psychiatric disorders before the birth of their child.

Statistical analysis: Cox regression was used to estimate the hazard ratio (HR), including 95%CI, for ADHD for children with prenatal VPA exposure, with the age of the child as the underlying time scale and separate strata for each birth year group to adjust for the decreasing use of valproate in pregnancy and the increasing prevalence of ADHD. The HRs were adjusted for risk factors for ADHD, including maternal age at conception (15-24, 25-29, 30-34, or ≥35 years), maternal psychiatric history (yes or no), maternal epilepsy (yes or no), maternal diabetes (yes or no), sex of the child, and parity (1, 2, or ≥3). Competing risk regression was used to estimate the absolute risk (cumulative incidence) of ADHD in the first 15 years of life after prenatal valproate exposure in pregnancy.

Confounding by indication was assessed by comparing the risk of ADHD in offspring of women who used VPA during pregnancy with previous uses (women who discontinued VPA at least 30 days before the EDC). Sensitivity analyses included stratifying the risk according to VPA dose, trimester of exposure (first vs later), monotherapy vs polytherapy, and maternal use of other AEDs, after adjusting for maternal smoking (yes or no) and after excluding children with congenital malformations. Further sensitivity analyses included excluding children with epilepsy and children whose mother had a diagnosis of ADHD and increasing the exposure period before the ETC from 30 days to 90 days.

HR of ADHD with follow up at 3 years of age was also estimated.

Results

The cohort comprised 913,302 children contributing more than 10.2 million person-years of observation. The mean age at end of study was 10.1 years, median age 9.4 years, interquartile range 7.2-12.8 years. Males comprised 51.3%. VPA exposure during pregnancy occurred in 580 children (monotherapy and polytherapy combined); 912,722 had no VPA exposure.

ADHD was identified in 29,396 (3.2%) of the 912,722 children who were unexposed to VPA, and in 49 (8.4%) of the 580 children who had been exposed to VPA.

Overall, children who were prenatally exposed to VPA had a 48% increased risk of ADHD (adjusted HR 1.48; 95% CI 1.09-2.00) compared with the unexposed children. When restricting the cohort to the 7620 children born to women with epilepsy, VPA use during pregnancy (n=516) was associated with a 39% higher risk of ADHD (adjusted HR 1.39; 95% CI 1.00-1.93) compared to no use of VPA during pregnancy (n=7104).

Among the 905,682 children born to women without epilepsy, VPA use during pregnancy (n=64) was not associated with an increased risk of ADHD (aHR 1.89; 95% CI 0.76-4.68) compared to no use of VPA during pregnancy (905,618). (Table 4)

Compared to LTG, prenatal exposure to VPA more than doubled the risk of ADHD (aHR 2.16; 95% CI 1.34-3.48). Prenatal exposure to CBZ increased the risk by 79% (aHR, 1.79; 95%CI, 1.06-3.04) compared to LTG. (Table 6)

Strengths and limitations

Strengths: population-based study, completeness of follow-up without attrition, and combined use of diagnostic and prescription-based data to identify children with ADHD.

Limitations: VPA is contraindicated in pregnancy, so women who continue to require VPA in pregnancy are likely to differ from those who do not in terms of their disorder presentation and severity. Sensitivity analyses aimed to address confounding by indication, but residual confounding may persist. However, more than 50% of VPA-exposed children were born from 1997-2002, before it was widely recognised that VPA was associated with adverse birth outcomes, and its use in pregnancy was not contraindicated in Denmark at that time.

[2] Table published in online supplementary material (eTable1).

Register data does not confirm actual use of the medicine. However, analysis of dose estimated the average daily dose based on the amount redeemed on prescription from pharmacies. It is unlikely that women would repeatedly purchase medicine if it was not consumed.

The study did not control for other types of medicine taken during pregnancy.

Several of the subgroup analyses for specific medicines and patient groups had low power, as indicated by the wide confidence intervals., so the findings must be interpreted with caution.

Conclusions

Maternal use of valproate during pregnancy was associated with a small but significantly increased risk of ADHD in the offspring, even after adjusting for maternal psychiatric disease, maternal epilepsy, and other potential confounding covariates.

Comments:

In a review of this study, Meador [37] highlights the strengths and limitations as follows:

> *Strengths of the study include the large population-based sample, lack of attrition, confirmed ADHD diagnosis combined with drug prescriptions for ADHD, and control for multiple potentially confounding factors such as maternal diagnosis of psychiatric disease, epilepsy, or diabetes; maternal age; maternal smoking; and child's sex, parity, year of birth, and presence of other disorders such as congenital malformations. Limitations of the study include the observational nature, no assessment of seizures or of drug concentrations in the blood, and lack of control for all other fetal medication exposures, including prescription, recreational, and abused drugs (eg, alcohol).*

This study indicates that prenatal exposure to VPA is associated with an increased risk of ADHD in children. LTG has a lower risk of ADHD than VPA, CBZ and clonazepam.

