Prenatal exposure to sodium valproate and levetiracetam: consequences for neurodevelopmental outcomes?

A thesis submitted to the University of Manchester for the degree of Doctorate of Clinical Psychology in the Faculty of Medical and Human Sciences

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Thank you to the supervisors of this project, Dr Penny Bunton and Prof Gus Baker for their thoughts, comments and support during the undertaking of this thesis.

Finally, I would like to thank my husband for his support through yet another thesis. This is the last one I promise!
1. Abstract

Prenatal exposure to sodium valproate and levetiracetam: consequences for neurodevelopmental outcomes?

Rebecca L. Bromley, PhD.

For the award: Doctorate of Clinical Psychology. Submitted to the University of Manchester June 2012.

Research has demonstrated that prenatal exposure to antiepileptic drugs is associated with an increased risk of physical malformations. The potential risk such exposure conveys to the developing brain and therefore the later cognitive functioning of the child is now the focus of both national and international research. This thesis investigated the relationship between prenatal exposure to antiepileptic drugs and child cognitive functioning. This investigation was undertaken in three phases: a systematic review of the published literature; an original research piece investigating prenatal exposure to sodium valproate and levetiracetam and finally a critical review of the research undertaken as part of this thesis and in the wider published literature.

The systematic review identified 30 studies which had investigated the cognitive abilities of children with a history of prenatal exposure to antiepileptic drugs. Methodological quality of the studies was considered against the criteria of the Newcastle Ottawa Scale. Differential findings were noted across the antiepileptic drug types, with the largest number of studies documenting increased risks associated with prenatal exposure to sodium valproate. A lack of high quality research across all antiepileptic drugs, and in particular the more recently licensed antiepileptic drugs is highlighted.

In the research paper presented here children aged between five and nine years of age exposed to either levetiracetam (n=37), sodium valproate (n=40) or who were born to women with epilepsy but did not require medication (n=43) were recruited from throughout the UK. Demographic and health information was collected from prospective records and supplemented with maternal interview. Formal standardised neuropsychological assessments were undertaken to inform on the child’s current level of intellectual, memory, language, attentional and executive functioning. Following adjustment for variables likely to influence child cognitive ability, prenatal exposure to sodium valproate was found to be associated with poorer intellectual and language functioning in a dose dependent manner. When stratified by dose, 57.9% of children exposed to doses of sodium valproate above 800mg daily scored below the average range for their global intellectual ability. Prenatal exposure to levetiracetam was not found to be associated with poorer cognitive functioning. The critical review highlighted a number of methodological strengths of this research, despite time and resource implications. However, consideration should be given to the retrospective nature of this cohort and the potential for recruitment bias.

This thesis concludes that women who require continuation of their treatment during pregnancy to control their seizures should be counselled regarding the risks and the benefits of their treatment to allow them to make informed decisions.
2. Declaration
No proportion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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4. Introduction
This thesis presents original research undertaken by the author for the award of Doctorate of Clinical Psychology (ClinPsyD). This project was part of a wider project undertaken by the Liverpool and Manchester Neurodevelopment Group, which was funded by Epilepsy Research UK and began in 2009. The wider project aimed to investigate the cognitive functioning of children exposed in utero to monotherapy topiramate, levetiracetam or gabapentin in comparison to no medication controls, and was designed by this thesis author in collaboration with the members of the UK Epilepsy and Pregnancy Register. The addition of a group of children exposed to sodium valproate was undertaken for the purposes of this ClinPsyD study. The aim of this addition was to provide reliable evidence of risk to neurodevelopment regarding prenatal exposure to levetiracetam and sodium valproate from simultaneously recruited groups.

Recruiting from a national register from which participants from all over the UK and Northern Ireland self enrol or are enrolled by their healthcare professional presented challenges in terms of data collection. To reduce the amount of investigator travel and in order to ensure that the assessments for this ClinPsyD project were conducted in a blinded fashion, assessments were allocated across the thesis author and one of two trained research assistants by geographical area, for the period of data collection for this thesis. The thesis author conducted 41 assessments for this project which included local cases, two trips to Scotland, two trips to the North East of England, a trip to the South East, multiple trips to the Midlands and a trip to Northern Ireland. All participant neuropsychological assessments were scored by the administrator of the assessment (e.g. the thesis author or the research assistant) and then second scored by the thesis author. The thesis author and the research assistants were required to have completed training on the neuropsychological measurements and be signed off in their use to ensure reliability.

The conception, design and analysis of the research presented here was the authors work. The paper presented in Chapter 1 is formatted for Developmental Medicine and Child Neurology (Appendix 1). The paper presented in Chapter 2 is formatted for Neurology (Appendix 2).
5. Chapter 1. Prenatal Exposure to Antiepileptic Drugs: Should We Be Concerned About Neurodevelopment?

5.1. Abstract

Aim
This systematic review aimed to summarise the literature pertaining to the neurodevelopmental outcome of children prenatally exposed to antiepileptic drugs (AEDs).

Method
Searches were conducted through MEDLINE, EMBASE, and PsycINFO. Studies were eligible for inclusion if they reported on the neurodevelopmental abilities of children or adults born to women with epilepsy who were exposed to a monotherapy AED.

Results
Thirty studies were identified. Most studies found no association between carbamazepine or lamotrigine exposure and neurodevelopmental outcome. Prenatal exposure to phenytoin was not associated with reduced neurodevelopment in larger cohorts. The majority of studies found an association between exposure to sodium valproate and neurodevelopmental outcome. Limited evidence pertaining to phenobarbital monotherapy meant that conclusions could not be drawn. Only single studies investigating the neurodevelopment of infants exposed to levetiracetam or topiramate were identified. No studies identified investigated prenatal exposure to ethosuximide, gabapentin, oxcarbazepine or zonisamide. The methodological quality of studies varied and only a small number considered the effect of AED dose.

Interpretation
Prenatal exposure to sodium valproate was associated with an increased risk to neurodevelopment in a dose dependent manner. Further research with improved methodology is required to delineate the potential risks associated with newer AEDs.
5.2. What this Paper Adds

- Evidence that research investigating neurodevelopment following prenatal exposure is increasing.
- Accumulation of evidence highlights significant risk associated with sodium valproate
- Research needs to delineate the risks associated with AED dose
- Methodological quality varies across studies

5.3. Introduction

There is growing concern regarding the use of antiepileptic drugs (AEDs) in women of child bearing age\(^1\). An accumulation of data highlights a significant and substantial increase in risk for the development of major congenital malformations for certain AED treatments\(^2\). Prenatal exposure to AEDs reportedly carries a dose dependent risk to the physical development of the child in utero, with sodium valproate doses over 1500mg daily carrying the highest risk (adjusted odds Ratio 16.1, 95% CI 8.22-31.54, p<0.001)\(^2\).

Historically, research has focused on physical outcomes of infants exposed to AEDs. However, a growing body of research highlights the susceptibility of the brain to prenatal exposure to AEDs, particularly sodium valproate\(^3\). The nature and prevalence of neurodevelopmental difficulties associated with prenatal exposure to AEDs is unclear. Knowledge regarding the risks associated with AED treatment in those of child bearing potential is of clinical use to prescribers. Health care professionals in paediatrics should also be aware of the potential associations between prenatal exposure and child health and development. This systematic review aims to summarise the scientific literature to date regarding the neurodevelopmental outcome of children prenatally exposed to commonly prescribed AEDs.
5.4. Method

5.5. Inclusion Criteria

Types of participants

Studies were included if they reported on the neurodevelopmental outcome of participants (children or adults) born to women with epilepsy treated with a monotherapy AED. Offspring born to women without epilepsy who were treated with AEDs (e.g., for mood disorders) were not included to limit cohort variability. Studies were eligible for inclusion if they reported on neurodevelopmental outcome (see outcome measures below) in children or adults following prenatal exposure to one or more specific monotherapy AEDs (listed below). An a priori hypothesis, based on previous research reporting differential outcomes across AED types\(^4\)\(^6\), predicted that studies, which reported on single groups that included multiple monotherapy AEDs together, would be high in bias. Therefore, studies which failed to reported outcome by specific monotherapy AED type were not included.

Studies reporting exposure to the following commonly prescribed AEDs were considered: sodium valproate, lamotrigine, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, topiramate, gabapentin, zonisamide, levetiracetam, ethosuximide.

Types of studies

Study types eligible for inclusion were:

- case-control
- randomised controlled trials (although such a methodology is considered to be unethical in this area of research)
- prospective observational
- retrospective observational
- record linkage
Included studies were limited to full articles. Conference abstracts were excluded due to the limited amount of information on the methodology utilised.

**Types of outcome measures**

Neurodevelopmental outcomes are broad and include discrete diagnosed conditions and continuous outcomes generated through formal assessment. The following neurodevelopmental outcomes were eligible for this review:

- Neurodevelopmental disorders including, but not limited to: autism, Asperger’s, dyspraxia, persistent pervasive developmental disorder, attention deficit hyperactivity disorder.
- Formally assessed cognitive functioning including, but not limited to: intelligence (IQ), language, memory, attention, executive function, processing speed and motor abilities.
- Formally assessed behavioural functioning (adaptive or maladaptive) measured by maternal report or structured clinical observations.
- Educational outcomes such as exam results or need for specialist intervention.

**5.6. Search Strategy**

Searches were conducted using MEDLINE (OVID 1946-week 2 2012), EMBASE (OVID 1980-week 15 2012) and PsycINFO (OVID 1946- June 2012). The search strategy was constructed utilising three main concepts or levels: pregnancy variables (concept 1); maternal epilepsy and treatment variables (concept 2) and finally outcome variables (concept 3). Search terms were (1) pregnancy OR prenatal OR fetus OR fetal OR foetal OR in utero OR exposure OR teratogen OR teratology AND (2) epilepsy OR seizure OR anticonvulsant OR antiepileptic OR valproic acid OR sodium valproate OR lamotrigine OR carbamazepine OR phenytoin OR phenobarbital OR phenobarbitone OR oxcarbazepine OR topiramate OR gabapentin OR levetiracetam OR ethosuximide OR zonisamide (3) AND development OR neurodevelopment OR IQ OR intellectual OR neuropsychology OR mental retardation OR memory OR language OR speech disorder OR cognitive OR learning OR attention OR autistic OR
autism OR Aspergers OR hyperactivity OR attention deficit OR dyspraxia OR motor OR educational ability OR behaviour OR behavior.

Reprotox, a teratology specific database, was also searched for each of the AEDs listed above. The reference lists of each Reprotox summary was cross referenced with the search results. Reference lists from review articles over the last five years were also referenced to ensure the validity of the search strategy.

5.7. Review of Studies

Identified studies were downloaded into reference management software and duplicates were removed. The study abstracts were reviewed against the inclusion criteria. A full text review was undertaken if inclusion was not clear from the abstract. The full text of potential relevant articles was reviewed to confirm inclusion. Multiple publications from the same study cohort are common in this area, particularly in the cohorts with longitudinal designs. Publications were linked through dates and sites of recruitment and are described as cohorts rather than by individual publication.

Data was extracted using a data extraction form designed for this systematic review.

5.8. Assessment of Quality

The Newcastle Ottawa Scale (NOS)\(^7\) has previously been utilised by a Cochrane Review into this subject area\(^8\) and is also implemented here, in an adapted form, to highlight methodological quality and limitation. The NOS assesses study quality in three broad areas: selection, comparability and outcome. The complexity of the assessment of outcomes in this area, and the wide range of child outcomes reviewed here, meant that the NOS was not utilised in full but adapted. In addition to the quality areas highlighted by the NOS, the issues of dose and power were felt to be important considerations in this subject area. The principle of dose is an important consideration in teratology research with agents such as AEDs unlikely to display teratogenic potential below a threshold dose\(^9\). Further, the power of studies to detect levels of difference is of paramount importance. Whether a study is adequately powered depends on four aspects: the sample size, the significance level
adopted, the ability of a test to detect an effect of a given size (power) and whether the hypothesis is directional or not\(^9\). Whilst the complexity of power is noted, the guidance by Cohen\(^{10}\) is utilised here to highlight studies which had 80% power to detect at least a large effect size at the commonly used significance level of 0.05. The majority of research in this area looks to identify significant differences across independent means. Therefore, based on Cohen’s guidance a group size of at least 26 would be required to detect a large effect on outcome. Considering these issues, two additional criteria were included when highlighting the quality of indentified study methodologies.

The following criteria were implemented to consider study quality:

1) Selection
   a. Was the cohort truly or somewhat representative of the women with epilepsy in the community (e.g. community recruited or hospital recruited)?
   b. Was a control (or comparison group) recruited from the same cohort?
   c. Did pregnancy related information and maternal health information come from medical records or structured interview with the mother at the time of the pregnancy?
   d. Was the study prospective (outcome was not known at onset of the study)?

2) Comparability
   a. Were the groups comparable on the basis of design (matching) or analysis (adjustment) for key confounding variables (e.g. maternal and child demographics)?

3) Outcome
   a. Were outcomes assessed in a blinded fashion or taken from formal records?

4) Additional criteria
   a. Was the dose of AED and its relationship to outcome investigated?
   b. Did the study include a sample size equal to or larger than 26 participants for the AED type being considered?
Details regarding individual study methodology is displayed in Tables 1-2. A positive response to each of the criteria above resulted in a higher quality study.

5.9. Results

The search strategy identified 3,928 articles. Eligibility checking at the abstract level removed 3,828 with 100 going forward to the full text review. A further 61 studies were removed, as they did not meet the criteria of reporting on specific monotherapy AED groups or for not undertaking formal assessment of neurodevelopment outcome. Five additional publications were identified through cross reference with previous review articles. All five were published prior to 1990. In total 30 studies were indentified across the indentified 44 publications. The methodologies included record linkage studies but the majority (n=28) were observational studies. Fifteen observational studies were truly prospective, seven studies were retrospective observational and six studies utilised retrospective enrolment but with prospective ascertainment of information pertaining to the pregnancy and treatment. This latter study type often included neurodevelopmental data from Pregnancy Registers, designed for the assessment of physical malformations, where neurodevelopmental follow ups were introduced later. No randomised controlled trials were indentified, which is not unexpected given that implementation of randomisation to AED treatment is felt to be unethical in pregnant women. Tables 1 and 2 display the methodological details of each study alongside reported results.

The results pertaining to specific AEDs are discussed below.

5.9.1. Carbamazepine

Carbamazepine had received the largest research attention with regards to neurodevelopmental outcome following prenatal exposure. Neurodevelopmental outcomes had been reported in 22
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>AED group</th>
<th>Control group</th>
<th>Controls Recruited from same source?</th>
<th>Outcome reported</th>
<th>Collection of pregnancy and epilepsy information</th>
<th>Child Age</th>
<th>Adjusted or matched for confounders</th>
<th>Reported outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shapiro et al. 1976 44</td>
<td>Prospective observational</td>
<td>PHT 40, PB 35, 35</td>
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<td>8 mths &amp; 4 years</td>
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<td>PHT 16, PB 7</td>
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<td>N/A</td>
<td>IQ</td>
<td>NR</td>
<td>9, 18, 36 &amp; 48 mths</td>
<td>Y</td>
<td>N</td>
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<td>Prospective longitudinal observational</td>
<td>DPH 13, CBZ 4, VPA 9, PHT 4</td>
<td>No med 12</td>
<td>NR</td>
<td>IQ or DQ</td>
<td>NR</td>
<td>15 mths, 4 &amp; 6 years</td>
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<td>No med 17, Gen pop 105 None</td>
<td>Y</td>
<td>IQ</td>
<td>Medical records</td>
<td>5.5 years</td>
<td>N</td>
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<td>N/A</td>
<td>DQ and IQ</td>
<td>Retrospectively from medical record</td>
<td>6-30 months</td>
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<td>Y</td>
<td>Educational ability</td>
<td>NR</td>
<td>6-13 years</td>
<td>N</td>
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<td>Vanoverloop et al. 1992 ^46</td>
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<td>CBZ 41</td>
<td>Gen pop 41 Gen pop 19</td>
<td>Y</td>
<td>IQ</td>
<td>Records</td>
<td>Adults</td>
<td>N</td>
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<td>Leavitt et al. 1992 ^46</td>
<td>Prospective observational</td>
<td>CBZ unclear PHT unclear, Study 1 PB 33, Study 2 PB 81 CBZ 41, PHT 12, Other 19, Poly 23</td>
<td>Gen pop 41 Gen pop 2000 Gen pop 47 No Med 13, Gen pop 49 None</td>
<td>UC</td>
<td>DQ or IQ</td>
<td>Maternal interview, medical records</td>
<td>1-8 years</td>
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<td>Educational and health needs</td>
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Cross-sectional Studies with Single Publication

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<th>Study</th>
<th>Study type</th>
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<th>Control group</th>
<th>Controls Recruited from same source?</th>
<th>Outcome reported</th>
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<td>Medical records</td>
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<td>N/A</td>
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<td>D’Souza et al. 1990 ^5</td>
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<td>Analysis of dose</td>
<td>Reported outcome</td>
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<tr>
<td>Katz et al. 2003</td>
<td>Retrospective observational</td>
<td>CBZ 56, VPA 56, PHT 22</td>
<td>No med 176</td>
<td>Educational needs</td>
<td>Maternal interview, medical records</td>
<td>0-16 years 12mths</td>
<td>N N N N N N</td>
<td>No mediation found</td>
<td>No association found</td>
</tr>
<tr>
<td>Arulmozhi et al. 2006</td>
<td>Prospective observational</td>
<td>CBZ 63, VPA 56, PHT 22, CBZ 37, VPA 17, PB 15, PHT 12, PHT 18, CBZ 7, VPA 3,</td>
<td>No med 176</td>
<td>Educational needs</td>
<td>Maternal interview, medical records</td>
<td>0-16 years 12mths</td>
<td>N N N N N N</td>
<td>No mediation found</td>
<td>Phenobarbitone was associated with motor development</td>
</tr>
<tr>
<td>Forsberg et al. 2010</td>
<td>Record linkage</td>
<td>PHT 316, CBZ 243,</td>
<td>No med 160, Gen pop 1,307,083</td>
<td>Educational needs</td>
<td>Educational needs</td>
<td>0-16 years</td>
<td>N N N N N N</td>
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<td>No association found</td>
</tr>
<tr>
<td>Cummings et al. 2011</td>
<td>Retrospective observational</td>
<td>VPA 58, CBZ 49, LTG 35</td>
<td>Gen pop 44</td>
<td>DQ</td>
<td>Maternal interview, records</td>
<td>9 mths - 5 years</td>
<td>Y Y Y Y Y N</td>
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<td>No association found</td>
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<tr>
<td>Shallcross et al. 2011</td>
<td>Retrospective observational</td>
<td>LEV 51, VPA 44, CBZ 70, PHT 31</td>
<td>Gen pop 97</td>
<td>DQ</td>
<td>Maternal interview, records</td>
<td>&lt;24 mths 3-6 years</td>
<td>N Y Y Y Y N</td>
<td>No association found</td>
<td>No association found</td>
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<tr>
<td>Råhtman et al. 2012</td>
<td>Retrospective observational</td>
<td>TPM 9</td>
<td>Gen pop 18</td>
<td>IQ, motor, behaviour</td>
<td>Maternal interview</td>
<td>3-6 years</td>
<td>NR N N Y N</td>
<td>No association found</td>
<td>No association found</td>
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</table>

