Neurodevelopmental Outcomes in Children Exposed to Newer Anti-Seizure Medications in the Womb

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Rebecca Knight

School of Health Sciences, Division of Psychology and Mental Health

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Total:	28,082 (*17,259*)

Thesis Abstract

This thesis comprises three papers investigating neurodevelopmental outcomes of children exposed to newer anti-seizure medications (ASMs) in the womb: a systematic review, an empirical study and a critical appraisal.

Within the review, systematic searching techniques were used to identify all available literature pertaining to child neurodevelopmental outcomes following in-utero exposure to newer ASMs. Thirty-five publications were identified for inclusion in the review. All studies underwent quality assessment and results were brought together using narrative synthesis, with ongoing recommendations for clinical practice and research discussed thereafter. Overall, it was highlighted that the effect of in-utero exposure to many newer ASMs remains unclear, with concerning implications for mothers with epilepsy and their children.

The empirical research project explored adaptive behaviour outcomes in children exposed to a newer ASM, topiramate, in the womb. Mothers with epilepsy completed parental report assessments about their children's adaptive behaviour skills (n = 25), with prospective pregnancy and ASM information available via the research registry from which they were recruited. When compared to normative data, topiramate-exposed children had significantly poorer adaptive behaviour skills. There were also high rates of Autism Spectrum Disorder and low birthweights within the topiramate-exposed sample. Potential explanations for these findings and suggestions for future research and clinical implications are presented.

Finally, the critical appraisal included a discussion of the strengths and limitations of the systematic review and empirical study. Reflections on process and contributions to research are discussed, in addition to the clinical implications of the findings.

Declaration

No portion of the work referred to in the 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.

Copyright Statement

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My sincerest thanks are extended to the women who contributed towards this research, volunteering their free time to help further knowledge within this important area of study. Acknowledgements go to wider members of the research team and key collaborators across the University of Manchester and the UK Epilepsy and Pregnancy Register: Dr John Craig, Ms Beth Irwin, Ms Sarah Rushton and Ms Simran Johal.

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Paper 1

Neurodevelopmental outcomes in children exposed to newer anti-seizure medications: a systematic review

Knight, R.,[1,2] Wittkowski, A.,[1,2] & Bromley, R. L.[3,4*]

[1]Division of Psychology and Mental Health, the University of Manchester

[2]Greater Manchester Mental Health NHS Foundation Trust

[3]Division of Evolution and Genomic Science, the University of Manchester

[4]Royal Manchester Children's Hospital, Manchester Academic Health Sciences, Manchester, UK.

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Manuscript prepared in line with guidance for *Epilepsia* (see Appendix A for author guidelines), with additional information provided for context.

Abstract

Objective: As prenatal exposure to certain older anti-seizure medications (ASMs) has been linked with poorer neurodevelopmental outcomes in children, the use of newer ASMs throughout pregnancy has increased. The current review aimed to delineate the impact of in-utero exposure to newer ASMs on child neurodevelopment. ***Method:*** A systematic search of MEDLINE, Embase, Web of Science, CINAHL Plus and PsycINFO was conducted, limiting results to articles available in English and published after the year 2000. Studies investigating neurodevelopmental outcomes following in-utero exposure to the following ASMs were eligible for inclusion in the review: eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, topiramate and zonisamide. ***Results:*** Thirty-five publications were identified and a narrative synthesis was undertaken. Methodological quality was variable, with distinct patterns of strengths/weaknesses attributable to design. Most studies examined lamotrigine or levetiracetam exposure and reported non-significant effects on child neurodevelopment. Data for topiramate, gabapentin and oxcarbazepine were limited, such that no conclusions could be drawn. Concerningly, no studies investigated eslicarbazepine, lacosamide, perampanel and zonisamide. ***Significance:*** Exposure to certain newer ASMs, such as lamotrigine and levetiracetam, does not thus far appear to impact certain aspects of neurodevelopment, but further delineation across the different neurodevelopmental domains is required. A lack of data cannot be inferred to represent safety of newer ASMs which are yet to be investigated.

Keywords: In-utero; Antiepileptic drugs; Epilepsy; Pregnancy; Teratogens

Introduction

Certain older anti-seizure medications (ASMs) act as teratogens in the womb (Weston et al., 2016; Tomson, Battino & Perucca., 2019), causing harm to the developing brain and leading to poorer neurodevelopmental outcomes in childhood (Bromley et al., 2014). Mounting evidence regarding older ASM exposure has prompted changes to prescribing guidelines (Medicines and Healthcare products Regulatory Agency [MHRA], 2018), in turn facilitating better-evidence prescribing and preconceptual counselling for women with epilepsy of childbearing age. Most notable is the evidence for sodium valproate, a now established human teratogen linked with a confirmed syndrome presentation, fetal valproate spectrum disorder (Bromley, Baker, Clayton-Smith & Wood, 2019). Comparatively, conclusions regarding newer ASM exposure remain limited and cannot be extrapolated from data on older ASMs due to the diversity of medicinal compounds which fall into the ASM category. In a Cochrane review of 28 studies, a paucity of research into lamotrigine, levetiracetam and topiramate was highlighted, with no data available for oxcarbazepine, perampanel, eslicarbazepine or zonisamide (Bromley et al., 2014). Although the study of newer ASMs has since increased, findings are mixed and methodologies used to investigate child neurodevelopment following in-utero exposure vary widely. Few studies have the remit to assess short- and long-term outcomes, both of which are crucial to understanding the impact of ASMs on the trajectory of brain development from infancy to early adulthood (Hill, Wlodarczyk, Palacios & Finnell, 2010).

To date, there has been no focussed attempt to synthesise and explicate research into newer ASMs and neurodevelopment. Newer ASMs are a varied group of medicinal compounds and their safety or risk profiles cannot be predicted via older ASMs or each other. Reviews are headlined by the large effect sizes associated with valproate teratogenicity, to the detriment of reaching a consensus on newer medications that are

increasingly used (Meador et al., 2018). The current review sought to bridge this gap in knowledge by offering a dedicated focus on newer ASMs only. Primary aims were to delineate child neurodevelopmental outcomes associated with in-utero exposure to eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, topiramate and zonisamide. Additionally, the review aimed to inform the direction of future research and practice, eventually facilitating informed decision-making for key stakeholders including women with epilepsy and prescribers alike.

Method

A narrative systematic review method, designed to provide high quality levels of evidence, was employed to synthesise the current research base for all available literature pertaining to newer ASM exposure and child neurodevelopment. The specific ASMs of interest were: eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, topiramate and zonisamide. These were selected on the basis of their prevalence of use (Meador et al., 2018).

Search strategy and selection criteria

Following PRISMA guidance (Moher et al., 2015), a search strategy was developed and adapted for use across five medical and psychological bibliographic databases: MEDLINE, Embase, Web of Science, CINAHL Plus and PsycINFO. Search term blocks related to in-utero exposure, child neurodevelopment and the ASMs of interest were constructed and tabulated for each database (see Appendix B). The review was PROSPERO-registered prior to commencement (ID: CRD4202012266). Searches were run in December 2019 and updated in May 2020. Databases were searched by the first author (RK) for published literature containing key search terms and concepts within titles or abstracts. Results were

restricted to articles published in/after the year 2000, given the increased use of newer ASMs from this timepoint (Meador et al., 2018). Results were also restricted to human studies available in English. Reference lists of all eligible papers and seminal review papers were also searched for not previously identified studies.

A-priori selection criteria were agreed by the review team (see Table 1), following the PICOT framework (Schardt, Adams, Owens, Keitz, & Fontelo 2007). No exclusions were made on the basis of methodological quality as it was planned that all included articles would be quality assessed. Titles and abstracts of all literature retrieved were screened by two authors (RK, RB) independently. Full text screening was then undertaken to confirm full eligibility for inclusion in the review by the two authors (RK, RB) independently.

Table 1. Selection criteria for eligibility

Population	Children of mothers with epilepsy (CME).
Intervention	In-utero exposure to ASM monotherapies: lamotrigine, topiramate, levetiracetam, oxcarbazepine, eslicarbazepine, zonisamide, perampanel, gabapentin and lacosamide.
Controls/ Comparators	• CME who did not take ASMs during pregnancy • Children of mothers without epilepsy • Children of mothers who took ASMs other than those under investigation during pregnancy • Normative sample data
Outcomes	• Global cognitive outcomes (e.g., IQ, DQ, presence of LD) • Specific cognitive outcomes (e.g., memory, attention, language etc.) • Other outcomes, including estimates of functional outcomes (e.g., adaptive functioning, academic attainment) and signals of atypical neurodevelopment (e.g., incidence and/or traits of ASD, ADHD, developmental delay etc.)
Type of Study	• Observational cohort studies • Population dataset studies • Randomised controlled trials • Pregnancy registry studies

Data extraction, quality appraisal and synthesis

The first author (RK) undertook data extraction. There was high variation of statistical data arising from diverse and disparate outcome measures, with necessary statistics missing from certain studies. This is a challenge commonly encountered in the synthesis of observational studies (Snilsveit, Oliver & Vojtkova, 2012). Though meta-analysis can provide the highest standard of synthesis in most circumstances (Stroup et al., 2000), inappropriate combining of heterogeneous data risks arriving at invalid and unreliable conclusions (Colliver, Kucera & Verhulst, 2008). A narrative synthesis of findings, following Popay et al.'s (2006) guidance was therefore selected to ensure a clear and useful summary of the literature to date (Egger, Schneider & Smith, 1998).[1]

Two reviewers independently completed quality appraisals for all included studies (RK, RB) using the Newcastle Ottawa Scale (NOS, Wells et al., 2012); a tool recommended for non-randomised studies (Cochrane Scientific Committee, 2017). The NOS was adapted (see Appendix C) to suit the review question and allow comparisons with a previous Cochrane review (Bromley et al., 2014). Risk of bias across selection, comparability and outcome domains were rated as 'poor', 'fair' or 'good' based on a star-rating system. *Selection* related to the representativeness of cohorts, exposure ascertainment and dose investigations. *Comparability* concerned whether cohorts were comparable at baseline. *Outcome* assessment concerned issues including blinding, missing data and attrition.

[1] See 'Data synthesis' (pp.116) section of Paper 3 for fuller discussion of the rationale for narrative approach.

Results

Search results

A PRISMA flowchart capturing the return and selection of relevant articles can be seen in Figure 1. Using the above search strategy and selection criteria, a total of 6632 results were returned across the five databases. After the removal of duplicates and exclusion of ineligible papers, a total of 35 articles were identified for inclusion in the review, with a good level of agreement between reviewers ($\kappa = .935$, $p < .001$) No further articles were identified via reference searching of included article bibliographies.

Study characteristics

A summary of study characteristics and findings from included papers can be seen in Table 2. All 35 publications were quantitative, employing retrospective cohort ($n = 2$), prospective cohort ($n = 16$), pregnancy registry ($n = 11$) or population dataset designs ($n = 6$). Most cohorts were sampled from the UK, the USA and Scandinavia, with outcomes available for cohorts between the ages of 4 months to 15 years of age. Using either cross-sectional or follow-up assessments, methods included direct neuropsychological assessment, parental report and diagnoses of neurodevelopmental conditions. Outcomes were global ability estimates (e.g., IQ/DQ), specific cognitive skills (e.g., language, executive functioning, attention) and other outcomes (e.g., functional ability, academic attainment and traits/incidence of neurodevelopmental conditions).

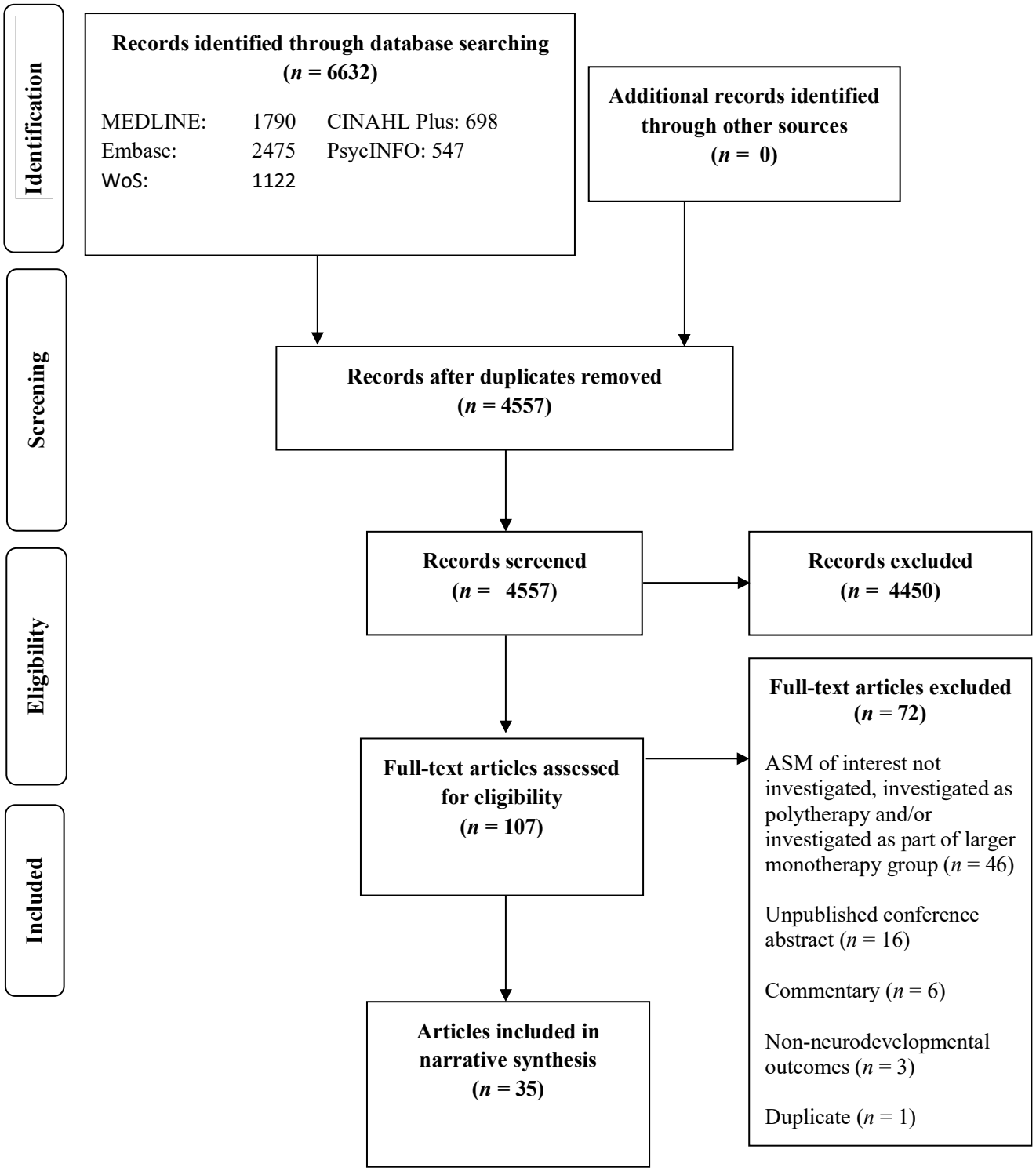

Figure 1. PRISMA flowchart

Table 2. Study characteristics and findings

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
Dutch Neurodevelopmental Study *Netherlands*	Huber-Mollema et al. (2020)	Pregnancy registry	161 exposed CME	CBZ (32) **LTG (82)** **LEV (25)** VPA (22)	6 years–7 years and 11 months	IQ (WISC-II-NL)	Domains (WISC-II-NL); attention/executive function, language, memory and learning, fine motor skills and visuospatial skills (NEPSY-II-NL)	NA	LTG and LEV-exposed groups performed significantly better on all outcomes compared to VPA-exposed group. LTG and LEV-exposed groups were comparable on almost all outcome measures. LTG and CBZ-exposed groups were comparable on almost all outcome measures. LTG and LEV-exposed groups performed at average to above levels on FSIQ and specific cognitive functions. N.S dose-effect for LEV or LTG.	*****	**	***

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
	Huber-Mollema et al. (2019)	Pregnancy registry	183 exposed CME	CBZ (37) **LTG (88)** **LEV (30)** VPA (26)	6 years – 7 years and 11 months	NA	NA	Child behavioural problems (CBCL and SEV)	N.S. differences in behavioural problems between ASM groups. LTG group had significantly higher parental ratings of ODD, CD and clinical symptoms of autistic behaviour compared to population norms (SEV), LEV group had significantly higher parental ratings of CD compared to population norms (SEV). LTG group had significantly fewer social problems compared to VPA group. LEV groups had significantly fewer social problems, ADHD symptoms and attentional problems compared to VPA group. LTG group had significantly more symptoms of ADHD compared to LEV group. LEV group had significantly higher parental ratings of anxiety than LTG group. N.S. dose-effect for LTG or LEV.	*****	**	*

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
Danish Population Studies ***Denmark***	Christen-sen et al. (2019)	Populat-ion	2923 exposed 899,941 un-exposed	CBZ (423) CZP (314) **LTG (1383)** **OXC (372)** VPA (431)	3-15 years (mean age 10.1 years)	NA	NA	Risk of ADHD (diagnoses)	N.S. difference between risk of ADHD for LTG group compared to unexposed group. N.S. difference between risk of ADHD for OXC group compared to unexposed group. N.S. increase in risk of ADHD between LTG group and OXC group. VPA group at significantly greater risk of ADHD compared to LTG group. N.S. high- versus low-dose differences in risk of ADHD for LTG or OXC when compared to unexposed group.	*****	*	***

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
	Bech et al. (2018)	Populat-ion	636 exposed 434 un-exposed	CBZ (35) CZP (43) **GBP (29)** **LTG (290)** **LEV (12)** **OXC (44)** PHB (11) **TPM (27)** VPA (55) Other (13)	6 – 7 years (median age 6.1 years)	Risk of LD (diagnoses)	NA	NA	N.S. differences in risk of LD for GBP, LTG or OXC groups when compared to unexposed group. Significantly increased risk of LD for LEV group versus unexposed group. Significantly increased risk of LD for TPM group versus unexposed group. Significantly lower risk of LD for LTG groups when compared with VPA group or 'other ASM' group. N.S. differences in risk of LD for GBP, TPM, LEV, OXC or TPM groups when compared with other ASM group. High-dose LTG decreased the risk of LD compared with other ASM group. Low does LTG increased the risk of LD compared to unexposed group. No dosage calculations made for other drugs.	*****	*	**

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
	Elkjær et al. (2018)	Population	1865 exposed 477,162 unexposed	CBZ (294) CZP (188) **LTG (396)** **OXC (236)** PHB (86) VPA (253)	7-14 years (mean age 12.9 years)	NA	NA	Academic performance (language and maths tests)	N.S. differences on academic performance in maths and language tests at all grades between LTG group and unexposed group. N.S. differences on academic performance in language tests between OXC group and unexposed group. OXC group performed significantly worse than unexposed group on Grade 6 maths tests. LTG group performed significantly better than VPA group on all tests. N.S. high- versus low-dose differences in test results at 6th Grade for LTG or OXC groups.	*****	*	**
	Christensen et al. (2013)	Population	2644 exposed 655,1027 unexposed* *includes comparators	CBZ (386) CZP (269) **LTG (647)** **OXC (321)** VPA (388)	4- 14 years (mean age 8.8 years)	NA	NA	Risk of ASD (diagnoses)	N.S. differences in risk of ASD for LTG group compared to unexposed/comparator group. N.S. differences in risk of ASD for OXC group compared to unexposed/comparator group.	*****	*	***

Study (year) *Country*	Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
					Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
Richards et al. (2019) *New Zealand*	Popula-tion	606 exposed 286,966 un-exposed	CBZ (201) **LTG (149)** **LEV (10)** **TPM (28)** VPA (161) Poly (57)	4 years	Developmental difficulties (parental report on PEDS)	NA	Emotional and behavioural development (parental report on SDQ) Referrals to 2º care.	Significantly greater proportion of LTG group referred to/seen by 2º care compared to unexposed group. LTG group were significantly more likely to have abnormal SDQ scores compared to unexposed group. N.S. differences in risk of parents reporting concerns in PEDS/SDQ assessments between LTG and VPA. N.S. differences in risk of parents reporting concerns in PEDS/SDQ assessments between LTG and CBZ. TPM and LEV groups were not statistically analysed due to small numbers.	****	*	**

Neurodevelopmental Effects of Anti-Epileptic Drugs (NEAD) ***UK; USA***	Cohen et al. (2019); Cohen et al. (2013); **Meador et al., (2013)**; Meador et al. (2012); Cohen et al. (2011); Meador et al (2011); Meador et al. (2009)	Pro-spective cohort	305 exposed CME	CBZ (93) **LTG (99)** PHT (52) VPA(61)	3 years, 4.5 years and 6 years (follow-up of same cohort)	IQ (DAS) DQ (BSID)	DQ domains (BSID) Memory (CMS) Executive functioning (BRIEF, NEPSY)	Adaptive behaviour (ABAS-II) Behavioural problems (BASC) Stress in child/parent relationship (PSI)	**Global outcomes** Significantly higher IQ scores in LTG group compared to VPA group at 3 years, 4.5 years and 6 years. N.S. dose-effect for LTG and IQ at 3 years, 4.5 years or 6 years. **Specific outcomes** Significantly higher index scores in LTG group compared to VPA group at 3 years and 6 years. Within LTG group, verbal abilities were significantly worse than non-verbal abilities at 3 years, 4.5 years and 6 years. LTG group performed significantly lower than normative sample on attention/concentration and learning indexes at 6 years. N.S. differences between LTG group at normative sample on overall CMS score at 6 years. **Other Outcomes** N.S. differences between LTG group and other ASMs on adaptive and emotional/behavioural functioning at 3 years. Significant differences between LTG and VPA group on adaptive and emotional/behavioural functioning at 6 years. N.S. effect of high dosage LTG on adaptive functioning at 3 years or 6 years.	***** *	**	****

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
									Significantly fewer atypical behaviours and attention difficulties for LTG group compared to VPA group.			
	McVearry et al. (2009) [NEAD sub-study]	Pro-spective cohort	42 exposed CME	CBZ (16) LTG (17) VPA (9)	3.5 – 5.5 years (mean age 4.2 years)	NA	Divergent thinking (TCAM)	NA	LTG group cognitive fluency and originality was significantly superior to VPA group. High-dose LTG subgroup scored better on TCAM compared to low-dose LTG group.	***** *	**	****