3.1.2.2 Elkjaer et al, 2018 (JAMA Neurol)

Association Between Prenatal Valproate Exposure and Performance on Standardized Language and Mathematics Tests in School-aged Children [38]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5885204/

Objective

To estimate the association between **long-term school performance** and prenatal exposure to valproate and other antiepileptic drugs (AEDs).

Methods

In this prospective, population-based cohort study, all children born alive in Denmark between 1997 and 2006 (n=656,496) were identified using the Danish Medical Birth Registry. Children were excluded from the cohort for the following reasons:

- did not participate in the national tests (n=115,175)
- participated in testing only in 2015, because tests performed that year were not comparable with previous years (n=56,573)
- presumed coding errors in gestational age (≤ 21 or ≥ 45 weeks), (n=2336)
- information on the mother's education (n=3260) and household income (n=125) was missing

After exclusions, the study cohort comprised 479 027 children, 1865 of whom were exposed prenatally to an AED.

Exposures: Information on AED exposure was retrieved from the Danish Register of Medicinal Product Statistics. The exposure window was 30 days before first day of last menstrual period (LMP) to 1 day before birth. The first day of the LMP was estimated by subtracting the length of gestation from the DOB.

Outcome measures: Information on school performance was provided by the Danish Agency for Information Technology and Learning. The primary outcome measure was cognitive ability assessed using academic tests conducted in Danish primary (grades 1-6) and lower secondary (grades 7-9/10) state schools from 2010 to 2014. All students enrolled in state education are required by law to participate in these tests. Danish tests are performed in grades 2, 4, 6 and 8; mathematics tests are performed in grades 3 and 6.

Covariates: Information on maternal epilepsy diagnoses was retrieved from the National Patient Register. The date of the first registered epilepsy diagnosis was used to distinguish between maternal epilepsy diagnosed before or after birth of the child.

Information on parents' income (quartiles) and maternal education at birth (<10 years, 10-15 years, ≥16 years of education) was provided by Statistics Denmark. Not all persons with psychiatric disorders are captured in the national patient registers, prescription data for antidepressants (N06A), antipsychotics (N05A), or anxiolytics (N05B) (excluding N05BA09 [clobazam]) was used as a proxy for psychiatric disorders in the parents.

Analysis: Test scores were standardized to *z* scores and adjusted for risk factors. Linear regression was used to examine differences in school performance among children prenatally exposed to valproate and unexposed children. Analyses were adjusted for calendar year, sex, maternal education, and parents' income.

Sensitivity analyses included comparison between school performance in children exposed to LTG and VPA, stratification on maternal epilepsy diagnosis before birth, epilepsy subtypes and use of psychiatric medicines in pregnancy. Prior use of VPA monotherapy (between 6 months and 30 days before LMP, but not during pregnancy) was compared with use during pregnancy. School performance was also analysed according to paternal use of VPA. Mean daily dose of AED during pregnancy was calculated based on gestation length. The effect of VPA dose was investigated by categorising estimated daily exposure into doses of < or ≥ 1000 mg/ day. The influence of exposure at first trimester vs second or third trimester was also examined.

Inverse probability weighting was used to assess the possibility of bias from missing data on excluded children.

Results

Among the 479 027 children who participated in the national tests, 1865 were prenatally exposed to one or more AEDs, of which 1576 children were exposed to AED monotherapy (VPA 253, PB 86, OXC 236, LTG 396, clonazepam 188, CBZ 294, and other AEDs 123).

Valproate exposed children scored worse on the sixth-grade Danish tests (adjusted difference, −0.27 SD; 95% CI, −0.42 to −0.12) and sixth-grade mathematics tests (adjusted difference, −0.33 SD; (95% CI, −0.47 to −0.19) compared with unexposed children and children exposed to lamotrigine (adjusted difference, −0.33 SD; 95% CI, −0.60 to −0.06). Children exposed to clonazepam scored worse in the sixth-grade Danish tests (adjusted difference, −0.07 SD; 95% CI, −0.12 to −0.02). CBZ, LTG, PB, and OXC were not linked to poor school performance compared with unexposed children. (See results table in the following link: www.ncbi.nlm.nih.gov/pmc/articles/PMC5885204/table/noi170121t2/?report=objectonly)

The Danish and mathematics sixth-grade results for all AED monotherapy groups are illustrated in Figure 8.

Strengths and limitations

Strengths: objective results without evaluator variability.

Limitations: Registry-based exposure information does not confirm that medicines were consumed, and there may be inaccuracies in timing of actual exposure. The data does not provide information on children with special education needs, and a relatively high proportion of children were missed for this reason. Information on folic acid use in pregnancy is missing. Information on other covariates such as AED blood levels during pregnancy, maternal seizure frequency, obstetric complication, use of alcohol, smoking or illicit drugs, and breast-feeding is also missing.

Conclusions

Maternal use of valproate was associated with a significant decrease in school performance in offspring compared with children unexposed to AEDs and children exposed to lamotrigine.