Cross-sectional Studies with Multiple publications

Aberdeen Study Group

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>AED group</th>
<th>Control group</th>
<th>Outcome reported</th>
<th>Collection of pregnancy and epilepsy information</th>
<th>Child Age</th>
<th>Adjusted or matched for confounders</th>
<th>Analysis of dose</th>
<th>Reported outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dean et al. 2002</td>
<td>Retrospective observational</td>
<td>CBZ 69, PB 61, VPA 46, PHT 24</td>
<td>No Med 38</td>
<td>Motor or speech delay</td>
<td>Maternal interview, records</td>
<td>2 days – 39 years</td>
<td>N N N N N N</td>
<td>No association found</td>
<td>Carbamazepine, phenytoin, phenobarbitone and valproate associated with poorer neurodevelopmental outcome</td>
</tr>
<tr>
<td>Rasalam et al. 2005</td>
<td>Retrospective observational</td>
<td>VPA 56, CBZ 80 Poly 51</td>
<td>None N/A</td>
<td>Autism</td>
<td>Maternal interview and records</td>
<td>6-13 years</td>
<td>N N N N N N</td>
<td>No association found</td>
<td>Carbamazepine, phenytoin, phenobarbitone and valproate associated with poorer neurodevelopmental outcome</td>
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Motherisk Study

<table>
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<tr>
<th>Study</th>
<th>Study type</th>
<th>AED group</th>
<th>Control group</th>
<th>Outcome reported</th>
<th>Collection of pregnancy and epilepsy information</th>
<th>Child Age</th>
<th>Adjusted or matched for confounders</th>
<th>Analysis of dose</th>
<th>Reported outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoelnik et al. 1994</td>
<td>Prospective observational</td>
<td>CBZ 36, PHT 34</td>
<td>Matched gen pop 70</td>
<td>DQ or IQ, language</td>
<td>Maternal interview, medical records</td>
<td>18-36 mths</td>
<td>Y N Y N Y N</td>
<td>No association found</td>
<td>Phenytoin was associated with reduced IQ and language ability</td>
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<tr>
<td>Rovet et al. 1995</td>
<td>Prospective observational</td>
<td>CBZ 29, PHT 29</td>
<td>Matched gen pop 58</td>
<td>DQ</td>
<td>Maternal interview, medical records</td>
<td>7-85 mths</td>
<td>Y Yes N Y Y N</td>
<td>No association found</td>
<td>Phenytoin was associated with poorer language ability and IQ</td>
</tr>
<tr>
<td>Study</td>
<td>Study type</td>
<td>AED group^</td>
<td>Control group</td>
<td>Controls Recruited from same source?</td>
<td>Outcome reported</td>
<td>Collection of pregnancy and epilepsy information</td>
<td>Child Age</td>
<td>Reported outcome</td>
<td></td>
</tr>
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<tr>
<td><strong>Finnish Study 1</strong></td>
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<tr>
<td>Eriksson et al. 2005^1</td>
<td>Retrospective *</td>
<td>VPA 13, CBZ 13</td>
<td>No med 13</td>
<td>Y</td>
<td>IQ</td>
<td>Maternal interview, records</td>
<td>7-11 years</td>
<td>Valproate was associated with decreased IQ</td>
<td></td>
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<tr>
<td>Viinkainen et al. 2006^2</td>
<td>Retrospective *</td>
<td>VPA 13, CBZ 13</td>
<td>No med 13</td>
<td>Y</td>
<td>Educational abilities Behaviour</td>
<td>6-11 years</td>
<td>Valproate was associated with increased educational support</td>
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<td></td>
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<tr>
<td><strong>Finnish Study 2</strong></td>
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<tr>
<td>Gaily et al 2004^6</td>
<td>Retrospective *</td>
<td>CBZ 86, VPA 13</td>
<td>Gen pop 141</td>
<td>Y</td>
<td>IQ</td>
<td>Medical records</td>
<td>5-9 years</td>
<td>Valproate was associated with decreased VIQ</td>
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<tr>
<td>Kantola Sorsa et al. 2007^21</td>
<td>Retrospective *</td>
<td>CBZ 76, VPA 8</td>
<td>Gen pop 141</td>
<td>Y</td>
<td>Attention, language, executive, memory</td>
<td>5-11 years</td>
<td>Valproate was associated with decreased VIQ</td>
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<td></td>
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<td><strong>Liverpool and Manchester Neurodevelopment Group Retrospective Study</strong></td>
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<tr>
<td>Adab et al. 2004^22</td>
<td>Retrospective *</td>
<td>VPA 41, CBZ 52</td>
<td>No med 80</td>
<td>Y</td>
<td>IQ</td>
<td>Maternal interview, records</td>
<td>6-16 years</td>
<td>Valproate was associated with decreased VIQ</td>
<td></td>
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<tr>
<td>Vinten et al. 2005^23</td>
<td>Retrospective *</td>
<td>VPA 41, CBZ 52</td>
<td>No med 80</td>
<td>Y</td>
<td>IQ</td>
<td>Maternal interview, records</td>
<td>6-16 years</td>
<td>Valproate was associated with decreased VIQ</td>
<td></td>
</tr>
<tr>
<td>Vinten et al. 2009^24</td>
<td>Retrospective *</td>
<td>VPA 41, CBZ 49</td>
<td>No med 80</td>
<td>Y</td>
<td>Behaviour</td>
<td>Maternal interview, records</td>
<td>6-16 years</td>
<td>Valproate was associated with decreased VIQ</td>
<td></td>
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<tr>
<td><strong>Australian Study</strong></td>
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<tr>
<td>Nadebaum et al. 2010^25</td>
<td>Retrospective *</td>
<td>VPA 23</td>
<td>None</td>
<td>N/A</td>
<td>IQ</td>
<td>Maternal interview, records</td>
<td>6-8 years</td>
<td>Valproate was associated with decreased VIQ</td>
<td></td>
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<tr>
<td>Nadebaum et al. 2011^26</td>
<td>Retrospective *</td>
<td>VPA 23, CBZ 34</td>
<td>None</td>
<td>N/A</td>
<td>Language</td>
<td>Maternal interview, records</td>
<td>6-8 years</td>
<td>Valproate was associated with decreased VIQ</td>
<td></td>
</tr>
</tbody>
</table>

^ through matching or analysis. *numbers completing neuropsychological assessment if different from enrolled. *retrospective recruitment into follow up study but with prospective collection of pregnancy information. AED = antiepileptic drug, VPA = Sodium valproate, PHT = Phenytoin, PB = Phenobarbital, CBZ = carbamazepine, LEV = levetiracetam TPM = topiramate Y= yes, N=No, NR= not reported, N/A= not applicable. IQ= intelligence quotient, DQ= developmental quotient, VIQ= verbal intelligence.

Table 1. Cross-sectional studies reporting on infant outcomes following prenatal exposure to AEDs.
identified studies. Seventeen of these studies failed to find an association between prenatal carbamazepine exposure and reduced neurodevelopmental outcome\textsuperscript{4-6, 11-36}.

Early global neurodevelopmental outcome in infants under three years of age had been found to be superior in infants exposed to carbamazepine when compared to infants exposed to other AEDs \textsuperscript{4, 5, 28, 31} and has frequently been reported to be comparable to control infants \textsuperscript{17, 18, 28-31}. In school aged children, a similar pattern was reported by both longitudinal and cross sectional studies for both cognitive and behavioural functioning \textsuperscript{6, 13, 15, 16, 19-23, 26, 33}. Of the 17 identified studies which failed to demonstrate an association between carbamazepine and neurodevelopment, only three studies met the criteria above for high quality methodology \textsuperscript{4, 5, 28, 31, 33}, two of which report partially overlapping cohorts \textsuperscript{4, 5, 28, 33}.

Four studies found that prenatal exposure to carbamazepine was associated with poorer infant development \textsuperscript{37-41}. Three of these studies utilised formal investigator conducted assessments with children of a wide age range, and due to this used more than one measure to assess outcome. In addition to formally assessed outcomes by researchers, one study identified found an association between carbamazepine exposure and increased prevalence of autistic spectrum disorders\textsuperscript{38}. This was not replicated by a prospective blinded study\textsuperscript{27}. None of these studies demonstrating an association between carbamazepine and neurodevelopmental outcome met the criteria above for high quality methodology (Tables 1&2).

Dose of carbamazepine had been associated with reduced verbal abilities in three year olds in the longitudinal study by the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group \textsuperscript{5}. However, when this cohort was reassessed at 4.5 years of age this association was no longer significant\textsuperscript{33}. Other cohorts have investigated a dose association for carbamazepine but failed to find a significant association with child outcome \textsuperscript{13, 22, 28, 31}. Finally, the study by Ornoy and Cohen\textsuperscript{39} demonstrated an association between carbamazepine exposure and child outcome but failed to demonstrate that dose exerted an effect.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Group n^</th>
<th>Control group</th>
<th>Controls ascertained from same source?</th>
<th>Outcome reported</th>
<th>Collection of pregnancy and epilepsy information</th>
<th>Child age</th>
<th>Adjust for confounders</th>
<th>Analysis of dose</th>
<th>Reported outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide et al 2000</td>
<td>Prospective observational</td>
<td>CBZ 35, PHT 21</td>
<td>Gen pop 81</td>
<td>Y</td>
<td>DQ</td>
<td>Maternal interview, records</td>
<td>9 mths</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Wide et al 2002</td>
<td>Prospective observational</td>
<td>CBZ 35, PHT 15</td>
<td>No med 66</td>
<td>Y</td>
<td>DQ</td>
<td>Maternal interview, records</td>
<td>4.5 years</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Bromley et al 2008</td>
<td>Prospective observational</td>
<td>VPA 64, CBZ 76, LTG 51, Other 14</td>
<td>Gen pop 336</td>
<td>Y</td>
<td>Autistic spectrum disorder DQ</td>
<td>Maternal interview, records</td>
<td>3-6 years</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Bromley et al 2010</td>
<td>Prospective observational</td>
<td>VPA 42, CBZ 48, LTG 34</td>
<td>Gen pop 230</td>
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<td></td>
<td>Maternal interview, records</td>
<td>6-23mths</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>McVeary et al 2007</td>
<td>Retrospective* observational</td>
<td>CBZ 16, LTG 17, VPA 9</td>
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<td>N/A</td>
<td>Originality and fluency IQ</td>
<td>Maternal interview, records</td>
<td>3.5-5.5 years</td>
<td>NR</td>
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<td>Y</td>
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<tr>
<td>Meador et al 2009</td>
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<td>CBZ 73, LTG 84, PHT 48, VPA 53</td>
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<td>N/A</td>
<td></td>
<td>Maternal interview, records</td>
<td>3 years</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Meador et al 2011</td>
<td>Prospective observational</td>
<td>CBZ 59, LTG 70, PHT 39, VPA 43</td>
<td>None</td>
<td>N/A</td>
<td>Verbal and non verbal abilities IQ</td>
<td>Maternal interview, records</td>
<td>3 years</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Meador et al 2012</td>
<td>Prospective observational</td>
<td>CBZ 53, LTG 72, PHT 40, VPA 38</td>
<td>None</td>
<td>N/A</td>
<td>IQ</td>
<td>Maternal interview, records</td>
<td>4.5 years</td>
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<tr>
<td>Cohen et al 2011</td>
<td>Prospective observational</td>
<td>CBZ 61, LTG 76, PHT 40, VPA 46</td>
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<td>N/A</td>
<td>Motor and behaviour</td>
<td>Maternal interview, records</td>
<td>3 years</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Thomas et al 2007</td>
<td>Retrospective* observational</td>
<td>PB 14, PHT 5, CBZ 14, PHT 12</td>
<td>Gen pop 201</td>
<td>NR</td>
<td>IQ, language</td>
<td>Maternal interview, records</td>
<td>6 years</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Thomas et al 2008</td>
<td>Prospective observational</td>
<td>CBZ 101, VPA 71, PB 41, PHT 29</td>
<td>No med 32</td>
<td>Y</td>
<td>DQ</td>
<td>Maternal interview, records</td>
<td>12-24 months</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

^ through matching or analysis. ^numbers completing neuropsychological assessment if different from enrolled. AED = antiepileptic drug, VPA = Sodium valproate, PHT = Phenytoin, PB = Phenobarbital, CBZ= carbamazepine, LEV = levetiracetam TPM = topiramate  Y= yes, N=No, NR= not reported, N/A= not applicable. IQ= intelligence quotient, DQ= developmental quotient, VIQ= verbal intelligence.

Table 2. Longitudinal studies reporting on infant outcomes following prenatal exposure to AEDs.
5.9.2. Ethosuximide

No studies were identified which documented neurodevelopmental outcome in children exposed to ethosuximide prenatally.

5.9.3. Gabapentin

No studies were identified which documented neurodevelopmental outcome in children exposed to gabapentin prenatally.

5.9.4. Lamotrigine

Only four identified cohorts (two of which have a degree of overlap) have investigated neurodevelopmental outcome in children exposed to lamotrigine \[4, 5, 26-28, 33-35, 40\], with only three being of adequate power \[4, 5, 27, 28, 33, 40\]. All three failed to find an association between lamotrigine and poorer neurodevelopmental outcome, with two meeting the criteria for high quality methodology \[4, 27, 28, 33, 42\]. The large study by Meador and colleagues \[4, 5, 33\] included 74 lamotrigine exposed infants and found no association between exposure and IQ or other cognitive abilities, following assessment at 3 and 4.5 years of age. The lack of control group in this study limits interpretations. However, similar findings by Bromley et al \[28\], who used a general population control group, support a lack of association with negative neurodevelopmental outcome.

The related cohorts of Meador et al \[4, 33, 42\] and Bromley et al \[28\] failed to find an association between lamotrigine dose and neurodevelopmental outcome, with the study of Cummings et al \[40\] failing to investigate dose of lamotrigine.

5.9.5. Levetiracetam

Only one study was identified which reported on infants exposed prenatally to levetiracetam \[43\]. Fifty-one infants prenatally exposed to levetiracetam were assessed in terms of their global cognitive development and compared to infants exposed to sodium valproate (n=44) or control infants (n=97) \[43\]. No association was found between levetiracetam exposure and child assessment scores following adjustment for confounding variables. The abilities of children exposed to levetiracetam
prenatally were significantly higher than infants exposed to sodium valproate across certain domains. Recruitment into this study was however retrospective with the control children recruited from a different source. No correlation between dose of levetiracetam and child neurodevelopment was identified in this study$^{43}$.

5.9.6. Phenytoin

In total, 19 published cohorts were identified to have conducted follow up studies in cohorts of infants exposed to phenytoin in utero. Thirteen studies failed to find an association between phenytoin exposure and infant outcome$^{4, 5, 12, 13, 15, 16, 22-24, 31-33, 36, 44-48}$. Of these 14, only two studies however were of high quality$^{4, 5, 31, 33}$. Six cohorts reported an association between phenytoin exposure and child functioning at one or more age points$^{17, 18, 29, 37, 49-51}$. Reduced motor ability$^{29, 51}$ and a reduction in IQ$^{18, 49}$ were the most frequently reported deficits. All the indentified studies which demonstrated an association between phenytoin exposure and child neurodevelopment failed on one or more methodological point (Tables 1 and 2) to meet the criteria for high quality.

The studies of Meador et al.$^{4, 5, 33}$ and Thomas et al.$^{31}$ have investigated the possible association between phenytoin dose and child neurodevelopmental outcome. Both reports failed to demonstrate a significant correlation between dose and child global cognitive ability in infants under the age of 4.5 years.

5.9.7. Phenobarbital

Seven identified studies investigated prenatal exposure to monotherapy phenobarbital and its potential effects on child neurodevelopment. Four studies failed to find an association between phenobarbital exposure and neurodevelopmental outcome$^{31, 36, 44, 48}$. Forty-eight infants exposed to phenobarbital during gestation were assessed between 12-24 months in the Kerala Registry$^{31}$. The infants were less likely to demonstrate below average rates of performance than other AED exposed groups. However, direct comparisons between the phenobarbital treated groups and controls, or
other AED exposed groups were not undertaken and phenobarbital monotherapy was not considered in the regression analysis specifically\textsuperscript{31}, which limited the interpretation of the results.

Three studies found an association between prenatal exposure to phenobarbital and neurodevelopmental outcome \textsuperscript{37, 52, 53}. The study in Scotland by Dean and colleagues\textsuperscript{37} reports that children exposed to phenobarbital were at an increased risk of poorer motor and language development. However, no formal objective assessments were conducted and the authors failed to adjust for confounding influences. In a small number (n=13) of four year olds, van der Pol et al.\textsuperscript{52} found that phenobarbital exposed children had poorer reading and mathematics abilities in comparison to control children, but also failed to adjust for confounding influences. There was evidence from a large record linkage study that the IQ of male adults prenatally exposed to phenobarbital was significantly poorer than control males, following the adjustment for confounding influences\textsuperscript{53}. The study by Reinisch et al\textsuperscript{53} demonstrates an effect of higher dose on poorer adult IQ.

5.9.8. Sodium Valproate

Fifteen cohorts were identified to have investigated neurodevelopmental outcome in children exposed to sodium valproate prenatally. Thirteen studies demonstrated an association between prenatal exposure to sodium valproate and poorer child neurodevelopmental outcome\textsuperscript{4-6, 12, 15, 19-28, 31, 33, 37, 38, 40, 43, 50}. Of these 13, three meet the high quality criteria \textsuperscript{4, 5, 27, 28, 31, 33}, although two have a degree of cohort overlap\textsuperscript{4, 5, 27, 28, 33}. Only two identified studies failed to find that exposure to sodium valproate was associated with poorer infant neurodevelopment\textsuperscript{36, 51}, and the numbers of participants were small.

Motor and language milestone attainment was reported to be delayed in sodium valproate exposed infants\textsuperscript{37}. Longitudinal cohorts have documented poorer global neurodevelopment in young infants with a history of exposure\textsuperscript{4, 5, 28, 31, 33, 40, 43}. At school age, the same infants displayed lower verbal and non-verbal cognitive abilities\textsuperscript{33}, which was consistent with a number of cross sectional studies investigating school aged outcomes\textsuperscript{6, 21-23, 25, 26}. The level of deficit was reported to be between 6-9 IQ
points (adjusted for confounding variables) when compared with other AED exposed groups, with similar levels of deficit reported in comparison to general population controls. Poorer language or verbal functioning was the most commonly reported cognitive deficit, although non-verbal abilities are also reportedly affected as are motor skills. Differences between the abilities of children exposed to sodium valproate and control children or those exposed to other AEDs (e.g. carbamazepine, lamotrigine or levetiracetam) appear to be more than statistical and translated into increased rates of below average IQ; need to access additional educational support and speech therapy services.

In addition to cognitive deficits reported across the identified studies, there were also reports of an association between prenatal exposure to sodium valproate and an increased prevalence of a diagnosis of autistic spectrum disorder. In a retrospective case review, Dean et al and Rasalam et al supported what had been suggested by case reports that children prenatally exposed to sodium valproate were at an increased risk of autistic spectrum disorders (prevalence of 6.5% for monotherapy). This increased prevalence of diagnosis was replicated by the preliminary findings from a large prospective cohort study who also reported a prevalence of around six percent. Both of these studies are however limited by a lack of adjustment for confounding variables.