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
Mother and Child Cohort Study (MoBa) *Norway*	Husebye et al. (2019)	Pro-spective cohort	346 exposed CME 388 un-exposed CME 133,674 un-exposed	CBZ (72) *17 **LTG (112) *41** **LEV (17) *6** **TPM (11) *4** **OXC (8) *1** **GBP (8) *1** VPA (40) *16 *Complet-ers at 8 years.	5 – 8 years	NA	Language impairment (parental report-partial ASQ and SLS)	NA	Risk of language impairment at age 5 and 8 years did not differ significantly between LEV, LTG or TPM groups when compared to the unexposed group. Mean scores on language outcomes at ages 5 and 8 did not differ significantly between LEV, LTG or TPM groups when compared to the unexposed group. N.S. ASM concentration-effect for LTG, LEV or TPM and language outcomes. OXC not analysed.	***** *	**	*

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
	Bjørk et al. (2018)	Pro-spective cohort	179 exposed CME 75,497 un-exposed	CBZ (41) **LTG (76)** **LEV (12)** **OXC (4)** **TPM (6)**	1.5 – 3 years	NA	NA	Autistic traits (partial SCQ, partial CHAT)	When both groups used a folic acid supplement, there was N.S. difference in rate of autistic traits in the LTG group compared to the unexposed group. When neither group used a folic acid supplement, there was a significantly higher proportion of autistic traits in LTG group compared to unexposed group. There were N.S. differences between risk of autistic traits in LEV, OXC or TPM groups compared to un-exposed group, regardless of folate use. N.S. correlation between ASM concentration and autistic traits for LEV or LTG.	***** *	*	*

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
	Veiby et al. (2013a)	Pro-spective cohort	182 exposed CME 77,770 un-exposed	CBZ (48) **LTG (71)** VPA (27) Poly (41)	0.5 years and 3 years	NA	Language skills (Dale et al. sentence completeness criteria)	Motor, social and communication skills, autistic traits, ADHD symptoms and aggressive-ness (as assessed by partial ASQ, BSID, CHAT, CBCL and full SCQ)	N.S. difference in risk of adverse outcomes for LTG group when compared to unexposed group at 6 months. N.S. difference in language skills when compared to unexposed group at 36 months.	****	*	**

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
	Veiby et al. (2013b)	Pro-spective cohort	184 exposed CME 221 un-exposed CME 60,583 un-exposed	CBZ (41)*31 **LTG (65)*44** VPA (25)*19 Poly (26)*25 *Complet-ers at 3 years.	1.5 years and 3 years	NA	Language skills (Dale et al. sentence complete-ness criteria)	Motor, social and communicati on skills, autistic traits, ADHD symptoms and aggressive-ness (as assessed by partial ASQ, BISD, CHAT, CBCL and full SCQ)	N.S. differences between LTG and unexposed group on any outcome assessed at 1.5 years. Significantly higher adverse outcomes for LTG group at 3 years compared to unexposed group on sentence completeness and autistic traits. N.S. differences on all other measures at 36 months.	****	*	**
Lacey et al. (2018) *Wales*		Popula-tion	440 exposed CME 1756 un-exposed	CBZ (84) **LTG (24)** VPA (115) Poly (39)	7 years	NA	NA	Educational attainment (KS1 assessment: core subject indicator, maths, language and science)	N.S. differences between LTG group and unexposed group on any aspect of KS1 score.	****	*	**

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
Liverpool and Manchester Neurodevelopment Group (LMNG) ***UK***	Baker et al. (2015)	Pro-spective Cohort	145 exposed CME 25 un-exposed CME 213 un-exposed	CBZ (50) **LTG (30)** VPA (51) Other (14)	6 years	IQ (DAS)	Intelligence indexes (DAS)	Special educational needs (SEN)	N.S. differences in FSIQ, verbal abilities, non-verbal abilities and spatial abilities in LTG group when compared to unexposed group. N.S. increased rate of special educational needs in LTG group compared to unexposed group. Significantly better scores on FSIQ, verbal abilities and spatial abilities for LTG group when compared to high-dose VPA.	***** *	**	****
	Bromley et al. (2013)	Pro-spective Cohort	243 exposed CME 285 un-exposed	CBZ (59) **LTG (36)** VPA(59) Other (14) Poly (41)	1 year, 3 years and 6 years	NA	NA	Neurodevelopmental conditions (frequency of ASD, ADHD and dyspraxia)	N.S. difference in risk of neurodevelopmental disorder between the LTG group and unexposed group.	***** *	**	****
	Bromley et al. (2010)	Pro-spective Cohort	198 exposed CME 230 un-exposed	CBZ (48) **LTG (34)** VPA (42) Other (14)	4 months – 2 years	DQ (GMDS)	Develop-mental domains (GMDS)	NA	N.S. differences between LTG group and unexposed group for overall development (DQ). Significant differences in non-verbal abilities (poorer hand and eye coordination) for LTG group compared to control group. N.S. dose-effect relationship between LTG and DQ.	***** *	**	****

Study (year) *Country*	Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
					Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
Kasradze et al. (2017) *Georgia*	Pregnancy registry	50 exposed CME 50 unexposed	CBZ (16) **LTG (3)** PB (3) VPA (30) Poly (9)	3 – 6 years	IQ (WPPSI-IV)	Intelligence indexes ability (WPPSI-IV)	NA	LTG group had significantly lower FSIQ scores than unexposed group. LTG group had significantly poorer verbal and visual comprehension scores than unexposed group.	**	**	****

UKEPR Follow-up Studies ***UK***	Bromley et al. (2016)	Pregnancy registry	130 exposed CME 55 unexposed CME	**GBP (14)** **LEV (42)** **TPM (27)** VPA (47)	5 – 9 years	IQ (WISC-III; WPPSI-III)	Intelligence indexes (WISC-III; WPPSI-III); attention and executive functioning (NEPSY-II); language (CELF-IV)	Behaviour (parental rating on BASC)	GBP excluded from statistical analysis but comparable means observed with unexposed group. N.S. differences in FSIQ, verbal abilities, non-verbal abilities or processing speed between LEV group and unexposed group. N.S. differences in language, memory, attention, and executive functioning or behavioural variables between LEV group and unexposed group. N.S. dose-effect relationship between LEV and poorer outcomes. At half the median dose of VPA, N.S. differences in outcomes were found in comparison to half the median dose of LEV. N.S. differences in FSIQ, verbal abilities, non-verbal abilities or processing speed between TPM group and unexposed group. TPM group scored significantly better on one aspect of attention and executive functioning compared to unexposed group. N.S. differences in language, memory or behavioural variables between TPM group and unexposed group. N.S. dose-effect relationship between TPM and poorer outcomes. At half the median dose of VPA, N.S. differences in outcomes were found in comparison to half the median dose of TPM.	*****	**	****

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
	Shallcross et al. (2014)	Pregnancy registry	97 exposed CME 131 unexposed	**LEV (53)** VPA (44)	3 – 4.5 years (mean age 42 months)	NA	DQ subdomains(GMDS) Language (RDLS)	NA	N.S. differences between LEV group and unexposed group on any GMDS subdomains. N.S. differences between LEV group and unexposed group for comprehension or expressive language on RDLS. LEV group scored significantly higher (average 15.8 points) than VPA group on gross motor skills subdomain. N.S. differences between VPA and LEV on social, hand and eye or performance skills subdomain. LEV scored significantly higher than VPA on comprehension and expressive language on RDLS. N.S. dose-effect relationship detected for LEV.	*****	**	**

Study (year) *Country*		Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
						Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
	Shallcross et al. (2011)	Pregnancy registry	95 exposed CME 97 unexposed	**LEV (51)** VPA (44)	< 2 years	DQ (GMDS)	Locomotor skills, personal and social skills, hearing and language skills, eye and hand coordination skills and nonverbal performance (GMDS)	NA	N.S. difference in overall DQ between LEV group and unexposed group. LEV group obtained significantly higher DQ scores than VPA group. LEV group were at significantly reduced risk of delayed development (below average DQ) compared to VPA group. LEV group obtained significantly higher subscale scores than VPA group on locomotor skills, hand/eye coordination and performance skills. N.S. differences between LEV group and unexposed group on any subscale of GMDS. N.S. dose-effect relationship between LEV and overall DQ.	*****	**	**

Study (year) *Country*	Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
					Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
Deshmukh et al., (2016) *North America*	Pregnancy registry	252 exposed CME	CBZ (97) **LTG (104)** VPA (51)	3 – 6 years	NA	NA	Adaptive behaviour (VABS-II)	LTG-exposed children were significantly less likely than VPA-exposed children to score low or moderately low in the ABC, socialisation, and motor domains, and in the expressive, interpersonal, play, and gross motor subdomains. N.S. differences were observed between the LTG and CBZ groups. N.S. dose–response effects were observed LTG on ABC scores.	*****	*	*
Videman et al. (2016) *Finland*	Prospective cohort	56 exposed CME 67 unexposed	CBZ (9) **OXC (10)** **LTG (9)** **LEV (7)** **TPM (1)** VPA (5) Poly (16)	7 months	NA	Neurological outcomes (subquotients of GMDS; HINE)	Perceptual abilities (eye tracking test)	TPM excluded from statistical analysis. N.S. differences in developmental sub-quotients between LTG or LEV groups compared to unexposed group. OXC group had significantly lower scores in 'hearing and speech' sub-quotient compared to unexposed group. N.S. differences in perceptual abilities between any ASMs, when compared with each other or when compared with unexposed group.	*****	*	****

Study (year) *Country*	Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
					Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
Guveli et al. (2015) ***Turkey***	Retro-spective cohort	28 exposed CME 13 un-exposed CME	CBZ (4) CLZ (1) **OXC (1)** PB (5) PHT (2) VPA (2) Poly (5)	6 – 15 years (mean age 8.3 years)	IQ (WISC)	NA	Behaviour (CPRS)	N.S. difference between OXC group and unexposed group on IQ scores or CPRS scores.	***	-	**

Rihtman et al., 2013 ***Israel***	Preg-nancy registry	69 exposed CME 52 un-exposed	**LTG (40)** VPA (29)	3 years–6 years and 11 months	IQ (SBS)	Verbal and non-verbal domain scores (SBS) Visual Perception (Beery)	Motor co-ordination problems (DCDQ; M-FUN) Sensory profile (parental report) Behaviour (BRIEF and BRIEF-P; CPRS)	Significant unexposed versus LTG group differences on Beery subscales of Visual Perception and Motor Control, with worse scores for LTG group Significant unexposed versus LTG group differences on M-Fun areas of Fine Motor and Gross Motor skills, with worse scores for LTG group. Significantly worse scores for LTG group on sensory measures when compared to unexposed group. N.S. differences between LTG group and unexposed group on any behavioural measure. N.S. differences between LTG and VPA groups on any measure. N.S. dose-effect relationship between LTG and any measure except Fine Motor skills on M-FUN better scores (r = +0.33)	****	*	****

Study (year) *Country*	Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
					Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
Rihtman et al., 2012 *Israel*	Pregnancy registry	9 exposed CME 18 unexposed	**TPM (9)**	3 years – 6 years and 11 months (mean age 47.4 months)	IQ (SBS)	Verbal and non-verbal domain scores (SBS) Visual Perception (Beery)	Motor coordination problems (little DCDQ; M-FUN) Behaviour (CPRS)	The TPM group obtained significantly lower IQ scores and fluid reasoning, visual spatial, verbal IQ and non-verbal IQ subscores compared to the unexposed group. Significantly worse scores on five/ten scores on the DCDQ in the TPM group compared to the unexposed group (visual perception; motor control; general coordination; fine motor; gross motor) Significant worse scores were found for two/fourteen scales on the CPRS (cognitive problems/inattention and for the perfectionism) in the TPM group compared to the unexposed group. The TPM group scored significantly lower than the unexposed group on the assessor questionnaire of the M-FUN.	**	*	**
Cummings et al. (2011) *UK*	Pregnancy registry	127 exposed CME 53 unexposed	CBZ (49) **LTG (44)** VPA (58)	Up to 8 years	DQ (BSID [<42 months] or GMDS [>42 months])	NA	NA	N.S. differences in outcomes between LTG group and unexposed group. N.S. difference in risk of developmental delay for LTG group compared to control group.	**	*	****

Study (year) *Country*	Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
					Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)
Nadebaum et al. (2011) *Australia*	Pregnancy registry	102 exposed CME	CBZ (34) **LTG (9)** VPA (26) Other (2) Poly (34)	6 – 8 years (mean age 7.4 years)	NA	Language (CELF)	NA	N.S differences in proportion of language delay within LTG group compared to normative population rate. N.S. difference in core language score for LTG group compared to expected mean of 100. Significantly better language scores in LTG group compared to VPA monotherapy and VPA polytherapy groups.	*****	**	***
Dean et al. (2002) *Scotland*	Retrospective cohort	210 exposed CME 28 unexposed CME (sibs of exposed cohort)	CBZ (69) **GBP (1)** PHB (61) PHT (24) PRM (2) ETH (2) Poly (4)	2 days – 39 years (mean age 9 years)	NA	NA	Risk of adverse outcomes (records or parental report of developmental delay and/or behavioural difficulties)	No significant differences between GPB child and unexposed group on any outcome assessed.	**	-	*

Study (year) *Country*	Design	Sample size	ASMs (*n*)	Age	Outcomes (measures)			Results	Quality assessment		
					Global Cognitive	Specific Cognitive	Other		Selection (/6 stars)	Comparability (/2 stars)	Outcome (/4 stars)

Abbreviations: CME = Children of Mothers with Epilepsy; LTG = Lamotrigine; VPA = Valproate; CBZ = Carbamazepine; TPM = Topiramate; LEV = Levetiracetam; OXC = Oxcarbazepine; GBP = Gabapentin; CLZ = Clozapine; PB = Phenobarbital; PHT = Phenytoin; WISC-II-NL= Wechsler Intelligence Scale for Children, 2nd Edition, Netherlands; NEPSY-II-NL = Developmental Neuropsychological Assessment, 2nd Edition, Netherlands; CBCL = Child Behaviour Checklist; SEV = Social Emotional Questionnaire; PEDS = Parental Evaluation of Developmental Status; SDQ = Strengths and Difficulties Questionnaire; BSID = Bayley Scales of Infant Development; CMS = Children's Memory Scale; DAS = Differential Ability Scales; BASC = Behaviour Assessment System for Children; PSI = Parental Stress Index; BRIEF = Behaviour Rating Inventory of Executive Function; ABAS-II = Adaptive Behaviour Assessment System; ASQ = Ages and Stages Questionnaire; CHAT = Checklist for Autism in Toddlers; WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition; GMDS = Griffiths Mental Development Scales; CELF-IV = Clinical Evaluation of Language Fundamentals, Fourth Edition; RDLS = Reynell Developmental Language Scales; HINE = Hammersmith Infant Neuropsychological Examination; CPRS = Child-Parent Relationship Scale; VABS-II = Vineland Adaptive Behaviour Scale, 2nd Edition; DCDQ = Developmental Coordination Disorder Questionnaire; M-FUN = Miller Function and Participation States; IQ = Intelligence Quotient; DQ = Developmental Quotient; FSIQ = Full-Scale Intelligence Quotient; ODD = Operational Defiance Disorder; CD = Conduct Disorder; ADHD = Attention Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder; LD = Learning Disability; KS1 = Key stage 1; SEN = Special Educational Needs.

Quality assessment rating key:			
Good	5 or 6 stars in selection	2 stars in comparability	3 or 4 stars in outcome
Fair	4 stars in selection	1 star in comparability	2 stars in outcome
Weaker	1 – 3 stars in selection	0 stars in comparability	0 or 1 star in outcome

Quality assessments of included studies

An overview of quality appraisal outcomes can be seen in Table 2. There was a good level of agreement between reviewers on the NOS ($\kappa = .973$, $p < .001$). Key strengths and weaknesses attributable to design are summarised in Table 3.

Table 3. Study designs

Design	Defining Features	Strengths	Weaknesses
Population dataset	Prospective enrolment and data collection	Large datasets Representativeness Generalisability	Limited covariate analysis Unclear blinding Exposure/dosage ascertainment often limited to prescription patterns. Often unequal sample sizes Missing data
Prospective cohort	Prospective recruitment and data collection	Cohort comparability Covariate analysis Clear blinding Exposure/dosage ascertainment based on individual records. Scope for attrition/missing data analyses	Variable representativeness Attrition/missing data
Retrospective cohort	Retrospective recruitment and data collection	Cohort comparability Covariate analysis Clear blinding conditions. Scope for attrition/missing data analyses.	Selection bias Recall bias/demand effects Variable representativeness Retrospective exposure/dosage ascertainment
Pregnancy registry	Retrospective recruitment Prospective data collection	Cohort comparability Covariate analysis Exposure/dosage ascertainment based on individual records. Scope for attrition/missing data analyses.	Selection bias Variable representativeness Attrition

Most studies scored well for *selection*, with 12 studies achieving 'good' ratings. Four achieved 'fair' ratings and four achieved 'poor' ratings. Cohorts from population dataset studies were rated 'truly representative', whereas prospective cohort studies and pregnancy registry studies were rated 'somewhat representative'. Of the 14 studies investigating dose, ten ascertained dosage information via individual medical records, scoring better than those extrapolating dose from prescription patterns. One study group ascertained dosage objectively via blood/ASM concentration (Husebye et al., 2019; Bjørk et al., 2018). One study ascertained dose from retrospective reporting (Dean et al., 2002), risking recall bias.

Twelve studies demonstrated 'fair' *comparability* of cohorts by considering key covariates established as impacting on neurodevelopment (Bromley et al., 2014). Prospective cohort and pregnancy registry studies considered additional covariates. Population dataset studies generally scored poorly on this item. Both retrospective cohort studies (Guveli et al., 2016; Dean et al., 2002) failed to consider covariates.

Most studies included in the review (n = 14) achieved 'good' or 'fair' ratings for *outcome*. Direct, blinded assessment conferred higher ratings (Neurodevelopmental Effects of Anti-Epileptic Drugs, NEAD; Liverpool and Manchester Neurodevelopment Group, LMNG; Kasradze et al., 2017; Rihtman, Parush & Ornoy, 2013; Nadebaum et al., 2011). Thirteen studies used non-blinded assessment via routine review (n = 5), parental report (n = 6) or unblinded direct assessment (n = 2). Five papers were rated poorly (Bjork et al., 2018; Husebye et al., 2019; Huber-Mollema, Oort, Lindhout & Rodenburg, 2020; Deshmukh et al., 2016; Dean et al., 2002), owing to blinding conditions and/or incomplete attrition information.

Results of narrative synthesis

A summary of study characteristics and findings is provided in Table 2.

Eslicarbazepine, Lacosamide, Perampanel and Zonisamide

There were no data available regarding neurodevelopmental outcomes following in-utero exposure to eslicarbazepine, lacosamide, perampanel or zonisamide.

Gabapentin

Two studies reported child outcomes following in-utero gabapentin exposure, a Danish population-based study (Bech et al., 2018) and a retrospective cohort study including a single exposed case (Dean et al., 2002). Additional studies recruited gabapentin-exposed children but subsequently excluded these data from statistical analysis, citing small sample sizes (Husebye et al., 2019; Bjørk et al., 2018; Nadebaum et al., 2011; Bromley et al., 2010; Baker et al., 2015; Bromley et al., 2016). As such, findings must be interpreted with caution and particular attention should be paid to the quality level of the study reporting gabapentin outcomes.

Global outcomes for gabapentin

Gabapentin versus controls: Bech et al. (2018) examined the educational records of 29 children exposed prenatally to gabapentin for evidence of learning disabilities at 6 years, including developmental and emotional-behavioural conditions or special educational needs. Risk of learning disability was no different for exposed (n =29) versus unexposed (n = 434) children. In 14 cases, assessed in blinded fashion, Bromley et al. (2016) observed comparable mean IQ scores in gabapentin-exposed children compared to a control group, however, this difference was not analysed for significance.

Gabapentin versus other ASM: When gabapentin-exposed children were compared to an 'other ASM' group, there was no significant difference in child risk of having a learning disability at 6 years of age (Bech et al., 2018). Data regarding gabapentin outcomes were

obtained prospectively but analyses did not adjust for key covarying factors, limiting the strength of these findings.

Specific outcomes for gabapentin

Gabapentin versus controls: No studies assessing specific cognitive outcomes compared gabapentin-exposed children with controls.

Gabapentin versus other ASM: No studies assessing specific cognitive outcomes compared gabapentin-exposed children with a comparator ASM.

Other outcomes for gabapentin

Gabapentin versus controls: Dean et al.'s (2002) findings were not interpretable given the single case sample.

Gabapentin versus other ASM: No studies assessing other types of outcomes compared gabapentin-exposed children with a comparator ASM.

Dose of gabapentin

No dose-response relationships were investigated for children exposed to gabapentin.

Lamotrigine

Thirteen studies, leading to 27 publications, reported outcomes for lamotrigine with cohorts across a range of countries. Designs comprised seven pregnancy registry studies, two population-based studies and four prospective cohort studies. Assessment points ranged from 4 months to 12 years, investigating myriad outcomes including IQ/DQ, specific cognitive skills (e.g., divergent thinking, memory, language), functional outcomes (e.g., educational attainment) and frequency of neurodevelopmental conditions. Comparisons

mostly utilised an unexposed cohort and/or a comparator ASM cohort, with normative data comparisons forming the main analysis in two studies (Huber-Mollema et al., 2019; Deshmukh et al., 2016).

Global outcomes for lamotrigine

Lamotrigine versus controls: Six studies assessed global cognitive outcomes. The LMNG assessed DQ at 4-24 months (*n* = 34, Bromley et al., 2010) and IQ at 6 years (*n* = 30, Baker et al., 2015) using a prospective design with blinded direct neuropsychological assessment. After adjusting for multiple covariates, no significant differences in global ability estimates were found for lamotrigine-exposed children compared to unexposed children. These findings were replicated at 7 months (Videman et al., 2016) and up to 8 years (Cummings, Stewart, Stevenson, Morrow & Nelson, 2011; Rihtman et al. 2013; Huber-Mollema, van Iterson, Oor, Lindhout & Rodenburg, 2020). The largest lamotrigine-exposed cohort (*n* = 82) was provided by Huber-Mollema et al. (2020), who failed to find poorer outcomes for the exposed children following adjustment for numerous confounding variables. Kasradze et al. (2016) reported lower IQ in lamotrigine-exposed children but this was not reliable due to sample size (*n* = 3). A large population dataset study identified no differences in risk of learning disabilities for lamotrigine-exposed children (*n* = 290, Bech et al., 2018).