3.1.2.3 Bech et al, 2018 (J Neurol Neurosurg Psych)

In utero exposure to antiepileptic drugs is associated with learning disabilities among offspring [39]

Objective

To investigate **learning disabilities** among offspring exposed to AEDs *in utero* and further assess which AEDs carry the highest risk.

Methods

Register-based case-cohort study design. All children born during a 4-year period from 2005-2008 were identified in the Danish Medical Birth Register, and were followed up from birth until the first

year of compulsory education during a 5-year period from 2011-2015. Only singleton births of mothers exposed to AEDs. Children were assigned as cases if their mother was exposed to an AED within the period from 90 days prior to conception to birth, or controls if their mother was exposed to AED at any time but not during pregnancy.

Study data was obtained from Danish registers as follows:

- Danish Medical Birth Register: child's DOB, sex, gestational age, birth weight and Apgar score, and the maternal age and smoking status
- Danish National Patient Register and Danish Psychiatric Central Research Register: maternal comorbidities
- Danish National Prescription Register: redeemed prescriptions using ATC codes
- Danish Population Education Register: highest achieved maternal education, as a proxy for socio-economic status.

Exposures: From the prescription register, AEDs (ATC N03A) and the period in which the prescription was redeemed were identified. Periods of exposure were defined as first trimester (90 days prior to conception to day 84 of pregnancy), second trimester (day 85 to day 196) and third trimester (day 197 to birth).

Outcome measures: Learning disabilities among offspring in the first year of compulsory education, defined as: mental retardation (ICD-10: F7x), specific developmental disorders (ICD-10: F80–83), autism spectrum disorders (ICD-10: F84), emotional/behavioural disorders (ICD-10: F9x) or having special educational needs (receiving special class lessons, additional time for a special education programme or having been classified with a learning disabilities obtained from the Special Education Register as part of the Danish Population Education Register.

Statistical analyses: (1) association between *in utero* exposure to any AED during any trimester and learning disabilities using a logistic regression model, and (2) ORs of learning disabilities among cases exposed to specific AEDs *in utero* compared with controls, and compared with cases exposed to another AED *in utero*.

Results

Of 117,475 incident singleton births in Denmark from 2005-2008, 636 were identified as cases (exposed to AEDs *in utero*) and 434 were identified as controls (mother redeemed prescription for AED more than 90 days prior conception but not during pregnancy). Median age of children was 6.1 years, 55.7% males. Maternal epilepsy was more frequently identified among cases (37.9%) compared to controls (11.5%), and the opposite for maternal psychiatric disorders (cases 21.4% vs controls 27.4%).

Learning disabilities were identified in 45 cases (7.1%) and 16 controls (3.7%) in the first year of compulsory education (adjusted OR 2.20, 95% CI 1.16 – 4.17). (Figure 9A)

Among cases exposed to monotherapy (n=556), the risk of learning disabilities for each AED was compared to no exposure (Figure 9B) and to monotherapy exposure to any other AED (Figure 9C).

In utero exposure to LTG compared with another AED during any trimester was associated with the lowest adjusted OR for learning disabilities (adjusted OR 0.42, 95% CI 0.19 to 0.92). VPA and PB were associated with significantly higher adjusted ORs compared to another AED.

Strengths and limitations

Strengths: As with other Danish registry studies, the data sources are robust.

Limitations: Possibility of residual confounding. Data on fathers was not available. Unable to adjust for parental learning disabilities. Possibility of selection bias and confounding by indication. Additional confounding factors could not be accounted for, including disease severity, seizure frequency, AED dose and serum levels, prescribing practices, exposure to other potential teratogens or use of folic acid during pregnancy. Exposure information based on redeemed prescriptions does not necessarily indicate that the medicine was consumed.

Conclusions

In utero exposure to antiepileptic drugs was significantly associated with learning disabilities among offspring. Lamotrigine should preferentially be considered over, for example, valproate if clinically feasible.

Comments:

As discussed by the authors, the composite outcome of mental retardation, specific developmental disorders, autism spectrum disorders, emotional/behavioural disorders or special educational needs are a vague proxy for assessing the effect on prenatal exposure to AEDs compared with more specific measures for learning disabilities such as low IQ score or poor performance on national school tests. However, the findings are consistent with a similar study by Elkjaer *et al* [38], which reported on specific measures of school performance.

3.1.2.4 Lacey et al, 2018 (J Neurol Neurosurg Psych)

Educational attainment of children born to mothers with epilepsy [40]

Objective

To identify whether children exposed to AEDs *in utero* have poorer **school performance**.

Methods

This Welsh study used anonymised, linked, routinely collected healthcare records in the Secure Anonymous Information Linkage (SAIL) databank to identify children born to mothers with epilepsy. SAIL contains medical records for approximately 2.3 million people (77% of the Welsh population).