Prenatal exposure to sodium valproate had also been linked to poorer adaptive and maladaptive behaviours. In the NEAD study cohort, Cohen and colleagues demonstrated that adaptive behavioural functioning was poorer in sodium valproate exposed infants (3 years of age) and that they also displayed an increase in maladaptive behaviours following adjustment for a range of influential variables. Vinten et al demonstrated that the child’s full scale IQ, maternal IQ and exposure to sodium valproate prenatally were independent predictors of poorer behavioural ability, demonstrating that behavioural difficulties are often multi-factorial in terms of causality.

A relationship between the daily dose of sodium valproate and child neurodevelopmental outcome was demonstrated in four indentified cohorts, which was consistent with a wealth
of evidence highlighting a dose relationship for major congenital malformations following sodium valproate exposure\(^2\). Doses over 800mg daily appeared to convey a larger risk to the infant in the identified studies\(^4, 22, 28\).

5.9.9. Topiramate
A single identified study investigated the impact of prenatal exposure to topiramate on child neurodevelopmental outcome. The study by Rihtman et al\(^{54}\) reported on nine topiramate children aged between three and six years of age. The authors made preliminary conclusions that prenatal topiramate exposure may have subtle effects on child neurodevelopment, although the study was not adequately powered to reliably detect levels of difference. Dose of topiramate was not assessed in this study.

5.9.10. Oxcarbazepine
No studies were identified which documented neurodevelopmental outcome in children exposed to oxcarbazepine prenatally.

5.9.11. Zonisamide
No studies were identified which documented neurodevelopmental outcome in children exposed to zonisamide prenatally.

5.10. Discussion
There is little evidence that prenatal carbamazepine exposure is associated with an increased risk to infant neurodevelopment across research completed with both infants and school aged children. There is limited research into a potential relationship between higher doses of carbamazepine and child neurodevelopmental outcome. The majority of identified studies investigating prenatal exposure to phenytoin failed to find an association between exposure and child neurodevelopmental outcome, although findings were limited by a lack of consideration of dose, and in most cases studies were not of high quality which limits the conclusions that can be drawn.
For phenobarbital, no reliable evidence exists to confirm that the risk phenobarbital in monotherapy poses to the physical development of the child is transferred into a risk to neurodevelopmental outcome. The largest, and the only, study to report an affect of dose of phenobarbital reports an association with poorer adult IQ\textsuperscript{53} highlighting that further research is needed.

Evidence regarding child neurodevelopmental outcome following prenatal exposure to lamotrigine was limited to three adequately powered studies (two of which have a degree of cohort overlap). These were consistent in their finding that prenatal exposure to lamotrigine is not associated with an increased risk to neurodevelopment in young children\textsuperscript{4, 5, 27, 28, 33, 40}. Despite a reported increase of major congenital malformations at higher doses, lamotrigine is reported to convey one of the lowest risks within the AEDs\textsuperscript{5}. The prescription of lamotrigine to women of child bearing age has rapidly increased over the last decade, due to its indication for idiopathic generalised epilepsy and the risks reported for sodium valproate\textsuperscript{55}. Despite lower risk of infant abnormalities, reports of decreased serum levels during later pregnancy in some women\textsuperscript{56} and a failure to reach the effective levels of seizure control demonstrated by other AEDs\textsuperscript{57}, means that lamotrigine may fail to offer a panacea for women in their child bearing years\textsuperscript{58}.

There is a growing body of evidence highlighting that prenatal exposure to sodium valproate is associated with a range of poorer neurodevelopmental outcomes. Daily dose of sodium valproate >800mg daily was found by a number of identified studies to be associated with reduced neurodevelopmental outcome\textsuperscript{4,5,22,23,25,26,28,33}. Reduced performance on formal neurodevelopmental assessments in infancy and in school aged children demonstrate that deficits are unlikely to be transient\textsuperscript{53}. The reported deficits following prenatal exposure appeared to be global, particularly in younger children\textsuperscript{4, 28, 33, 40}, with a suggestion that verbal mediated abilities are differentially effected\textsuperscript{5}. The increased prevalence of educational support, speech and language therapy and diagnoses of autistic spectrum disorders reported, highlight that these deficits are not merely statistical, but transfer into real life deficits. The studies of Bromley et al\textsuperscript{28} and Cummings et al\textsuperscript{40}
demonstrate that 23-29% of infants fall below the average range following prenatal exposure to sodium valproate and highlight the need for surveillance of exposed infants during childhood to facilitate early intervention.

Single studies were identified investigating prenatal exposure to levetiracetam monotherapy and topiramate monotherapy. No association was found between prenatal levetiracetam exposure and neurodevelopmental outcome and levetiracetam exposed infants demonstrated improved outcomes in a direct comparison to sodium valproate exposed infants. Replication in older aged cohorts of levetiracetam exposed children is required before conclusions can be drawn. Rihtman et al reported that prenatal topiramate exposure was associated with reduced cognitive performance, however the group only contained nine topiramate exposed children and extension is required.

No studies were identified which investigated monotherapy exposure to oxcarbazepine, gabapentin, zonisamide or ethosuximide and child neurodevelopmental outcome, a question that needs to be addressed in future research cohorts, as these AEDs become more frequently prescribed.

Research into the neurodevelopmental outcomes of infants exposed to AEDs has increased since the turn of the century. Research methodologies are becoming more refined with a shift from single centre retrospective recruitment towards a higher frequency of multisite prospective studies with either cross sectional or longitudinal assessments. Alterations in prescribing practices over time and differences in utilisation of AED types across countries leads challenges in comparing studies across cohorts. The adaption of pregnancy registers to conduct longer term outcome studies allows for the currently less commonly prescribed medications to be investigated, reducing the latency between monotherapy licence and risk information, but often instigate retrospective recruitment of mother-child pairs.

This review has a number of strengths including: an a priori inclusion criteria; the systematic searches; cross validation of the search strategy and systematic extraction of findings. The adaption
of the NOS to highlight pertinent methodological issues enhanced the reporting of identified studies and sought to highlight the reliable sources of evidence. Further, this review highlights that there are differential outcomes in terms of the neurodevelopment of children exposed prenatally and justifies the a priori decision to limit inclusion to studies that reported infants exposed to specific monotherapy AEDs.

Limitations of this review include the exclusion of studies which report outcomes pertaining to children exposed to polytherapy prenatally. However, combination of different exposure types is likely to introduce bias leading to conflicting outcomes across cohorts. The assessment for eligibility for this review would have been enhanced if verified by a second independent reviewer, although cross referencing findings against the Reprotox database and recent review articles, sought to validate the search strategy and the eligibility decisions. Comparing groups of polytherapy exposed infants across cohorts is difficult due to their likely differential composition. It is of note that many report poorer outcomes following polytherapy treatment\textsuperscript{22}, \textsuperscript{31}, although recently the influence of sodium valproate within the combination treatments has been suggested as causal in this effect\textsuperscript{25}.

\textbf{5.11. Future Research}

Further research is required to delineate the risks higher doses pose to neurodevelopment across AED types. Investigations into the potential risks associated with the increasingly prescribed newer AEDs are urgently required to ensure that females and their treating physicians have comprehensive information to allow for informed decisions about the risks and benefits of treatment. Further, the majority of research to date is limited by its focus on global cognitive/ neurodevelopmental functioning and future studies should consider that specific cognitive functions may be differentially affected. A comprehensive understanding of specific cognitive impairments, if present, would facilitate the targeting of interventions. Limited investigation into the neurodevelopmental outcomes of children diagnosed with a fetal anticonvulsant syndrome exist. Fetal anticonvulsant syndromes have been described in the literature for valproate (Fetal valproate syndrome),
 carbamazepine (Fetal carbamazepine syndrome), as well as phenytoin (Fetal hydantion syndrome) and phenobarbital (Fetal phenobarbital syndrome)\textsuperscript{59-61}. Such syndromes are diagnosed predominantly on the physical presentation. Research is required to delineate to what extent infants with the physical sequelae of prenatal AED exposure also experience neurodevelopmental deficits and whether the physical symptoms are indicators of later cognitive difficulties.

Adequately powered, prospectively recruited AED and control groups, with blinded longitudinal assessments into later childhood and analysed adjusting for confounding variables are required to provide the comprehensive information to women requiring AED treatment. The importance of dose should be given priority in future research. Record linkage and case-control methodologies should be utilised to investigate rarer outcomes, such as autistic spectrum disorders, where larger cohorts are required.

5.12. **Practical Applications**

There are a number of practical implications for the conclusions of this review. Women who require treatment with AEDs during their child bearing years should be counselled about the potential risks treatment options pose to the longer term health and neurodevelopment of the future child. Girls and women of childbearing potential should be provided with information at each opportunity about the risks and benefits of AED treatment. Further, the superiority of sodium valproate in the treatment of idiopathic generalised epilepsies means that paediatric health professionals need to be vigilant for infants who have been exposed to sodium valproate, provide regular monitoring and intervene early.

5.13. **References**


54. Rihtman T PS, Ornoy A. Preliminary findings of the developmental effects of in utero exposure to topiramate. Reproductive Toxicology 2012;In Press.


6.1. Abstract
Objective: To investigate the effects of prenatal exposure to monotherapy levetiracetam and sodium valproate on child cognitive functioning.

Methods: Children exposed to monotherapy levetiracetam (n=37), sodium valproate (n=40) and a group of children born to women who had an untreated epilepsy (n=43) were enrolled from the UK Epilepsy and Pregnancy Register. Assessor blinded neuropsychological assessments were conducted utilising standardised measures between five to nine years of age. Information was collected on demographic and health variables and adjusted for utilising multiple regression analyses.

Results: Prenatal exposure to levetiracetam was not found to be associated with reduced cognitive performance within the adjusted model across all assessed domains. Significant dose effects were demonstrated for prenatal sodium valproate exposure across child intelligence and language functioning. Higher doses of sodium valproate (>800mg daily) were associated with a significantly increased risk of a full scale IQ below the average range (57.6%).

Conclusions: Prenatal exposure to levetiracetam did not convey a risk to later child cognitive functioning. Replication and extension of this finding is required. Consistent with findings from other cohorts prenatal exposure to sodium valproate was associated with reduced cognitive functioning in a dose dependent manner. Women should be counselled specifically on the risks and benefits associated with antiepileptic drug treatment, including the potential risks to the cognitive functioning of the child.
6.2. Introduction
There is increasing concern about the use of sodium valproate in women of child bearing age due to its teratogenic risks\(^1\). An increased risk of major congenital malformations is documented, with the risk being as high as 24% for daily doses exceeding 1500mg\(^2\). Less research has been undertaken into the potential neurodevelopmental consequences of prenatal exposure to sodium valproate, but a dose effect is suggested\(^3\)-\(^7\). In recent years, there has been a decrease in the use of sodium valproate in women due to a growing concern about teratogenicity\(^8\). This has been paralleled by an increase in prescriptions of newer antiepileptic drugs (AEDs) including levetiracetam\(^8\).

There is limited research into the safety of prenatal exposure to levetiracetam. There is evidence that levetiracetam exposure is not an independent risk factor for an increase in major congenital malformations\(^9\), \(^10\). Previous research from our group demonstrated that prenatal exposure to levetiracetam is not associated with poorer neurodevelopmental outcome under 24 months of age\(^11\). Neurodevelopment is a dynamic process throughout childhood, with the complexity of cognitive abilities increasing and new skills emerging\(^12\). Assessment during infancy is therefore unlikely to produce reliable and stable conclusions in terms of the longer term neurodevelopmental outcome. To date, no study has reported on the school aged abilities of children prenatally exposed to levetiracetam. This study aims to delineate the cognitive abilities of school aged children exposed prenatally to monotherapy levetiracetam or sodium valproate in comparison to children born to women with untreated epilepsy.

6.3. Methods
The study design was a retrospective cross-sectional observational study. Mother-infant pairs were identified from the UK Epilepsy and Pregnancy Register, a national pregnancy register with the primary aim to investigate the prevalence of major congenital malformations following exposure to AEDs. Detailed information about the register and its methodology have been reported previously\(^13\).
Women with epilepsy are enrolled onto the register through self referral or through referral by their health professional. Recruitment occurs within the first or early second trimester, facilitating prospective documentation about the health and well being of mother and the pregnancy. At birth, or within three months, details about the birth and health of the child are reported to the register by local health care services.

Mother-infant pairs were eligible for inclusion in this neurodevelopment follow up study: if there had been a live birth between September 2004 and May 2007; they were taking either levetiracetam or sodium valproate monotherapy or they were untreated during their pregnancy and the infant was not diagnosed at birth with a serious health condition. There were approximately three times more eligible participants for the sodium valproate exposed group and the no medication group, than for the levetiracetam exposed group and therefore each third mother identified was included in the recruitment list for these two groups. Recruitment letters and information sheets were sent to those identified (Appendix 3). Follow-up letters were issued after 2-4 weeks if no response had been received. Addresses of participants were checked against the General Practitioner Database for England. No address check could be undertaken for participants residing in other areas of the UK. Mother-infant pairs who returned a positive response were formally enrolled into the study, informed consent taken and a mutually convenient appointment arranged for the assessment of the child.

Pregnancy details and details about the mother’s epilepsy, including AED dose and seizure information, were collected from the prospective pregnancy records. Details of the mother and father’s educational history and employment were collected through a semi-structured interview. Alcohol, nicotine and concomitant medication use for the second and third trimesters, which is not routinely collected by the register, was collected through maternal report retrospectively. Maternal intellectual functioning was measured with the Test of Non-verbal Intelligence (TONI)\textsuperscript{14}. 

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Sixty percent of children exposed to levetiracetam and 20% of children exposed to sodium valproate enrolled into this study were previously assessed at three years of age as part of an ongoing study (unpublished), but were not part of the infant cohort reported by Shallcross et al.\textsuperscript{11}

Neuropsychological assessments were conducted by author R.B or one of two trained research assistants either in the child’s home or their school. Assessors were blinded to the group the child belonged to. The assessment battery included the Wechsler Intelligence Scale for Children – IV edition (WISC-IV)\textsuperscript{15} or the Wechsler Preschool and Primary Intelligence Scale (WPPSI-III)\textsuperscript{16} if the child was five years of age. The outcome measures were full scale intelligence quotient (FSIQ), verbal intelligence quotient (VIQ), non-verbal intelligence quotient (PIQ) and processing speed. Analysis of these outcomes adjusted for test version (WISC-IV or WPPSI-III). Domain specific cognitive abilities were assessed utilising subtests of the NEPSY, A Developmental Neuropsychological Assessment, second edition (NEPSY-II)\textsuperscript{17} and the Clinical Evaluation of Language Fundamentals-IV edition (CELF)\textsuperscript{18}. Index scores were created for the outcome measures from the NEPSY-II by taking an average across administered subtests using the NEPSY-II pre-determined cognitive domains. The attention and executive skills domain comprised of the auditory attention combined, inhibition and design fluency scores. The memory index comprised of scores from the subtests memory for faces, designs, names and narrative memory cued and free recall. Finally, scores from the CELF-IVs subtests comprehension of instructions, formulated sentences and expressive naming were averaged to create the language index. Assessments were double scored to minimise errors and scores were entered onto a database which was double checked. Feedback was provided to the family on the outcome of the assessments, and where required referrals to specialist services were made.

The normal distribution of each outcome measure was assessed through exploration statistics and graphical representation. The primary analysis tested the hypothesis that prenatal exposure to sodium valproate but not levetiracetam would be associated with reduced child cognitive functioning. This primary analysis utilised multiple regression models with adjustment for covariates.
(parental and child), with the no medication group as the reference group. An a priori hypothesis was generated, based on previous work in this area, that maternal IQ, socioeconomic status and dose of AED would be influential variables\textsuperscript{4, 19} and therefore were entered into the model through forced entry. Dose of AED was transformed into a standardised dose based on specific AED dose range \((100 \times (\text{observed dose} - \text{minimum dose})/ \text{range of dose})\). Graphical representation of the dose correlations were created for each AED treatment when significant results were found for AED dose within the regression models.

Other potential covariates were entered into the model in a stepwise fashion with significance values less than 0.05 being retained and those above 0.1 being removed. Confounding variables investigated for inclusion were: child age at assessment; assessment used (for IQ outcomes); gender; gestational age at birth; maternal age; maternal epilepsy type; exposure to seizures; exposure to alcohol; exposure to nicotine and paternal education level. Relationships between covariates were inspected for multicolinearity, which led to the removal of birth weight due to its strong correlation with gestational age. The final regression models differed by the outcome measured, resulting in different covariate models. The data was analysed using SPSS version 20.0 by author R.B, employing a Bonferroni correction to the analysis of the outcome variables \((0.05/10 = 0.005)\) to minimise type one error.

Approval was obtained from the North West Regional Ethics Committee, UK (Appendix 4). All participants provided informed written consent.

**6.4. Results**

Three hundred and fifty five mother-infant pairs were eligible for recruitment. The positive response rate overall was 36%, but this differed significantly between the no medication controls (35.4%), the sodium valproate group (28.9%) and the levetiracetam group (72.2%) \((\chi^2(2)=34.28, \ p<.001)\). No response from the recruitment letter was the most common reason for a lack of enrolment (62.1%).
Only 17.2% of invitations to participate resulted in a decline. No significant differences were found between those who participated and those who did not in terms of maternal age, gestational age at birth and by child gender. Following recruitment, five children were lost to follow up (levetiracetam exposed) and a two children required exclusion: one due to a diagnosis of epilepsy and the other attention deficit hyperactivity disorder respectively (both sodium valproate exposed).

One hundred and twenty mother-child pairs completed the study. Table 1 displays the demographic information for each group. The age of the mothers at the child’s birth and gestational age of the child at birth were comparable across the groups. Experience of seizures generally or seizures of a convulsive nature did not differ across the groups and neither did socioeconomic status based on paternal employment. Significant differences were present between the groups in terms of the age at which the child was assessed ($F_{(2,114)}=2.38, p<0.001$) and the IQ of the mother ($F_{(2,116)}=3.33, p=0.039$). Significant differences were also demonstrated across the groups in terms of maternal epilepsy type ($X^2_{(4)}=12.88, p<.012$) (Table 1).

Multiple linear regression found that dose of levetiracetam was not associated with a significant change in child performance across any of the neuropsychological measures administered, following adjustment for confounders (Table 2). In contrast, dose of sodium valproate was associated with a significant reduction on VIQ ($p<0.001$), PIQ ($p=0.001$), FSIQ ($p<0.001$) and language ability ($p=0.001$), with large effect sizes noted (Table 2).
Table 1. Cohort demographic information and mean scores by AED group.