Lamotrigine versus other ASM: Most comparisons were with valproate. Research using high quality designs indicated favourable outcomes for lamotrigine-exposed children in comparison to children exposed to valproate (Meador et al., 2009; Meador et al., 2013; Bromley et al., 2010; Baker et al., 2015; Huber-Mollema et al., 2020). Rihtman et al. (2013) reported comparable IQ performance between lamotrigine-exposed (*n* = 40) and valproate-exposed (*n* = 29) cohorts at 3-7 years, but doses of both valproate and lamotrigine were

lower than in other studies and the cohorts' representativeness were weakened as a result of convenience sampling.

Meador et al. (2013) observed comparable IQ scores between carbamazepine-exposed children ($n = 93$) and lamotrigine-exposed children ($n = 99$). This was more recently replicated by Huber-Mollema et al. (2020), who also provided the first IQ data pertaining to lamotrigine ($n = 88$) in comparison to levetiracetam ($n = 38$), observing comparable IQ scores at 6-7 years.

Specific outcomes for lamotrigine

Lamotrigine versus controls: In infants, comparable performance to controls at 7 months on all developmental sub-quotients by a lamotrigine-exposed cohort ($n = 9$) has been observed (Videman et al., 2016). One study reported lower verbal and visual comprehension index scores for lamotrigine-exposed children ($n = 3$) at 3-6 years but the exposed cohort was small (Kasradze et al., 2017). The LMNG observed poorer hand/eye coordination on unadjusted scores in their lamotrigine-exposed cohort ($n = 34$) at ≤ 2 years (Bromley et al. 2013) but not at the 6-year follow-up, with comparable verbal, non-verbal and spatial abilities between lamotrigine-exposed ($n = 30$) and unexposed controls (Baker et al., 2015). Within NEAD's lamotrigine-exposed group, verbal abilities were significantly worse than non-verbal abilities at 4.5 years and 6 years, whereas normative sample abilities were equal (Meador et al. (2012; 2013), although the absence of a study-specific control group renders the validity of this finding unclear.

A number of papers examined language development from the MoBA dataset. At 3 years, comparable communication skills were observed between lamotrigine-exposed ($n = 44$) versus unexposed children (Veiby et al., 2013a), however, poorer use of complex sentences was more frequent in lamotrigine-exposed children than in the control group (14%

versus 4.5%, respectively). Comparable language performance and low risk of language impairment in lamotrigine-exposed children was reassuringly observed at 5 years (n = 39) and 8 years (n = 41) relative to controls (Husebye et al., 2019). Nadebaum et al. (2011) observed lamotrigine-exposed children to have comparable language skills at 6-8 years when compared to a normative sample; although the sample was small (n = 9), a comprehensive and direct assessment of language was employed.

Rihtman et al. (2013) reported poorer fine/gross motor skills and visual perception in lamotrigine-exposed children (n = 40) compared to controls, however, baseline differences in socio-economic status was a potential confound.

Lamotrigine versus other ASM: Drug-versus-drug comparisons suggested favourability of lamotrigine. NEAD and LMNG compared a lamotrigine-exposed group with a valproate-exposed group. Across follow-up, children exposed to lamotrigine performed better in domains of verbal abilities at 3 years (Meador et al., 2012), language (Nadebaum et al., 2011), cognitive fluency at 3.5-5.5 years (McVearry, Gaillard, VanMeter & Meador, 2009), in memory and executive functioning at 6 years (Meador et al., 2012) and on index scores of IQ (Meador et al., 2013; Baker et al., 2015). Similar mean scores for lamotrigine-exposed and carbamazepine-exposed children on verbal and spatial abilities were observed (Baker et al., 2015), although mean differences were not analysed for significance. At 6-7 years, significantly better performance was seen in lamotrigine-exposed children (n = 82) on verbal abilities, attention and executive function compared to valproate (n = 22), with comparable performance to levetiracetam-exposed children (n = 25) and carbamazepine-exposed children (n = 32, Huber-Mollema et al., 2020).

Other outcomes for lamotrigine

Lamotrigine versus controls: Studies reported comparable levels of autistic traits and symptoms of ADHD between lamotrigine-exposed children and control samples at 18 months (Veiby et al., 2013a; Veiby et al., 2013b), 3 years (Cohen et al., 2011) and 6 years (Cohen et al., 2013). At 6 years, comparable rates of neurodevelopmental conditions (ASD, ADHD, dyspraxia, developmental delay and SEN) for exposed versus unexposed cohorts were reported by LMNG (Baker et al., 2015; Bromley et al. 2013). Population dataset studies investigated long-term outcomes by assessing rates of ADHD, ASD and learning disabilities up to 14 years of age. The risk of being diagnosed with one of these conditions was comparable between exposed (*n* between 290 – 1383) and unexposed cohorts for ADHD (Christensen et al. 2019) and ASD (Christensen et al., 2013).

When folate supplementation was absent, a prospective cohort study noted a significantly higher proportion of autistic traits in lamotrigine-exposed children (50% of *n* = 12) relative to the unexposed cohort (11% of *n* = 16, 229) at 1.5-3 years (MoBa, Bjørk et al., 2018), although numbers were small and the children were young in age. A linked study observed higher levels of autistic traits in lamotrigine-exposed children at 3 years (*n* = 44) but not at 1.5 years (*n* = 65) and interpreted these findings as representing the increasing stability of autistic traits with age (MoBa, Veiby et al., 2013b). At 4 years, Richards, Reith, Stitely and Smith (2019) reported poorer outcomes for lamotrigine-exposed children (*n* = 149) on routinely administered developmental and emotional/behavioural measures, as reported by parents. However, rates of referrals for intervention were low, at 6% (n = 9) in lamotrigine-exposed children. Comparisons to population norms found that lamotrigine-exposed children (*n* = 88) had significantly higher parent-rated proportions of autistic behaviour and defiance/conduct difficulties at 6-8 years (Huber-Mollema et al., 2019).

Academic attainment has been reported by two population datasets, with comparable performance in maths, science and English between exposed (n = 24) and unexposed cohorts up to the age of 7 in the smaller study (Lacey et al., 2018). The larger study replicated comparable performance for lamotrigine-exposed children (n = 396) and unexposed children on maths and language tests throughout schooling until age 14 (Elkjær, Bech, Sun, Laursen & Christensen, 2018). These findings are more robust given the long-term follow-up and adjustment for maternal education, child age and socio-economic status.

Lamotrigine versus other ASM: Compared to valproate, several studies indicated favourable outcomes for lamotrigine-exposed children. These included fewer social problems and ADHD symptoms at 6-8 years (Huber-Mollema et al., 2019), reduced risk of ADHD (Christensen et al., 2019) and greater academic test performance (Elkjær et al., 2018) in lamotrigine-exposed children. Better adaptive behaviour skills in lamotrigine-exposed children (n = 104) versus valproate-exposed children (n = 51) were also revealed at 3-6 years (Deshmukh et al., 2016). These findings tied with prospective cohort studies indicating better adaptive and emotion/behavioural outcomes in children exposed to lamotrigine (Cohen et al., 2011) and fewer instances of lamotrigine-exposed children requiring special educational adjustments (Baker et al., 2015). Notably, research citing comparable outcomes for lamotrigine and valproate-exposed children reported lower mean dosages of lamotrigine and valproate in their samples (Rihtman et al., 2013 Richards et al., 2019). Furthermore, Rihtman et al. (2013) did not find correlations between valproate and cognitive outcomes which are well-established (Bromley et al., 2014), suggesting that methodological issues (e.g., small sample and lower dosage) influenced findings.

Comparisons to other drugs were less common but reaped comparable outcomes in relation to oxcarbazepine (Christensen et al., 2019), and carbamazepine (Deshmukh et al., 2016). When compared with levetiracetam-exposed children, one study found mixed

differences, with parents of lamotrigine-exposed children reporting more symptoms of ADHD but lower parental anxiety (Huber-Mollema et al., 2019).

Dose of lamotrigine

No dose-response relationships were found for lamotrigine across a range of outcomes assessed between the ages of 2 and 8 years (NEAD studies; Husebye et al., 2019; Bjørk et al., 2018; Huber-Mollema et al., 2019, 2020; LMNG studies). Bech et al. (2018) observed improved outcomes with high-dose lamotrigine dose (>100mg) and poorer outcomes with low-dose lamotrigine but these findings were not replicated by linked studies (Elkjær et al., 2018; Christensen et al., 2019) and contradict typical dose-associations (Vorhees, 1986); they were therefore likely a chance finding.

Levetiracetam

Six studies, resulting in 10 publications, investigated neurodevelopmental outcomes of children exposed to levetiracetam in the womb, using population datasets (Bech et al., 2018), prospective cohort designs (Videman et al., 2016; MoBa) and pregnancy registers (Dutch Neurodevelopmental Study; UKEPR Follow-up Studies).

Global outcomes for levetiracetam

Levetiracetam versus controls: Comparable DQ scores at 7 months were reported for exposed-versus-control groups, despite significantly poorer parental educational attainment for levetiracetam-exposed children (n = 7, Videman et al., 2016). According to the UKEPR group, levetiracetam exposure did not affect global cognitive ability in children up to 2 years (n = 53; Shallcross et al., 2011), 3-4.5 years (n = 51; Shallcross et al., 2014) or 9 years (n = 42; Bromley et al., 2016), with similar proportions of children falling into the below average

range for levetiracetam (8%) and controls (12%; Bromley et al., 2016). Supporting this, a recent study found that levetiracetam-exposed children (*n* = 25) had average to above average IQ levels, after controlling for maternal IQ (Huber-Mollema et al., 2020). Contrastingly, a population dataset study found an increased risk of learning disability in children exposed to levetiracetam when compared to controls (Bech et al., 2018). However, the sample was small (*n* =12). Furthermore, analyses did not adjust for direct maternal ability, ASM dosage or prescribing indication and it is unclear whether other causes of learning disability were excluded.

Levetiracetam versus other ASM: Levetiracetam-exposed children (*n* = 51) under two years of age demonstrated higher global ability than valproate comparators (*n* = 44; Shallcross et al., 2011). Significantly fewer levetiracetam-exposed children fell within the below average range (8%) compared to valproate-exposed children (40%), with risk of delayed development in the valproate group being 3.38x greater (Bromley et al., 2016). Huber-Mollema et al. (2020) observed favourable scores for levetiracetam-exposed children (*n* = 25) in relation to valproate exposed children (*n* = 22), however, both group sizes were smaller relative to Bromley et al. (2016, *n* = 42 levetiracetam-exposed and *n* = 47 valproate-exposed). Despite reporting an increased risk of learning disability in comparison to unexposed controls, Bech and colleagues (2018) reported that risk level was no different than that observed for an 'other' ASM group at 6-7 years.

Specific outcomes for levetiracetam

Levetiracetam versus controls: At the index level, the UKEPR group observed no exposed-versus-unexposed differences on motor, personal, practical, hand/eye or performance developmental sub-quotients in children up to 2 years old (Shallcross et al., 2011) and at 3-4.5 years old (Shallcross et al., 2014) on verbal abilities, nonverbal abilities, or processing

speed at 5-9 years (Bromley et al., 2016). Language abilities were also comparable (Shallcross et al. 2014; Bromley et al., 2016) and this finding was replicated at 5 (*n* = 17) and 8 years of age (*n* = 6) when assessing language skills and risk of language impairment (Husebye et al., 2019).

In Bromley et al.'s (2016) investigation of attention and executive functioning, levetiracetam exposure (*n* = 42) was not associated with poorer outcomes compared to controls (*n* = 55), even after adjustments for covariates. Finally, a novel, young infant visual perception task similarly revealed no differences between a small levetiracetam-exposed cohort (n = 7) and controls (*n* = 67) Videman et al., 2016).

Levetiracetam versus other ASM: Compared with valproate (*n* = 44), research indicated better performance for levetiracetam-exposed children (*n* = 51) on developmental sub-quotients up to 2 years of age, with significant differences on locomotor, hand/eye coordination and performance domains (Shallcross et al., 2011). This trend held at a subsequent follow-up (Shallcross et al., 2014), with levetiracetam-exposed children also demonstrating better language comprehension and better gross motor skills (+15.8 point difference). Only one small study reported no differences in perceptual ability between levetiracetam and valproate-exposed children (Videman et al., 2016). Huber-Mollema et al. (2020) observed comparable performance between levetiracetam-exposed (*n* = 25) and lamotrigine-exposed children (*n* = 82) on almost all cognitive domains assessed, with better executive functioning and attentional skills than valproate-exposed children (*n* = 22).

Other outcomes for levetiracetam

Levetiracetam versus controls: Functional outcomes, as assessed by parent-rated child behaviour, were no different between levetiracetam-exposed children (*n* = 42) and controls (*n* = 55, Bromley et al., 2016). This was consistent with a pregnancy registry study that

reported comparable levels of behavioural difficulties between levetiracetam-exposed children (*n* = 30) and a normative sample at 6-8 years (Huber-Mollema et al., 2019). After adjusting for key covariates including maternal behaviour, sub-analyses remained non-significant for anxiety and ADHD but revealed higher proportions of parent-rated conduct disorder (Huber-Mollema et al., 2019). Bjørk et al. (2018) found no difference in risk of autistic traits at 3 years, although findings were limited by the use of a small sample (n = 12).

Levetiracetam versus other ASM: Compared to valproate, fewer attentional problems or symptoms of ADHD were reported for levetiracetam-exposed (Huber-Mollema et al., 2019). Comparisons with lamotrigine were mixed, indicating more ADHD symptoms but less anxiety in levetiracetam-exposed children (Huber-Mollema et al., 2019).

Dose of levetiracetam

No studies identified a significant dose-response relationship between levetiracetam exposure and neurodevelopmental outcomes up to the age of 9 (Huber-Mollema et al., 2019, 2020; Bromley et al. 2016; Shallcross et al., 2011, 2014). This included research using an objective means of dose ascertainment, blood sampling, although analyses may not have been sufficiently powered (n = 15, Bjørk et al., 2018).

Oxcarbazepine

Oxcarbazepine exposure was investigated by a prospective cohort study (Videman et al., 2016), a single-case retrospective cohort study (Guveli et al., 2015) and a study using Danish population datasets (Christensen et al., 2019, 2013; Bech et al., 2018; Elkjær et al., 2018).

Global outcomes for oxcarbazepine

Oxcarbazepine versus controls: Three studies reported comparable global abilities between oxcarbazepine-exposed children and controls. Although the sample sizes of the exposed cohorts within two studies (Videman et al., 2016; Guveli et al., 2015) were very small (*n* = 10 and *n* = 1, respectively), similar findings were obtained by Bech and colleagues (2018) who, using a larger sample drawn from a general population, found no elevated risk of learning disability for oxcarbazepine-exposed children (*n* = 44) at 6-7 years.

Oxcarbazepine versus other ASM: When compared to an 'other' ASM group (n = 13), risk of learning disability for oxcarbazepine-exposed children (*n* = 44) at 6-7 years was not significantly different (Bech et al., 2018).

Specific outcomes for oxcarbazepine

Oxcarbazepine versus controls: Poorer hearing and speech was observed in an oxcarbazepine-exposed cohort (*n* = 10) relative to controls (Videman et al., 2016), although this finding is weakened by the small sample. No differences were observed in the single case cohort (Guveli et al. 2015).

Oxcarbazepine versus another ASM: No studies assessing specific cognitive outcomes compared oxcarbazepine-exposed children with a comparator ASM.

Other outcomes for oxcarbazepine

Oxcarbazepine versus controls: With the largest oxcarbazepine-exposed cohorts to date (*n* = 236 – 372), the Danish Population Studies assessed oxcarbazepine-exposed cohorts from 6 years of age to 14 years of age, for risk of autism, ADHD (Christensen at el., 2013, 2019) and academic performance (Elkjær et al., 2018). Results indicated comparability between

controls on all outcomes at all timepoints except on one test of mathematics, where performance of the exposed cohort was marginally lower (Elkjær et al., 2018). Similarly, MoBa observed comparable rates levels of risk of autistic traits between oxcarbazepine-exposed children and controls, although the sample was likely insufficiently powered (n = 4; Bjørk et al., 2018).

Oxcarbazepine versus other ASM: Only one study compared oxcarbazepine to another ASM. Christensen et al. (2019) observed no differences in risk of ADHD associated with oxcarbazepine exposure (n = 372) when compared with lamotrigine (n = 1383) up to 15 years of age.

Dose of oxcarbazepine

No dose-effect relationships were examined for oxcarbazepine. The Danish Population Studies assessed high-versus-low dosage of oxcarbazepine, finding non-significant differences in ADHD outcomes (Christensen et al., 2019) and test performance outcomes (Elkjær et al., 2018), although dosage estimates were less reliable, having been calculated from prescription patterns rather than individual records.

Topiramate

Four studies assessed neurodevelopmental outcomes in topiramate-exposed children, comprising two pregnancy registry papers (Bromley et al., 2016; Rihtman, Parush & Ornoy, 2012), a population dataset study (Bech et al., 2018) and MoBa's prospective cohort study (Husebye et al, 2019; Bjørk et al., 2018). Despite decades of its use, the largest sample achieved was 27 topiramate-exposed children (Bromley et al., 2016; Bech et al., 2018).

Global outcomes for topiramate

Topiramate versus controls: Findings from the two largest topiramate cohorts (*n* = 27) were mixed, with one study reporting IQ scores comparable to controls at 5-9 years of age (Bromley et al., 2016) and the other citing a significantly increased risk of learning disability compared to controls at 6-7 years (Bech et al., 2018). However, in the latter it was not stated whether children were excluded when there were other possible explanations for their learning disabilities (i.e. head injury, epilepsy etc). Poorer IQ scores in topiramate-exposed children were reported elsewhere but these findings may be biased by the undertaking of unblinded assessments in just nine children (Rihtman et al., 2012).

Topiramate versus another ASM: Outcomes from one study indicate comparable levels of risk of learning disability in topiramate-exposed children (*n* = 27) relative to an 'other' ASM group (*n* = 13) at 6-7 years (Bech et al., 2018). Bromley et al. (2016), reported comparable mean IQ scores to children exposed to lamotrigine, however, no statistical comparison was undertaken.

Specific outcomes for topiramate

Topiramate versus controls: Poorer outcomes were observed in a small cohort of topiramate-exposed children (*n* =9) on verbal IQ, non-verbal IQ and motor functioning (Rihtman et al., 2012). However, differences in any IQ index scores or on any measure of language, executive functioning or attention were not replicated in a larger cohort of 27 children between the ages of 5-9 years (Bromley et al., 2016). Husebye et al. (2019) similarly found no difference in language skills between exposed and control cohorts, although this was based on only 4 topiramate cases at the 8-year follow-up. Thus, language development outcomes were unclear.

Topiramate versus another ASM: No studies assessing specific cognitive outcomes compared topiramate-exposed children with a comparator ASM.

Other outcomes for topiramate

Topiramate versus controls: Bromley et al. (2016) observed comparable levels of behavioural difficulties between topiramate-exposed children (n = 27) and controls (n = 55), contrasting with Rihtman et al. (2012) who observed poorer outcomes for topiramate-exposed children (n = 9). Findings in both papers were based on parental report. Bjørk et al. (2018) examined risk of autistic traits, also through parental report, in a small cohort of topiramate-exposed children (n = 6) and found non-significant differences.

Topiramate versus other ASM: No studies assessing other outcomes compared topiramate-exposed children with a comparator ASM.

Dose of topiramate

Only two studies investigated dose of topiramate, with neither reaping significant results. Although one study used an objective measure of dosage via blood sampling (Husebye et al., 2019), the lack of significant association between topiramate concentrations and language outcomes was likely due to the size of the cohort (n = 4 at 8-year follow-up). In the largest topiramate sample to date (n =27), no significant difference in cognitive outcomes was seen when comparing half the median dose of topiramate to half the median dose of valproate at 5-9 years, although higher doses of valproate affected cognitive functioning more greatly than higher doses of topiramate (Bromley et al., 2016).

Discussion

This systematic review was the first to offer a comprehensive synthesis of literature into newer ASMs and child neurodevelopment. Through the identification of 16 newly published articles we extended a previous review in this area (Bromley et al., 2014). The novel focus on newer medicines alone afforded an unobscured view of the research base as it is currently; that is, starkly and disproportionately neglected relative to the research base for older medicines. Since the 2014 Cochrane review (Bromley et al.), it is only lamotrigine for which some insights have been delineated. Without any published studies investigating perampanel, eslicarbazepine, lacosamide or zonisamide, the effects of these medicines remain entirely unknown. Although research has emerged for oxcarbazepine and gabapentin, findings are mixed and drastically limited by the use of single-case cohorts and retrospective designs. Overall, the evidence base for newer ASMs has been slow to evolve, with concerning implications for timely practicing of pharmacovigilance (Adam, Polifka & Friedman, 2011; Friedman, 2012).

Reflecting current prescribing trends in the UK and USA (Meador et al. 2018), lamotrigine was the most commonly studied medicine, with data available for children up to 14 years. Research consistently indicated comparable lamotrigine-versus-control performance and favourable lamotrigine-versus-valproate performance across a range of global and specific cognitive outcomes, with initial evidence of comparability with carbamazepine and levetiracetam. Data for other lamotrigine outcomes, namely autism/autistic symptoms and diagnoses, were less clear. When based on parental rating, there were indications of increased traits/features associated with autism spectrum disorders in lamotrigine-exposed children (Bjørk et al., 2018; Veiby et al., 2013b). However, this risk did not translate into elevated diagnosable cases of autism (Christensen et al., 2013; Bromley et al., 2013). Further work is required to understand the emotional and behavioural outcomes

of children exposed to lamotrigine in utero; specifically, whether there are sub-diagnostic levels of social communication difficulties in lamotrigine-exposed children which are being highlighted via parental report, or whether these results have arisen from aspects of uncontrolled biases.

Findings for levetiracetam were suggestive of non-detrimental effects on child neurodevelopment, although the pool of research was much smaller, with data available for children up to the age of 9 only and with cohorts typically smaller than those reported for lamotrigine. Topiramate findings were substantively limited by cohort size and heterogeneity of outcomes assessed and measurement techniques. An association between topiramate exposure and fetal growth (Hernandez-Diaz et al., 2017) and an increased risk of oral clefts has been demonstrated previously (Margulis et al., 2012; Hernandez-Diaz et al., 2012), indicating that topiramate is a drug with human teratogenic capabilities. However, it is not yet possible to determine whether there is any impact on brain development when exposed to topiramate in-utero. Further, it remains unclear whether children born with possible physical symptoms of teratogenicity also present with neurodevelopmental difficulties, as with other ASM teratogen syndromes such as Fetal Valproate Spectrum Disorder (Clayton-Smith et al., 2019) and Fetal Hydantoin Syndrome (Hanson & Smith, 1976).