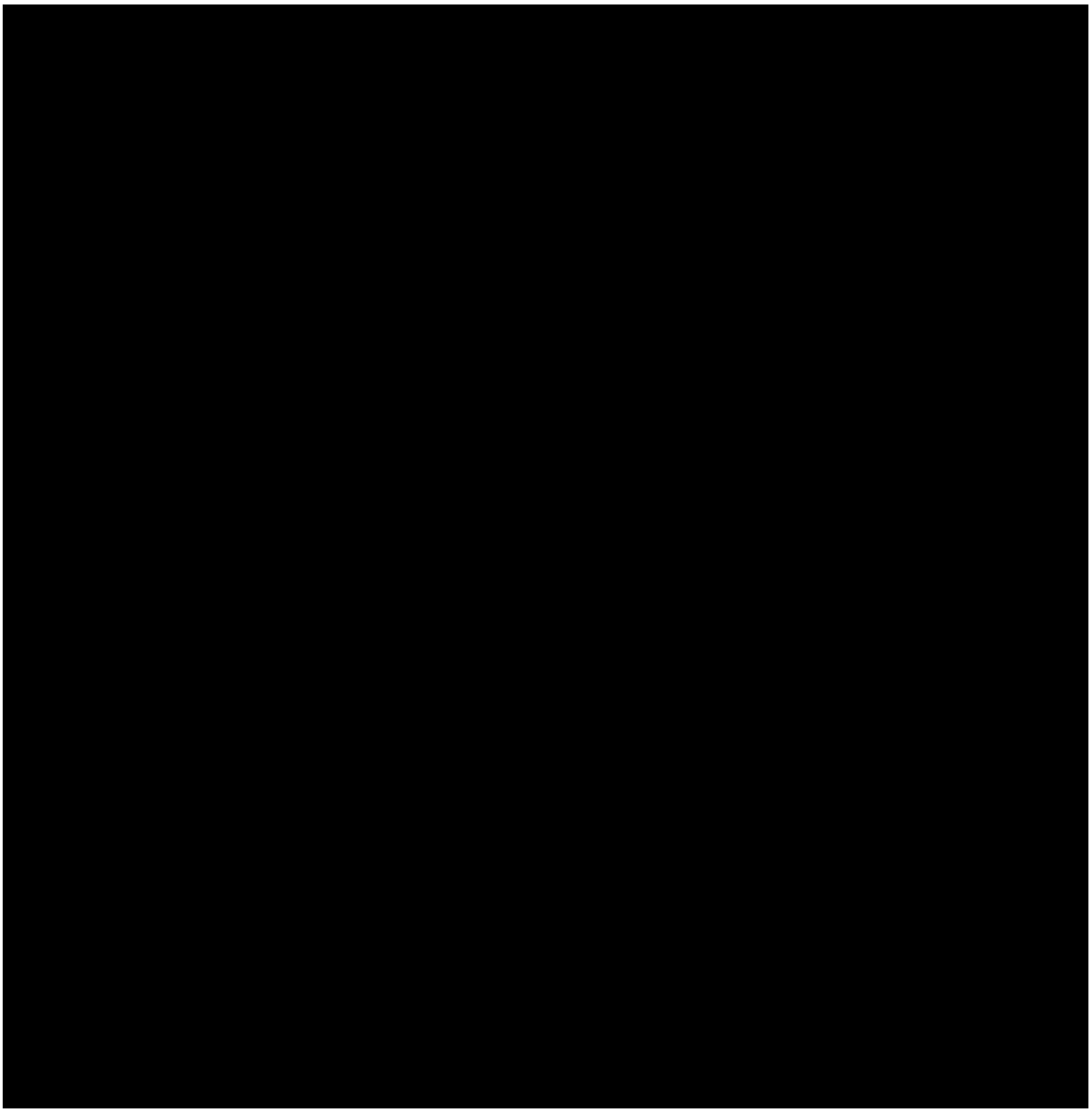
From 1999 to 2011, the Welsh national assessments of educational achievement were performed at five Key Stage (KS) between 7 and 16 years of age. Children were tested in mathematics, language (English or Welsh) and science, and awarded a level between 1 (lowest) and 3 (highest). KS1 took place at age 7 years. The core subject indicator (CSI) was the proportion of children achieving a minimum standard (≥ level 2) in all three KS1 subjects. A new system for assessment of educational attainment has been used since 2011. KS1 results were available in SAIL for the years 2003-2008.

SAIL was searched for women with epilepsy who gave birth between 1996-2001 and had children who had KS1 results that were accessible in SAIL. Mothers were grouped according to the AED they were prescribed during pregnancy. A control group was created matched for maternal age, gestational age and deprivation at time of birth (4:1 ratio).

Results

440 children were born to mothers with epilepsy with available KS1 results available between 2003 and 2008.

Compared with a matched control group, fewer children with mothers who were prescribed VPA during pregnancy achieved the national minimum standard in CSI (-12.7% compared to the control group), mathematics (−12.1%), language (−10.4%) and in science (−12.2%). No significant difference was observed in children exposed to CBZ, LTG or no AED compared to the control group. (Figure 10)



Strengths and limitations

Due to limitation of data availability, the study was limited to examining educational attainment in 7-year-olds during the period 2003-2008. Consequently, newer AEDs such as LEV were not included in the analysis.