<table>
<thead>
<tr>
<th>Parental Demographics</th>
<th>Levetiracetam (n=37)</th>
<th>No Medication (n=43)</th>
<th>Sodium valproate (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (range, mg daily)</td>
<td>500-4000</td>
<td>-</td>
<td>400-2000</td>
</tr>
<tr>
<td>Enrolled</td>
<td>72.2%</td>
<td>35.4%</td>
<td>28.9%</td>
</tr>
<tr>
<td>Maternal age (years, M, CI)</td>
<td>29.8 (28.1-31.6)</td>
<td>30.5 (28.4-32.7)</td>
<td>32.5 (31.1-33.9)</td>
</tr>
<tr>
<td>Maternal IQ (M, CI)</td>
<td>91.4 (87.0-95.7)</td>
<td>89.8 (86.2-93.4)</td>
<td>97.1 (92.1-102.1)</td>
</tr>
<tr>
<td>SES(^a) (% professional employment)</td>
<td>56.2%</td>
<td>33.3%</td>
<td>55.3%</td>
</tr>
<tr>
<td>Father Education (% degree)</td>
<td>35.3%</td>
<td>25.7%</td>
<td>35.1%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>14.7%</td>
<td>20.5%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Nicotine</td>
<td>14.7%</td>
<td>28.2%</td>
<td>17.9%</td>
</tr>
<tr>
<td>Epilepsy Type (%)</td>
<td>IGE 66.7%</td>
<td>50.0%</td>
<td>80.0%</td>
</tr>
<tr>
<td></td>
<td>FOC 33.3%</td>
<td>40.5%</td>
<td>20.0%</td>
</tr>
<tr>
<td></td>
<td>UC 0%</td>
<td>9.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Seizures (%)</td>
<td>any 41.7%</td>
<td>41.5%</td>
<td>27.5%</td>
</tr>
<tr>
<td></td>
<td>CVS 26.0%</td>
<td>24.4%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Child Variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child Age (months, M, CI)</td>
<td>72.8 (70.7-75.9)</td>
<td>85.0 (79.9-90.2)</td>
<td>86.7 (79.3-94.1)</td>
</tr>
<tr>
<td>Gestational Age (weeks, M, CI)</td>
<td>39.5</td>
<td>38.7</td>
<td>38.8</td>
</tr>
<tr>
<td></td>
<td>(38.9-40.1)</td>
<td>(37.8-39.5)</td>
<td>(37.8-39.6)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>62.2%</td>
<td>55.8%</td>
<td>55.0%</td>
</tr>
<tr>
<td>Mean Scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ(^b) (M, CI)</td>
<td>97.4 (93.1-101.7)</td>
<td>100.5 (96.4-104.7)</td>
<td>95.8 (91.0-100.6)</td>
</tr>
<tr>
<td>VIQ(^b) (M, CI)</td>
<td>99.5 (96.0-103.0)</td>
<td>103 (98.9-106.8)</td>
<td>93.5 (88.4-98.6)</td>
</tr>
<tr>
<td>PIQ(^b) (M, CI)</td>
<td>98.0 (93.7-102.4)</td>
<td>100.8 (96.1-105.4)</td>
<td>102.0 (97.1-106.9)</td>
</tr>
<tr>
<td>PS(^b) (M, CI)</td>
<td>95.0 (90.8-99.2)</td>
<td>97.8 (93.8-101.9)</td>
<td>94.3 (90.3-98.3)</td>
</tr>
<tr>
<td>Attention &amp; Executive Index (M, CI)</td>
<td>9.3 (8.7-9.9)</td>
<td>8.7 (8.0-9.4)</td>
<td>9.3 (8.6-9.9)</td>
</tr>
<tr>
<td>Memory (M, CI)</td>
<td>9.9 (9.2-10.7)</td>
<td>10.3 (9.7-10.9)</td>
<td>10.2 (9.6-10.8)</td>
</tr>
<tr>
<td>Language (M, CI)</td>
<td>9.1 (8.3-9.9)</td>
<td>9.7 (9.0-10.4)</td>
<td>8.9 (8.0-9.7)</td>
</tr>
</tbody>
</table>

Values rounded up to the nearest decimal. M = mean, CI = confidence interval, SES = socioeconomic status, IGE = idiopathic generalised epilepsy, FOC = focal epilepsy, UC = unclassified, CVS= convulsive.

\(^a\) Socioeconomic status measured by paternal employment (6 cases maternal employment as father unknown).

\(^b\) Adjustment for test used (WISC-IV or WPPSI-III).
Table 2. Linear Regression coefficients for AED groups and covariates.

<table>
<thead>
<tr>
<th></th>
<th>FSIQ</th>
<th>VIQ</th>
<th>PIQ</th>
<th>Processing Speed</th>
<th>Attention &amp; Executive</th>
<th>Memory</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β Coef. (SE)</td>
<td>S β</td>
<td>P*</td>
<td>β Coef. (SE)</td>
<td>S β</td>
<td>P*</td>
<td>β Coef. (SE)</td>
</tr>
<tr>
<td>No Medication (n=43)</td>
<td></td>
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<td></td>
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<tr>
<td>AED</td>
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<tr>
<td>LEV (n=37)</td>
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<tr>
<td></td>
<td>-0.095 (.056)</td>
<td>-0.147</td>
<td>.093</td>
<td>-0.076 (.055)</td>
<td>-0.116</td>
<td>.167</td>
<td>-0.100 (.062)</td>
</tr>
<tr>
<td>VPA (n=40)</td>
<td></td>
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<tr>
<td></td>
<td>-0.272 (.049)</td>
<td>-0.471</td>
<td>&lt;.001</td>
<td>-0.346 (.048)</td>
<td>-0.588</td>
<td>&lt;.001</td>
<td>-0.193 (.055)</td>
</tr>
<tr>
<td>Entered</td>
<td></td>
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<tr>
<td>Maternal IQ a</td>
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</tr>
<tr>
<td></td>
<td>0.277 (.090)</td>
<td>0.271</td>
<td>.003</td>
<td>0.172 (.086)</td>
<td>0.166</td>
<td>.052</td>
<td>0.304 (.100)</td>
</tr>
<tr>
<td>SES b</td>
<td>4.400 (2.479)</td>
<td>0.157</td>
<td>0.079</td>
<td>4.640 (2.425)</td>
<td>0.163</td>
<td>.059</td>
<td>3.446 (2.757)</td>
</tr>
<tr>
<td>Child age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.090 (0.088)</td>
<td>0.087</td>
<td>0.305</td>
<td>-0.055 (0.086)</td>
<td>-0.052</td>
<td>.527</td>
<td>-0.012 (.098)</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.575 (2.210)</td>
<td>0.227</td>
<td>0.007</td>
<td>0.411 (2.025)</td>
<td>0.160</td>
<td>.048</td>
<td>0.673 (2.330)</td>
</tr>
<tr>
<td>Stepwise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>4.545 (2.260)</td>
<td>0.160</td>
<td>0.047</td>
<td>5.864 (2.211)</td>
<td>0.203</td>
<td>.009</td>
<td>0.000</td>
</tr>
<tr>
<td>Alcohol c</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Missing covariate variables occurred in 11 cases. *Only p-values equal to 0.005 or less were considered to be statistically significant due to multiple comparisons (p = 0.05/10 = 0.005). Significant variables are highlighted.

Covariates entered but not retained due to p > .1 were gestational age at birth, epilepsy type, seizure exposure, convulsive seizure, paternal education and exposure to nicotine.

a Measured by Test of Non-verbal Ability (TONI)
b Socioeconomic status measured by paternal profession (in 6 cases maternal profession used as father unknown)
c Defined as report of any alcohol consumed.

R² were .379 for VIQ, .372 for FSIQ, .262 for PIQ and .090 for processing speed. For the language index R² was .367, for attention and executive it was .129 and for the memory index it was .271.
The dose effect of sodium valproate on child VIQ, PIQ, FSIQ and the language index is displayed in Figure 1, highlighting the reduction in child score following doses of sodium valproate above the mean (adjusted for covariates). The distribution of FSIQ scores in Figure 2 demonstrates the implications of the dose effect. Fifty seven percent of children exposed to higher doses of sodium valproate fell below the average range (standard score less than 90), which was higher than children exposed to lower doses of sodium valproate (OR 5.84 95% CI 1.4-24.1, p=0.03), no medication (OR 7.01 95% CI 2.1-23.9, p=0.001) and the levetiracetam exposed group (OR 3.7 95% CI 1.2-11.9, p=0.02).

In terms of the covariates, maternal IQ was significantly associated with the child performance on the FSIQ (p=0.003), PIQ (p=0.003), memory (p=0.004) and the language index (p<0.001), but fell above the corrected significance level on the other outcome measures. Standardised Beta values demonstrated that dose of sodium valproate was a stronger predictor of child performance on FSIQ, VIQ and PIQ than maternal IQ (Table 2). Of clinical interest, the maternal epilepsy variables of epilepsy type, exposure to seizures or exposure to convulsive seizures were not significantly associated with child performance across the outcome variables.
Figure 1. Partial regression plots for VIQ, PIQ, FSIQ and the Language index by standardised sodium valproate dose.

Adjusted for maternal IQ, child age, socioeconomic status, gender and maternal age.
Figure 2. FSIQ score classification for AED groups alongside low dose and high dose sodium valproate.

6.5. Discussion
This retrospective, cross-sectional study demonstrates that there was no significant risk to cognitive functioning during middle childhood for children exposed to levetiracetam in utero. No relationship was found between dose of levetiracetam and child outcome across child intelligence, language, memory or attentional and executive abilities. This study was adequately powered to detect a medium effect size (.15) with 89% power (GPower 3.1.3). A lack of an association is consistent with our group’s earlier finding pertaining to levetiracetam in infants under 24 months of age. A negative finding also supports the work reported from preclinical studies where levetiracetam is reported, even at high doses, to be exempt from the increased neuronal apoptosis seen following administration of other AEDs in rodents. Levetiracetam is reportedly becoming an encouraging alternative to sodium valproate in the treatment of generalised epilepsy and has been reported to
be without significant teratogenic potential in relation to major congenital malformations\textsuperscript{9, 10}. Further support to its safety is presented here, but caution is required. Although results are encouraging, replication is required with larger cohorts to rule out milder levels of effect on child cognitive ability.

In relation to sodium valproate, the findings of this study are consistent with that of other cohorts in the demonstration that prenatal exposure to sodium valproate is associated with significant risks to child cognitive ability in a dose dependent manner\textsuperscript{3, 4, 19}. Prenatal exposure to sodium valproate appears to have a significant effect on VIQ, PIQ, FSIQ and language skills, which is consistent with the results of others\textsuperscript{3,7,19}. Doses over 800mg daily carried an increased risk, with 57.9% falling below the average range for their FSIQ, which was higher than the other groups. Reductions in FSIQ are reported to carry long term implications for the educational and later occupational attainment of the child\textsuperscript{23}.

Verbal abilities are reportedly differentially affected following sodium valproate exposure\textsuperscript{24}, which is replicated here, with VIQ demonstrating the largest effect size. Such a pattern has been hypothesized to be linked to disruptions in lateralisation of skills\textsuperscript{24}. However the age at which the children are assessed and the corresponding complexity of cognitive functioning expected at that age may also account, at least in part, for the strong association with verbal abilities above that of other skills.

No significant association between dose of sodium valproate and memory ability was found in the adjusted model, which may represent a type two error due to the strict Bonferroni correction of the significance level, as the value was $p=0.009$ with a medium effect size reported. Further research is required to clarify this as little research has addressed memory functioning following prenatal exposure to sodium valproate. The attention and executive skills of children exposed to sodium valproate were also found to not be associated with prenatal exposure. Due to the age of the children this should be viewed with caution. Executive and attentional abilities mature over later
childhood and adolescence and therefore the non-significant findings reported here may not be a reliable or stable indicator of longer term outcome.

A number of recent guidelines have highlighted that where possible sodium valproate should be avoided as a first line treatment in women of childbearing age and if required, monotherapy treatment at the lowest possible dose should be the aim. Such advice is based primarily on findings pertaining to major congenital malformations. The results presented here for neurodevelopment support such advice. Women should be provided with information both in terms of the physical risks to the potential child as well as the potential risks to that child’s longer term neurodevelopment, allowing her to make an informed decision about her treatment.

No significant influence of maternal epilepsy type or exposure to seizures was found to be associated with child cognitive functioning, supporting previous results. Maternal IQ was found to be influential on child functioning but the standardised beta values across child IQ scores were higher for dose of sodium valproate than for maternal IQ (Table 3), which replicates the findings of Meador and colleagues (2009). A major strength of this study is its utilisation of a national register to reduce the latency between AED monotherapy licence and teratology risk information which can be provided to women. Sodium valproate for example was licensed for monotherapy use in the 1970s across Europe and the USA but the consequences it poses for the cognitive functioning of the child are only now being delineated. Such a delay in information undermines clinical risk-benefit decision making. The inclusion of sodium valproate alongside an alternative treatment for idiopathic generalised epilepsy allows data pertinent for clinical decision making to be viewed from a simultaneously recruited cohort and increases the clinical application of this study. Further methodological strengths of this study include: its prospective collection of pregnancy details which limits recall bias; the utilisation of blinded formal neuropsychological assessment; the collection and control for a number of influential covariates, follow up of the children at school age and adequate power to
detect large effect sizes. Finally, the consideration of AED dose is important considering the principles of teratology\textsuperscript{26} and the lack of such an effect in this cohort for levetiracetam is reassuring.

There are a number of limitations to the present study. Firstly, the low rate of recruitment highlights the challenges of adjusting Pregnancy Registers designed to collect congenital malformation data for investigation of neurodevelopmental outcomes. The recruitment rate, although low, is consistent with the challenges experienced by others\textsuperscript{27}. The higher rate of participation in the levetiracetam group is felt to be multi-faceted with 60% of this group being assessed as part of an earlier study at three years of age (unpublished), increasing the likelihood that a more current address was on file. A further influential factor on recruitment rates may have been the explanation on the participant information sheet. The information sheet outlined that the study aimed to investigate levetiracetam, whilst those on no medication and those on sodium valproate were acting as comparison groups. Higher recruitment/retention rates are reported for longitudinal studies with multiple follow ups across the early childhood years\textsuperscript{5,19}. Such methodologies are costly in terms of finance and time, and may not facilitate collection of data for less frequently prescribed AEDs. Secondly, the lack of information about AED dose alterations and seizure exposure in the second and third trimesters means that we are unable to comment on the implications these two factors may present to the cognitive functioning of the child. Seizure exposure prior to register enrolment (typically first trimester or early second) was not associated with reduced cognitive functioning. Thirdly, the retrospective nature of the invitation to participate may have influenced the nature of the cohort. The three groups were recruited and assessed in the same manner and therefore it is not felt that the differential outcomes for levetiracetam, sodium valproate and no medications are simply due to retrospective recruitment bias. A fourth consideration is the age of these children at assessment. In middle childhood, cognitive development is still dynamic and it should be considered that, as this cohort further develops and the age appropriate cognitive skills become more complex, differential results may be seen. Future research should aim to follow up levetiracetam and sodium valproate
exposed children in later childhood and into adolescence, to provide reliable information to aid clinical decision making.

6.6. Conclusion
Prenatal exposure to levetiracetam is not found to be significantly associated with reduced cognitive functioning in childhood. Prenatal exposure to sodium valproate carries a dose dependent risk, which may carry lifelong implications for the child. If effective seizure control can be maintained on levetiracetam, this may be a more preferential treatment for women of childbearing age. Due to the dynamic nature of neurodevelopment over the childhood and adolescent years, it is unlikely that the results reported here represent a stable measure of ability or deficit and longer-term follow up is required.

6.7. References


7. Chapter 3. Critical Reflection Chapter

7.1. Overview of this Project

This thesis aimed to investigate the cognitive functioning of children prenatally exposed to antiepileptic drugs (AEDs). This aim was executed in two parts: a systematic review of published literature and a research project which investigated the cognitive functioning of children prenatally exposed to levetiracetam or sodium valproate.

Both the first and second parts of this thesis conclude that prenatal exposure to sodium valproate is associated with an increased prevalence of poorer cognitive functioning. Levels of deficit were statistically significant and are reported here and in the wider literature, to be to a level of clinical significance. Limited research has been undertaken into the longer term consequences of prenatal exposure to levetiracetam and the results reported in Chapter 2 replicated the results previously demonstrated in infants under 24 months of age (Shallcross, Bromley, Irwin, Bonnett, Morrow, Baker, et al., 2011).

This chapter critically appraises the work undertaken in Chapters 1 and 2, highlights the ethical and professional issues raised and discusses the implications for clinical practice. Finally, the need for future research is outlined.

7.2. Context of this Research

Epilepsy is a chronic condition and in most cases will require continued treatment during pregnancy to lower the risk of seizure reoccurrence (Pennell, 2008). It is estimated that 0.3-0.4% of children are born to women who have epilepsy (Tomson & Battino, 2009). Since the 1960s and early 1970s there has been evidence that AEDs cross the human placenta (Pruitt & Dayton, 1971) and may be associated with an increased risk of neonatal withdrawal and major congenital malformations (Meadow, 1968). Commonly reported major congenital malformations include spina bifida, heart
defects, limb reductions, cleft lip and cleft palate (Jentink, Loane, Dolk et al., 2010). Since this time the methodological approach and international research interest has evolved. Case reports (Barr, Poznanski & Schmickel, 1974), led to single site studies (Koch, Jager-Roman, Losche, Nau, Rating & Helge, 1996) which in turn led to multicentre studies (Nelson & Ellenberg, 1982), pregnancy registers (Morrow et al., 2006) and finally analysis of outcomes from a number of pregnancy registers (Tomson et al., 2012). This body of research has produced fairly consistent outcomes: that prenatal exposure to certain AEDs convey an increased level of risk for major congenital malformations. Differential levels of risk are present across the AEDs types (Samren, Van Duijn, Christiaens, Hofman, & Lindhout, 1997). Interestingly, King, Lie and Irgens (1996) documented a change in the type of major congenital malformation seen in the offspring of women with epilepsy between 1967 and 1992, a period which saw a decline in the use of phenytoin and phenobarbital, and the increased prescription of carbamazepine and sodium valproate. Recently data from an international collaboration has published combined results from 42 different countries, representing the largest cohort of AED exposed infants ever reported (Tomson et al., 2011). The results confirm earlier reports that there is differential risk across AED types and highlighted the significant role dose plays in the teratogenicity of AEDs. Sodium valproate is reported to be associated with the largest risk to foetal physical development, in a dose dependent nature (Tomson et al., 2011). Due to the relative rarity of major congenital malformations, around 2% of the general population (although this varies by geographical region) large numbers are required to detect a significant increase in risk (Hernandez-Diaz et al. 2012). For example to detect a three-fold increase in risk of congenital malformations (any type), with 80% power at an alpha level of 0.05 a cohort of 300 exposed infants would be required, with substantially larger cohorts (>5000) required to detect significant increases in specific malformations (Holmes & Hernandez-Diaz, 2012).

The large amount of research interest into the physical malformations associated with AED treatment is not mirrored in research considering neurodevelopmental outcomes in children prenatally exposed. The brain is unique in that it develops across the entire gestational period and
into the postnatal years (Stiles, 2008), whilst other major organs develop during the period of organogenesis which extends from gestational weeks 3 though to 8 (Moore & Persaud, 2008). The brain is vulnerable to disruption from environmental influences therefore for a prolonged period (Stiles, 2008). There is evidence from animal models that administration of AEDs causes alterations in neuronal developmental processes and an increased rate of programmed neuronal pruning (Bittigau, Sifringer, & Ikonomidou, 2003; Kim, Kondratyev & Gale, 2007). It has been hypothesised that such alterations to neuronal developmental convey a risk to the cognitive functioning of human infants exposed prenatally to AEDs (Bittigau et al., 2003).