An area which was unclear across newer ASMs related to dosage: fewer than half of the reviewed articles investigated dose, despite dose associations being a key principle in neurobehavioural teratology and despite more established literature for older ASMs espousing this as having a significant moderating effect on neurodevelopmental outcomes (Bromley et al., 2014). Of note, most comparisons were made to an unexposed cohort or a valproate comparator cohort. In most cases, it is unlikely that women who require medicine to manage seizures will be titrated off ASMs completely. Valproate is now counter-indicated

for women of childbearing age (MHRA, 2018); although its use as a 'positive' control has utility in contextualising the relative risks associated with more widely used ASMs, comparisons between newer ASMs should be of greater prominence within the dissemination of results.

Across ASMs, mixed findings on parent-rated functional outcomes were observed and, in some cases (e.g., lamotrigine as noted above), these findings clashed with clinician-led diagnoses. This discrepancy may suggest that parents are well equipped, both in experience and knowledge of their children, to alert researchers to more subtle neurodevelopmental differences not yet reaching diagnostic thresholds. Alternatively, parent-completed measures may be at greater risk of biased reporting due to parents being unblinded to exposure status. The vast difference in findings pertaining to behavioural traits versus diagnoses requires further exploration.

Alongside our synthesis of the literature regarding ASMs, this review also revealed patterns of strengths and weaknesses attributable to study design (see Table 3). Although the retrospective cohort studies in our review scored most poorly, this finding was partly due to the use of single-case samples which is not typical of this design. Well designed and adequately powered retrospective cohort studies, utilising blinded and standardised assessment, can serve as a useful 'first look' in the absence of existing research, as evidenced by early, subsequently validated, findings on valproate risk which gave momentum to this previously lagging research area (Adab et al., 2004). Population designs were well-suited to investigations of the prevalence of rare conditions and diagnosable neurodevelopmental outcomes (e.g., ASD and ADHD) as the large datasets offered large numbers conveying improved power. Population datasets also offered representativeness of the mothers due to the numbers and pattern of enrolment, although it is uncertain whether they are wholly representative of the child outcomes, given that only those referred for clinical appointments

through typical diagnostic pathways are reviewed. Pregnancy registry and prospective cohort designs, with standardised blinded assessments of all exposed children, provided robust outcome data and could better assess relevant confounding factors, cohort comparability and investigations around dose. Each research design was thus seen to have some unique utility and as such, no single approach could be considered superior without consideration of the outcome in question and its most meaningful means of assessment.

Strengths and limitations

Strengths of this review included the rigorous systematic searching in line with current guidelines (Moher et al., 2015), including two authors independently reviewing abstracts for inclusion and undertaking quality assessments. The focus on newer ASMs was novel and its findings outlined clear recommendations regarding the direction of future research. That there remains a dearth of empirical studies into the impact of particular ASMs on child neurodevelopment was a concerning but important issue that this review highlighted through its synthesis of available literature. The review was undertaken with an in-depth knowledge of the outcomes under investigation; this avoided the combining of outcomes which were too distinct to discuss in unitary terms. In terms of limitations, grey literature was excluded, introducing possible publication bias. However, within this specific field, non-significant findings have clinical relevance and the number of non-significant findings reported in included published studies suggests this was not an issue. It was beyond the scope of this review to synthesise publications in languages other than English.

A meta-analysis was considered for the current review because this method often provides stronger levels of evidence over narrative synthesis (Centre for Reviews of Dissemination, 2009). However, bringing together highly heterogenous statistics describing clinically distinct domains of neurodevelopment risked generating invalid findings (Colliver

et al., 2008), losing insight into the review question through over-transformation of data into overly simplified constructs/outcomes (Snilsvelt et al., 2012). Here, we did not support the findings of a previously published meta-analysis (Veroniki et al., 2017). Veroniki et al. (2017) combined outcomes for studies investigating parent-reported autistic traits with studies investigating clinician-made autism diagnoses and reported a relationship between lamotrigine and oxcarbazepine exposure with an increased risk of ASD symptomatology. The results of the current review suggested that the literature for lamotrigine did not support this and, in fact, highlighted a difference between parent-completed questionnaire data and ASD diagnoses. Due to substantial heterogeneity, it was considered that the use of a narrative synthesis offered the most appropriate and meaningful way of summarising the newer ASM literature to date. Furthermore, bringing the literature together with this method also enabled the parsing apart of the specific areas of neurodevelopment that are more or less impacted upon by individual ASMs.

Future directions

The results of this review highlighted several avenues for future researchers to consider. It is established that the brain continues to develop well into adulthood (Kolb & Whishaw, 2015), with antecedents for its trajectory beginning in utero (Stiles, 2008). Existing teratology research indicates that the impact of prenatal exposures may not be observable until later years, as the gap between affected children and their peers widens (Bath & Scharfman, 2013; Bromley et al., 2019). Follow-ups reflecting the longevity of these developmental trajectories are required across ASMs if we are to attain a fuller understanding of their impact on neurodevelopment over the long-term. Greater attention to the impact of dose will similarly permit a more sophisticated understanding, aiding real-world clinical decision making. It may be prudent to compare the relative safety and risks of

newer ASMs against each other, as well as with unexposed or valproate cohorts. Regarding specific research questions, further research is needed for topiramate using larger sample sizes with, ideally, prospectively collected, blinded outcome data and consideration to whether those noted to have poorer birth outcomes (e.g., small for gestational age or oral clefts) are at greater risk of neurodevelopmental difficulties. The literature for gabapentin and oxcarbazepine would be strengthened by methodologies enabling attention to covarying factors, such as prospective cohort or pregnancy registry designs. For those ASMs where there is no research at all, there may be some utility in scoping for possible associated risks via retrospective cohort designs as a starting point. Further exploration of functional outcomes and outcomes related to conditions such as autism are required to explicate the currently mixed findings is also needed for lamotrigine.

Broader recommendations concern the due consideration of design and methodology. Researchers should consider with full cognizance the strengths and weaknesses of study designs to guide the selection of that which is best suited to the empirical hypothesis. Given that certain parental, perinatal and child factors influence neurodevelopment (Bromley et al., 2014; Tong, Baghurst, Vimpani & McMichael, 2007), adjustment for covariates, through matching or statistical adjustment, should be employed. Other recommendations include responsible reporting of missing data/attrition, drawing upon prospectively-collected data when available and the ascertainment of exposure/dose via more reliable methods such as individual medical records). Finally, future researchers should endeavour to supplement parental measures with a direct and blinded component (i.e., clinician-rated) when possible. Attention to these areas of methodology will be key in producing research from which reliable and firm conclusions can be made.

Clinical implications

The immediate clinical implications of this review concern how women with epilepsy are counselled about their medications, if they are counselled at all. Previous literature indicates poor levels of pre-conceptive counselling around teratogenic effects (McGrath, Sharpe, Lah & Parratt, 2014), with further issues around the provision of misinformation (Gerard et al., 2014). Unfortunately, more recent studies cite ongoing variability in how and whether healthcare professionals discuss medicines with women with epilepsy (Kirkpatrick et al., 2020). Anecdotal evidence suggests that many women are told that their medicines are safe due to an absence of data confirming risk (Epilepsy Society, 2016). Consistent with recent amendments to clinical guidelines (NICE, 2020), lack of data cannot be inferred to represent safety of ASMs.

In line with principles of informed decision making and evidence-based practice, a key clinical recommendation is that women should be informed about the impact of ASMs on neurodevelopment, including instances when data are limited and conclusions are not possible (NICE, 2020). Long-term, it is anticipated that the findings of this review will open avenues of research into those ASMs less well studied, shaping prescribing practices and ensuring that women can be appropriately counselled on risk, with greater availability of evidence.

Conclusion

Overall, this review highlighted the starkly inequitable levels of evidence available regarding newer ASMs. Although some important insights have been realised, a full understanding of neurodevelopmental outcomes is far from complete. The recommendations arising from this review will serve as an impetus for ongoing study that works towards evidence-based

practice for prescribers and informed decision making for women with epilepsy who are, alongside their children, at the heart of this important issue.

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Paper 2

Adaptive behaviour in children exposed to topiramate in the womb

Knight, R.,[1,2] Wittkowski, A.,[1,2] & Bromley, R. L.[3,4*]

[1]Division of Psychology and Mental Health, the University of Manchester

[2]Greater Manchester Mental Health NHS Foundation Trust

[3]Division of Evolution and Genomic Science, the University of Manchester

[4]Royal Manchester Children's Hospital, Manchester Academic Health Sciences, Manchester, UK.

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Abstract

Objective: Many women with epilepsy need to continue anti-seizure medications (ASMs) throughout pregnancy. The current study aimed to investigate adaptive behaviour outcomes in children exposed to topiramate monotherapy in the womb. ***Method:*** An observational, cross-sectional study was designed, recruiting mother-child-pairs from the UK Epilepsy and Pregnancy Register (UKEPR). Developmental histories and Vineland Adaptive Behaviour Scale-Third Edition (VABS-III) assessments were administered via telephone by a blinded researcher to examine neurodevelopmental outcomes, supplemented with prospectively collected pregnancy and medication information. Topiramate-exposed children were compared to normative data and correlational analyses were used to investigate outcomes and dosage while taking key confounders into account. **Results:** Thirty-four women with epilepsy opted into the study from 135 (25%) invitations and 26 women completed telephone interviews about their children (n = 28). Children ranged from 2.5 to 17 years of age at the time of assessment. Significantly lower adaptive behaviour scores were observed in topiramate-exposed children (n = 21) with a significant dose-response relationship established after adjustment for parental educational level. High dosages of topiramate (>200mg/day) were associated with a 12-point reduction in ABC scores. Six topiramate-exposed children were born small for gestational age, with significant associations identified between birthweight, dose and adaptive behaviour. Additionally, four topiramate-exposed children (19.05%) had diagnoses of Autism Spectrum Disorder, which was significantly higher than UK prevalence rates (1.1%). ***Significance:*** The findings of poorer adaptive behaviour, higher incidence of ASD and links with birthweight are of concern and require further validation and repetition using larger samples and comparator cohorts. Implications for research and clinical practice are discussed.

Keywords: Neurodevelopment; Antiepileptic drugs; Epilepsy; Pregnancy; In-utero

Introduction

Epilepsy is a neurological condition affecting 0.5-1% of the UK population (National Institute of Health and Care Excellence, NICE, 2020). For many individuals, the abnormal seizure activity within the brain caused by epilepsy can be managed with anti-seizure medications (ASMs; NICE, 2020). The majority of women continue treatment throughout pregnancy to protect the welfare of both mother and child (Morrow et al., 2006). Sodium valproate was the first-line epilepsy treatment until April 2018, when mounting evidence of teratogenicity alongside a consistent dose-response association (Bromley et al., 2014; Weston et al., 2016) and confirmation of a syndrome presentation (Bromley, Baker, Clayton-Smith & Wood, 2019) led the Medicines and Healthcare products Regulatory Agency (MHRA) to prohibit its use during pregnancy and childbearing years.

Prescribing practices have thus shifted and women of childbearing age are offered alternative, newer medicines, such as topiramate (Meador et al., 2018). In the UK, approximately 2.3% of women with epilepsy are prescribed topiramate to manage seizures during pregnancy (Meador et al., 2018). Two animal studies have reported that topiramate exposure is not associated with abnormal levels of cell death in developing rat fetuses (Kim, Kondratyev & Gale, 2007; Glier et al., 2004), whereas a more recent publication identified decreased survival and increased rates of malformation in topiramate-exposed zebrafish offspring (Lai, Ding, Moses & Chen, 2017). Initial human research suggests that topiramate may act as a physical teratogen, carrying higher levels of risk to the developing foetus with respect to major congenital malformations (Hunt et al., 2008). Replicated evidence of increased incidences of oral cleft (Margulis et al., 2012; Hernández-Díaz et al., 2012), alongside evidence of higher numbers of babies born small for gestational age (Hernández-Díaz et al., 2017; Ornoy et al., 2008; Veiby, Dalveit, Engelsen & Gilhus, 2014) further indicates that topiramate has human teratogenic tendency. Evidence regarding the impact of

topiramate on the developing fetal brain and later neurodevelopmental outcomes, however, is incredibly limited. This is concerning given the known potential of medicines to impact the developing brain, as demonstrated by the severity of neurodevelopmental outcomes in valproate-exposed children. Only four studies have sought to delineate the neurodevelopmental outcomes associated with topiramate, with the two largest studies (n = 27) reaping conflicting findings from different methodological approaches. In a blinded prospective cohort study, the cognitive abilities of children exposed to topiramate were no different to unexposed controls (Bromley et al., 2016). In direct contrast, a population dataset study reported elevated risk of learning disability for topiramate-exposed children (Bech et al., 2018). Rihtman, Parush and Ornoy (2012) observed significantly poorer behavioural and cognitive outcomes compared to a control cohort; however, these findings were based on an extremely small sample (n = 9). Two linked papers reported non-significant differences in either language skills (Husebye et al., 2018) or autistic traits compared to controls (Bjørk et al., 2018) but as above, cohorts were small (n = 4 and n = 6, respectively). Mixed findings likely resulted from studies being powered to detect large effects only, alongside inconsistencies in outcome selection and measurement.

The gap in knowledge regarding how in-utero topiramate exposure impacts neurodevelopment is alarming, given its increased use over recent years (Meador et al., 2018), a trend anticipated to accelerate in response to recent restrictions on valproate (MHRA, 2018). With scant empirical findings upon which to base clinical guidelines, women and prescribers alike are, at present, unable to make informed choices about epilepsy treatment during pregnancy (Tomson, Battino & Perucca, 2019). Guidance around the use of topiramate to manage seizures during pregnancy and/or childbearing years is inconsistent; the British National Formulary (BNF, 2020) suggest the consideration of alternative medications, whereas NICE (2020) recommend topiramate as a treatment option during

childbearing years. Currently, the patient information leaflet for topiramate states a risk of oral clefts, hypospadias and growth suppression (Electronic Medicines Compendium, 2020).

This study sought to investigate neurodevelopmental outcomes in children with in-utero topiramate exposure. The primary aim was to determine whether topiramate exposure impacted adaptive behaviour skills. Subsidiary aims were to consider potential covarying factors and their impact on main outcomes, and to explore associations between topiramate exposure and/or dose with other neurodevelopmental outcomes.

Based on the above indications of possible teratogenicity, it was hypothesised that:

- H_{E1} – Topiramate-exposed children would show significantly **poorer overall adaptive behaviour**, as indicated by lower composite scores on the Vineland Adaptive Behaviour Scale 3rd Edition ([VABS-III], Sparrow, Cicchetti & Saulnier, 2016), relative to the normative mean of 100.
- $H_{E2\text{-}4}$ – Topiramate-exposed children would show significantly **poorer development in communication skills, daily living skills and socialisation skills** when compared to normative domain scores of 100 on the VABS-III.

Method

Design

The study used a cross-sectional and observational design. The primary dependent outcome was adaptive behavioural skills, including communication, daily living and socialisation skills, as measured by the VABS-III. Secondary outcomes and factors included incidence of neurodevelopmental conditions, birth outcomes, maternal and paternal educational level, socio-economic status, child gender, alcohol exposure and nicotine exposure.

Recruitment and participants

Recruitment was national across the UK. Mother-child-pairs were identified from the United Kingdom Epilepsy and Pregnancy Register (UKEPR), a prospective research database established in 1996 to investigate major congenital malformation prevalence following in-utero exposure to ASMs (Morrow et al., 2006). The UKEPR provided a letter of support for the study (Appendix D) Enrolment onto the register takes place via self-referral or by a health professional within the first/second trimester of pregnancy, facilitating prospective collection of medication use, health/pregnancy data and birth outcomes. Mother-child-pairs were eligible for inclusion in the study if the child had been a live birth and was up to 17 years of age at the time of participation and mothers with epilepsy were taking topiramate monotherapy during pregnancy *or* were untreated during therapy. Families were not invited to participate in cases where conditions associated with neurodevelopment impairment were suspected (e.g., maternal learning disability).

Although registration with the UKEPR is prospective, recruitment into the current follow-up study was retrospective. There were approximately three times more eligible participants for the unexposed cohort than for the topiramate-exposed group and therefore each third mother-child-pair identified from the register was included in the recruitment list. Potentially eligible participants were invited to participate via letter including an information sheet (Appendix E), with follow-up invitations sent if no response had been received (Appendix F). When possible, addresses were verified via GP systems. On receipt of a positive response, mothers were contacted and screened for eligibility before formal enrolment into the study. Ethical approvals were obtained from the Health Research Authority (HRA, study reference: 19/NW/0299, Appendix G), with local approvals also granted by Manchester University Hospitals NHS Foundation Trust and Belfast Health and

Social Care Trust which host the UKEPR. All participants provided informed written consent (Appendix H).

Procedure and measures

Data collection took place via telephone interviews lasting 40 – 60 minutes, with assessments conducted by a blinded researcher. A brief, semi-structured health and background interview was undertaken with mothers (Appendix I), followed by a parent-rated measure of adaptive behaviour. Adaptive behaviour was the primary outcome, measured using the VABS-III (Sparrow et al., 2016). The VABS-III is widely used within the field, has strong psychometric properties (Floyd et al., 2015; Pepperdine & McCrimmon, 2018; Price, Morris & Costello, 2018) and has been validated in studies of ASM exposure during pregnancy (Bromley et al., 2019; Deshmukh et al., 2016; Vinten et al., 2009). The measure provides overall estimates of adaptive behaviour skills (ABC) as well as domain-specific estimates of communication, daily living and socialisation skills (see Table 4).

Table 4. Overview of Vineland Adaptive Behaviour Scale- Third Edition (VABS-III)

	Domain	**Description**
Global Adaptive Behaviour Composite (ABC)	Communication (COM)	Comprises receptive, expressive and written communication
	Daily living skills (DLS)	Comprises personal, domestic and community daily living skills
	Socialisation (SOC)	Comprises interpersonal relationships, play and leisure time and coping skills.

N.B. Additional domains of motor skills and maladaptive behaviour were not included due to unavailability of normative estimates across the age range under study.

On the VABS-III, domain and ABC scores are standardised, with lower scores conferring poorer adaptive behaviour skills. Scores can be classified using qualitative descriptors, depending on how far scores deviate from the expected mean (100, *SD* = 15). Scores of 85 or lower are classified as being below the average range. Full details of classifications can be seen in Appendix J).

Prospectively collected data on additional factors, such as exposure status, dosage and pregnancy/birth outcomes, were obtained via the UKEPR database. Individual dosage information was available and represented dose of topiramate around the time of enrolment on the register, with any changes to medication since conception documented. UKEPR data on birth weight and gestational age were input into UK World Health Organisation (WHO, 2013) growth charts in order to calculate the birth weight for gestational age centiles for each study child and identify those children falling below the 10th centile and therefore classed as small for gestational age (Royal College of Obstetricians and Gynaecologists, RCOG, 2013). Estimates of socio-economic status were generated by inputting postcodes into nationally-held and freely available statistics on deprivation indices (Ministries of Housing, Communities & Local Government, MHCLG, 2019; Northern Ireland Statistics & Research Agency, NISRA, 2017).

Relevant to the study's subsidiary aims, a semi-structured interview format was used to gather health and background information that was not available on the UKEPR database (Appendix I). This included information about incidence of health and neurodevelopmental conditions within the study children and parental factors including educational attainment and family history of special educational needs, illnesses and neurodevelopmental conditions. Following data collection, participants were debriefed, with ethical standards adhered to throughout. VABS-III data were double scored and data entry was checked by a second researcher to reduce scoring and data entry errors.

Data analysis

Although a comparison between a topiramate-exposed cohort and a 'no medication' unexposed control cohort was initially planned, an adequately-sized control cohort was not obtained due to recruitment difficulties. Thus, comparisons to the VABS-III normative sample (n = 2560) were made, an approach previously utilised in this area (Bromley et al., 2019; Deshmukh et al., 2016).

After tests for normality were completed, the primary analysis was a comparison of adaptive behaviour skills, as assessed by the VABS-III, to normative sample data (Sparrow et al., 2016). Mean adaptive behaviour scores were calculated from ABC scores and domain standard scores in communication skills, daily living skills and socialisation skills. One-sample t-tests were then used to test whether group means differed from the test normative value of 100. The comparison to the mean of 100, rather than age-adjusted means, was deemed most appropriate given the cross-sectional sample including infants, children and adolescents. This approach has been adopted in this area previously (Nadebaum et al., 2011; Deshmukh et al., 2016).

Potential confounding variables were explored by assessing their relationships with VABS-III scores, using mean difference and correlational analyses. As these were exploratory analyses undertaken prior to regression, the conventional significance value of .05 was adopted. Variables explored were socio-economic status, parental educational attainment, parental age at birth, employment status, maternal epilepsy type, seizure exposure, other maternal health conditions, folate status, breastfeeding status, alcohol exposure, nicotine exposure, gestational age at birth, birth weight, child gender, child age at assessment and other child health factors. It was planned that variables significantly associated with adaptive behaviour scores would be entered into hierarchical multiple regression analyses to establish the impact of high-versus-low topiramate dose on ABC and

domain scores on the VABS-III, taking into account covarying factors. Cut-off values for low and high dosages (≤200mg/day and >200mg/day, respectively) were informed by the BNF (2020) guidance for topiramate.

In line with our subsidiary aims, correlational and mean difference analyses were completed to examine the impact of topiramate exposure/dose on other outcomes, including gestational weight at birth, birth weight centile, incidence of malformations, incidence of neurodevelopmental conditions, presence of special educational needs.

All data analysis was performed using IBM SPSS Statistics 25.

Results

One hundred and thirty-five invitations were sent out to potentially eligible mother-child-pairs (n = 106 invitations to the topiramate group and n = 29 invitations to the 'no medication' group). Two mothers declined participation (1.5%) and for four mothers, invitations were returned to sender (3.0%). Thirty-four positive responses were received (25.0%). Of these thirty-four, two mothers (5.9%) were not contactable. The remaining thirty-two mothers were eligible and were enrolled into the study (94.0%). However, four mothers did not complete interviews, either due to a change in circumstances (n = 2, 5.9%) or due to not attending the arranged appointment (n = 2, 5.9%). Therefore, of the 135 mothers who were sent letters, data was provided for 28 children, corresponding to a 20.7% completion rate with 12.5% attrition of those enrolled.