Conclusions

In utero exposure to AEDs in combination, or sodium valproate alone, is associated with a significant decrease in attainment in national educational tests for 7-year old children compared with both a matched control group and the all-Wales national average. These results give further support to the cognitive and developmental effects of *in utero* exposure to VPA as well as multiple AEDs, which should be balanced against the need for effective seizure control for women during pregnancy.

Comments:

The control group was matched for maternal age, gestational age and deprivation at time of birth, but the group is not well described. It is not explicit that the controls are children of women without epilepsy.

3.1.2.5 Charlton et al, 2017 (Drug Safety)

Sensitivity of the UK Clinical Practice Research Datalink to Detect Neurodevelopmental Effects of Medicine Exposure in utero: Comparative Analysis of an Antiepileptic Drug-Exposed Cohort [41]

Objective

To determine whether data from the UK Clinical Practice Research Datalink (CPRD) produces similar risk estimates to a prospective cohort study in relation to the risk of **neurodevelopmental disorders (NDDs)** following prenatal AED exposure.

Methods

A cohort of mother-child pairs of women with epilepsy (WWE) was identified in the CPRD and matched to a cohort of mother-child pairs of women without epilepsy (WWO). The study period ran from 1 January 2000 to 31 March 2007, and children were required to be in the CPRD at age 6 years. AED exposure during pregnancy was determined from prescription data and Read codes were used to identify children with NDDs by age 6 years. The prevalence and risk of NDDs was calculated for mother-child pairs in WWE stratified by AED regimen, and for WWO.

Comparisons were made with the results of the prospective Liverpool and Manchester Neurodevelopment Group study which had previously competed assessment on 201 WWE and 214 WWO at age 6 years [42].

Results

1030 eligible mother-child pairs of WWE were identified in the CPRD and were matched with 6180 mother-child pairs of WWO. After exclusion of mother-child pairs in which mother or child had a condition that could influence neurodevelopment, there were 1018 WWE and 6048 WWO. Fifty-four percent of WWE received an AED during pregnancy: 79% monotherapy and 21% polytherapy.

There were 87 Read code diagnoses for NDDs of interest in 84 children: 47 for ASD, 30 for ADHD, four for dyspraxia and three children had codes for both ASD and ADHD.

NDDs were more frequently reported in the children of WWE than children of WWO. The prevalence of NDDs was increased amongst offspring antenatally exposed to CBZ, VPA (monotherapy and polytherapy) and non-VPA polytherapy when compared with offspring born to women without epilepsy, but these increases did not reach statistical significance. (Table 7)

Conclusions

This study identified a lower prevalence of NDDs in the CPRD than in a prospective observational study matched for calendar time and age of the child, and did not produce a signal that valproate as monotherapy is a neurodevelopmental teratogen.

Comments:

The main purpose of this study was to compare risk estimates obtained from the CPRD through data-linkage with those obtained in a prospective observational cohort study. The CPRD data was compared with data from the Liverpool and Manchester Neurodevelopment Group study published by Bromley *et al* [42]. The latter was included in both the network meta-analysis by Veroniki *et al* [21] and the Cochrane review by Bromley *et al* [7] described in section 3.1.1 above.

This study showed an increase in NDDs in children of WWE who were not taking an AED during pregnancy compared to controls (children born to women without epilepsy). An increase in the risk of NDD was detected for children with prenatal exposure to VPA or CBZ compared to controls, but it was not statistically significant.

A more appropriate comparator group for children of WWE exposed to AED monotherapies would be children of WWE with no prenatal AED exposure (instead of the children of women without epilepsy who were the control group in this study).

3.1.2.6 Christensen et al, 2013 (JAMA)

Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism [43]

Objective

To determine whether prenatal exposure to valproate is associated with an increased risk of **autism** in offspring.

Methods

Population-based cohort study on risk of autism in children exposed prenatally to VPA. Risk estimates were adjusted for known risk factors for autism. The effects of VPA dose, trimester of exposure, VPA polytherapy, congenital malformations, and maternal history of epilepsy were also estimated.

Study population: Children born alive in Denmark from 1 January 1996 to 31 December 2006, using data from the Danish Civil Registration System. Children were excluded from the cohort if they had errors or missing gestational age, or missing information about the mother, were adopted, or died during the first year of life.

Medicine exposure: Data obtained from the Danish Prescription Register. AED exposure was defined as any filled prescription with ATC codes N03A (antiepileptic drugs) and N05BA09 (clobazam). Exposure window was 30 days before EDC to DOB for children with EDC after 1 February 1996, who were born up until 31 December 2006. The mean daily dose of AED was estimated from the total amount of AED redeemed from 30 days before pregnancy to birth, divided by the number of days in the same period. Monotherapy and polytherapy were defined as redemption of prescriptions for only one type of AED and more than one type of AED, respectively, during exposure window. Mothers may also have redeemed prescriptions for other types of medicines in the exposure window.