As early as the 1970s there were reports that children exposed to AEDs performed significantly poorer on measures of cognitive functioning (Hill & Tennyson, 1986) and early case reports regarding valproate teratogenicity noted ‘neurodevelopmental delay’ or ‘mental retardation’ (Ardinger et al., 1988; DiLiberti, Farndon, Dennis, & Curry, 1984). Despite such reports, substantially less research effort has focused on the delineation of the risk prenatal exposure to AEDs conveys to the developing brain and the later cognitive development of the child. This is thought to be multifactorial in nature including: historical views about teratology and the physical outcomes of the child; differences in prescribing patterns across countries; the prolonged period of follow up required and the additional untangling of postnatal influences. Despite these challenges Chapter 1 demonstrates there is now an accumulating body of evidence addressing this fundamental question. The majority of research to date, however, is limited by the methodologies utilised and in the main, is limited to follows ups within the childhood years only.

The classification of AEDs as teratogens has a number of clinical implications. Women who require treatment during their child bearing years should be provided with comprehensive information about the risks associated with their treatment and the benefits of seizure control (Crawford, 2005). This is a difficult decision required to be made by women with epilepsy. Failure to control seizures places the women at an increased risk of sudden unexpected death in epilepsy (SUDEP),
demonstrating the difficult balance between the protection of the foetus and the protection of the mother (Ryvlin & Rheims, 2012). Careful considerations are therefore required to maximise treatment efficacy whilst limiting the risk to the foetus (Harden et al., 2009). Due to growing concerns about the teratogenic risk of sodium valproate, women and their prescribers are seeking alternative treatments (Meador et al., 2009). This is particularly so for the treatment of idiopathic generalised epilepsy (Craig, 2012), an epilepsy type for which sodium valproate is regarded as first line treatment, due to its superior efficacy in terms of seizure control (Marson et al., 2007). It has been suggested that levetiracetam may offer an alternative treatment to sodium valproate in women with idiopathic generalised epilepsy (Craig, 2012). Prescriptions of the newer AEDs levetiracetam, lamotrigine and topiramate are increasing (Meador et al., 2009). There is however limited information about their safety in terms of congenital malformations (Holmes & Hernandez-Diaz, 2012) and as highlighted in Chapter 1, in relation to the neurodevelopment of the child.

7.3. Reflections of the Systematic Literature Review

Systematic literature reviews are designed to allow for systematic searching and review of all available literature in line with an a priori hypothesis about inclusion criteria to limit review bias (Higgins & Green, 2009). The systematic review in Chapter 1 highlighted that the expanding evidence base concerning neurodevelopmental outcomes following prenatal exposure to AEDs demonstrates differential outcomes across AEDs. Consistent with research pertaining to congenital malformations, sodium valproate was associated with a significant reduction in neurodevelopmental outcome. Additionally, the systematic review highlighted a significant lack of research delineating the risks to newer AEDs. Such conclusions have implications for preconceptual counselling for women with epilepsy and for paediatric services.

The undertaking of this review and the decisions taken in the design and execution of this systematic review are critically discussed below.
7.3.1. Was a Review Needed?

Over the last five years a large number of reviews have been published pertaining to exposure to AEDs (e.g. Adab, Tudur, Vinten, Williamson, & Winterbottom, 2004; Bromley, Baker, & Meador, 2009; Meador, Baker, Cohen, Gaily, & Westerveld, 2007; Nadebaum, Anderson, Vajda, Reutens, & Wood, 2012; Nicolai, Vles, & Aldenkamp, 2008), the majority of which were not systematic, with an a priori plan for inclusion and often only briefly reported on neurodevelopmental issues. The three exceptions to this are the Cochrane Review by Adab and colleagues (2004), the recently published review by Nadebaum et al. (2012), and the critical review by Nicolai and colleagues (2008). The Cochrane review by Adab et al (2004) reviews data published prior to 2003, and concluded that, at that time, there was no clear evidence about differential risks between AEDs in terms of child neurodevelopment. However, since 2003 in excess of 12 new studies pertaining to neurodevelopmental outcomes have been published. The more recent systematic reviews by Nadebaum et al. (2012) and Nicolai et al. (2008) focused on neurodevelopmental outcomes, conducted searches in a systematic way but failed to outline fully the quality of individual studies and did not include the recent publications (Cummings, Stewart, Stevenson, Morrow, & Nelson, 2011; Meador et al., 2011, 2012; Nadebaum et al., 2011b; Rihtman, Parush & Ornoy, 2012; Shallcross et al., 2011). Considering these issues it is felt that a systematic review of the literature pertaining to neurodevelopmental outcomes, aimed at publication in a paediatric journal and highlighting the quality of methodologies was a useful addition to the literature base.

The Paper in Chapter 1 has been formatted for submission to Developmental Medicine and Child Neurology, an international journal with an interest in child development and child neurology. Developmental Medicine and Child Neurology was chosen due to its readership, its impact factor (3.264) and its previous interest in research into prenatal exposure (Christianson, Chesler, & Kromberg, 1994; Rasalam et al., 2005).
7.3.2. Inclusion Criteria

The inclusion criteria for the systematic review was multifaceted across type of participants, types of study and types of neurodevelopmental outcome but was limited to commonly prescribed AEDs. In short studies were included if they reported on an aspect of neurodevelopmental outcome following prenatal exposure to an AED prescribed for the treatment of maternal epilepsy. Studies where AEDs had been solely prescribed for conditions other than epilepsy (e.g. bipolar disorder or migraine) were not included. This is justified on the basis that such a strict inclusion policy limited the potential bias inherent across health conditions such as dose and type of AED and also concomitant medication use.

An a priori decision was made to exclude studies which only reported on a single ‘exposed’ group which comprised of children exposed to a number of different AED treatments. If the risk to neurodevelopmental disorders varied by monotherapy AED type, consistent with the malformation literature, possible associations between specific AED treatment and child functioning would be masked in such ad hoc groups. This argument also applies to the exclusion of polytherapy AED treatment. As noted in Chapter 1, comparing outcomes from groups of children exposed to polytherapy across different cohorts is challenging due to the different AED combinations included. For example, the use of sodium valproate is lower in countries like Finland (Gaily et al., 2004), with the majority of polytherapy combinations therefore not including sodium valproate. In publications from the UK and Australia, approximately half of polytherapy groups are treatments which contain sodium valproate (Bromley et al., 2010, Nadebaum et al., 2011). With this in mind, the comparison of polytherapy combinations across cohorts is likely to be unreliable and would have likely produced conflicting results. The decision to limit the review to specific monotherapy exposures are felt to be justified by the differential outcomes across AEDs reported in the review.

The decision to include such a wide range of outcome variables requires defending. The inclusion of a wide range of neurodevelopmental outcome types was due to author knowledge of the area and
could be argued, therefore lead to review bias. Alternatively, it could in fact be argued that knowledge of the area and outcome range enhanced the review. If for example, just IQ had been the subject of the systematic review important information for clinicians and researchers about other aspects of neurodevelopmental outcome would have been overlooked leading to unreliable conclusions and practice. The selection of outcomes to be included in the review by initial searches or author experience/ knowledge of the area is recommended by the Centre for Reviews and Dissemination at York University (Centre for Reviews and Dissemination, 2008) and the Cochrane Collaboration (Higgins & Green, 2009). The inclusion of a wide range of outcomes is unlikely to account for the review outcome; namely the differential findings across the AED groups.

### 7.3.3. Searches

Searches were conducted using MEDLINE (OVID 1946-week 2 2012), EMBASE (OVID 1980-week 15 2012) and PsycINFO (OVID 1946- June 2012). Results were cross-referenced across individual AED reports in Reprotox Database, a teratology specific information resource which contains reviews on individual drugs. Previous review articles were also cross referenced with the search results to ensure research reliability.

The search strategy was constructed utilising three main concepts or levels: pregnancy variables (Concept 1), maternal epilepsy and treatment variables (Concept 2) and finally outcome variables (Concept 3). Such a method is consistent with the advice of the Centre for Reviews and Dissemination (2008). Each concept or level was constructed individually (e.g. pregnancy or teratology or exposure or fetal etc) and then combined (Concept 1 terms AND Concept 2 terms AND Concept 3 terms). Searches were limited to human outcomes only. Medical subject heading terms (MeSH) were utilised and terms were exploded. This strategy may have led to the over generation of citations and the large number of results which required to be checked against the inclusion criteria (n=3928). The wide range of outcomes included along with the large number of AEDs eligible for inclusion may also have been causal in the large number of citations generated. Over inclusion was
felt to be preferable to under inclusion. The majority of unrelated citations surrounded paediatric epilepsy or the treatment of preeclampsia related seizures with AEDs. Papers pertaining to both of these areas met the search criteria concepts and therefore had to be hand removed.

Eligibility was checked using abstracts and full text articles by a single reviewer. This represents a weakness of the review methodology, and would have been enhanced by an independent review of eligibility at both the abstract and full text stages (Centre for Research and Dissemination, 2008). It is felt that the search strategy and inclusion decisions were verified by the cross referencing against reference lists in Reprotox and the reference lists of other review articles.

7.3.4. Data Extraction

Data extraction was conducted onto a specifically designed data extraction form. Details of the methodology, results and overlap with other publications were recorded. A series of publications from a single cohort are common in this area, particularly in the longitudinal cohort studies, and therefore studies are reported rather than individual publications. Data extraction was not cross checked by an independent reviewer which represents a weakness of the systematic review methodology employed here (Higgins & Green, 2009). The involvement of a second independent reviewer was not plausible given the time and resource restraints of this thesis.

7.3.5. Quality Appraisal

Quality assessment tools and risk of bias tools are routinely utilised in systematic reviews of randomised controlled trials (Higgins & Green, 2009). Quality assessment tools for investigating the methodological quality of non-randomised studies are without consensus and with the Cochrane Systematic Review Group and the York Centre for Reviews and Dissemination failing to define best practice (Higgins & Green, 2009, Centre for Reviews and Dissemination, 2008). The Newcastle Ottawa Scale (NOS)(Wells et al., 2008) has been utilised and is recommended by the York University based group and has been used by a Cochrane Review into this area (Adab et al., 2004). The decision was therefore taken to utilise it to highlight study methodology here.
The general areas of the NOS were utilised here to highlight methodological quality. The NOS was adapted for use in the review presented in Chapter 1. Two items of the NOS were not implemented here: was follow up long enough for outcome to occur and was follow up complete or minimised? The first of these items is difficult to apply when considering paediatric neurodevelopmental outcomes. It could be argued that, depending on the outcome which you are measuring, observation hours after birth would result in the response to this question being yes. Therefore it was felt that this would not assist in the stratification of quality across studies. The second item removed: was follow up complete or minimised, was omitted in Chapter 1, due to the challenges of applying this across study types. Cross-sectional studies for example are likely to have a high completion rate due to the proximity of recruitment to assessment. Longitudinal studies will however, by their nature suffer from loss to follow up. Two additional considerations were made regarding the methodology of the identified studies: was dose of AED considered and was the study adequately powered. Dose is one of the key principles of teratology (Beckman & Brent, 1984). Even the most potent teratogens do not convey an increase in risk to foetus until it reaches a critical dose (Beckman & Brent, 1984). Failure to consider AED dose, may lead to a masking of an effect when large and smaller doses of AED are considered together. The issue of an adequately powered study has been discussed for decades in medical and social science research (Cohen, 1992). Few studies in this area reported on adequacy of their cohort to detect a predetermined level of effect. Consideration of the studies sample size and its power is an important issue and was included to assist readers in their understanding of the level of quality of the research under review. Power is a complex issue and depends on four aspects: the sample size, the significance level adopted, the ability of a test to detect an effect and whether the hypothesis is directional or not (Cohen 1992). In order to provide the reader with information on the number of adequately powered studies and to avoid wordy and complex descriptions of each of these four aspects of power for each study the minimum criteria for power in observational studies investigating independent means as suggested by Cohen (1992) was taken as a benchmark: 80% power to detect a large effect size at the significance level of 0.05. It is
acknowledged that more stringent measures (e.g. 90% power, detection of a medium or small effect size and with an accepted probability level of 0.01) would have stratified the research results further, but this would have lead to an overly elongated discussion about the power of each study.

The following criteria were implemented to consider study quality:

1) Selection
   a. Was the cohort truly or somewhat representative of the women with epilepsy in the community (e.g. community recruited or hospital recruited)?
   b. Was a control (or comparison group) recruited from the same cohort?
   c. Did pregnancy related information and maternal health information come from medical records or structured interview with the mother at the time of the pregnancy?
   d. Was the study prospective (outcome was not known at onset of the study)?

2) Comparability
   a. Were the groups comparable on the basis of design (matching) or analysis (adjustment) for key confounding variables (e.g. maternal and child demographics)?

3) Outcome
   a. Were outcomes assessed in a blinded fashion or taken from formal records

4) Additional criteria
   a. Was the dose of AED and its relationship to outcome investigated?
   b. Did the study include a sample size equal to or larger than 26 participants for the AED type being considered

7.3.6. **Review Bias**

There are a number of aspects of the review methodology which may have introduced bias into the review. These include limiting studies to the English language, limiting the inclusion to published results and not having a second independent reviewer to undertake eligibility checking and data
extraction (Centre for Research and Dissemination, 2008). All three of these decisions were taken due the time and resource limitations for the ClinPsyD thesis. It is thought that review bias is unlikely to account for the differential outcomes across AED groups as the results for each AED were ascertained in the same way. Publication bias remains possible in this area, but this was not formally assessed here. Demonstrating the safety of medicine use in pregnancy is as important as demonstrating risk, as both are informative to clinical practice. Negative findings from studies are publishable for this reason, and may reduce the chance of publication bias. Gaily et al. (2004) for example, published a paper entitled ‘Normal intelligence in children with prenatal exposure to carbamazepine’ in a high impact factor journal. It is therefore felt, although the limitations of not assessing publication bias are noted, that publication bias would have been strong enough to alter study conclusions.

7.3.7. Implications of this Review

The systematic review presented in Chapter 1, had a number of implications for future research and clinical practice both across neurology and paediatric specialties. The review highlighted that varying methodologies have been employed to investigate whether prenatal exposure to AEDs are associated with neurodevelopmental difficulties. At the end of the review a guide to enhance and ensure consistent methodologies was outlined. In the main such suggestions were consistent with those made by Meador et al. (2007), Nicolai et al. (2008) and Bromley et al. (2009) for observational studies but highlights the role record linkage studies may place in neurodevelopmental disorders such as autistic spectrum disorders, where the prevalence is small and large cohorts are required to demonstrate reliable differences.

The review also had implications for clinicians who work in paediatric services and those who prescribe AEDs who are required to counsel women about the risks and benefits of treatment. This is discussed in more detail below (Sections 7.6 & 7.7).
7.4. Critical Reflections of the Main Paper

7.4.1. Summary of Results

The empirical paper in Chapter 2, found no association between prenatal exposure to levetiracetam and impaired cognitive outcome in children aged between five and nine years of age across IQ, language, memory, executive and attentional skills. In contrast prenatal exposure to sodium valproate was associated in a dose dependent manner, with impaired cognitive functioning across IQ and language skills. In the group of children exposed to doses over 800mg daily of sodium valproate, below average full scale IQ was significantly increased (57.9%). The implications of these results for clinical practice are discussed further below in Section 7.7.

7.4.2. Comparability to the findings of others

**Levetiracetam**

There is only a single published cohort investigating the potential association between prenatal exposure to levetiracetam and human cognitive development. Taken together, the results from Shallcross and colleagues (2011) paper and the empirical paper presented here demonstrate that throughout early and middle childhood, prenatal levetiracetam exposure is not associated with large reductions in cognitive functions. A failure to increase neuronal apoptosis in the immature brain is reported for levetiracetam exposure in rats, even at high doses, and as part of polytherapy, which sets it apart from the other AEDs (Kim et al., 2007), and may account for the lack of association with human cognition reported here.

Investigation into the risks prenatal levetiracetam exposure may convey to the physical development of the child is limited, but fails to find an association with major congenital malformations (Hernandez-Diaz et al., 2012; Hunt et al., 2012). It should be highlighted that the cohort of levetiracetam exposed infants in the paper by Hunt et al. (2006) includes those assessed as part of this study. Recently a larger study reporting on 450 levetiracetam exposed infants demonstrated
that it carried the lowest risk of malformations across the AED types (Hernandez Diaz et al., 2012). Systematic studies of minor congenital malformations and facial dysmorphia have not been undertaken and therefore milder developmental anomalies cannot be ruled out following levetiracetam exposure.

**Sodium Valproate**

The finding here that sodium valproate is associated, in a dose dependent manner, with reduced cognitive functioning across Verbal IQ (VIQ), Non-verbal IQ (PIQ), Full scale IQ (FSIQ) and poorer language ability is consistent with previous studies (Adab et al., 2004; Gaily et al., 2004; Meador et al., 2009; Nadebaum et al., 2011a). It is concerning that the effect sizes for dose of sodium valproate were large (>0.30) and the standardised beta values highlighted that sodium valproate dose was a stronger predictor of child outcome than maternal IQ, a predictor noted to be highly influential on child cognitive ability (Santos et al., 2008). The finding that 57.9% of children exposed to doses of sodium valproate over 800mg daily scored below the average range (standard score of less than <90) is consistent with the reports of others of an increased incidence of below average performance (Meador et al., 2009b, 2012; Nadebaum et al., 2011a, 2011b). Inspection of the spread of the FSIQ scores demonstrates (Figure 2, Chapter 2, page 43) that sodium valproate is associated with an increased prevalence of scores across the extremely low, borderline and low average ranges, highlighting the clinical significance of the results. Taken alongside research from three other independent cohorts (Gaily et al., 2004; Meador et al., 2012; Nadebaum et al., 2011a) there is an accumulation of evidence that prenatal exposure to sodium valproate is associated with deleterious effects on cognitive functioning in middle childhood, which is consistent with the reports pertaining to infant cognitive development (Bromley et al., 2010; Cummings et al., 2011). The clinical implications for such findings are discussed further in Section 7.7.

Verbal abilities are reportedly differentially affected following sodium valproate exposure (Meador et al., 2011) which is replicated here with VIQ demonstrating the largest effect size across the
adjusted models. Such a pattern has been hypothesized to be linked to disruptions in lateralisation of skills (Meador et al., 2011), however it is proposed here that the age at which the child is assessed and the corresponding complexity of that cognitive domain expected at that age may also account, at least in part, for the strong association with verbal abilities above that of other skills. No association between sodium valproate dose and memory abilities or early attention and executive abilities were demonstrated.

Research into the longevity of the effects of sodium valproate are limited to the childhood years. Meador et al. (2012) highlighted that between two and 4.5 years of age children exposed to sodium valproate who were impaired at two years of age did not catch up with their peers by four and a half years of age. There is limited research into school aged children exposed to sodium valproate, but their findings are consistent with the findings reported in Chapter 2 (Kantola-Sorsa, Gaily, Isoaho, & Korkman, 2007; Nadebaum et al., 2011a).

There is evidence that the difference in cognitive ability between sodium valproate exposed children and their peers is more than simply small mean differences. Reports of increased incidence of below average IQ, impaired language abilities and the need for educational support highlight the real life nature of the reported deficits (Adab, Jacoby, Smith, & Chadwick, 2001; Adab et al., 2004; Meador et al., 2012; Nadebaum et al., 2011a). Extrapolation from the general neuropsychological literature suggest that the described deficits are likely to impact on final level of educational attainment and impact on occupational attainment (Deary, Strand, Smith & Fernandes, 2007). Therefore the consequences of prenatal exposure to sodium valproate are potentially life long.