Participants

A total of 26 mothers took part in the study and provided information about 28 children (including two sibling pairs). The topiramate-exposed and 'no medication' groups were unequal in size (n = 25 and n = 3, correspondingly) and not appropriate for statistical

comparison. Thus, the alternative analytic approach was taken whereby the topiramate-exposed group were compared to the test normative group. Cohort demographics for the sample recruited can be seen in Table 5. Demographics for the no medication group are displayed due to being included in subsequent dose analyses.

Table 5. Cohort demographic information by exposure status

	Topiramate	**No medication**
Sample size	25	3
Maternal demographics		
ASM dose, mg/d, mean (range min-max)	279.00 (100.00-800.00)	-
Maternal age at birth, y, mean (*SD*)	30.80 (*5.30*)	33.67 (*2.51*)
Maternal higher education[a] *n* (%) yes	21 (84.00)	3 (100.00)
Maternal undergraduate degree, *n* (%) yes	14 (56.00)	3 (100.00)
Maternal employment, *n* (%) yes	21 (84.00)	3 (100.00)
Low socioeconomic status[b], *n* (%) yes	12 (48.0)	0 (0.00)
Folate supplementation, *n* (%) yes	22 (91.7)	2 (66.70)
Alcohol exposure, *n* (%) yes	2 (8.00)	1 (33.30)
Nicotine exposure, *n* (%) yes	4 (16.00)	0 (0.00)
Maternal epilepsy type, *n* %		
Idiopathic generalised	13 (52.00)	1 (33.33)
Focal	2 (8.00)	1 (33.33)
Juvenile myoclonic	8 (32.00)	1 (33.33)
Partial with secondary generalisation	1 (4.00)	0 (0.00)
Symptomatic	1 (4.00)	0 (0.00)
Seizure exposure, *n* (%) yes	9 (36.00)	1 (33.33)
Convulsive seizure exposure, *n* (%) yes	4 (16.00)	0 (0.00)
Breastfeeding, *n* (%) yes	6 (24.00)	1 (33.33)
Paternal demographics		
Paternal age at birth, y, mean (*SD*)	31.84 (*5.92*)	32.33 (*1.53*)
Paternal higher education, *n* (%) yes	19 (76.00)	3 (100.00)
Paternal undergraduate degree, *n* (%) yes	11 (44.00)	3 (100.00)
Paternal employment, *n* (%) yes	24 (96.00%)	3 (100.00)
Child demographics		
Age at assessment, y, mean (*SD*, range min-max)	10.96 (*3.90*, 2.58-17.33)	4.00 (*1.00*, 3.00-5.00)
Gestational age at birth, wks, mean (*SD*)	40.12 (*1.42*)	40.00 (*1.00*)
Birth weight, g, mean (*SD*, range)	3162.24 (*572.83*, 1620-4330)	3630.00 (*296.07*, 3330-3850)
Child sex, *n*, female (%)	12 (48.00)	1 (33.33)
Sibling enrolled in study, *n* (%) yes	2 (8.00)	0 (0.00)
Family history of major malformations, *n* (%) yes	2 (8.00)[b]	0 (0.00)
Family history of special educational needs, *n* (%) yes	0 (0.00)	0 (0.00)
Family history of developmental conditions, *n* (%) yes	0 (0.00)	0 (0.00)

[a] Education beyond that which was compulsory.
[b] Low socio-economic was defined as mothers falling in the bottom three centiles of the Multiple Deprivation Decile.
[c] Sibling pair.

In the topiramate-exposed group, children ranged from 2.5 years to 17 years of age at the point of assessment (M = 10.96, SD = 3.90). The gender split was approximately equal (48% female, 52% male). Forty-eight percent of the children were calculated as being low in socio-economic status. On average, children were carried to full term with a mean gestational age of 40.12 weeks at birth (SD = 1.42). Dose of topiramate ranged from 100-800mg total daily dose, with a mean daily dose of 280.21mg. Twenty-three mothers took topiramate throughout the duration of pregnancy. One mother stopped topiramate at six weeks gestation; this child was included in the topiramate cohort.

Nine children (36%) were exposed to maternal seizures in utero, with exposure to convulsive seizures in four cases (16.0%). Six children (24%) were breastfed and almost all children (n = 22, 92%) were exposed to pre/peri-conceptual folate. There was no family history of special educational or developmental conditions. Two children who were siblings (8%) had a paternal family history of malformations.

Regarding parental demographics, mothers were a mean age of 30.80 years at the time of birth. Women had diagnoses of generalised epilepsy (n = 13), focal epilepsy (n = 2), juvenile myoclonic epilepsy (n = 8), partial with secondary generalisation epilepsy (n = 1) and symptomatic epilepsy (n = 1). At the time of assessment, 84% (n = 21) of mothers were in employment. Higher education and university degrees were reported in 84% and 56% of cases, correspondingly. Paternal demographic information was obtained via maternal report. Fathers were 31.84 years (SD = 5.92) at the time of birth. Rates of employment were high (n = 26, 96%). Seventy-six percent (n = 19) of fathers attended higher education, with 44% (n = 11) obtaining an undergraduate degree.

Adopting a conservative approach, four children were excluded from the main analysis due to conditions that may have impacted neurodevelopment (e.g., acquired brain injury, genetic conditions, neurological conditions). Therefore, of the 24 children entered into the

analysis, 21 were prenatally exposed to topiramate and three were not exposed to any medication. The 'no medication' group were included in dose investigations only due to the size of this group.

Adaptive behaviour outcomes

Adaptive behaviour data, as ascertained via the VABS-III were analysed for 21 topiramate-exposed children. Unadjusted means, standard deviations and rates of performance below average adaptive level for those included in the study are presented in Table 6. An equivalent table summarising the outcomes for the children excluded from the analysis (n = 4) is presented in Appendix K.

Table 6. Unadjusted means, standard deviations and rates of below average performance

Topiramate-exposed children (n = 21)		
VABS-III	**Mean (SD)**	**No. (%) ≤85[a]**
ABC	91.10 (16.55)	9 (42.90%)
Communication	94.90 (19.78)	5 (23.80%)
Daily Living Skills	90.38 (13.25)	7 (33.33%)
Socialisation	90.86 (17.66)	5 (23.80%)

Abbreviations: VABS-III = Vineland Adaptive Behaviour Scale, Third Edition; ABC = Adaptive Behaviour Composite.

[a] The VABS-III normative sample mean is 100 with SD of 15 points. A score ≤85 would therefore be classified as below average adaptive levels.

Compared to the normative sample, children exposed to topiramate had poorer levels of adaptive behaviour (see Table 7 and Figure 2). After aforementioned exclusions (n = 4), topiramate-exposed children (n = 21) had significantly lower mean scores in global ABC (M = 91.10, p = .023), daily living skills (M = 90.38, p = .003) and socialisation skills (M = 90.86, p = .028). A similar trend was observed for communication skills (M = 94.90);

however, this difference did not reach significance. Frequency analyses revealed that 42.9% of the topiramate-exposed cohort fell beneath the 'average' range ($M = \leq 85$) for global ABC, with up to a third children also falling beneath the 'average' range on communication skills (23.80%), daily living skills (33.33%) and socialisation skills (23.80%).

Table 7. Results of comparisons against normative sample

VABS-III	t-value	Mean difference	95% CI		p-value (2-tailed)
			Lower	Upper	
ABC	-2.465	-8.91	-16.44	-1.37	**.023***
Communication	-1.181	-5.10	-14.10	+3.91	.252
Daily living skills	-3.327	-9.62	-15.65	-3.59	**.003***
Socialisation	-2.372	-9.14	-17.18	-1.10	**.028***

Test value = 100.00; *$p < .05$

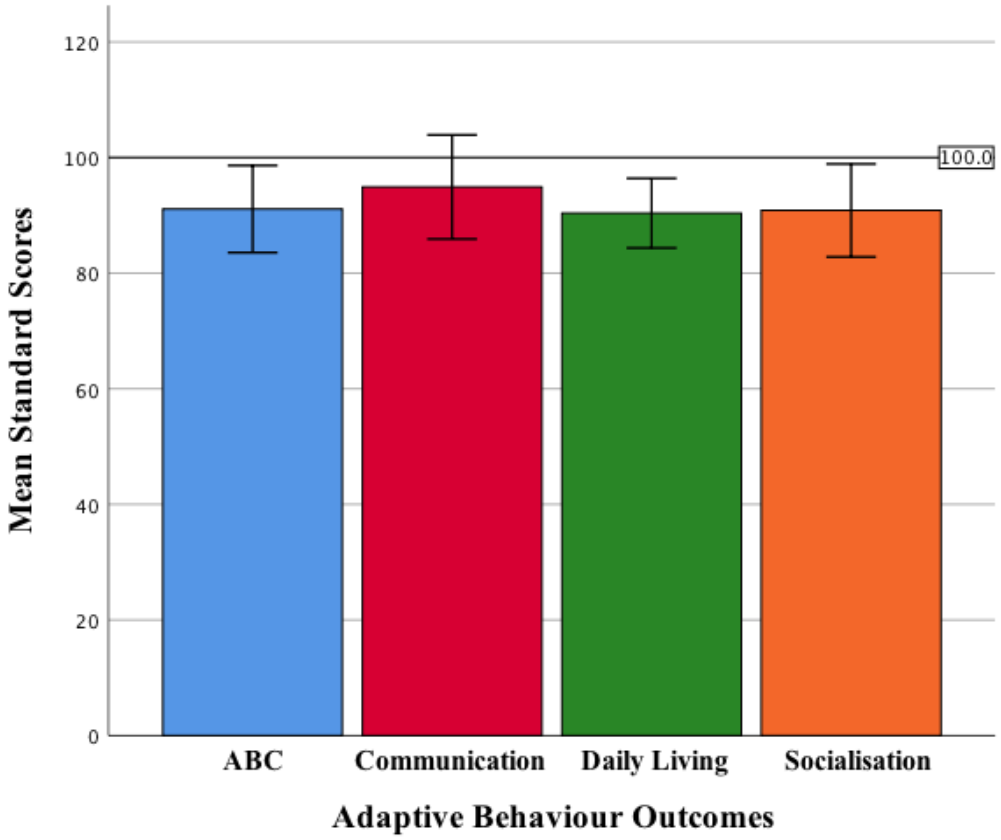

Figure 2. Mean scores and error bars with reference line of normative mean

Influence of non-exposure variables

Demographic and clinical variables were investigated for their influence on ABC and domain scores, including socio-economic status, parental educational attainment, parental age at birth, employment status, maternal epilepsy type, seizure exposure, other maternal health conditions, folate status, breastfeeding status, alcohol exposure, nicotine exposure, gestational age at birth, birth weight, child gender and child age at assessment and other child health factors. As it was planned that significantly influencing variables would be adjusted for in subsequent regression analyses, Bonferroni corrections were not applied.

Parental educational attainment yielded significant differences on adaptive behaviour outcomes. Topiramate-exposed children with at least one parent who attended education

beyond compulsory requirements had substantially higher ABC scores (*MD* = 20.29, *p* = .005), communication skills domain scores (*MD* = 30.07, *p* <.001) and socialisation skills domain scores (*MD* = 18.43, *p* = .020) than topiramate-exposed children with no parents having attended higher education. Alcohol exposure also led to significantly different Daily Living Skills domain standard scores; however, on review of alcohol-exposed cases, alcohol consumption was very low and infrequent and was thus considered a chance finding. No other significant influences on VABS-III scores were identified.

Dose investigations

Associations between topiramate dosage (low dose = ≤200mg/d, high dose = >200mg/day) and neurodevelopmental outcomes were analysed using hierarchical multiple regression. Following adjustment for parental higher education, there was a significant negative association between topiramate dose and ABC scores (Figure 3, β = -.405, 95% *CI* [-22.347 - -3.006], *p* = .013), whereby children exposed to high dose topiramate scored over two thirds of a standard deviation below children exposed to low dose topiramate (*B* = -12.678). Significant dose-response relationships were also observed for communication domain scores (*B* = -12.530, 95% *CI* [-22.139 - -2.920], *p* = .013) and socialisation domain scores (*B* = -14.703, 95% *CI* [-26.145 - -3.262], *p* = .014). Thus, once the expected influence of parental education was adjusted for, increasing doses of topiramate were associated with poorer communication, socialisation and global adaptive behaviour scores.

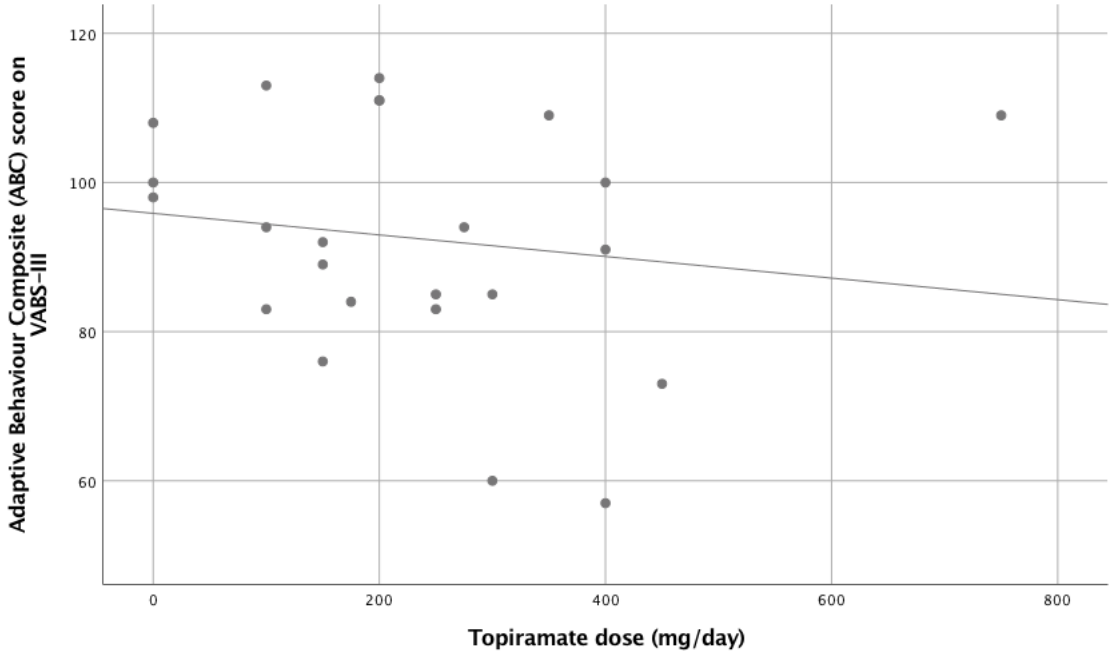

Figure 3. Scatterplot depicting relationship between ABC scores and topiramate dose

Other outcomes

As part of the study's subsidiary aims, further health and neurodevelopmental outcomes were explored in relation to topiramate exposure. Within the topiramate-exposed cohort (n = 21), two children (9.5%) were born with major congenital malformations. Six children (28.6%) were born small for gestational age and when compared with UK population estimates (10%, NHS, 2016) using a binomial test, this proportion was significantly greater than expected (p = .014). A significant negative relationship was identified between birthweight centile and dose of topiramate (see Figure 4, r (24) = -.407, p = .048). Furthermore, birthweight centile was significantly correlated with VABS-III outcomes, with lower centile children obtaining poorer for overall ABC scores (Figure 5, r (21) = .479, p = .028) and socialisation skills scores (r (21) = .504, p = .020).

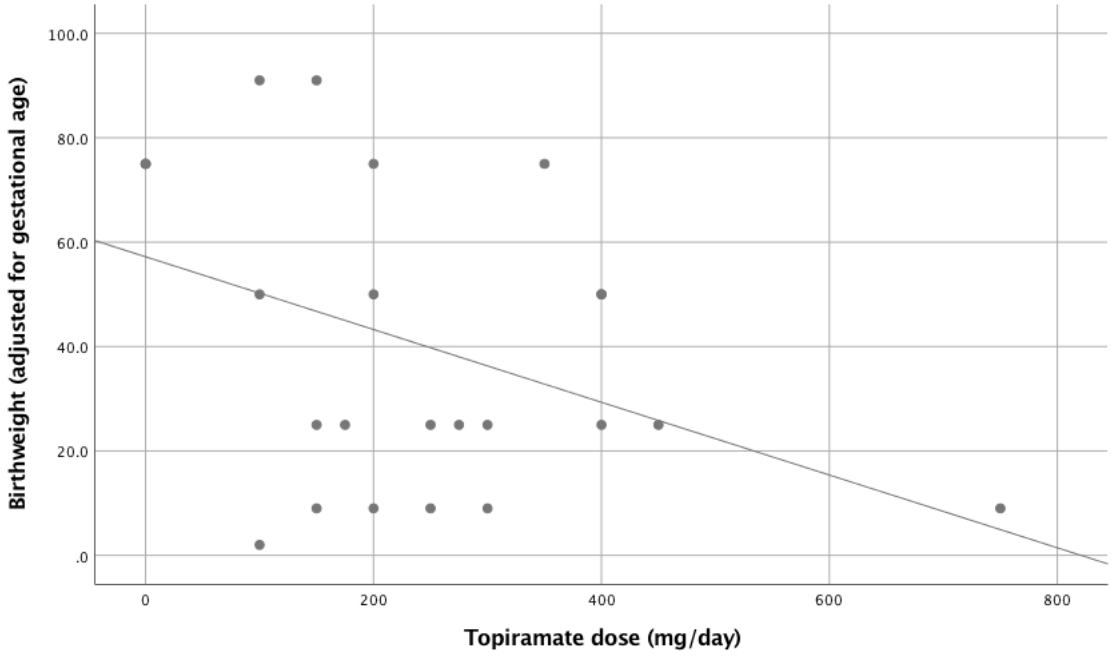

Figure 4. Scatterplot depicting relationship between birthweight and topiramate dose

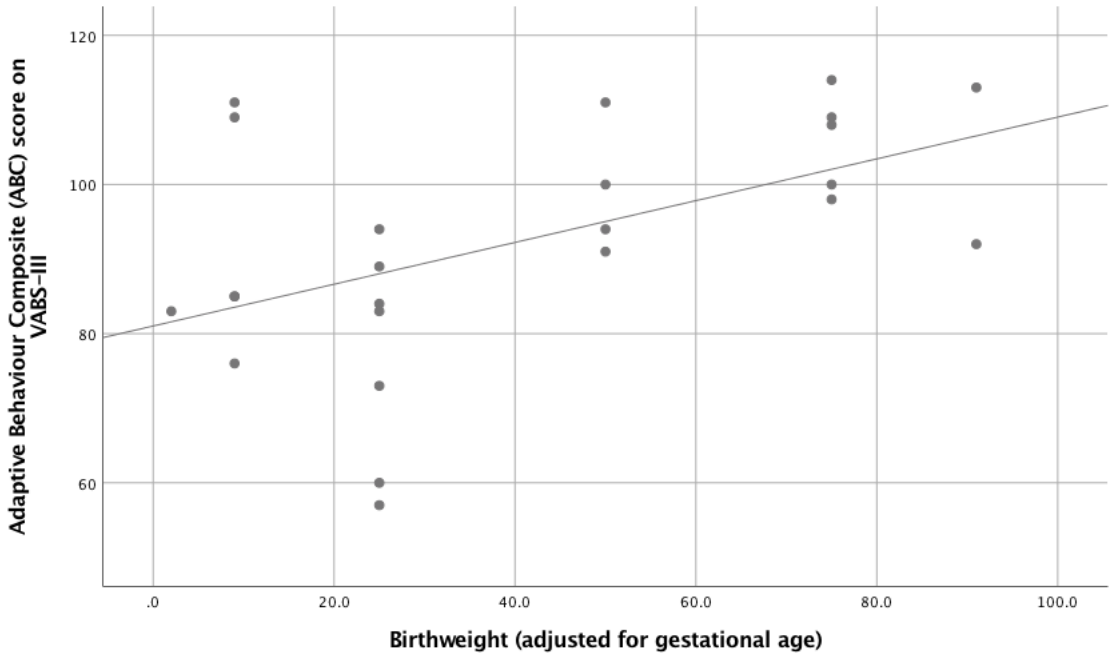

Figure 5. Scatterplot depicting relationship between ABC scores and birthweight

Maternal report identified five children (23.8%) that did not meet their early developmental milestones on time. Six children (28.6%) were reported as having difficulties

with learning at school and three children (14.3%) were in receipt of formal supported learning provision. Six children (28.6%) were reported as having difficulties with social interaction.

Amongst the total sample recruited (n = 28), there were six cases of children with existing diagnoses of Autism Spectrum Disorder (ASD) made via routine clinical services and independent of the study. All six children had been exposed to topiramate; however, two children represented those excluded from analyses due to the presence of other possibly influencing conditions. Therefore, four children (19.05%) in the included topiramate-exposed cohort had formal diagnoses of ASD. A binomial test of proportion was conducted using 1.1% population estimates as the prevalence value (Office of National Statistics, ONS, 2011; Baron-Cohen et al., 2009). This revealed that the observed incidence of ASD was significantly higher in the current cohort compared to estimates of ASD prevalence within the general UK population ($p < 0.001$). A summary of the demographics and outcomes for the four topiramate-exposed children diagnosed with ASD can be seen in Table 8.

For all four children with diagnoses of ASD, there was no family history of congenital malformations, special educational needs, ASD or other neurodevelopmental conditions. The mean daily topiramate exposure dose was 285.00mg/daily, with three children (60%) exposed to high-dose topiramate in-utero. There were no cases of major congenital malformation; however, one child was born with a congenital heart problem at birth that was self-resolving. Adaptive behaviour skills were below average levels for all children (100%) on all outcomes except daily living skills, where 75% of children (n =3) fell below average levels. Three children (75%) had formal learning support in place. All four children were born smaller than average for gestational age at birth ($\leq 25^{th}$ centile), with one child below the 10^{th} centile.