Outcomes: The Danish Psychiatric Central Register was used to identify children with a new diagnosis of autism spectrum disorder (ASD) or childhood autism (ICD-10 codes F84.0, F84.1, F84.5, F84.8, and F84.9).

Information on covariates was obtained from national registers as follows:

- Danish Psychiatric Central Register: parents with psychiatric disorders before birth of child
- Danish Birth Register: gestational age, birth weight and parity
- National Hospital Register: children diagnosed with congenital malformations, and parents diagnosed with epilepsy before birth of the child

Children were followed up from birth until the day of autism spectrum disorder diagnosis, death, emigration, or 31 December 2010, whichever came first.

Data analysis: Absolute risk (cumulative incidence) and the hazard ratio (HR) of autism spectrum disorder and childhood autism in children after exposure to VPA in pregnancy. Data were analysed by Cox regression adjusting for potential confounders (maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations, and parity)

Results

After exclusions, 655,615 children were born from 1996 -2006. The mean age of the children at end of follow-up was 8.84 years (range, 4-14; median, 8.85).

During the study period, 5437 children were identified with autism spectrum disorder, including 2067 with childhood autism. 2644 children were exposed to antiepileptic drugs during pregnancy, including 508 exposed to valproate.

The estimated absolute risk after 14 years of follow-up was 1.53 (95% CI 1.47 - 1.58) % for autism spectrum disorder and 0.48 (95% CI 0.46 - 0.51) % for childhood autism.

Compared to no exposure (n=655,107), prenatal exposure to VPA (monotherapy or polytherapy; n=508) was significantly associated with:

- ASD: absolute risk 4.42 (95% CI 2.59-7.46) %, adjusted HR 2.9 (95% CI, 1.7-4.9)
- Childhood autism: absolute risk 2.50 (95% CI 1.30-4.81) %, adjusted HR 5.2 (95% CI, 2.7-10.0).

(Table 8)

VPA monotherapy was associated with a significantly higher risk of both ASD (HR 3.0, 95% CI 1.7 – 5.4) and childhood autism (HR 4.9, 95% CI 2.3 – 10.3). Prenatal exposure to LTG, CBZ, OXC and clonazepam monotherapies was not associated with a statistically significant increase in ASD or childhood autism (Figure 11).

Strengths and limitations

Strengths: Population based cohort of children followed for up to 14 years with less than 3% loss to follow-up. Analyses adjusted for parental psychiatric history, which is a known risk factor for autism

Weaknesses: Exposure data based on filled prescriptions does not confirm that the medicine was taken. Information on alcohol use (except for abuse) or folic acid use in pregnancy was not available.

Conclusions

Maternal use of VPA during pregnancy was associated with a significantly increased risk of autism spectrum disorder and childhood autism in the offspring, even after adjusting for maternal epilepsy. For women of childbearing potential who use antiepileptic medications, these findings must be balanced against the treatment benefits for women who require valproate for epilepsy control.

Comments:
This study was included in the NMA by Veroniki *et al* [21], but is described separately here due to its size and robust methodology.

3.1.3 Other studies

A search of the literature for studies of neurodevelopmental outcomes associated with prenatal exposure to AEDs identified only one recent study that was not included in any of the three systematic reviews described in section 3.1.1.

3.1.3.1 Cohen-Israel et al, 2017 (BJCP)

Short- and long-term complications of in utero exposure to lamotrigine [44]

https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bcp.13437

Aim

To evaluate further the short and long-term physiological, cognitive and emotional development of children exposed to lamotrigine *in utero* to the age of 12 years.

Methods

Retrospective cohort study of 83 women who gave birth at a single hospital in Israel between January 2004 and August 2014, who had been treated with lamotrigine during the first trimester of pregnancy. Study participants were identified using the local teratology information service. Only women for whom complete records were available were included in the study. Women were excluded if they had chronic diseases other than epilepsy or were taking medicines known to affect their child's short or long-term outcome (eg, opioids, SSRIs or SNRIs).

Perinatal data were obtained from the medical charts of the mothers and neonates. Long-term data were obtained from medical files and telephone interviews using an *ad hoc* questionnaire. The questionnaire covered: child's age, growth, chronic diagnoses, medicines, hospitalisations, and development (including delays in global developmental, speech, motor function or coordination, sensory disturbance, emotional disturbance, leaning disabilities and autism).

Results

Lamotrigine was used as monotherapy in 76 mothers with epilepsy (91.6%) and in combination in 7 (8.4%) as follows: clonazepam 4 women, carbamazepine (2), quetiapine, levetiracetam and phenytoin (1 each).

Long-term follow-up was made at a single point up to the age of 12 years. The results were compared to an equal number of children born at the same hospital to healthy women matched for gestational age and date of birth. Forty-seven children (56.6%) were aged 6-12 years when evaluated.