Reflections on the relationship between maternal use of sodium valproate and child cognitive functioning

Due a lack of randomisation of human participants in this area of research direct causation is difficult to conclude from human studies alone. Control for known influential variables decreases the change
of a third known factor influencing the relationship between sodium valproate exposure and child cognitive functioning, but it remains that an additional unknown influential variable may influence the association. The NEAD study group have undertaken one of the most comprehensive review of confounding variables to date, making adjustments for maternal illness (epilepsy type, seizure frequency, adherence to medication), child variables (age, gestational age at birth, birth weight, breastfeeding, whether it was a wanted pregnancy) and parental socioeconomic variables (maternal IQ, maternal stress, educational level, maternal age, folate use, employment, ethnicity) and a significant association between prenatal exposure to sodium valproate and child cognitive functioning remained (Meador et al., 2009, 2011, 2012). The replication of this results across independent cohorts, including the cohort reported here, further decreases the likelihood that an additional unknown variable accounts wholly for the relationship between sodium valproate exposure and child cognitive functioning.

Additional evidence regarding the nature of the relationship between prenatal exposure to sodium valproate and child cognitive functioning comes from the physical symptoms associated with such exposure. Since 1987, it has been documented that there is a recognisable phenotype associated with prenatal exposure to sodium valproate (Winter, Donnai, Burn, & Tucker, 1987) which includes facial dysmorphia and characteristic malformation patterns. Whilst authors have questioned (Janz, 1982) whether a common mechanism may be present between maternal epilepsy itself and the cognitive outcome in the child, such a mechanism is does not account for the physical defects in the child (Bromfield, Dworetzky, Wyszynski, et al., 2008) which are reported to correlate with cognitive outcome (Kini, Adab, Vinten, Fryer, & Clayton-Smith, 2006).

Children within the same family where maternal epilepsy medication has been changed for subsequent pregnancies offers an interesting ‘control’ over unknown intra-familial variables. To date no cohort studies have been presented but case reports demonstrate differential outcomes across
siblings both in terms of their physical presentation and cognitive functioning, with those exposed to sodium valproate performing significantly poorer (Vinten, 2004).

Further evidence on the issue of causation can be drawn from animal models. Animal models provide data which separates out the presence of maternal epilepsy in the mother and the effects of sodium valproate on the developing brain. Whilst the challenges of application of animal models to humans are noted, they have provided evidence which demonstrates that exposure to sodium valproate leads to alterations in the development of the premature brain (Miyazaki, Narita & Narita, 2005; Rinaldi, Silberberg, & Markram, 2008).

Finally, it should be considered that other documented human teratogens such as alcohol and lead are also found to be associated with a decrease in child cognitive functioning, with some authors proposing a similar mechanism between alcohol and valproate exposure through the GABA (Olney, Farber, Wozniak, Jevtovic-Todorovic, & Ikonomidou, 2000).

On the balance of probability, considering research across human cohorts and with knowledge of animal findings, it is likely that sodium valproate plays a causal role in the alteration of child cognitive functioning. Further research into specific epilepsy types with different antiepileptic medications and also research recruiting cohorts of families where medications have been altered between pregnancies will provide further evidence to this issue.

Mechanisms of effect on the fetal brain

Limited information is available to delineate the exact effect prenatal exposure to sodium valproate may exert on the premature human brain. Extrapolation from animal studies suggests that exposure to valproate may lead to alterations in disrupted neuronal development (Rice & Barone, 2000) which may be due to induce alterations in the GABA neurotransmitter (Olney, et al., 2000). Research utilising neuroimaging to investigate the morphology of brains of individuals exposed to antiepileptic drugs are beginning to emerge and demonstrate that subtle morphological alterations are present
within the brains of children and adults exposed to antiepileptic drugs, including sodium valproate (Ikonomidou, Scheer, Wilhelm, et al., 2009).

It is hypothesized that such alterations in brain morphology likely lead to functional alterations, which in turn are associated with altered neuropsychological functioning and account for the cognitive difficulties associated with prenatal exposure to sodium valproate (Bittagü et al., 2003; Rice & Baron, 2000). Findings of poorer language functioning following prenatal exposure to sodium valproate has been the most commonly reported finding to date, leading some to conclude that verbal abilities are differentially effected (Adab et al., 2004; Meador et al., 2011). Meador and colleagues (2011) have proposed that such differential findings may be due to a failure of early cognitive abilities to lateralise to specific anatomical regions within the cortex and propose, although without evidence, that the lateralisation process is disrupted following prenatal exposure to certain antiepileptic drugs at certain doses (Meador et al., 2011). It should be considered however that methodological processes of data collection may also, in part account for such findings. The cohorts of Meador et al., (2009,2011), on which their hypothesis of a failure to lateralise is based, includes data from 3 year old infants, where cognitive abilities are far from their mature levels. It must also be considered that in younger children neuropsychological assessments may more easily document language abilities rather than other skills such as processing speed or memory, which require complex and abstract language comprehension abilities to explain the task. It should be considered that differential effects of the neuroanatomical regions of the brain are possible (Olney et al., 2000) and should be investigated through future research.

7.5. Review of Methodology

Study design
Recruitment into this cross-sectional study came from the UK Epilepsy and Pregnancy Registry, a nationwide registry of women with epilepsy who enrol during pregnancy. Women can either choose
to self enrol or are approached about enrolment by their health care provider (Russell et al., 2004). Utilisation of this design has a number of advantages. Historically, there has been a considerable latency between monotherapy AED licence and adequate teratology risk information. Sodium valproate for example was licensed in the UK and Europe in the 1970s but only recently have the risks posed to neurodevelopment become known (Bromley, Leeman, Baker, & Meador, 2011). Single or even multicentre studies are unlikely to be able to provide information on new AED treatments due to the time required to recruit adequate numbers of exposed infants. The utilisation of a national registry provides access to an increased number of infants exposed to new AEDs. This large advantage however must be considered alongside the weaknesses of such a methodology.

Cross-sectional results provide useful information about the neurodevelopmental outcome of the child at that particular age and its potential relationship with prenatal exposure, and are commonly utilised in this area of research (Cummings et al., 2011; Gaily et al., 2004; Nadebaum et al., 2011a). Cross section studies however fail to provide information on early risk markers or the development of deficits over time. Due to the gravity of the time and financial commitment required there are only a small number of truly prospective cohorts, where the infants are followed from the prenatal period into school age (e.g. Bromley et al., 2010; Meador et al., 2009b, 2011, 2012). The results of which are consistent with the majority of cross-sectional findings (e.g. Cummings et al., 2011; Gaily et al., 2004).

The study presented in Chapter 2 was limited to a cross-sectional design due to the time limitations of the ClinPsyD.

Finally, cross-sectional studies employ retrospective recruitment which may increase bias due to parental knowledge about the development of the child. The inclusion of comparison and control groups from the same source and in the same manner are likely to reduce this bias, but it is difficult to make reliable risk estimates.
Case Ascertainment

Both the experimental and the control groups were recruited from the same source to minimise source bias. Children with a major congenital malformation likely to cause neurodevelopmental difficulties (e.g. spina bifida with hydrocephalus) were excluded. Children with known genetic mutations were also excluded. There was approximately three times the number of children exposed to sodium valproate or who were control no medication children in comparison to levetiracetam exposed infants. Each third mother-infant pair for sodium valproate and no medication groups were selected, without any knowledge of participant information (e.g. dose or maternal epilepsy type). Increased resources and time would have enabled the inclusion of all eligible children which would have provided a more comprehensive insight into the cognitive functioning of the sodium valproate exposed group.

Recruitment

The recruitment procedure was the same across the three groups. All participants received an invitation to participate along with the study information sheet (Appendix 3) and a prepaid envelope. Enrolment into this study was significantly different across the groups. The uptake for levetiracetam was 72.2% with sodium valproate and the no medication acceptance rate being 28.9% and 34.5% respectively. The higher rate of participation in the levetiracetam group is felt to be multifaceted. Sixty percent of the levetiracetam group had been assessed as part of an earlier study at three years of age (unpublished), increasing the likelihood that a current address was on file. A further influential factor on recruitment rates may have been the explanation on the participant information sheet that this study aimed to investigate levetiracetam, inviting those on no medication and those on sodium valproate to act as comparison groups, which may have reduced acceptance. Cummings and colleagues (2011) who also recruited participants from the UK Epilepsy and Register, but report a higher acceptance rate (58%), which may be due in part to the younger age of the children. A large number of invitations to participate were met with no response, highlighting the challenges of attempting to contact families six years post enrolment. The reported acceptance rates
are substantially lower than those reported for prospectively recruited studies where recruitment occurs in pregnancy, and highlight the difficulties of adding neurodevelopmental follow up studies to registers. Although the conversion of pregnancy register recruited families into a cohort for neurodevelopmental follow up facilitates the recruitment of newer AED exposed groups, they present a challenge in terms of the acceptability and tracing of families.

Women who did not participate were comparable to participants across maternal age, gender of child and gestational age of the child at birth. No information was available to determine whether the socioeconomic status of participants differed from non-participants, a factor which has been reported to be influential in other cohorts (Bromley et al., 2010).

**Control groups**

A control group is of paramount importance in this type of research to ensure that biases present in the cohort are reduced and reliable risk estimates can be generated. The majority of studies in the literature use a control group or a comparison group. The term comparison group is coined to refer to another AED exposed group to which comparisons across treatment type are made (e.g. Meador et al. 2009b, 2011, 2012). Control and comparison groups answer different questions, and the utilisation of one or both depends on the primary study questions: control groups for estimates of risk and comparison groups for risks across treatment types. Debate within the literature has emerged about the type of control group which offers the most benefit. Nicolai et al. (2008) outline that controls should be women of epilepsy who are not medicated as they offer ‘control’ for the maternal disease state, although this has been questioned by others who outline that non-treated epilepsy is likely to represent a different maternal disease state than epilepsies that require long term AED treatment (Meador et al., 2007). A general population control group, typically a group of women who do not have epilepsy or other chronic health condition and who are not taking medications during pregnancy, have been employed by others who feel that true risk estimates should be generated against such a population (e.g. Bromley et al., 2010; Cummings et al., 2011;
Gaily et al., 2004). This debate remains unsettled but may in fact be academic as the majority of studies, with adequate adjustment for confounding factors, fail to demonstrate a significant difference between the abilities of children born to women with an untreated epilepsy and children born to women representative of the general population (Bromley et al., 2010; Holmes, Rosenberger, Harvey, Khoshbin, & Ryan, 2000).

The decision to employ a no medication control group here was made on the basis that recruitment bias could be reduced by recruitment from the same source as those in the experimental groups (levetiracetam or sodium valproate). The UK Epilepsy and Pregnancy Register, as the name implies, does not enrol the pregnancies of women without epilepsy.

**Collection of information**

Below the study protocol and processes are critically reviewed.

Confounding variables

Information collected during pregnancy limits recall bias (Werler, Nelson & Holmes, 1988) and by enrolment during pregnancy ensures prospective recruitment without prior knowledge of the infants neurodevelopmental status. This study utilised prospective collection of information pertaining the pregnancy (gestational age at birth, mode of delivery, health of the infant, presence of major congenital malformations) and the maternal illness status of the mother (AED type, dose, seizure exposure etc). However, other information such as maternal lifestyle (e.g. alcohol and nicotine consumption), socioeconomic status, educational level of the mother and the father were collected retrospectively through a structured interview with the mother. The retrospective collection of alcohol and nicotine exposure is likely to have been influenced by recall bias (Werler et al., 1988). To limit recall bias these questions were limited to a binary ‘yes’ or ‘no’ response, which proposes limitations to dose and frequency considerations for these factors. The accuracy of self reported information pertaining to use of alcohol, nicotine and drugs is likely influenced by social
acceptable practice (Werler et al., 1988) whether asked prospectively or retrospectively, and therefore should be viewed with caution.

The majority of research to date has failed to demonstrate an association between prenatal exposure to seizures and child cognitive functioning (Hattig & Steinhausen, 1987; Ornoy & Cohen, 1996; Gaily et al., 2004; Eriksson, Viinikainen, Monkkonen, et al., 2005; Kantola-Sorsa et al., 2007; Thomas, Sukumaran, Lukose, George, & Sarma, 2007; Thomas, Ajaykumar, Sindhu, Nair, & Sarma, 2008; Bromley et al., 2010; Meador et al., 2009, 2011, 2012) with two studies reporting an association, but for differential seizure types. Adab et al. (2004) for example reported that five or more generalised seizures were associated with poorer child outcome, whilst Gaily et al., (1990) failed to replicate such an association but found instead that partial seizures were associated with poorer child cognitive outcome. In the study by Adab and colleagues seizure frequency was collected retrospectively from maternal report which may have been associated with recall bias. In the study here, as noted above, limitations of the data collected during pregnancy meant that only the presence of seizures was recorded rather than seizure frequency. Whilst this should be viewed as a methodological limitation of the current study, consideration across the literature base suggests that prenatal exposure to transient seizures is not associated with significant implications to the cognitive abilities of the child. Consideration should be given however to the potential for fetal injury or loss posed by prolonged maternal seizures (status epilepticus) or through injury to the mother (e.g. falls and burns) during transient seizures.

Antiepileptic drug factors

Antiepileptic drug dose

A key strength of this study is the recognition of the importance of dose. Dose is a defining feature of a teratogenic substance (Beckman & Brent, 1984), although it is not always considered in the AED exposure literature (Kantola-Sorsa et al., 2007; Cummings et al., 2011; Gaily et al., 2004; Wide, Winbladh, Tomson, Sars-Zimmer, & Berggren, 2000). Further, prospective collection of dose
information at the time of enrolment into the UK Epilepsy and Pregnancy Register reduces recall bias.

A significant effect of sodium valproate dose was seen for VIQ, PIQ, FSIQ and language ability. A lack of consideration of dose may have led to the masking of a significant effect. The dose effect noted for sodium valproate is consistent with the reports of others (Adab et al., 2004; Meador et al., 2009b,2011,2012; Bromley et al., 2010; Nadebaum et al., 2011a,2011b). No association was found between levetiracetam dose and child cognitive functioning. A lack of a dose effect of levetiracetam will be of interest to clinicians and is consistent with the outcomes of levetiracetam exposed children at earlier ages (Shallcross et al., 2011), preclinical models of apoptosis (Kim et al., 2007) and human malformation rates (Hunt et al., 2005; Hernandez-Diaz et al., 2012).

There are limitations to the dose information available for the study in Chapter 2 which requires consideration alongside the results. AED information collected for this study at the time of enrolment into the UK Epilepsy and Pregnancy Register (typically within the first trimester or early second) fails to account for the changes that may occur later in pregnancy. This represents a challenge when neurodevelopmental follow up studies are added to pregnancy register enrolled women, where the primary concern of the register is dose in the first trimester during the period of major organs formation. They are not designed for longitudinal data collection throughout the gestational period. Development of the brain extends beyond the first trimester, with a peak in neuronal genesis, synaptogenesis and programmed cell death occurring in the second and third trimesters (Stiles, 2008). In the large (n= 345) study utilising pooled data from a number of pregnancy registers only 18% of women on sodium valproate altered their dose of sodium valproate (EURAP, 2007). There is evidence, although from a small cohort (n=23 monotherapy sodium valproate), that first trimester dose of sodium valproate was a stronger predictor of child language functioning compared to third trimester dose (Nadebaum et al., 2011a), which may justify its use
Future research is required to delineate dose by trimester effects for sodium valproate and all other commonly prescribed AEDs.

**Timing and duration of exposure**

A limitation of this study is the failure to consider the variance of prenatal exposure across participants. Timing of the exposure (e.g. gestational time point), duration of exposure and factors such as metabolism and placental transfer differ between individuals and therefore means that fetal exposure will also differ. Such factors are rarely considered, with the majority of studies assuming that AED consumption by the mother leads to a single uniformed exposure, assuming that AED placental transfer, timing of AED treatment, duration of AED treatment are equal across individuals. The results of this study and many others are limited by the theory of uniformed exposure (e.g. Kantola–Sorsa et al., 2007; Meador et al., 2009b,2011,2012; Bromley et al., 2010). There is a suggestion that altering AEDs during pregnancy is rare, particularly when women are seizure-free (EURAP, 2007) but considerations of potential alterations or halting of treatment should be assessed within cohorts. AED formulations differ with standard and slow release formulas available to prescribers for sodium valproate, but not levetiracetam. The potential differences in risk they convey were not considered here. Formulation type did not alter malformation rate in recent research from the UK Epilepsy and Pregnancy Register (Mawhinney et al., 2012), research into its potential relationship with neurodevelopmental outcomes is required.

**Cohort Size**

This cohort (n=120) had a power of 89% to detect a medium effect size (.15) utilising multiple regression analysis with a maximum of 10 confounding variables being entered into the model at a significance level of less than 0.01 (Gpower)(Faul, Lang & Buchner, 2007). The study reported in Chapter 2 was therefore adequately powered to detect a medium effect size in the levetiracetam exposed children but failed to do so. The consideration of effect size represents a strength of this
study. Milder levels of cognitive impairment would require larger cohorts to detect and therefore this study cannot rule about a small effect of levetiracetam exposure on child cognitive functioning.

**Data collection**

Neuropsychological assessment

Currently there is no consensus regarding the type of neuropsychological battery which is best placed to detect cognitive difficulties linked to prenatal exposure at different developmental points. Across behavioural teratology more generally measures of global cognitive ability (e.g. IQ) are often utilised as the primary outcome with measures of more specific domains often a secondary consideration (e.g. Nulman et al., 2002). It is not clear whether a score of global cognitive ability is the most sensitive measure to prenatal exposure deficits but its utilisation can be defended through the ease at which is can be translated to medical and educational colleagues. Good principles of neuropsychological practice would suggest that domain specific assessments are more likely to yield reliable results and are more likely to offer avenues for intervention (Baron, 2004; Lezak, Howieson & Loring, 2004).

The neuropsychological battery for this study comprised of:


- NEPSY, A developmental Neuropsychological Assessment 2nd edition (NEPSY-II)(Korkman et al., 2007)


The neuropsychological battery was designed to ensure breadth of coverage of skills whilst ensuring that the child is not under assessment conditions for longer than required to reduce fatigue. The assessment was designed to fit into a school morning, starting at 9am with the child having a
number of small breaks between assessments and attending their normal scheduled break period with their peers. The author and the research assistants were trained on test administration and general principles of neuropsychological assessment, including monitoring and avoiding fatigue. In a small number of cases (<5%) a follow up visit was arranged due to child fatigue.

All assessments were completed in the following order: WISC-IV or WPPSI-III, NEPSY-II, CELF-IV to ensure comparability of performance across the groups.

Due to considerations about assessment length and child fatigue the neuropsychological battery was required to be limited to IQ, language, memory and attentional or executive skills. If there had not been such constraints and multiple follow ups with each child could have been implemented assessment of the following would have been a useful addition:

- measures of fine and gross motor ability
- a measure of verbal working memory
- a measure of rate of learning
- measures of social and behavioural functioning

Such a battery would have provided a comprehensive understanding regarding the neuropsychological and behavioural functioning of the children prenatally exposed to antiepileptic drugs. However, the implications for the statistical analysis in terms of statistical multiple testing must be considered.