Table 8. Summary of included topiramate-exposed children with diagnosed ASD

	Case 1	Case 2	Case 3	Case 4
Demographics/background				
ASM dose, mg/d (high/low)[a]	300 (high)	400 (high)	450 (high)	150 (low)
Family history[b] of neurodevelopmental conditions, ×/✓	×	×	×	×
Family history[b] of learning difficulties, ×/✓	×	×	×	×
Family history[b] of major malformations, ×/✓	×	×	×	×
Birth and health outcomes				
Gestational age at birth, wks	39	42	41	40
Major[b] malformations, ×/✓	×	×	×	×
Birth weight centile	25	25	25	9
Small for gestational age (≤ 10th centile), ×/✓	×	×	×	✓
Long-term health conditions, ×/✓	×	✓	×	×
Hearing/eyesight conditions, ×/✓	✓	×	×	×
Educational outcomes				
Reported learning difficulties, ×/✓	✓	✓	✓	✓
Formal learning support provision in place, ×/✓	✓	✓	✓	×
Adaptive behaviour outcomes				
Below average[d] Adaptive Behaviour Composite (ABC) score, ×/✓	✓	✓	✓	✓
Below average[d] communication skills (COM), domain standard score, ×/✓	✓	✓	✓	✓
Below average[d] daily living skills (DLS), domain standard score, ×/✓	✓	✓	✓	×
Below average[d] socialisation skills (SOC) domain standard score, , ×/✓	✓	✓	✓	✓

[a] Low dose = <200mg, high dose = ≥200mg
[b] First degree relatives
[c] Requiring intensive and/or surgical intervention.
[d] Score of ≤85

Discussion

In line with initial hypotheses, the results of the current study suggested that prenatal exposure to topiramate was linked with poorer adaptive behaviour outcomes. Obtained in a relatively small sample this highlights how, decades following its medicinal approval in 1996, the neurodevelopmental trajectory of children exposed to topiramate in the womb is far from understood. When comparing parent-rated adaptive behaviour to normative sample data, children exposed to topiramate had significantly poorer skills in their daily living skills, socialisation skills and global adaptive behaviour. Our sample (n = 21) provided adequate power (90%, d = 0.6, VABS-III score MD = 10) to detect the large effect sizes observed, with mean scores falling over half a standard deviation from the norm. Findings were both statistically and clinically significant, with 42.9% of the exposed cohort falling below the average range for global adaptive behaviour. Significant dose-response associations were observed between topiramate dose and adaptive behaviour outcomes, with lower adaptive behaviour scores in cases of high-dose topiramate exposure. Additional associations were also identified between birthweight centile and adaptive behaviour outcomes and between topiramate dose and birthweight centile, in line with aforementioned research (Hernández-Díaz et al., 2017).

The paucity and inconsistency of existing human research limits the confidence with which we can interpret these findings. Consistent with our main observations, a population dataset study reported that children with in-utero topiramate exposure (n = 27) were at an increased risk of learning disability (Bech et al., 2018); however, it was unclear whether children with conditions established as impacting neurodevelopment (e.g., epilepsy, acquired brain injuries and genetic conditions) were excluded from the study. In contrast, two research groups have indicated comparable outcomes between topiramate-exposed and unexposed children (Bromley et al., 2016; Husebye et al., 2019), although the outcomes

assessed differed to this study. Establishing dose associations are key to establishing teratogenicity (Voorhees, 1986) and this information can offer some degree of clarity in ascertaining the validity of findings. The significant negative correlation observed in the current study between topiramate dose and birthweight (controlled for gestational age) centile were of note and were consistent with research reporting reduced fetal growth following in utero topiramate exposure (Hernández-Díaz et al., 2017). The finding also links with preclinical research which observed lower birthweights, limb malformations and problems with physical development animal models of topiramate exposure (Michelucci, Passarelli, Riguzzi, Volpi & Tassinari, 1998; Hill, Wlodarczyk, Palacios & Finnell, 2010; Lai, Ding, Moses & Chen, 2017). That we also observed a significant negative association between topiramate and adaptive behaviour outcomes is consistent with the position that teratogenic effects on neurodevelopment occur in a dose-response fashion (Friedman, 2010; Vajda et al., 2004). Together, these statistically and clinically relevant findings bolster our hypothesis that topiramate exposure may impact neurodevelopmental outcomes. However, due to our small sample size, further exploration with a large cohort is warranted to validate findings.

Subsidiary analyses also demonstrated clinically important findings requiring further investigation. After the cautious exclusion of children with other conditions or difficulties linked with neurodevelopmental outcomes, four of the 21 children exposed to topiramate had formally diagnosed ASD. The 23.8% incidence was starkly and significantly greater than population rates of autism which are estimated to be 1.1% (Baron-Cohen et al., 2013; Rutter, 2005). It is of further note that, had all invited families participated in the study, the rate of ASD observed would remain above typical estimates at 3.7%, suggesting that opt-in bias cannot fully explain this finding. In our three cases, dosage was high (>200mg/daily) and there was no family history of diagnosed neurodevelopmental conditions. Birthweights

were lower, with three children falling in the 25th centile and one child below the 10th centile. An increased rate of ASD has been repeatedly observed in children with in-utero exposure to valproate (Bromley et al., 2013; Christensen et al., 2013) and is also evident in animal data which indicates this to be associated with drug teratogenicity rather than risk associated with maternal disease (Schneider & Przewlocki, 2004). One study examining risk of autistic traits reported comparability between topiramate-exposed and unexposed children (Bjørk et al., 2018), however, the sample included only six children. Within our sample, children with a confirmed diagnosis of ASD also obtained socialisation skills that were, on average, nine points lower than the total topiramate-exposed group. This could represent a continuum of influence on social abilities and therefore, a question remains as to whether in-utero topiramate exposure confers a risk of neurodevelopmental impact which presents similarly to ASD. Further work should investigate this as a priority to ensure families are provided with adequate and evidence-based risk counselling and the risks to children of mothers with epilepsy are reduced as far as possible.

Strengths and limitations

Meeting our overarching research aim, this study was the first to examine long-term adaptive behaviour outcomes in children exposed to topiramate in the womb which, alongside the undertaking of dose investigations, brings novelty to this limited research area. Strengths included the blinded administration of a standardised measure with proven ability to detect functional deficits associated with teratogenic exposures (Bromley et al., 2019; Deshmukh et al., 2016; Vinten et al., 2009), undertaken by a small number of outcome assessors. Double scoring of outcome measures, data entry checks and the prospective collection of pregnancy and exposure information based on individual medical records further increased the reliability of our findings. Although, after relevant exclusions, our exposed cohort was limited to 21 children, the sample achieved was reasonable relative to existing topiramate

research (Knight, Wittkowski & Bromley, 2020) and the observation of significant findings with large effect sizes indicated adequate power, in line with aforementioned power calculations. Furthermore, the capacity to exclude children with conditions associated with neurodevelopmental outcomes ensured a purer investigation the impact of topiramate exposure. Attention to key covariates, including maternal, paternal and child variables, was another factor that strengthening the methodological quality of the study.

The main weakness of the study was the absence of an equally sized control group. The unexposed cohort data was utilised for dose investigations; however, main analyses were limited to contrasts against normative data, limiting the strength of our comparisons due to possible confounding via baseline differences between groups. Although potential covariates were assessed and associations with adaptive behaviour outcomes were carried out, planned regression analyses were not sufficiently powered to input several covariates at once. It is possible that our findings could have been confounded by multiple covarying factors that affected adaptive behaviour outcomes in a cumulative fashion. Further limitations were the use of a parental report measure and the retrospective enrolment into the study. Both of these factors could have contributed to the large effect sizes observed; mothers with concerns about their child's functioning might have been more eager to participate and although the VABS-III was administered by a blinded researcher, mothers were unblinded to their child's exposure status which could influence responses.

Future directions

Regarding the direction of future research, there are many ways in which the findings of the current study could be built upon. Our findings regarding adaptive behaviour skills and elevated incidence of autism warrant further investigation. Investigations into the links between topiramate, birthweight and neurodevelopmental outcomes are also indicated.

Extension of the current study to include a full, unexposed cohort, as originally planned, would enable better comparability between cohorts and greater reliability of results, if replicated. Replication studies using direct, clinician-rated methods of assessment would add weight to the current findings regarding adaptive behaviour. Researchers should also consider the use of a comparator drug-exposed cohort. Comparisons against established teratogenic ASMs, such as (e.g., valproate) or ASMs which appear to be less harmful (e.g., lamotrigine, Knight et al., 2020), serve as a clinically meaningful reference for medication regulatory authorities and would engender important insights into the relative risk of topiramate. Such insights are key, given that most women with epilepsy will need to continue treatment throughout pregnancy (Hill et al., 2010).

More broadly, studies recruiting larger sample sizes that are adequately powered to adjust for multiple confounding variables will be key to unpicking the inconsistencies that have arisen thus far within the literature. Careful attention should be paid to the outcomes under investigation and how best to measure these, using direct and blinded methods of assessment when possible. Similarly, due consideration should be given to selecting an appropriate design (Knight et al., 2020); the use of prospective data and ideally, prospective recruitment techniques would be of particular value. Any observations would have added strength if including dysmorphology reviews, as all major human teratogens have had a syndrome presentation (Friedman, 1992), including valproate (Bromley et al., 2019).

Clinical implications

There are myriad clinical implications arising from this study, most notably with regards to the ASMs offered to women of childbearing age and the information available to them and prescribing clinicians. The current findings are preliminary and require further replication and study in order to be fully understood but clearly demonstrate a need for routine and

systematic study of newly approved ASMs and better systems for pharmacovigilance (Adam, Polifka & Friedman, 2011; Friedman, 2012). If lessons are to be learned from previous failures to act upon harm evidence regarding valproate exposure, then this must proceed as a matter of urgency. Immediate implications relate to how women are counselled about the existing availability of evidence.

Conclusion

In sum, this novel study has reaped important results regarding poorer adaptive behaviour outcomes and higher incidence of ASD diagnoses for children exposed to topiramate in-utero. Alongside some indications of a possible dose-response relationship, these findings suggest that topiramate could act as a neurobehavioural teratogen. The proposed directions for future research should be undertaken as a matter of urgency to elucidate the reliability and validity of these findings. The timeliness with which these insights are gained will have lasting implications on the lives of women with epilepsy and their children.

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Paper 3

Critical appraisal

Word count: 4,900 (main text)

6,725 (all text), 1,825 (references)

Introduction

This paper comprises a critical review of the current thesis. A detailed examination of the systematic review and empirical study is firstly presented, with attention to the rationale for decisions made regarding methodology and the impact of these decisions on the overall quality of the work undertaken. Reflections on the process of undertaking research in this area are discussed throughout. Consideration is then given to the wider implications of our findings and their relevance within and beyond clinical psychology.

Paper 1: Systematic review

Topic choice

Teratogens are agents that interrupt typical fetal development (Hill, Wlodarczyk, Palacios & Finnell, 2010). Anti-seizure medications (ASMs) were first postulated as having teratogenic potential over four decades ago, when early human studies reported adverse birth outcomes following in-utero exposure (German, Kowal & Ehlers, 1970; Annegers, Elveback, Hauser & Kurland, 1974). Research into physical outcomes advanced steadily from this point (e.g. Kaneko et al., 1999; Meador et al., 2006; Weston et al., 2016; Tomson, Battino & Perucca, 2019), while attention towards the impact of ASMs on the developing brain lagged by comparison (Bromley et al., 2014). Neurodevelopmental outcomes became the subject of research much later, with studies investigating older ASMs due to their prevalent use at the time. Striking findings regarding valproate, now summarised in key reviews (Bromley et al. 2014; Veroniki et al., 2017; Bromley, Baker & Meador, 2009), highlighted the potentially devastating effects of in-utero exposure, such that valproate is now counter-indicated for women of childbearing age (MHRA, 2015). Despite these restrictions, alongside the increasing use of newer ASMs over the past decade (Meador et al., 2018), a predominance of studies investigating older ASMs prevails. Inequity of research into newer ASMs has been

highlighted as hindering appropriate synthesis of findings, in turn limiting evidence-based guidance and decision-making around epilepsy treatment throughout pregnancy (Bromley et al., 2014).

Scoping searches conducted in line with relevant guidance (Munn et al., 2018; Liberati et al., 2009) revealed that although the research base for newer ASMs had grown recent years, inconsistent findings had limited the impact of any individual study in furthering understanding. The decision to review newer ASMs only was therefore based upon the rationale that this would enable a more meaningful summary of this research area to date, undiluted and unshrouded by already established findings relating to older ASMs. A concentrated review of newer ASM research was also believed to be a high priority in terms of its implications for medical prescribing. As understanding into the relative risks of older ASMs has progressed, so too have prescribing patterns (Meador et al., 2018), guidelines around epilepsy treatment (NICE, 2018) and aforementioned restrictions of these medicines during pregnancy (MHRA, 2018), shaped by availability of literature, in line with principles of evidence-based practice (National Health Service, 2015; Health & Care Professions Council, 2016)). A study of teratogenicity reported a mean time of 27 years to fully understand the risks associated with a medicine (Adam, Polifka & Friedman, 2011). Without a galvanisation of efforts, this could well be the case for newer ASMs, some of which have been licensed for use since 1993 (Adam et al., 2011), with unknown consequences for women with epilepsy and their children.

In terms of relevance to clinical psychology, research reports poorer mental health outcomes for mothers with epilepsy who have had to make uninformed treatment decisions (Atarodi-Kashani et al., 2018). It was aimed that this review would contribute towards better pre-conceptual counselling of women with epilepsy, promoting informed decision making and, in turn, a sense of agency and control. The review was also hoped to encourage

consideration of the potential impact of maternal medications in general clinical practice, for example, within developmental history assessments and as part of the espoused biopsychosocial model of psychological formulation (Division of Clinical Psychology, 2011). Thus, from a number of perspectives, the review question was selected with the rationale that it had the greatest potential impact, both empirically and clinically.

Search strategy

When developing the search strategy, consideration was given to the selection of terms that would capture all available literature, with sufficient sensitivity to omit irrelevant research (Liberati et al., 2009). As the review question had relevance to medics, pharmacology, neuropsychology and neurology, a greater variety of key search terms was required to represent this overlap. It was therefore anticipated that despite developing a sensitive search strategy, large numbers of results would be returned. In line with recommendations, over-inclusion was agreed within the review team as preferable to the risk of developing a search that omitted relevant papers (Xiao & Watson, 2019).

When selecting search terms, existing reviews were consulted for guidance (Bromley, Baker & Meador, 2009; Tomson et al., 2019), with particular attention to Bromley et al. (2014) because this was a Cochrane-standard review that the current review aimed to extend. Three search term blocks were devised, encompassing key components of the review question. This was piloted on a single database before advice was sought to apply the search elsewhere. Guidance was sought from supervisors and the University of Manchester library team regarding the selection of appropriate databases that would best represent the different scientific disciplines of relevance to the review question. It was agreed to search MEDLINE, PsycINFO, Embase, Web of Science and CINAHL PLUS. To ensure an all-encompassing

search that was least variable across databases, limitations were restricted to dates and human studies, as outlined in exclusion/inclusion criteria.

Inclusion and exclusion criteria

Though the review question was broad, the paucity of research in this area was such that an exhaustive list of inclusion and exclusion criteria was not required to temper the number of results returned. Animal studies were excluded due to the need to understand the human teratogenic potential of newer ASMs. Studies not available in English were excluded; this was justified on the basis that Bromley et al. (2014) identified only one study in a different language, the findings of which were not relevant to this review. Results were also restricted to those entered onto databases after 2000, as the use of newer ASMs was seen to increase after this time (Meador et al., 2018). Given that the current review intended to follow on from Bromley et al. (2014), restricting results to those entered after 2014 was considered. However, this would have removed key data from the review, in turn weakening the quality of evidence, synthesis and overall conclusions. Although this meant including articles from nine studies that had been reviewed by Bromley et al. (2014) it was felt that the current review was able to explicate the findings more elaborately given the focus on newer ASMs.

Unpublished data were excluded from the study, in lieu of any further restrictions based on quality. Publication bias is an established issue within clinical research that can be amplified within systematic reviews (Knobloch, Yoon & Vogt, 2011). However, dependant on the methodological context within which they are obtained, non-significant findings can be of equal value in answering questions about comparative risks of ASMs within this research area (Bromley et al., 2014). For clarity on how this criterion would affect results returned, this restriction was removed; an additional 17 conference abstracts to those returned originally (Figure 1) were identified; however, 13 of these led to publications

included in the review. Of the remaining four, it was evident in the abstract that sufficient information would not have been available for data extraction or quality assessment and thus would not have added to the narrative synthesis.

Beyond database limits, key inclusion and exclusion criteria for screening decisions concerned the use of newer ASMs as monotherapy, rather than polytherapy treatments. Outcomes for polytherapy are not useful in ascertaining insight into the impact of a specific ASM (Vajda et al., 2004), as was intended in the current review. Furthermore, although polytherapy outcomes have purportedly been poorer than monotherapy outcomes, emerging evidence suggests that these are largely driven by the impact of valproate as a common combination treatment (Vajda et al., 2010; Tomson et al., 2015). Excluding studies reporting polytherapy outcomes only was thus made with the rationale of the review's aim to provide a clear, unmuddied, understanding of individual newer ASMs. No exclusions were made on the basis of study design, contrary to Bromley et al. (2014) who removed retrospective cohort studies from their review. In the case of this limited research area, including all available evidence alongside a transparent quality assessment was believed to offer a more meaningful synthesis and generate more relevant recommendations for the research base moving forwards. Regarding the main outcome assessment, our review question was intentionally broad, covering neurodevelopmental outcomes across a range of domains so that all available literature could be captured and discussed.

Quality assessment

When selecting an appropriate quality assessment tool, an important consideration was the novelty of this research base in comprising studies that were observational/non-randomised in nature. There is no consensus on a single assessment tool for such studies, and a general criticism is that the tools available tend to be highly subjective, leading to inconsistent

quality appraisals with poor inter-rater reliability, ultimately limiting the utility of quality appraisals and the conclusions of the narrative synthesis overall (Mallen, Peat & Croft, 2006). The current review opted to use the Newcastle Ottawa Scale (NOS, Wells, 2015) to assess the quality of risk of bias across included studies, on the basis that it was Cochrane-recommended and because it has been designed to appraise non-randomised studies specifically (Cochrane Scientific Committee, 2017). Bromley et al.'s (2014) tool was not selected because it included items relevant to a meta-analytic technique, although items around dose were integrated due to their centrality to the review question.

Consideration of key covarying factors were part of the standard NOS but required operationalising. Classifying the covarying factors that would be 'key' for the purposes of passing this quality appraisal criterion was given careful consideration by the review team, with reference to existing literature on influencers on child neurodevelopment. Research clearly indicated SES and other child/parent factors as having the strongest effect on child outcomes and so these were integrated into the NOS. To ensure fairness and consistency, all items and criteria were a priori, decided upon with full agreement from the review team before the undertaking of any quality assessments. A scoring key was also developed in order to translate scores to a quality rating (Appendix C). The finalised tool was piloted between two reviewers, with decisions made independently thereafter. Longitudinal studies assessing the same cohorts using the same methods (e.g., NEAD) were rated together whereas studies using different methodological approaches across publications (e.g., Huber-Mollema et al., 2019; 2020) were assessed separately to ensure ratings were representative and fair. One hundred percent of included papers were independently quality-assessed by two members of the review team, with levels of inter-rater reliability ($\kappa = .973$, $p < .001$) indicating that a consistent and methodological approach had been achieved.

Data synthesis

Our review concerned whether and how newer ASM exposure affected child neurodevelopment. It was always intended that the synthesis of findings would be structured via individual ASM type rather than by grouping together ASMs and structuring findings via outcomes. In light of the established differences between older ASMs and how they impact child outcomes in varied and distinctive ways (Bromley et al., 2014), this approach was deemed to best answer the research question and meet our aims of informing decision making and policy (Mays, Pope & Popay, 2005). After finalising those papers that were to be included in the review, inspection of available evidence per ASM revealed notably sparse and heterogenous data, with regards to both the types of outcomes assessed and the statistical methods of analysis employed. Although meta-analysis can be undertaken with as few as two data (Stroup et al., 2000), this can risk generating unreliable or invalid findings via inappropriate combination of outcomes/statistics (Bullock & Svyantek 1985; Sharpe, 1997). Quasi-experimental or observational studies, such as those encompassed in our review, are cited as yielding particularly disparate and dissimilar findings (Snilsvelt et al., 2012) which are particularly subject to bias by confounding (Egger, Schneider & Smith, 1998) and can lead to invalid conclusions if combined inappropriately (Stroup et al., 2000). A narrative approach to the analysis of data can provide syntheses of literature with due caution around and consideration of such factors (Egger et al., 1998; Colliver, Kucera & Verhulst, 2008). In addition to providing a meaningful, sophisticated and useful summary of data for key stakeholders, the primary and secondary structuring of results (via ASM type and neurodevelopmental outcomes, correspondingly) afforded by our approach highlighted those areas of research that were significantly lacking or absent altogether. As such, there was felt to be good rationale for undertaking a narrative synthesis analytic approach.

Reflections

While undertaking the review, there was a distinct and prevailing sense of frustration and shock regarding the availability of evidence and information available to mothers with epilepsy, prescribers and other key stakeholders. The discovery that there was no data at all for certain ASMs was particularly jarring when considered in the context of evidence-based practice and decision-making, an ethos held and espoused by health services and medication regulators alike. The knowledge that these medicines had been approved for use for decades without investigation brought about further feelings of indignation and disbelief. It was reflected that these reactions likely mirrored those felt by mothers with epilepsy and prescribers alike who faced, or currently face, the challenge of making potentially life-altering decisions without information or insight into the long-term implications for their children.

A further reflection concerned the issue of responsible reporting. Responsible reporting is essential to all areas of research (British Psychological Society, 2014) but is particularly crucial in areas where there is a lack of clarity and/or a reliance upon data to inform clinical practice and guidance, such as in health-related research (Simera, Hoey, Schulz and Altman, 2010). The process of undertaking data extraction and quality assessments brought to the fore the importance of reporting studies with sufficient detail and transparency so that fair and reliable conclusions could be reached. It seemed that a tension sometimes existed between responsible reporting and a pressure to undertake and disseminate high impact research, with the latter occasionally leading to the over-stating or over-generalising of findings inappropriately. This has been noted in existing literature (Kiyomi et al., 2017) and was a tension experienced first-hand when explicating the results of the review and subsequently, the empirical study. However, in a research area defined by

paucity and inconsistency, it is only those studies undertaken and reported with integrity that can have the most meaningful and long-term impact, both clinically and academically.