The only significant difference between the groups was found in speech delay, with a lower rate in the lamotrigine group compared to the control group (6 children, 7.2% vs. 15 children,18.0%, P = 0.036).

Comments:
Small single-centre study with poorly documented method. Age at which long-term follow-up occurred varied. Information on neurodevelopmental outcomes obtained using a questionnaire, but not clear how or by whom developmental delays were assessed. Comparator group were infants born to healthy women (presumably without epilepsy) matched for gestational age and date of birth only. No information comparability of the two groups on other neurodevelopmental risk factors, such as Apgar scores, birthweight, gestational age, maternal smoking/ alcohol, other medicine exposures or use of folic acid.

3.2 CARM data

A search of the CARM database to 31 March 2020 identified 34 cases of *in utero* exposure to AEDs (ATC group N03A). Twenty-six of the reports indicated neurodevelopmental abnormalities based on a review of the individual case reports.

All but one of these 26 reports were associated with prenatal exposure to VPA. Two reports were associated with exposure to VPA and another AED (LTG and PB, one report each) and one report concerned CBZ.

Of the 26 reports of neurodevelopmental abnormalities, 21 reports included fetal valproate syndrome (FVS) associated with prenatal exposure to VPA. Four reports were for autistic disorders (3 associated with VPA and 1 with CBZ), and one report was for developmental delay and congenital mental deficiency associated with VPA and LTG exposure. (Table 9)

In total, six reports specifically reported an autistic disorder, of which five were related to VPA and one to CBZ.

A full line listing of the cases is provided in Annex 6.

Table 9. Summary of adverse reaction reports in the CARM database for neurodevelopmental adverse effects associated with *in utero* exposure to antiepileptic medicines (to 31 March 2020).

Adverse drug reaction	Antiepileptic medicine	Reports (n)
Fetal valproate syndrome	VPA	17
Autistic spectrum disorder	VPA	3
Fetal valproate syndrome + autistic spectrum disorder + developmental delay	VPA	2
Fetal valproate syndrome + developmental delay	VPA	1
Fetal valproate syndrome	VPA + PB	1
Developmental delay + congenital mental deficiency	VPA + LTG	1
Autistic spectrum disorder	CBZ	1

4 DISCUSSION AND CONCLUSIONS

Neurodevelopmental outcomes in children may take some years to become apparent. Unlike major congenital malformations, which may be apparent at birth, neurodevelopmental adverse effects require longer term follow-up studies to ascertain their frequency. Many studies have been undertaken to assess neurodevelopmental outcomes in children exposed to AEDs, but they are often small and have methodological limitations such as retrospective design, loss to follow-up, or inappropriate control groups.

This review focused on large scale meta-analyses and register-based studies. Register-based studies, such as those undertaken in Denmark, lend themselves to this type of investigation, as they allow for a large cohort, without the cost of a prospective observational study, and do not rely on recall of medicine exposure. However, register studies also have limitations. Exposure data based on dispensing records does not confirm that a medicine was consumed (although repeat dispensings do suggest that it was), and confounding factors such as maternal IQ, paternal diagnoses of ADHD or autism, seizure control during pregnancy, concurrent medicines, smoking, cannabis and alcohol consumption are not well accounted for.

Autism

In a large Danish register-based study [43], prenatal exposure to VPA (monotherapy or polytherapy) was significantly associated with autism spectrum disorder (HR 2.9, 95% CI 1.7-4.9) and childhood autism (HR 5.2, 95% CI 2.7 – 10.0). Prenatal exposure to LTG and CBZ monotherapies was not associated with a statistically significant increase in ASD or childhood autism.

The NMA [21], which included the Danish register study, found that VPA was significantly associated with autism/dyspraxia (OR 17.29, 95% CrI 2.40 to 217.60), and the association remained when the analysis was restricted to use in epilepsy. LTG was also significantly associated with autism/dyspraxia (OR 8.88, 95% CrI 1.28 to 112.00), but statistical significance was lost in the sensitivity analyses using only higher quality studies.

ADHD

In the Danish register-based study, Christiansen *et al* [12] found that among women with epilepsy, maternal use of VPA was associated with a 39% higher risk of ADHD (adjusted HR 1.39; 95% CI 1.00-1.93) compared to no use of VPA during pregnancy. VPA was also associated with an increased risk of ADHD (adjusted HR 1.52; 95% CI 1.05 – 2.19 when compared to non-use of any AED in pregnancy.

Prenatal exposure to CBZ or LTG was not associated with and increased risk of ADHD compared to non-use of any AED in pregnancy [12].

In the large NMA [21], none of the treatment comparisons reached statistical significance for ADHD.

Cognitive impairment and developmental delay

In the NMA by Veroniki *et al* [21], VPA was associated with significantly increased odds of cognitive developmental delay compared with control (OR 7.40, 95% CrI 3.00 to 18.46), although this association was lost when the analysis was restricted to studies rated highly for 'adequacy of follow-up'.