In order to obtain an adequately powered sample it was necessary to include children aged between five and nine years of age. The WISC-IV has an age range of from six to 16 years and therefore the
WPPSI was required for the assessments of children who were five years of age. These two measures were standardised around the same time, with 182 children completing both measures and demonstrating differences of less than one point (Wechsler, 2004). Differences between the WISC-IV and the WPPSI-III were adjusted for in all analyses undertaken. Both the WISC-IV and the WPPSI-III have been utilised together and separately in other previous research investigating outcomes following prenatal exposure to AEDs (Jones, Lacro, Johnson, & Adams, 1989; Gaily, Kantola-Sorsa, & Granstrom, 1988; Gaily et al., 2004). Both the WISC-IV and the WPPSI-III demonstrate high levels of reliability, with the average retest coefficients across the IQ domains of 0.86-0.93 for the WISC-IV (Wechsler, 2004) and between 0.88-0.91 for the WPPSI-III (Wechsler, 2003).

The use of more than one measure of global cognitive ability, whilst not ideal, has been used in research where the age range of the intended sample is not covered by a single measure (e.g. Ornoy & Cohen, 1996; Cummings et al., 2011).

The primary outcome measure for this study was IQ. The utilisation of a measure of IQ as the primary outcome could be criticised for its lack of domain specificity and its drawing on a number of more specific cognitive domains (Baron, 2004; Lezak et al., 2004), which may lead to domain specific effects being unreliably reported. For example, Adab et al., (2004) reported that sodium valproate exposure was associated with a reduction in verbal IQ in their retrospective study, but highlight that the language abilities of the children were not assessed and it remained to be seen whether the deficits noted in verbal IQ were in fact a deficit in the language domain. It is therefore of paramount importance that more specific cognitive domains are investigated. The utilisation of IQ as the primary outcome is defended however through its consistency with other research cohorts (e.g. Meador et al., 2009b,2012) and through the ease in which it can be translated to medical colleagues, the largest target audience for this research. It should be noted that that WISC-IV manual (Wechsler, 2004) redefines the index scores of VIQ, PIQ and FSIQ as verbal comprehension,
perceptual reasoning and full scale. This terminology was not adopted here to ensure clarity and consistency with the reports of others (Nadebaum et al., 2011b).

The neuropsychological battery also assessed the memory and the attentional and executive abilities of the cohort. The NEPSY-II subtests: auditory attention; design fluency; inhibition; memory for names; narrative memory; memory for faces and memory for designs were administered. The use of the NEPSY-II is consistent with previous publications (Kantola-Sorsa et al., 2007) and has good evidence of reliability across the domains administered (0.5-.75) (Korkman et al., 2007)). The language abilities of the children were assessed using the CELF-IV. To avoid excessive assessment length subtests were limited to: comprehension of instructions; formulated sentences and expressive naming. The CELF-IV has evidence of high reliability (0.7-0.9) (Semel et al., 2006)) and has been utilised by other researchers in this area (Nadebaum et al., 2011a).

To reduce the number of analyses required and to reduce the chance of a type one error domain index scores were created. The three index scores were created by dividing the sum of relevant subtest scaled scores by the number of subtests relevant to that domain. This is consistent with the practice of other authors (Meador et al., 2011). Whilst reporting individual subtest scores as a single index may reduce the likelihood of a significant effect by chance, it does create the possibility that specific ability types may be differentially effected which may be masked or may dominate the index score reporting. For example, are verbally mediated memory abilities more susceptible to the effects of sodium valproate than non-verbally mediated memory abilities? This was not investigated here due to an a priori analysis plan and the number of multiple tests that are required to investigate this, but should be considered when reviewing the results and in future research.

Finally, this study is weakened by the lack of ‘real’ life cognitive functioning indicators. Despite considering FSIQ results by the classifications outlined in the Wechsler Manual (Wechsler, 2004), this study failed to provide real life implications of reduced cognitive functioning such as prevalence of educational support and healthcare utilisation.
Blinding

Recruitment and child assessments were both completed in a blinded fashion for the present study to reduce bias. This is consistent with the recommendations of Nicolai and colleagues (2008) and represents an important strength of this study. The appointment letters, sent to confirm the details of the arranged appointment, reminded mothers not to disclose whether they were or were not treated for their epilepsy.

Age at assessment

Neuropsychologic functioning in children is dynamic due to evolving development of the brain across childhood (Baron, 2004). This study investigated the cognitive abilities of children aged between five and nine years of age. Assessment beyond the infant years provides an original contribution to the evidence base regarding prenatal exposure to levetiracetam and provides confirmation of the results of others pertaining to outcomes at school age, following prenatal exposure to sodium valproate (Nadbaum et al., 2011a, 2011b; Kantola-Sorsa et al., 2007). Due to the dynamic nature of neurodevelopment over the childhood and adolescent years, it is unlikely that the results reported here represent a stable measure of ability or deficit. It remains possible that prenatal exposure to levetiracetam may be associated with deficits in skills that are not matured in this age group. The most prominent example of this is the maturation of the frontal lobes and development of executive functioning skills which develop across later childhood and adolescence (Baron, 2004; Lezak et al., 2004).

Analysis

This study had a directional hypothesis based on the findings from previously published cohorts: Prenatal exposure to sodium valproate but not levetiracetam would be associated with reduced child cognitive functioning.

Exploration of the data was undertaken to ensure that the data met with the parametric principles of the a priori analysis plan. Analysis of the data for the primary question was undertaken using
multiple regression analysis allowing with adjustment for confounding factors. The reference group within the regression was set as the no medication group. Discussions were held prior to the finalisation of the statistical plan regarding whether the levetiracetam exposed group should be set as the reference group, to facilitate direct comparisons between levetiracetam exposure and sodium valproate exposure. With limited information about the potential association between prenatal exposure to levetiracetam and child cognitive functioning it was decided that it would limit the conclusions which could be made pertaining to the risks associated with prenatal sodium valproate exposure.

Univariate regression models were constructed to gain an understanding of the relationship between the independent variables and the dependent variables. Correlation matrices were created to investigate the potential relationships between each of the independent variables and to check for multicolinearity. At this stage a strong relationship was found between gestational age and birth weight. Gestational age is known to have implications for later cognitive development and therefore this variable was retained to be considered in the multivariate model. There are a range of methods of entry which can be utilised to construct a multiple variable linear regression model: simultaneous entry, stepwise and hierarchical (Tabachnick, & Fidell, 2007). Entry into the multiple regression model was completed in two stages: variables with known clinical significance and had demonstrated a statistically significant relationship with the main outcome variable (FSIQ) in the univariate regression models were entered through simultaneous entry; variables with unknown clinical significance were entered using the more exploratory method of stepwise entry with variables being retained if they had a p value of <0.1. Once a variable is included using stepwise entry its interpretation within the model would be the same if another method of entry would have been utilised and once a this new independent variable is retained in the model the independent contribution of the other independent variables previously entered is recalculated (Tabachnick, & Fidell, 2007). Stepwise entry is not without its controversies, due to its being based on statistical rather than clinical relevance to the dependent variable, but this method can be used when there
are a large number of variables with largely unknown significance within the cohort in question. It is felt that the balance of known clinically relevant entry using simultaneous entry methods and the additional entry using stepwise of other variables with a less clearly defined relationship with the dependent variable (Field, 2009), balanced the consideration of important clinical variables against the number of independent variables to be considered. This method is also consistent with that of other authors conducting research in this area (Meador et al., 2009, 2011, 2012).

Hierarchical entry to the regression model could have been utilised but this method draws heavily on prior knowledge of the relationship between each of the independent variables and the dependent variable; something which was not clearly defined for all variables in this type of population. Consideration to this method of entry has been given and a repeat multivariate analysis of the main dependent variable, full scale IQ, confirmed what the earlier model had found: that dose of sodium valproate was significantly associated with outcome and displayed the highest standardised beta value.

Another consideration when considering the analysis was whether multiple analysis of covariance could have been utilised instead of multiple regression analysis. This would have been feasible if the groups had been analysed as single exposure groups, rather than by dose, but a larger number of additional follow up analysis of covariance analyses would have been required to provide information specific to individual AED comparisons. Further the important issue of dose could not be reliably assessed in such a model. The utilisation of multiple regression is consistent with the majority of published research (Nadebaum et al., 2011a; Bromley et al., 2010; Gaily et al., 2004), facilitating comparisons of the results across cohorts.

A Bonferroni correction was applied due to the number (n=10) of analyses that were undertaken. This gave an adjusted p value threshold of 0.005. This will have decreased the likelihood of a type one error but increased the chances of a type two error. Bonferroni corrections have been criticised (Perneger, 1998), but such adjustment was felt to be important considering the clinical implications.
of this research. Consideration is required that an association between sodium valproate dose and child scores on the memory index fell subject to such a stringent significance level. In the multiple regression a large effect size is reported (Table 2, page 41) but the significance of level of 0.009 did not meet the adjusted level of acceptance. Further research is therefore required to investigate whether in fact reductions in memory ability are also noted following prenatal exposure to sodium valproate.

Finally, no attempt was made to replace missing data as done by others by using intention-to-treat analysis (Meador et al., 2009b, 2011, 2012). Intention-to-treat analysis or other forms of computation however requires reliable knowledge of the non assessed cohort. The majority of this cohort had not been previously assessed and therefore such imputation was not feasible.

**Journal Choice**

The paper in Chapter 2 was formatted for the Journal Neurology. This journal is a widely renowned journal which specialises in the reporting of high quality research pertaining to a wide range of aspects of neurology. AEDs are prescribed for a range of neurological conditions and therefore a journal with a general neurology readership would ensure adequate dissemination of results. Neurology has a high impact factor (8.17) and has published a large number of articles pertaining to prenatal exposure to AEDs over the last 10 years (e.g. Bromley, Mawer, Clayton-Smith, & Baker, 2008; Meador et al., 2012; Shallcross et al, 2011).

**7.6. Ethical Considerations and Professional Issues**

The provision of information to women with epilepsy who are of childbearing potential is a major ethical issue. Preconceptual counselling is now a standard recommendation, however it appears to be dominated by the physical risks to the child (Crawford, 2005). In order for evidence based decision making to be undertaken by the female and her Physician, reliable research needs to be undertaken with reliable methodologies. The slow accumulation of research delineating the risks AED exposure poses to neurodevelopmental outcomes has led to a lack of evidence based decision
making in such preconceptual counselling sessions. Commentaries published by Neurologists have demonstrated that they are cautious in the provision of information pertaining to neurodevelopmental outcomes due to concerns about methodology (Penovich & Gaily, 2005). Further, the view that neurodevelopmental outcomes are only ‘minor’ anomalies (Craig, 2012) may also direct the central focus of counselling towards malformation risk estimates. The recent accumulation of research regarding neurodevelopmental outcome is likely to impact on preconceptual counselling practice (Harden et al., 2009). In order to be ethical, to allow women to make evidence based decisions, they should be provided with all the information pertaining to the risks and benefits of their treatment. Preconceptual counselling cannot be classed as comprehensive unless all the risks posed to the future child are discussed.

A further ethical issue relates to the care for children prenatally exposed to AEDs who are at risk of poor neurodevelopmental outcome. There is currently no formal pathway within the National Health Service for children exposed to AEDs, or other medicines, who display delayed neurodevelopment. Whilst those with severe neurodevelopmental delay or a major congenital malformation are likely to be picked up through routine Health Visiting Services, those who fall below the average range but above the severely impaired range are likely to be missed. As noted in the distribution of IQ scores reported in Chapter 2 for children exposed to sodium valproate prenatally, the majority of children exposed to this AED are likely to fall within this range. Such a service would facilitate early intervention to maximise child outcome. The difficult decisions women with epilepsy make about their treatment, should be supported with the knowledge that postnatally all will be done to maximise the infants development, should problems become apparent.

A final consideration surrounds the conduct of research into this sensitive matter. There is concern that women may decide to halt their medication during pregnancy due to knowledge of research results or following contact with the research team. Both the Liverpool and Manchester Neurodevelopment Group and the UK Epilepsy and Pregnancy Register research teams have had
experience of women calling to enquire about the level of risk the medication they are taking may convey. At the onset of this study plans were made to tackle such questions and involved signposting the women to her health care professional and highlighting the importance of not stopping her medication without medical assistance. When the results of the neuropsychological assessments indicated that the child required clinical review from local services referrals were made.

7.7. Clinical Applications

There are wide reaching clinical issues pertaining to this research. As highlighted by the systematic review there is limited information about the safety profile of levetiracetam during pregnancy. Although there is now a reliable evidence base of information pertaining to pre-school outcomes in children prenatally there is limited information about the cognitive consequences of prenatal exposure to sodium valproate in school aged children. The demonstration of a dose effect for sodium valproate, leaves clinicians with the option of reducing the dose of sodium valproate rather than immediately switching to an alternative treatment. It is anticipated that the results of the study presented in Chapter 2 will be used in preconceptual counselling for women with epilepsy in their childbearing years or who are planning a pregnancy.

The results of this study also present clinical implications to Paediatric Services and Health Care Professionals, including psychologists, who may come into contact with children exposed prenatally to AEDs. Children exposed to sodium valproate should be considered at risk for poorer neurodevelopmental functioning across the infant (Bromley et al., 2010; Cummings et al., 2011) and middle childhood years. Such at risk cohorts of infants should be closely monitored to allow for early intervention. The results of this study also add to that of other studies to help Paediatricians and Clinical Geneticists if their diagnosis of children exposed to sodium valproate in utero and who present with neurodevelopmental and cognitive difficulties.
7.8. Future Research

The expansion of research interest in this area will provide clinicians and women with epilepsy with evidence based information on which to base their treatment decisions. There remains a wealth of outstanding questions which future research needs to address.

Further neurodevelopmental outcomes

Further research into the neurodevelopmental outcomes across AED type, considering dose and other AED variances is required. Such detailed information will further enhance the information conveyed to women, the treatment options available to prescribers and will reduce the risk to the developing child. As outlined in Chapter 1, studies should be prospective in nature, utilise standardised neuropsychological assessment periods, conduct blinded assessments and follow up into the adolescent years.

Record linkage and case-control studies should be utilised to facilitate the reliable investigation between maternal AED use and rarer neurodevelopmental outcomes. Conditions such as autistic spectrum disorder, attention deficit hyperactivity disorder and dyspraxia have been reported to be at an increased prevalence following prenatal sodium valproate exposure (Adab et al., 2004; Bromley et al., 2008), but these observations require replication in large samples.

Consideration is also required into the types of neurodevelopmental outcomes investigated and with adaptive behavioural skills and social communication skills being considered in addition to more typical cognitive functions.

Knowledge provision in preconceptual counselling

Future research should address the methods of risk-benefit information delivery to women with epilepsy in preconceptual counselling, as there is evidence that current practice is limited, with women displaying poor levels of recall (Pack, Davis, Kritzer, Yoon, & Camus, 2009).
Research into other indications

AEDs are prescribed across a range of neurological conditions, including pain and mood disorders. Future research should aim to replicate the results documented in women with epilepsy in users of AEDs for other neurological symptoms, to confirm the reliability of findings reported.

Defining best practice

Future research needs to investigate the most reliable and cost effective ways of delineating the risks to neurodevelopment associated with prenatal exposure. The delineation of cognitive strengths and weaknesses is required and should be used to facilitate interventions to maximise child neurodevelopmental outcome.

Intervention

Finally, research is required to investigate the optimum way to intervene when children with a history of prenatal exposure are delayed in their development in infancy to maximise their neurodevelopmental outcome.

7.9. Conclusion

This ClinPsyD project aimed to delineate the risks associated with prenatal exposure to levetiracetam and sodium valproate. The results from the systematic review and the empirical paper demonstrated that prenatal exposure to sodium valproate is associated with an increased risk to child cognitive functioning, in a dose dependent manner. No association was demonstrated between prenatal exposure to levetiracetam and large effects on cognitive functioning, but replication and extension is required. Due to the dynamic nature of neurodevelopment over the childhood and adolescent years, it is unlikely that the results reported here represent a stable measure of ability or deficit. It remains possible that prenatal exposure to levetiracetam may be associated with deficits in skills that are still to mature in this age group.
Women with epilepsy should be provided with information about the risks and benefits of her treatment and should be supported in her decision making to maximise outcome. Finally, Healthcare Professionals within Paediatrics are required to be vigilant regarding the development of infants prenatally to medications, particularly sodium valproate, to allow for early intervention to maximise child outcome.

7.10. References


Cummings, C., Stewart, M., Stevenson, M., Morrow, J., & Nelson, J. (2011). Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Archives of Disease in Childhood, 96*(7), 643-647.


Olney, JW, Farber NB, Wozniak DF, Jevtovic-Todorovic V, & Ikonomidou C (2000a). Environmental agents that have the potential to trigger massive apoptotic neurodegeneration in the developing brain. *Environmental Health Perspectives, 108*, 383-388.


### Developmental Medicine and Child Neurology

#### Presentation and formatting of your paper

#### Maximum length requirements

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#### All papers

**General** Use single-line spacing for all parts of the submission. Include tables and figure legends in your main article file, after the references. Submit figures (illustrations) as separate files, as described below. Name all files using the surname of the first author (e.g. Smith.doc, Smith fig1.tif, etc.).

**Title page** Include the title of the paper, authors’ names, main appointments and primary affiliations (i.e. one affiliation only per author), and word count. Identify the corresponding author and give his or her postal address, fax number, and e-mail address.

**Abstract** On the second page of original articles and systematic reviews, provide a full structured abstract of no more than 200 words, with the following headings: Aim; Method, Results, Interpretation. Where relevant the Method section should follow Equator guidelines and should include means (sd) or medians and sex for study and control groups, definition of clinical characteristics, entry criteria for study, assessments used, duration and frequency of intervention, and timing of outcome assessments. Where relevant “Results” should follow Equator guidelines and should summarize significant results with statistical values, including negative findings if related to the study hypothesis. Non-significant trends should not be noted in the abstract. Non-systematic reviews and case reports should have a non-structured abstract without headings of up to 150 words, covering the aims, method, results, and conclusions of the study. On the abstract page, also provide a shortened form of the title (up to six words) for use as a running foot.
'What this paper adds' All original articles and systematic reviews should have a section ‘What this paper adds’ after the abstract. This should comprise up to five bullet points of 5-10 words each, summarizing the new knowledge contributed by the study. Other articles should have one or two similar bullet points.

Reviews

We publish two types of review. One is a fully detailed comprehensive review of a subject, such as a systematic review, with full referencing and a word-count appropriate to the topic and amount of material to be covered. The other is intended to be a more personal view providing the reader with a systematic review, with full referencing and a word-count appropriate to the topic and amount of material to be covered. The journal does not recognize abstracts or submitted (as opposed to accepted, or ‘forthcoming’) papers as proper citations; such material should not be listed with the references but cited only in text, followed by ‘(personal communication)’.

List all authors unless more than six, in which case list the first three followed by ‘et al’, using Index Medicus abbreviations for journal names (see www.nlm.nih.gov/tsd/serials/lji.html). Order and punctuate bibliographic information as follows, omitting issue month and number unless needed to distinguish issues. For additional citation formats, adapt appropriate examples from the NLM’s Citing Medicine (www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=citmed).


For references to online sources, supply the author names, full title, and full URL including the date on which the site was accessed.