Paper 2: Empirical study

Topic choice

Topiramate is a newer ASM that was approved for medicinal use by the Food and Drug Administration in 1996 (Adam, et al., 2011). As noted, prescribing of ASMs shifted towards newer medicines in recent years (Meador et al., 2018); thus, there was a clear rationale for the selection of a newer ASM to study. In the UK, the most commonly-prescribed ASMs are lamotrigine and levetiracetam (31.1% and 27.6%, respectively, Meador et al., 2018) and the systematic review revealed that the research base for these medicines were relatively more developed. Among ASMs less commonly prescribed were topiramate, zonisamide and oxcarbazepine. A study of topiramate was decided upon the basis of existing animal data and early human research indicating babies born small for gestational age and with higher rates of malformation (Margulis et al., 2012), physical signatures which have been closely linked with brain impacts in the case of alcohol and valproate (Carter et al., 2016 and Clayton Smith et al., 2019, respectively). Although topiramate only accounts for 2.3% of prescriptions (Meador et al., 2018), this equates to large numbers when it is considered that 2,500 women with epilepsy give birth in the UK each year alone (Epilepsy Society, 2016). Combined with possible indicators of teratogenicity, these numbers were seen to indicate a more urgent need to study topiramate specifically. In addition, although limited, the scant research available for topiramate suggested some possibility of impacted neurodevelopmental outcomes and specifically, adaptive behaviour. Thus, there was a well-defined research question to be addressed with clear relevance to clinical neuropsychology and developmental psychology.

Designing the study

When devising the study, foremost considerations centred on addressing the research question (BPS, 2014), using a design and method that were feasible as a doctoral project. The selection of a registry cohort design offered several strengths in investigating the research question and these have been discussed in the empirical paper. The design was also well-suited to the limited time and resources afforded by the doctorate. For example, prospective information available on the registry enabled the ascertain of pregnancy and birth information, increasing the reliability and quality of data by minimising recall bias and reducing burden on both participant and researcher at the point of data collection. The cross-sectional element facilitated long-term outcome assessment without the need for longitudinal follow-up.

As mentioned, it was initially intended that the study would investigate neurodevelopmental outcomes of a topiramate-exposed cohort compared to a 'no medication' control cohort. Had a full cohort been achieved, an additional strength would have been the recruitment of comparable cohorts drawn from the same source. The registry source was the UK Epilepsy and Pregnancy Register (UKEPR), chosen due to established links within the supervisor team and due to successful recruitment into past publications with high uptake rates (Shallcross, 2011; Shallcross, 2014; Bromley et al., 2016, Cummings, 2011). It could be argued that the high uptake rates seen from the UKEPR resulted from a self-selection bias, wherein women concerned about their child's development would be more eager to participate. Inspection of the frequency of mothers reporting concerns about their child's development and social skills in the current study indicated that this was unlikely to be the case. Furthermore, in the 2014 Cochrane Review (Bromley et al.), follow-up studies based within pregnancy registers provided results that were consistent with prospective longitudinal studies.

Regarding outcome assessment, the inconsistent findings to date regarding functional outcomes (Bech et al., 2018; Rihtman, Parush, & Ornoy, 2012; Bromley et al., 2016) indicated sufficient rationale for the investigation of adaptive behaviour. Furthermore, it was possible to ascertain a measure of adaptive behaviour skills indirectly via maternal report rather than via direct observation or assessment (Sparrow, Cicchetti & Saulnier, 2016). While this limited the strength of our findings to some degree, it was a cost-efficient and time-efficient means of collecting data which enabled the largest sample possible to be achieved. When considering possible assessment tools, the Adaptive Behaviour Assessment System (ABAS) was considered before opting for the Vineland Adaptive Behaviour Scale-Third Edition (VABS-III, Sparrow et al., 2016). Both the ABAS and VABS-III are widely used have been reviewed as having the strongest psychometric properties of assessment tools available (Price, Morris & Costello, 2018). The VABS-III had been used within the research area previously (Deshmukh et al., 2016), demonstrating its ability to detect ASM teratogenicity. Importantly, the measure enabled cross-sectional assessment spanning childhood into adulthood and could be administered via telephone, as evidenced by Deshmukh et al. (2016). On this basis, the tool was felt to be an appropriate means of assessment.

Ethical approval

The study was undertaken in line with guiding ethical principles (BPS, 2014; 2018). The study required sponsorship from the University of Manchester and ethical approvals from the Health Research Authority (HRA) and from the local research approval departments of Manchester University Hospitals NHS Foundation Trust and Belfast Health and Social Care Trust. Unfortunately, significant delays in the processing of HRA applications had substantive consequences for the study.

Recruitment

Due to the above-mentioned delays to obtaining ethical approval, recruitment did not begin until October 2019, approximately six months following its anticipated start-date. Although the recruitment phase was extended and the uptake rate was reasonable (25%), it fell below the rate expected based on previous studies using a similar recruitment method (e.g., Shallcross, 2011; Shallcross, 2014; Bromley, 2016, Cummings, 2011). The delays had significant ramifications on the quantity of invitations that could be posted and number of data collection appointments that could be undertaken prior to the submission deadline, which had also been extended. Additional factors impacted recruitment and the total sample achieved. Uptake and data collection declined during the festive season and in the final block of recruitment, the Covid-19 pandemic led to several participants withdrawing from the study due to other home-work and home-school commitments and concerns.

Data collection and analysis

Necessitated by the small scale of the study in relation to the wide pool of participant which spanned the UK, data collection took place via telephone appointments. This was anticipated to have some effect on participation opt-in and completion, although the direction of this effect was uncertain. While some mothers may not have felt as invested in a telephone appointment, it was also considered that this means of data collection provided more flexibility for participants in terms of appointment times and managing other demands. Ultimately, rates of uptake and attrition were reasonable (25.0% and 12.5%, correspondingly), indicating some level of acceptability of the data collection method to potential participants. That said, relative to aforementioned studies recruited via the UKEPR, uptake was reduced. It is notable that this was the first study without any direct child assessment or feedback provided to mothers and the appeal of this element may have been

underestimated. Another possible explanation relates to findings that topiramate medicine affects language ability (Thompson, Baxendale, Duncan & Sander, 2000); the telephone format, unsupported by non-verbal communication, may have deterred women from participating who felt aware of any language difficulties.

A further implication of issues with ethical approvals and recruitment was on the size of the control group obtained. It was not possible to recruit an equally sized 'no medication' cohort against which to compare the adaptive behaviour skills of topiramate-exposed cohort, due to the challenges noted above. This undoubtedly weakened conclusions regarding our findings. Comparisons to normative data are limited; as participants are drawn from different sources, there is a greater likelihood that baseline differences between groups explains differences in outcome. However, this was felt to be the best use of data under the constraints of time and is a method employed in this area previously by other research groups (Nadebaum et al., 2011, Bromley, Baker, Clayton-Smith & Wood, 2019). Continuing planned statistical comparisons would have been wholly inappropriate given the size of difference between the exposed versus unexposed cohorts and may have introduced risk of Type 1 error, in turn affecting the validity of the results (Rusticus & Lovato, 2014).

At the point of data analysis, a total of four topiramate-exposed children were excluded from the main analyses as, despite appropriate screening, it became apparent during the course of data collection that existing factors (e.g., neurological condition, learning disability, genetic condition) were present that may have confounded the results. This represents a more cautious approach than other topiramate studies to date (e.g., Bech et al., 2018) but increases the likelihood that the associations found were genuine. Excluded children's data were represented in the demographics table; mothers had spent time and effort participating in the study and it was deemed unethical to exclude their data from the study completely. Although the 'no medication' cohort could not be used for planned group

comparisons due to group size (n = 3), the data were used within dose investigations. As such, all data collected was presented in the study, in line with key guidance around research ethics (Rosenthal, 1994; BPS, 2014).

Despite the relatively small sample size (n = 21 for comparisons against normative data and n = 24 for dose investigations), the study was calculated to be powered to detect the large effect sizes observed. Furthermore, in the context of this research area, the sample achieved was the second largest to date, with superiority of some aspects of methodology over the existing population dataset research (*n* = 27, Bech et al., 2018). For example, the current study attained prospective dose information using more reliable methods, was able to exclude data on the basis of child/family history (as described above) and enabled all participants to undergo data collection with only two researchers, increasing consistency of outcome assessment.

Reflections

Many mothers who took part in the study described having experienced a range of complex emotions when facing the dilemma of whether and how to treat their epilepsy during pregnancy, in addition to ongoing uncertainty and doubt regarding their choices. Mothers also described an altruistic sense of duty in relation to their participation in the study, expressing hope that doing so might contribute towards a future in which women with epilepsy could be appropriately counselled and informed about medication choices throughout pregnancy and risks to children reduced to a minimum. Receiving thanks and gratitude from participants for running the study was humbling, surreal and testament to the gravity of the issue at hand. The sense of duty in participants was mirrored by a growing sense of responsibility within the trainee to produce a study that would be of most clinical and empirical value to the research area and the individuals at its heart. Loss of time to recruit

the intended sample was a source of guilt and sadness, made more pertinent upon the emergence of significant findings which could not be fully interpreted due to the size of the cohort obtained. This brought about further consideration of ethics and the responsibility of researchers to take appropriate action when there is a discovery of potentially concerning findings with important clinical implications (Rosenthal, 1994).

Implications

The key clinical and academic implications of the research were addressed in the review and empirical papers. Further considerations are discussed herein.

Clinical implications and future research

Overall, the findings of the systematic review and empirical study clearly demonstrated that myriad insights remain to be attained in our knowledge of newer ASMs and their impact on the developing brain. Implications for ongoing clinical practice and future research endeavours were presented. There were also direct implications for those participating in the study which were deemed to require immediate action. Although the study design limited our ability to interpret the results fully, our finding of higher rates of ASD were seen as representing a moral and professional duty of care (BPS, 2018; HCPC, 2016). It was therefore agreed those mother-child-pairs concerned would be provided with a follow-up appointment to discuss the results of the study in greater detail. It was also decided between the research team that data collection would continue to recruit a larger sample overall, including an adequately sized ‘no medication’ group, in order ensure that findings were validated using the most rigorous methodology before publishing findings.

Implications of the research also extended to considerations of pharmacovigilance and the efficacy of the current regulatory systems in place regarding ASMs. In line with the

national strategy, our findings were reported to the MHRA via the Yellow Card Scheme (2015). This UK system follows a protocol whereby pharmacological companies and regulators rely on spontaneous reporting of adverse events and reactions as opposed to proactively seeking this information (Adams et al., 2011). Spontaneous reporting has utility in cases where medications have direct and immediate effects on the person using them (Friedman, 2012). However, it has been argued that this system works less well for increasing pharmacovigilance around teratogens; teratogenic adverse effects are less likely to be identified due to the indirect and longer term outcomes associated with them, in turn, reducing the likelihood of spontaneous reporting by mothers and prescribers alike (Friedman, 2012). The findings within the current study, obtained almost 25 years following the licencing of topiramate bolsters a position that the UK's current system for pharmacovigilance is not adequate and requires revision.

Dissemination

In addition to reporting findings via the Yellow Card System, findings were shared with the MHRA to support their regulatory review. The MHRA convened on 20 February 2020 to review evidence pertaining to the outcomes of children exposed to newer ASMs in utero. A member of the supervisory team was invited to contribute to this review opinion and due to the limited literature available for topiramate, data from this thesis were requested to be considered alongside published and unpublished data. The need for this data, evidenced by the committee's desire to include the preliminary study results, demonstrates both the importance of the study and its potential impact. It was further planned dissemination would take place at myriad levels including at the individual level to participants, at an organisational level to key stakeholders and at a societal level via publication. Mothers who participated in the study were to be provided with a newsletter-style summary of the findings,

described in lay terms. In addition, findings would be disseminated to the UKEPR, third sector epilepsy organisations, at relevant conferences and amongst clinicians with involvement in National Health Service (NHS) teratology clinics. Both the systematic review and empirical papers would be submitted for publication within Epilepsia. This journal has a high impact factor rating and has a varied readership of relevant healthcare professionals including neurologists, clinical psychologist and specialist epilepsy nurses. As such, the journal was selected with the rationale that findings would be disseminated to a large number of researchers and healthcare professionals in the field, in turn influencing both research and practice.

Conclusion

Overall, the process of undertaking the thesis was an invaluable experience within an important area of research, with skills, reflections and learning to take into future research and clinical practice.

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Appendix A

Author guidelines for Epilepsia

Epilepsia, **XX**(X):xxxx–xxxx, 2019
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Epilepsia®
Official Journal of the International League Against Epilepsy

INSTRUCTIONS FOR AUTHORS

Epilepsia is the official journal of the **International League Against Epilepsy (ILAE)**. The Journal publishes original articles on all aspects of epilepsy, clinical and experimental, especially of an international importance. Manuscripts should be the work of the author(s), must not have been published elsewhere, and must not be under consideration by another journal.

If you have a question not addressed in these pages, please contact the journal at epilepsia@epilepsia.com.

EDITORIAL POLICIES

(1) The Editors-in-Chief of *Epilepsia* invite authors to submit manuscripts in all areas of epilepsy-related research, especially if useful for an international audience. Manuscript submission is free. As a general guide, manuscripts will be considered for publication if they contribute significant new findings to the field. The primary aim of *Epilepsia* is to publish innovative and high-quality papers that provide clinical and/or basic science insights.

The Editors will make an initial evaluation of all manuscripts to determine whether they provide new important information in the field, are in the proper format, and are appropriate for the Journal (editorial review). Reports are not likely to be accepted for publication if they are not based on sound science and/or they provide only incremental knowledge of limited general usefulness. To assist authors in deciding whether to submit a manuscript to *Epilepsia*, we provide the following commonly encountered examples of reports that we are not likely to publish:

(a) Papers that describe clinical features or epidemiology in a given region of the world that do not provide new insights into epilepsy not already published;

(b) Correlative studies where the sample size is too low to provide statistically sound findings;

(c) Genetic association studies in which the association has already been confirmed;

(d) Investigatory articles describing the application of a new technical variation that is not likely to have clinical utility or impact;

(e) Correlative clinical studies, which are conceived without clear hypotheses and the results of which are of little clinical utility;

(f) Basic research studies that are not grounded in epilepsy-relevant hypotheses;

(g) Single group, before-after evaluations of therapeutic interventions and programs that do not include a control group;

(h) Small case series that largely replicate what is already known;

(i) Case reports (highly unlikely to be accepted unless they provide novel findings of theoretical or clinical importance).

Epilepsia will accept, review, and publish studies with negative results, provided that appropriate controls have been used, the study is adequately powered, and the results are important and/or useful to others in their research community.

Epilepsia encourages submissions regarding novel genes with compelling genetic data, as well as submissions regarding established epilepsy-related genes with new insights into their associated phenotypes. For both types of submissions, we strongly suggest that authors present genetic variants with sufficient detail for review, that is, accession number of the transcript, codon and amino acid position and substitution, in silico predictions, absence or ethnicity-matched allele frequencies in control datasets or gene-specific databases, and available published functional data, in keeping with current guidelines for variant interpretation set forth by the American College of Medical Genetics and Genomics. In the case of large cohort studies reporting novel associations, appropriate statistical methods must be demonstrated, and consideration for technical (eg, batch effects) and biologic (eg, genetic ancestry) confounders adequately discussed; underpowered studies will not be sent for review. As for all submissions to *Epilepsia*, case descriptions should provide sufficient detail regarding seizure types and epilepsy syndromes presented according to current ILAE guidelines and terminology.

(2) Manuscripts describing original research, and passing the initial editorial screen, will be subject to external peer review. An abstract of the work may have been published, however, if the material in the manuscript has been presented at meetings and the abstract has been published as part of meeting proceedings. At least two reviews are generally obtained for these submissions; additional reviews may be sought at the discretion of the Editors. Appeals of rejection

decisions will be considered by the Editors-in-Chief; decisions of the Editors-in-Chief are final.

(3) In the cover letter, authors should indicate that the material described in the manuscript is the work of the author(s) and has not been previously published including as preprint on servers. The authors should also specify that the material included in the manuscript is not simultaneously under consideration by any other journal.

(4) As a condition of publication, *Epilepsia* requires authors to transfer copyright to the ILAE. Authors will be asked to log in to Author Services and complete the appropriate license agreement via Wiley Author Licensing Service.

(5) *Epilepsia* complies with recommendations of the International Committee of Medical Journal Editors (http://www.icmje.org/)

(6) Authors are required to include a statement at the end of their manuscript affirming that the work described is consistent with the Journal's guidelines for ethical publication (see below). *Epilepsia* is a member of the Committee on Publication Ethics (COPE), and we adhere to its principles (https://publicationethics.org/). Data reporting should follow appropriate checklists and guidelines (eg, STROBE for observational trials; CONSORT for clinical trials), and other checklists should be consulted for other reports including diagnostic accuracy (STARD), systematic reviews and/or meta-analyses (PRISMA, with systematic review protocol registered on PROSPERO), or neuroepidemiologic studies (STROND). Checklists can be downloaded from the following:
STROBE – http://strobe-statement.org
CONSORT – http://www.consort-statement.org/
STARD – http://www.equator-network.org/reporting-guidelines/stard/
PRISMA – http:// www.prisma-statement.org/
PROSPERO – https://www.crd.york.ac.uk/prospero/

Epilepsia encourages authors to share the data and other artifacts supporting the results in the article by archiving it in an appropriate public repository. Authors should include a data accessibility statement, including a link to the repository they have used, in order that this statement can be published alongside their paper. A global registry, https://www.re3data.org/, is available to help authors identify relevant research data repositories. *Epilepsia* requires authors to cite data in the format proposed by the Joint Declaration of Data Citation Principles: authors; year; dataset title; data repository or archive; version (if any); or persistent identifier (eg, DOI). Source: Data Citation Synthesis Group: Joint Declaration of Data Citation Principles. Martone M. (ed.) San Diego CA: FORCE11; 2014 https://www.force11.org/datacitationprinciples.

(7) For animal experiments, the authors need to state that the experiments have been performed in accordance with all applicable national and/or international guidelines/laws. The authors should also provide their allowance number for performing animal experiments when available and should add a statement indicating that the principles outlined in the ARRIVE guidelines and the Basel declaration https://www.basel-declaration.org/ including the 3R concept have been considered when planning the experiments.

(8) Authors are also required to provide full disclosure of any conflicts of interest as a part of the submitted manuscript (see Disclosure of Conflicts of Interest in the Manuscript Format section under Manuscript Preparation). Manuscripts that do not conform to these guidelines will not be considered for publication. Discovery of or failure to comply will result in rejection of the manuscript, retraction of the published article, and/or a ban on future submissions by the author(s).

(9) In submitting a manuscript, the submitting/corresponding author must acknowledge the following: (a) that all coauthors have been substantially involved in the study and/or the preparation of the manuscript; (b) that no undisclosed groups or persons have had a primary role in the study and/or in manuscript preparation (ie, there are no "ghostwriters"); and (c) that all coauthors have seen and approved the submitted version of the paper and accept responsibility for its content. The Editors reserve the right to require authors to submit their original data for comparison with the manuscript's illustrations, tables, and results.

(10) Sometimes editors make mistakes. If an author believes an editor has made a decision in error, we welcome an appeal. Please contact the editor and in your appeal letter, clearly state why you think the decision is a mistake and set out specific responses to any comments related to the rejection. An appeal does not guarantee a re-review.

TYPES OF MANUSCRIPTS

The following types of material may be considered for publication:

(1) Peer-reviewed papers (to be submitted by uploading online via ScholarOne Manuscript Central (https://mc.manuscriptcentral.com/epilepsia)

a. Critical Review and Invited Commentary. The Editors-in-Chief encourage submission of reviews and commentaries on topical and controversial issues. Authors planning/proposing such papers should contact the Editors-in-Chief at epilepsia@epilepsia.com before submitting their manuscripts. Authors can also approach one of *Epilepsia*'s Associate Editors about possible reviews. Although there are no strict length limits on this type of paper, manuscripts generally should be around 5000 words and include a maximum of 100 references. Ample figures and tables are encouraged. Longer manuscripts will be considered at the discretion of the Editors-in-Chief, but justification should be provided by the authors.

b. Full-length Original Research. These articles should be limited in length to 4000 words, 50 references, and no more than 6 figures and tables (combined). Additional figures and tables will be permitted at the discretion of the Editors or

can be submitted for "online only" Supporting Information (which will be linked to the online version of the published article). Authors should aim for presenting material clearly and completely, in the most concise and direct form possible; the Introduction section should be brief (typically less than 600 words), and the Discussion section should be restricted to issues directly relevant to the Results (typically less than 1200 words).

c. Brief Communications. These articles, including short studies, small series, case reports, and so on, should describe previously unpublished material, including original research and/or clinical observations. The papers are limited generally to 1800 words (excluding the summary), 18 references, and no more than 2 figures and tables (combined). Please note that the Editors may use their discretion to request that Brief Communications be shortened to a length that they feel is appropriate and may provide for a larger number of figures and tables if justified. Brief Communications will be published online only (not in the print version of the journal). They will appear in a specific issue in the electronic (online) version and will be identified and described (Short Summary) in the Table of Contents of the printed version of that issue. The online versions will be dealt with by PubMed/Medline and other indexing/citation systems in the same manner as print articles; they will be referenced by their DOI number and date of online publication.

d. Controversy in Epilepsy. For emerging areas related to epilepsy care and research for which there is more opinion than high-quality data, *Epilepsia* uses the Controversy series as a venue. Authors can propose a pro and con position, with each limited to 2000 words. Contact the editors at epilepsia@epilepsia.com before submitting in this series.

(2) Editorially reviewed material (to be submitted by email to the Editors-in-Chief at epilepsia@epilepsia.com, except letters and commentaries, which should be submitted online at (https://mc.manuscriptcentral.com/epilepsia)

Other contributions that do not report original research will be published at the discretion of the Editors-in-Chief, with only editorial review. Such material includes workshop reports and conference summaries, obituaries, letters/commentary to the editors (500-word limit, and only exceptionally including figures or tables), special (brief) reports from the ILAE Commissions or other working groups, and announcements. Such material will usually be published in Gray Matters.

(3) Supplements (to be submitted as directed by the Editors-in-Chief)

Supplements, including meeting abstracts, will be published only after advance arrangements are made with the Editors-in-Chief. Guidelines for preparing supplements are given below. Proposals for, and questions about, supplements should be directed to one of the Editors-in-Chief (epilepsia@epilepsia.com). Such proposals must be explicitly approved by the Editors-in-Chief, who will also confirm the page rate charge for the proposed supplement.

(4) Special Reports: Special reports from the ILAE Commissions or other broadly constituted working groups may be published after peer review. The corresponding author of such papers should confer with the Editors-in-Chief to determine if the full manuscript will be peer-reviewed, or whether only a short version will be considered for publication in *Epilepsia's* Gray Matters (see below). Manuscripts are limited to 5000 words, 7 figures, and a maximum number of 100 references.