VPA was also significantly more harmful than control in the analyses of psychomotor developmental delay (OR 4.16, 95% CrI 2.04 to 8.75) and language delay (OR 7.95, 95% CrI 1.50 to 49.13) [21].

Haskey *et al* [13] reviewed 10 studies of neurodevelopmental outcomes associated with use of AEDs for mood stabilisation, but did not undertake a meta-analysis. Two of the studies found that higher dose VPA (> 800 mg/day) was associated with poorer IQ scores [30, 31]. Bromley *et al* [31] found decreased verbal, non-verbal and expressive language abilities with increasing doses of valproate.

The Cochrane review [7] found that prenatal exposure to VPA is associated with a reduction in IQ, to an extent that may affect education and occupational outcomes in later life. Reduced IQ was found in comparisons with children of women without epilepsy and children of women with untreated epilepsy, and when compared to children exposed to CBZ *in utero*. A dose effect was reported in six studies, with higher VPA doses (800 to 1000 mg daily or above) associated with a poorer cognitive outcome in the child.

For children exposed to CBZ *in utero*, the Cochrane review did not find a significant association with poorer IQ or DQ, compared to children of women without epilepsy. There was no convincing evidence of a dose effect for CBZ, PHT or LTG. There was insufficient data about newer AEDs.

Long-term school performance was studied by Elkjaer *et al* [38] in a Danish register-based study. Prenatal exposure to VPA was associated with a significant decrease in 6th grade school performance compared with children unexposed to AEDs, and compared with children exposed to LTG.

Learning disabilities were studied in another Danish register-based study by Bech *et al* [39]. Children exposed to VPA *in utero* had a significantly greater risk of learning disability compared to unexposed children (OR 5.31, 95% CI 2.13 – 13.93), and compared to children exposed to another AED during any trimester (OR 4.67, 95% CI 1.73 – 12.59). Prenatal exposure to PB compared to another AED during any trimester was also associated with significantly higher adjusted OR. Prenatal exposure to LTG

compared with another AED during any trimester was associated with the lowest adjusted OR for learning disabilities (adjusted OR 0.42, 95% CI 0.19 to 0.92).

In a Welsh register-based study, school performance was poorer in children exposed to VPA *in utero*, but no difference was observed for children exposed to CBZ or LTG compared to the unexposed matched control group [40].

The UK CPRD study [41] looked at neurodevelopmental disorders overall, using relevant Read codes. The prevalence was higher in children prenatally exposed to CBZ, VPA, and non-VPA polytherapy compared to children of women without epilepsy, but the increases were not statistically significant.

Summary

Overall, these studies consistently show poorer neurodevelopmental outcomes (including ASD, ADHD, cognitive impairment and developmental delay) for children exposed to VPA *in utero*. The risk was found to be greater with higher VPA doses (> 800 mg per day).

LTG was associated with an increased occurrence of autism in the NMA (although the result was not statistically significant when analyses were limited to studies with adequate follow-up) [21].

CBZ was not significantly associated with ASD, ADHD, cognitive impairment or developmental delay in any of the studies reported on in this review.

Little information was available for PHT, PB, LEV and TPM.

Newer unapproved AEDs (eg, retigabine and rufinamide), second-line AEDs (eg, vigabatrin, lacosamide), and medicines that are not indicated for tonic-clonic seizures (ethosuximide, gabapentin, pregabalin) were not included in this review.

The CARM data, in which 25 of the 26 reports of neurodevelopmental adverse effects were associated with prenatal exposure to VPA, is consistent with these findings.

Usage data indicates that exposure to VPA during pregnancy is declining, as newer AEDs including LTG and LEV are used in preference. However, there will remain some women for whom VPA is the most appropriate therapy to continue in pregnancy, and it is important for these women to have clear, up-to-date information about potential risks to the fetus, to enable informed treatment decisions and support for their children.

The current data sheets for VPA includes warnings about neurodevelopmental disorders in children exposed to VPA in utero (see Annex 1) [14].

The Committee is asked to consider whether the current data sheet wording for AEDs reflects the degree of risk reported in the literature.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the current evidence supports an association between prenatal exposure to any of the antiepileptic medicines and adverse neurodevelopmental outcomes in the child?
- Whether there is a need to update the data sheet for any of the antiepileptic medicines to reflect current knowledge on the risk of neurodevelopmental adverse effects associated with prenatal exposure?

6 ANNEXES

1. New Zealand data sheet wording for AED use in pregnancy
2. AED pregnancy usage data - National Collections:
    a. Base Data: count of women who gave birth in the years 2010-2020 who also have one or more dispensing record of any antiepileptic medicine in the 310 days preceding delivery
    b. Folic Acid: count of women who appeared in the Base Data who also have a record of folic acid dispensing during the same period.
3. Veroniki *et al*, 2017
4. Haskey *et al*, 2017
5. Bromley *et al*, 2014
6. CARM data – line listing (31 March 2020)

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