Figures and tables

Note that the Editors may decide that large figures or tables should be published online-only.

Tables, figure legends and short appendices Set out on separate pages at the end of (and as part of) the main document, after the references.

Tables and appendices to be published online only Present as separate files in Microsoft Word or Rich Text format.

Figures (e.g. illustrations, charts and photographs) Present electronically as separate files (not in the main text of the article). Guidelines about acceptable file formats and illustration preparation are provided at authorservices.wiley.com/bauthor/illustration.asp.
Please label radiographs, CT, or MRI scans with left [L] and right [R], and if appropriate with anterior [A] and posterior [P]. Areas of interest should be marked with an arrow. For EEGs please indicate the gain, timescale, and lead position.

Graphs should be as simple as possible, not three-dimensional, and not framed. Shading should be white, black, or strong hatching, not grey. No background lines should be used (except for bars and axes).

**Colour** If colour printing of figures is essential for their comprehension, please indicate this in the covering letter. There is normally a charge to the author for printing in colour. It is possible to publish a figure in black and white in the print version of the issue but in colour in the online version at no extra charge.

**Statistical reporting**

The Editors advise reading “Statistical recommendations for papers submitted to *Developmental Medicine & Child Neurology*” (Rigby AS, Dev Med Child Neurol 2010; 52: 293–298) for guidelines on appropriate use and reporting of statistical analyses.

**Supporting information (supplementary material)**

DMCN publishes online supporting information (including audio and video files, data sets, additional images, and large appendices) that cannot be included in the print version of an article. This material should be relevant to and supportive of the parent article. For guidelines see authorservices.wiley.com/bauthor/suppmat.asp.
9. Appendix 2: Formatting Guidelines for Neurology
**Neurology**

**Scientific Contributions**

**Articles**

Articles are full-length reports of original research. These include large-scale pivotal trials of new therapies (randomized clinical trials). According to ClinicalTrials.gov, clinical trials "are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined protocol. ClinicalTrials.gov includes both interventional and observational types of studies. Intervenional studies are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured. Observational studies are those in which individuals are observed and their outcomes are measured by the investigators."

**Specifications:**

Maximum of 3000 words (not including abstract, figure legends, table legends, references). This length equals about 15 double-spaced manuscript pages.

Structured Abstract containing Objectives, Methods, Results, and Conclusions, maximum 250 words.

Limit of 40 references. The best references should be included rather than duplicative citations for single points. Citations to non-peer-reviewed work should be avoided. If additional references are deemed important, they can be published online as supplemental data. Review articles may have up to 60 references.

Limit of 5 figures and tables total. Up to 3 additional figures or tables can be published online. Tables should not repeat data in the text.

If a table is longer than two double-spaced manuscript pages (including the legend), it will be published online as supplementary material.

Figure legends must explain what is represented in the figure rather than repeating results, methods, and conclusions.

If Methods contain widely available, detailed protocols, appropriate portions may be posted online only at the Editor’s discretion.

**General Formatting**

Manuscript submissions to *Neurology* should be prepared electronically and submitted in a standard word processing format; Microsoft Word is preferred. Although conversions can be made from other word processing formats and PDF files, the vagaries of the conversion process may introduce errors. Do not submit ASCII text files. The manuscript should be formatted so as to print out double-spaced at standard 8" x 11" or A4 (international) paper dimensions, using a 12-point font size and a default typeface (e.g., recommended fonts are Times, Times New Roman, Courier, Helvetica, and Arial). Set the left margin at one inch, and the right margin at one-half inch or more. Do not justify the right margin; leave it unaligned.
Place the page number and lead author’s last name in the upper right-hand corner of each page (including the reference pages, tables, and figure legends).

Observe the following guidelines in preparing your electronic manuscript file:

Use hard returns only at the end of paragraphs and display lines (e.g., titles, subheadings)

Do not insert a tab, indent, or extra spaces before the beginning of a paragraph or for list entries

Do not indent run-over lines in references

Set line spacing at 2 (not 1.5 or 2.5)

Turn off automatic hyphenation and justification

Do not use automatic references

Do not insert hard page breaks

Take care to enter "one" (1) and lowercase "el" (l), as well as "zero" (0) and capital "oh" (O), correctly

Key dashes as follows: Use a single hyphen with space before it for a minus sign, and a double hyphen (with space before and after) to indicate an em-dash (long dash) in text. Use only single hyphens in the references.

Nonstandard characters (Greek letters, mathematical symbols, etc.) should be coded consistently throughout the text. Please make a list of such characters and provide a key to the codes used.

**Abstract**

Articles require **structured** abstracts that should not exceed 250 words (one double-spaced typed manuscript page). Abstracts should be lucid and readable; minimum statistics are sufficient. A structured abstract should be organized as follows:

**Objective**

**Methods**

**Results**

**Conclusions**

**Classification of Evidence** (applicable for studies of therapeutic interventions)

Papers evaluated for classification of evidence must contain the section titled Classification of Evidence after the Conclusions section. In this section, please include the following in 25 words or less: Classification of Evidence: This study provides Class [I, II, III, or IV] evidence that [Treatment] [reduces/increases/decreases/is well tolerated] results.

For example:
Classification of Evidence: This study provides Class I evidence that certain dosages of mexiletine are well tolerated and effective in reducing handgrip relaxation.

This statement should be expanded to include other details in the Methods section. For Views & Reviews articles, provide a 150- to 250-word abstract, structured if possible. NeuroImages and Clinical/Scientific Notes do not require an abstract.

Introduction

The introduction should not be more than 250 words. Be specific and concise in stating information related to the study. Refrain from reiterating known information.

Methods

The Methods section or the accompanying supplemental materials must provide sufficient detail to allow replication of the study. As examples, the Methods should indicate nucleotide sequences used for RNA or DNA probes, what an antibody was made against and sources of antibodies, constructs for transgenic animals, and reagents and instruments used with the manufacturer’s names and locations.

If the study reports a therapeutic intervention (clinical trial or use of medication, procedure, maneuver, or change in patient environment intended to benefit the patient), the Methods must be sufficiently detailed to allow classification of level of evidence.

Papers evaluated for classification of evidence must contain a paragraph titled Classification of Evidence. In this paragraph, please state (a) the question(s) the investigation was designed to answer, specifically identifying the patient population, intervention of interest, and relevant outcomes; (b) the class of evidence (I, II, III, or IV) assigned to each question as determined by AAN criteria; and (c) a brief statement of the results of the study for each question. Detail dosages, percentages, years, and significance. Examples:

Classification of evidence: This interventional study provides Class I evidence that warfarin (target INR 1.7 to 2.5) is equivalent to aspirin 81 mg daily in preventing recurrent strokes during an average of 3 years of follow-up in patients aged 20 to 70 with a history of stroke (relative risk of stroke warfarin vs aspirin 0.98, 95% CIs 0.81 to 1.10).

Methods/Primary research question: Has the introduction of adjunctive dexamethasone in the Netherlands improved outcome in pneumococcal meningitis? This study provides Class III evidence that dexamethasone reduced the proportion of patients with unfavorable outcomes (Glasgow Outcome Scale score of one to four) in the 2006-2009 cohort, as compared to the 1998-2002 cohort (39 vs. 50%; odds ratio, 0.63%; 95% confidence interval, 0.46 to 0.86; p=0.002). Mortality rates (20 vs. 30%; absolute risk difference, 10%; 95% confidence interval 4 to 17%; p=0.001) was also significantly lower in 2006-2009.

In a subsection on Standard Protocol Approvals, Registrations, and Patient Consents, include the following:

A statement of approval by an ethical standards committee on human experimentation (institutional or regional) for any experiments using human subjects.
A statement identifying the institutional or licensing committee approving experiments performed on live vertebrates and/or higher invertebrates.

A statement that written informed consent was obtained from all patients (or guardians of patients) participating in the study (consent for research). For a retrospective analysis that is IRB-approved, state that approval from an ethical standards committee to conduct this study was received.

A statement that authorization has been obtained for disclosure (consent-to-disclose) of any recognizable persons in photographs, videos, or other information that may be published in the Journal, in derivative works by the AAN, or on the Journal's Web site (when applicable).

A statement, if the study reports on a clinical trial, providing the identity of the public trials registry and the clinical trial identifier number.

To report previously published methods, provide a statement in the manuscript as follows: We used the same methodology as the one employed in a previous study [citation]. Insert the published method verbatim immediately below, citing it appropriately. If the verbatim wording is more than 200 words, supply permission to republish the content from the publisher of the original article.

**Figures**

Authors should examine a recent issue of *Neurology* to plan the appropriate layout and size when preparing their figures.

*Neurology* is interested in 3-D or interactive figures. If you have figures that would be enhanced by this approach, please let the editors know and include these as part of your submission.

Proof of permission to reprint a figure from any source is required (as is permission to modify a figure, if applicable); figures previously published anywhere will not be published in *Neurology* without documented permission from the copyright holder.

Color figures are published with no charge to authors.

Use Arial type within figures, capitalizing the first letters of first words of labels only. Ensure that the spacing between letters (kerning) is even (no letters closer together than the others) and that the lettering is crisp.

Per Journal style, each figure has a short title above it (the detailed legend is placed under the figure). Provide a short title (15 words or less) for each figure at the beginning of the Figure Legend in the manuscript file.

Title and Figure legends should be double-spaced and appear on a separate page of the manuscript document file.

Footnotes should be noted as superscript a, b, c, etc.

Multipart figures should be labeled with capital letters A, B, C, (using Arial font) etc. in the upper left-hand corner of each panel. Please submit multipart figures as composite files. Panels should read from left to right, then down.
In graphs, standard symbols should be used for data points in the following order: □, △, ◆, ●, ○, ▽. Symbols like the following are not acceptable: ⊗, ⊘. To prevent wasted space, axes should end no more than one increment beyond the final data points. Explanatory lettering should not extend beyond the ends of the axes.

Remove extraneous lines from graphs (only include x, y axis).

Line graphs should be solid colored lines rather than dots and dashes.

Bar fill in bar graphs should be solid color rather than patterns.

Figures should not include titles or patient initials. Titles should be placed in the figure legend, not on the figure itself. Abbreviation keys should be placed in the figure legend unless they fit into the confines of the figure.

Internal scale markers must appear on microscopic photographs.

Remove white type from MRIs, CTs, etc.

Number figures (including figures to be published online only) in the order of their mention in the text.

For supported electronic file requirements, see the section Electronic Figure, Video, Supplemental Data Submission.

Tables

Tables should be created using a structured table format in Word and included as part of the manuscript document file. Do not embed image files of tables and do not use tabs in creating tables. Authors should consult a recent issue of Neurology before designing tables.

Tables should be brief and easily understood without referring to the text.

Do not use color or shading within tables.

Do not include patient names or initials in the tables.

Extensive tabular data may be posted on Neurology’s Web site when the article is published (see Supplemental Data/Additional Files).

Place each table, including a title and legend (if applicable), on a separate page.

All tables must be double-spaced.

Number tables in the order of their mention in the text.

References cited within a table should use numbers rather than author names.

Tables should be no longer than two double-spaced manuscript pages.

Supplemental Data
Tables and other illustrative material submitted to *Neurology* should be succinct and easily interpreted by the general readership. Often lengthy data difficult to summarize in print are important to the study. These data, which may take the form of tables, figures, data, references, or appendices, can be posted on the *Neurology* Web site and can also be referenced in the print journal.

Authors who wish to submit detailed data to be considered with their manuscript should upload these data upon submission. The data must be in a separate electronic file rather than included in the main document.

The list of Coinvestigators must be uploaded as a data supplement.

The online data should also be referenced within the text.

The title page of the paper should indicate "Supplemental Data" below the authors' affiliations. All Supplemental Data and electronic file names should also be listed on the title page (e.g., Supplemental Table, electronic file name: table e-1, Supplemental Appendix, electronic file name: appendix e-2). See section on Supplemental Data/Additional Files for upload information.

If the manuscript is accepted, this supplemental data will be posted as submitted and will not be professionally copyedited or proofread. For this reason, authors should carefully review their material. *Neurology* will not be responsible for errors or omissions. See Supplemental Data/Additional Files for upload information.

**Reference Style**

Cite references in *numerical order* according to their position in the Reference list in the text.

List all authors when there are six or fewer; for seven or more, list only the first three and add "et al."

Use PubMed abbreviations for journal names but eliminate U.S. cities cited in parentheses after the name of a journal.

Use continuous pagination (e.g., 33-37, not 33-7).

Do not reference papers that are "submitted"; unpublished papers must be accepted and in press.

Authors must provide "submitted" and "in press" manuscripts clearly labeled as such by uploading them as supplemental files with submission or faxing them to the editorial office.

Personal communications should be mentioned in the body of the manuscript (not in the references). The author must state in writing in the cover letter of the submission that permission was obtained by the author of any personal communication cited in the article.

*Neurology* reference style is similar to the style described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/), with the exception that
Journal article

Journal article published electronically ahead of print version

Published abstract

Conference paper

In press (forthcoming)

Letter

Book


Online book or Web site

Online journal article

Monograph in electronic format
10. Appendix 3: Information Sheet and Invitation to Participate
Cognitive Abilities of Children Exposed to Antiepileptic Drugs In the Womb

As you may remember, when you were pregnant you enrolled into our study looking at the development of children born to women with epilepsy. You may remember we were both interested in women that were taking these antiepileptic medications and women that were not.

You are being invited to continue to take part in a research study being carried out by members of the UK Epilepsy and Pregnancy Register and the Liverpool and Manchester Neurodevelopment group. Before you decide, it is important for you to understand why the research is being done and what it will involve.

Please take the time to read the following information carefully and discuss it with others if you wish. Please feel free to ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

In certain cases it is important that antiepileptic medication is continued even when you are pregnant. It is known that other medications taken for epilepsy can have an effect on the unborn child, for example in terms of school abilities. We do not know about the longer term effect of exposure to levetiracetam, topiramate, gabapentin and sodium valproate in the womb and that is why we have begun this study. We want to compare the development of children whose mothers took one of these newer medications to children whose mothers took no medication during the pregnancy.

The results of this study will be provided to doctors who treat women with epilepsy.

Why have I been chosen to participate?

We are looking for mothers who were taking levetiracetam (Keppra), topiramate (Topamax), gabapentin (Neurontin) and sodium valproate (Epilim) at the time of their pregnancy and also mothers who were not taking epilepsy medication during pregnancy.
Who is organizing the study?

The study is being organized by the UK Pregnancy Registry and the Liverpool and Manchester Neurodevelopment Group. It is being funded by a grant from Epilepsy Research UK.

What will taking part in the study involve for myself and my child?

If you agree to participate in the study one of the researchers will contact you to arrange a time to see you and your child in your home at your convenience. Alternatively you can request for you child to be assessed at school. We would write to gain permission from the school. Your child will be asked to complete a number of game-like tasks with the researcher to inform on their current cognitive abilities. The cognitive abilities we are assessing include reasoning, language memory and attention. You will be asked to complete a questionnaire looking at your child’s behavior. We will also ask you to complete a small reasoning task.

At the assessment we would also want to take some measurements from your child (height, weight and head circumference) to inform on their physical development. We would also request that photographs are taken of your child’s hands, feet and face. In previous research looking at the effects of exposure of other antiepileptic drugs in the womb, some children have been found to have facial features and other minor features of the hands and feet that are similar across children exposed to that particular drug. Whilst these are undetectable to the untrained eye in most cases, we will be asking your permission to take photographs of your child’s face, feet and hands. A geneticist will then examine these photos in order to determine if there are any features that could be attributable to exposure to a particular drug in the womb. The photographs will not be stored by your child’s name and will be stored on a secure, password protected disc which will be kept in locked cabinet in an office that is secure and locked out of hours. You can decide to take part in this study but refuse for this picture data to be collected.

Are there any disadvantages or risks in taking part in this study?

The study may involve some inconvenience in terms of having to be seen at your home or in their school, but we will try to minimize this where possible by arranging mutually convenient appointments. There is a risk that the assessment may uncover a problem with your child’s development that you were not aware of previously. If significant problems are identified we will discuss this with you and seek your permission to refer your child to someone who could help (i.e. a speech and language therapist).

What are the possible benefits of taking part?

The information we obtain from this study will help us to learn about any difficulties children exposed to levetiracetam, topiramate or gabapentin may experience. This information is especially helpful for mothers with epilepsy who are planning pregnancies in the future. If by any chance problems are identified in your own child, then we will arrange for your child to see a specialist.
Is my doctor being paid for including me in the study?

No, the money which has been provided for the study only covers necessary expenses.

What happens if something goes wrong?

In the unlikely event that you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed by someone else’s negligence then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you can contact our lead site NHS/HSC Belfast Health and Social Care Trust (0800 917 0222) or the lead academic institution Liverpool University’s research complaints department 0151 794 8727 for advice.

Who will know I am taking part in this study?

All information collected about you during the course of the research will be kept strictly confidential. Any information about you, which leaves the hospital, is made anonymous so that you cannot be recognized from it. We will also ask your permission to let your GP know that you have participated in this study.

What will happen to the results of the study?

Our aim is to publish the full results of this study in one of the national medical journals. We will also prepare a shorter summary of the results and send this out to the GPs of all the families who have participated. We will send all families who have participated a summary of the results.

Ethical approval for the study has been obtained from the North West Research Ethics committee.

What do I do now?

We ask that you return the slip at the bottom of the covering letter indicating whether you wish to participate. If we do not hear from you we will send a reminder letter to you in the next couple of weeks.

Thank you for reading this information and considering whether to take part.

Further information about the study can be obtained from:

Dr Rebecca Bromley
Trainee Clinical Psychologist
Division of Clinical Psychology
University of Manchester
Oxford Road
Manchester
M13 9PL
07736037612

Dr James Morrow
Consultant Neurologist
Department of Neurology
Royal Victoria Hospital
Grosvenor Road
Belfast
BT12 6BA
028 90240503
11. Appendix 4: Ethical Approval
Dear Dr Bromley

Study title: Cognitive Consequences of In Utero Exposure to New Antiepileptic Drugs

REC reference: 09/H1011/63

Amendment number: 2

Amendment date: 31 May 2011

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
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<tbody>
<tr>
<td>Participant Information Sheet</td>
<td>4</td>
<td>30 May 2011</td>
</tr>
<tr>
<td>Protocol</td>
<td>2</td>
<td>30 May 2011</td>
</tr>
<tr>
<td>Notice of Substantial Amendment (non-CTIMPs)</td>
<td>2</td>
<td>31 May 2011</td>
</tr>
<tr>
<td>Covering Letter</td>
<td></td>
<td>30 May 2011</td>
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</table>
Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H1011/63: Please quote this number on all correspondence

Yours sincerely

Dr Peter Klimiuk

Chair

Enclosures: List of names and professions of members who took part in the review
Copy to: Dr James Morrow (By email jim.morrow@belfasttrust.hscni.net)
         Ms Lindsay Carter, Research Office, University of Liverpool
         Professor Ian Young (By email I.Young@qub.ac.uk)

NRES Committee North West - Greater Manchester North Attendance at Sub-Committee of the REC meeting on 12 July 2011

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Ken Cook</td>
<td>Acute Care Manager - Later Life</td>
<td>Expert</td>
</tr>
<tr>
<td>Dr Peter Klimiuk</td>
<td>Consultant Rheumatologist</td>
<td>Expert</td>
</tr>
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</table>