MANUSCRIPT PREPARATION

General Style Guidelines

Manuscripts are to be submitted (and will be published) in English. Writers not fluent in English should seek assistance to ensure proper grammar and syntax and to help generate a manuscript organization that facilitates reader understanding. Authors for whom English is a second language may choose to have their manuscript professionally edited before submission to improve the English. A list of independent suppliers of editing services can be found at https://wileyeditingservices.com/en/. All services are paid for and arranged by the author and use of one of these services does not guarantee acceptance or preference for publication. The Editors will not rewrite papers submitted in unacceptable English and will return such manuscripts for revision before sending them out for review.

Use international nonproprietary (generic) names when referring to drugs; avoid proprietary (brand) names. All acronyms should be spelled out at first mention. Make sure to spell out all abbreviations at first use in summary and again in the body of the manuscript. Also spell out any abbreviations in figures and tables in legends and footnotes, respectively. Spell out numbers below 10 and all numbers that are used to begin a sentence; use Arabic numerals for numbers 10 or larger and for units of measure. Confirm that the correct names of tests, agencies, organizations, and manufacturers are being provided. Confirm that data that are presented in the manuscript are consistent in all parts of the manuscript: numbers, percentages, and so on. Numbers should be checked to be sure they add up correctly. Confirm that all tables and figures are correctly cited in text and numbered in the order that they appear and that all references are correctly cited in text. Locations for manufacturers are not required. Manuscript text should be double spaced with at least a 1-inch margin on all sides using size 12 font. Word limits for each type of submission will generally be enforced unless there are good reasons not to do so. If manuscripts exceed these guidelines, authors should submit a cover letter explaining why the additional length is necessary.

Authors are encouraged to use the most recent terminology of seizures and epilepsy.

Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of sei-

zure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30. (https://onlinelibrary.wiley. com/doi/abs/10.1111/epi.13670)

Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017:58:531–542. (https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.13671)

Epilepsy classification of the ILAE

Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512–21. (https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.13709)

Studies involving treatments should adhere to ILAE's classification of medically refractory epilepsy

Levira F, Thurman DJ, Sander JW, Hauser WA, Hesdorffer DC, Masanja H, et al. Premature mortality of epilepsy in low- and middle-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia. 2017;58:6–16. (https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.13603)

Manuscript Format

a. Critical Review and Invited Commentary

- ❑ **Title Page** (see Full-Length Original Research below)
- ❑ **Summary and Keywords**

  Reviews and commentaries should generally begin with a summary (less than 300 words) of the content. The unstructured summary should provide the reader with an outline of the main points of the paper. The Summary should be followed by a list of 3 to 6 Keywords; please provide Keywords that will assist in the indexing of your article (ie, make it easy for individuals who are searching PubMed to find your paper). Do not use words already incorporated into your title (those words are picked up automatically by the indexing service).

- ❑ **Body of review**

  There is no designated structure for the body of Reviews or Commentaries. Authors are encouraged, however, to use subheadings to separate major sections and to facilitate clarity, and to use figures and tables to illustrate the key issues of the document. Tables, figures, figure legends, references, acknowledgments, statement of compliance with the Journal's guidelines for ethical standards in publishing, disclosure of conflicts of interest, and Supplementary material as for *Full-Length Original Research* (see below)

b. Full-Length Original Research, Special Report, and Brief Communication

- ❑ **Title Page**

  Include the following information: Full title of the manuscript, which should be as concise and precise as possible; authors' names (first and last names, middle initial when commonly used by that author); institutional affiliation for each author named in English language and not in a national language (use superscripted numbers after each author's name, and a corresponding superscripted number before each institutional affiliation; names of institutions should be spelled out, but the abbreviation can be provided in parentheses); contact information for the corresponding author (name, address, telephone number, fax number, e-mail address; ensure name matches that given in author list); Keywords for use by abstracting services (same as following summary); number of text pages; number of words; number of references; number of figures; number of tables; ORCID number for the first and senior authors, and any authors designated as corresponding.

- ❑ **Summary and Keywords**

  Provide a summary of no more than 300 words (200 words for Brief Communication). The summary for Full Length Original Research should consist of four sections, labeled: Objective; Methods; Results; Significance. This structured summary should concisely and specifically describe why and how the study was performed, the essential results, and what the authors conclude from the results. To promote brevity, authors may use phrases rather than complete sentences. The summary for Special Reports, Invited Commentaries, and Brief Communications is not structured, but should cover the same topics as the structured summary. The summary (structured or unstructured) should be followed by 3 to 6 Keywords (see above). A second short summary (less than 100 words) is required for Brief Communications that can be used in the print issue Table of Contents. Submit the second short summary as a Supporting Document.

- ❑ **Key Points Box**

  Include 3 to 5 key bullet points that summarize your article after the main body of text. Please ensure that each bullet point is no longer than 140 characters. (Brief Communications do not require a Key Point box.)

- ❑ **Introduction**

  State the objectives of the study clearly and concisely and provide a context for the study by referring judiciously to previous work in the area. Do not attempt to present a comprehensive view of the field. Provide a statement about the significance of this research for understanding and/or treating epilepsy.

- ❑ **Methods**

  Describe the research methods in sufficient detail that the work can be duplicated; alternatively, give references (if they are readily accessible) to previous comprehensive descriptions. Identify the statistical procedures that were used and the rationale for choosing a particular method, especially if it is not standard. Reports of experimental studies on humans must explicitly certify that the

research received prior approval by the appropriate institutional review body and that informed written consent was obtained from each volunteer or patient. Studies involving animals must include an explicit statement that animal care and use conformed to institutional policies and guidelines. When animals are subjected to invasive procedures, details must be provided regarding the steps taken to eliminate/minimize pain and suffering, including the specific anesthetics, analgesics, or other drugs used for that purpose (amounts, mode of delivery, frequency of administration). If extensive descriptions of methods are needed, provide basic information within the text and submit supplementary information for online Supporting Information.

❑ **Results**

Results should be reported fully and concisely, in a logical order. Do not repeat methodologic details from the Methods section. Where possible, use figures and/or tables to present the data in a clear and concise format. Do not repeat data in the text that are given in a table but refer to the table. Provide textual explanations for all figures, with clear reference to the figure(s) under discussion. Descriptive information provided in figure legends need not be repeated in the text; use the text, however, to describe key features of the figures. When appropriate, give sample numbers, the range and standard deviation (or mean error) of measurements, and significance values for compared populations.

❑ **Discussion**

Provide an interpretation of the results and assess their significance in relation to previous work in the field. Do not repeat the results. Do not engage in general discussion beyond the scope of the experimental results. Conclusions should be supported by the data obtained in the reported study; avoid speculation not warranted by experimental results, and label speculation clearly. Discuss the significance of the data for understanding and/or treating epilepsy.

❑ **Statistical Methods**

The following guidelines assume familiarity with common statistical terminology and methods. We recommend that authors consult a biostatistician during the planning stages of their study, with further consultations during the analytical and interpretational stages.

1. Analysis guidelines:

- Use robust analytic methods when data are skewed.
- Use Kaplan-Meier methods, Cox proportional hazards, and mixed models analyses for longitudinal data.
- Account properly for statistical outliers.
- Use exact methods as much as possible in analyses of categorical data.
- Use appropriate correction procedures to account for multiple comparisons and conduct post hoc comparisons with statistically appropriate methods.

2. Presentation guidelines:

- Report means accompanied by standard deviations; standard errors should not be used.
- Present results with only as much precision as is appropriate.
- Present confidence intervals, whenever possible, including in figures.
- Describe quantity of missingness and methods used for handling such missingness.
- In general, present two-sided P values. P values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places, and those smaller than 0.001 should be reported as $P < 0.001$.
- In reporting clinical trials, include a flow diagram, a completed trial checklist, and trial registration information. The CONSORT flow diagram and checklist are recommended (http://www.consort-statement.org/).

❑ **Acknowledgments**

Acknowledge sources of support (eg, grants from government agencies and private foundations), including funds obtained from private industry. Also acknowledge (consistent with requirements of courtesy and disclosure) participation of contributors to the study who are not included in the author list.

❑ **Disclosure of Conflicts of Interest**

In addition, each author should provide full disclosure of any conflicts of interest. One of the following sentences must be included at the end of the paper: either "Author A has received support from, and/or has served as a paid consultant for; Author B has received support from. The remaining authors have no conflicts of interest." Or "None of the authors has any conflict of interest to disclose." Note: Disclosure is needed for financial income/payment from commercial sources, the interests of which are relevant to this research activity. Please identify sources from which financial assistance/income was obtained during the period of the research activity and generation of the current report. Grants from government and/or private agencies should be identified in the Acknowledgments section.

❑ **Ethical Publication Statement**

All papers must include the following statement to indicate that the authors have read the Journal's position on issues involved in ethical publication (see below) and affirm that their report is consistent with those guidelines: "We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines."

❑ **References**

Authors are responsible for the accuracy of their references. References should follow a modified Vancouver style format. Refer to PubMed to ensure accurate and complete reference information. Citation of references in the text should be in superscript numbers (including those in figure legends and tables). When names are given with reference citations, check the reference list to make sure spelling is consistent. Cite the end references in numerical order. The first six authors should be listed and followed by et al. Use PubMed abbreviations for journals in the reference list at the end of the paper (as opposed to journal names being written out in full). Reference program patches are available on the *Epilepsia* ScholarOne (https://mc.manuscriptcentral.com/epilepsia); in the "Instructions and Forms" link.

Number of references is limited to the following:
Full Length Original Research – 50
Brief Communication – 18
Review – 100
Special Report – 100

Sample References:

Journal Article

Faught E, Szaflarski JP, Richman J, Funkhouser E, Martin RC, Piper K, et al. Risk of pharmacokinetic interactions between antiepileptic and other drugs in older persons and factors associated with risk. Epilepsia 2018;59:715–23.

Journal article published electronically ahead of print version

Vakharia VN, Sparks R, Li K, O'Keeffe AG, Miserocchi A, McEvoy AW, et al. Automated trajectory planning for laser interstitial thermal therapy in mesial temporal lobe epilepsy. Epilepsia 2018 Mar 12 [Epub ahead of print].

Journal article In Press

Hirsch LJ, Gaspard N, van Baalen A, Nabbout R, Demeret S, Loddenkemper T, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES) and related conditions. Epilepsia (in press 2018).

Letter

Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. How long for epilepsy remission in the ILAE definition? Epilepsia 2017;58:1486–7. Letter

Published Abstract

Alsfouk BA, Brodie MJ. Tolerability of Antiepileptic Drugs. Epilepsia 2017;58(suppl 5): p0227. Abstract

Book

Arzimanoglou A, Cross JH, Gaillard WD, Holthausen H, Jayakar P, Kahane P, et al. Pediatric epilepsy surgery. Montrouge: John Libbey Eurotext; 2017.

Chapter in a Book

Noebels JL. Spontaneous and gene-directed epilepsy mutations in the mouse. In Pitkänen A, Buckmaster PS, Galanopoulou AS, Moshé S (Eds) Models of seizures and epilepsy. 2nd Ed. London: Academic Press, 2017:763–76.

Online

Center for Disease Control and Prevention. Epilepsy: one of the nation's most common neurological conditions— at a glance 2016. National Center for Chronic Disease Prevention and Health Promotion, 2016. Available at: http://www.cdc.gov/chronicdisease/resources/publications/aag/epilepsy.htm. Accessed November 20, 2016

❑ **Figure legends**

Number each legend sequentially to conform to the figure number (eg, Figure 1, Figure 2). The legend should provide a brief description of the figure, with explanation of all symbols and abbreviations. Written permission to use nonoriginal material must be obtained by the authors (from the original authors [where possible] and publishers). Credit for previously published material (author(s), date, journal/book title, and publisher) must be included in the legend. A figure legend should be listed at the end of the manuscript following the list of references. When references are made in the text to items within a figure (arrows, inserts, etc), make sure they are in the figure.

❑ **Tables**

Tables should be formatted in the manner that the authors wish the table to appear in print. Present all tables together at the end of the main text document or as separate table files. Do not embed tables in the main text file or upload tables in image formats. Each table should be given a number and a descriptive title. Provide notes and explanations of abbreviations below the table and provide clear headings for each column and row. Do not duplicate data given in the text and/or in figures. Written permission to use nonoriginal material must be obtained by the authors (from the original authors [where possible] and publishers). Credit for previously published material (author(s), date, journal/book title, and publisher) must be included in the table notes.

❑ **Figures**

All figures should be prepared with care and professionalism. Submissions that do not comply with the following formatting requirements will be returned for correction and resubmission. Figures should be submitted as TIF files in the size expected for final publication—approximately 3 inches (7-8 cm) for half columns and 6 to 7 inches (15-17 cm) for double columns. Do not embed figures within the main text document. Submit black and white figures with a minimum of 300 dpi (MRI scans) and for line drawings or figures that include embedded text (bar graphs with numbers) at least 600 dpi. Complex

figures (including photographs, micrographs, and MR-related images), either in color, in halftones, or in black and white, should also be submitted in TIF format with a resolution of at least 600 dpi. We recommend saving the TIF files with LZW compression (an option when you "save as" in packages like Photoshop), which will make the files smaller and quicker to upload without reducing the resolution/quality. Save each TIF file with a name that includes the first author's last name and the figure number as referenced in the text (eg, Smith-fig1.tif). Provide clear labels on the ordinate and abscissa. Figures with more than one part should be combined by the authors in the correct orientation and labeled with A, B, C, and so on. When relevant, include calibration information. Label figures using Calibri font and ensure that all labels are large enough to be clearly legible when the figure is reduced to fit onto a journal page. The maximum size of any figure is 7x9 inches (17×22.5 cm) and 40 megapixels; the total number of pixels for each figure (ie, height×width) must be less than 40 megapixels, otherwise the image will not convert to PDF format for review. There is no charge for color figures. We strongly encourage authors to generate figures in color (to enhance clarity of presentation and aesthetic appeal), using the color palette below.

Photographs or videos of patients should not reveal patient identity; masking eyes and/or other identifiers is compulsory unless the eyes are essential to the meaning of the photograph or video. In addition, such photographs and videos must be accompanied by a letter stating that signed consent forms authorizing publication have been obtained for all identifiable patients, and that the consents will be maintained by the author for 7 years or until the patient reaches 21 years of age, whichever is longer. Do not send *Epilepsia* the consent forms; U.S. Federal privacy rules prohibits sending signed consent forms to *Epilepsia* or Wiley Publishing without written permission from the patient to do so. A sample signed consent form can be found on the *Epilepsia* ScholarOne site (https://mc.manuscriptcentral.com/epilepsia); Click "Instructions and Forms" at the top right-hand corner of the homepage.

❑ Supporting Information

Supporting information, to be published online only, can be submitted for review. Such material may include additional figures, large tables, videos, and so on that cannot be accommodated within the normal printed space allocation for an article but provide important complementary information for the reader. As determined by the reviewers and Editors, supporting information will be posted on the Wiley Online Library *Epilepsia* server and integrated directly into the full-text HTML article. Explicit reference to the supporting information in the main body of the text of the article is recommended, and the material must be captioned at the foot of the text, below the reference list. Citations should be in the following format: Figure S1, Table S1, Appendix S1, etc. Supporting information will be published as submitted and will not be corrected or checked for scientific content, typographical errors, or functionality. Although this material is hosted on Wiley Online Library, the responsibility for scientific accuracy and file functionality remains entirely with the authors. A disclaimer will be displayed to this effect with any supporting information published.

Supporting Information files should be accompanied by detailed information (if relevant) about what they are and how they were created (eg, a native dataset from a specific piece of apparatus). Acceptable formats for Supporting Information include:

General – Standard MS Office format (Word, Excel, PowerPoint, Project, Access, and so on); PDF

Color #	RGB Definition	CMYK Definition
#e4b8b4	228/184/180	0/25/15/9
#ce8080	206/128/128	0/50/30/18
#a30234	163/2/52	0/100/60/37
#511d24	81/29/36	42/85/67/60
#f1b682	241/182/130	0/29/50/4
#e37c1d	227/124/29	0/58/100/8
#ffde76	255/223/118	0/11/64/0
#abb47d	171/180/125	13/0/47/27
#67771a	103/119/26	27/0/94/55

Color #	RGB Definition	CMYK Definition
#a1c5cb	161/197/203	25/0/7/16
#5698a3	86/152/163	50/0/14/32
#00545f	0/84/95	100/0/28/64
#002f30	0/47/48	87/34/47/77
#bacfec	186/207/236	25/11/0/0
#0076c0	0/118/192	100/46/0/0
#002157	0/33/87	100/75/0/60
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Graphics – GIF; TIF (or TIFF); EPS; PNG; JPG (or JPEG); BMP; PS (postscript); embedded graphics (e.g. a GIF pasted into a Word file) are also acceptable.)

c. Gray Matters

❑ **Title**

Letters, workshop reports, and so on, should be given a brief title. Letters should start with the opening *To the Editors:*

❑ **Authors and affiliations**

Provide authors' names (first and last names, middle initial when commonly used by that author); institutional affiliation in English for each author (use superscripted numbers after each author's name, and a corresponding superscripted number for each institutional affiliation); and an e-mail contact address for the corresponding author, ORCID number for the first and senior authors, and any authors designated as corresponding.

❑ **Body of submission**

Letters and commentaries should be restricted to 500 words or less, unless otherwise allowed by the Editors. Figures and tables will be included only in exceptional cases. Gray Matters will not be used to publish case reports. Tables, figures, figure legends, References, Acknowledgments, Disclosure of Conflicts of Interest, Ethical Publication Statement, and Supporting Information—as for *Full-Length Original Research* (see above).

(3) Details of Preparation

Detailed instructions for all aspects of electronic manuscript submission (including useful information on image files) is available on the *Epilepsia* ScholarOne site (https://mc.manuscriptcentral.com/epilepsia); click "Instructions and Forms" at the top right-hand corner of the home page; then click on the link "Instructions to Authors."

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Manuscripts should be prepared using a word processing program. Save text and tables as a Microsoft Word document. Place the lead author's name and the page number in the upper right-hand corner of each page. Begin numbering with the Title page as the first page, and number pages consecutively including references, figure legends, and tables. Text (including acknowledgements, disclosure statement, and figure legends) and references should be double-spaced, and be composed in 12-point font (preferably Times New Roman). When generating a revised manuscript, identify the altered portions of the manuscript with highlighted text, underlined, colored, or bold font to indicate where changes to the original version of the text have been made.

b. Tables, Figures, and Supporting Information

See above. Video–QuickTime; MPEG; AVI can be used for video clips. All video clips must be created with commonly used codecs, and the codec used should be noted in the supplementary material legend. Video files should be tested for playback before submission, preferably on computers not used for its creation, to check for any compatibility issues. Video clips are likely to be large; try to limit their size to less than 10 MB.

MANUSCRIPT SUBMISSION

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Manuscripts should be submitted via the Journal's website on ScholarOne at https://mc.manuscriptcentral.com/epilepsia. Instructions at the site will guide the author through the submission process. Separate files should be submitted for the cover letter to editors, manuscript text, tables, each figure, supplemental material, permissions to use previously published material, and patient consent declaration.

(2) Cover letter

All manuscripts should be submitted with a cover letter, addressed to the Editors-in-Chief, which explains why the manuscript should be published in *Epilepsia*. In particular, authors should identify novel findings, innovative approaches, and important insights that would make the manuscript of particular value to the broad readership of *Epilepsia*.

(3) Text, table and figure files

All files should be given a label that includes the first author's last name and the nature of the file (eg, Smith-manuscripttext.doc; Smith-Fig1.tif).

(4) Other materials/forms

At the time of submission, all other materials (eg, permission forms, supplemental material, patient consent) must be uploaded onto Manuscript Central, or emailed to epilepsia@epilepsia.com.

(5) Questions/Contacts

Questions and request for assistance should be addressed to the Journal at epilepsia@epilepsia.com. The Managing Editor, Ms. Laurie Beninsig, will in most cases be able to provide direction or will contact the Editors-in-Chief for further assistance.

MANUSCRIPT PUBLICATION

(1) Cover Image Art

The Editors may approach authors to provide one or two of their figures as possible cover material for the printed journal. These figures will need to be large enough and with the appropriate resolution. All authors of accepted manuscripts are welcome to submit ideas for the cover.

(2) Online tracking of your article

Online production tracking of your article is available through Wiley's Author Services. Author Services enables authors to track their article once it has been

accepted through the production process to publication online and in print. Authors can check the status of their articles online and choose to receive automated emails at key stages of production. The corresponding author will receive an email with a unique link that enables him/her to register and have the article automatically added to the system. To facilitate this service, please ensure that you provide a complete email address when submitting the manuscript. Visit https://authorservices.wiley.com/author-resources/Journal-Authors/index.html for more details on online production tracking and for other publication resources (including FAQs and tips on article preparation, submission, and more).

(3) Proofs

Authors will receive an e-mail notification with a link and instructions for accessing HTML page proofs online. Page proofs should be carefully proofread for any typesetting errors. Online guidelines are provided within the system. No special software is required, all common browsers are supported. Authors should also make sure that any renumbered tables, figures, or references match text citations and that figure legends correspond with text citations and actual figures. Proofs must be returned within 48 hours of receipt of the email. Return of proofs via e-mail is possible in the event that the online system cannot be used or accessed. The proof corrections stage is not the time for fine-tuning language or making any other substantive changes. Confine corrections to errors in printing; authors may be charged for major author-initiated changes.

(4) Early View

The publication-ready PDF of an article will be published initially online. Early View publication will precede print publication by a variable time period. The online publication date will be considered the official publication date. Early View published material will be indexed by PubMed and can be cited by DOI number. In general, manuscripts will be published on Early View within 28 days of the publisher's receipt of the complete accepted manuscript (including CAF and permission forms).

(5) Print issue publication

Publication of an article in a print issue will typically occur after Early View publication. Print issue articles carry their electronic publication date.

(6) Public access of accepted/published articles

Prior to acceptance, articles may be shared (print or electronic copies) with colleagues; at this time the article may be posted on the author's personal website, on his/her employer's website, and/or on free public servers in the author's subject area—with the acknowledgement that the article has been submitted to *Epilepsia*. After an article has been accepted, authors may share print or electronic copies of the article (accepted and revised to address peer review) with colleagues, and may use the material in personal compilations, other publications of his/her own work, and for educational/research purposes. Articles published in *Epilepsia* are freely accessible to the public via the Wiley Online Library website one year after publication. *Epilepsia* will automatically upload NIH-supported studies to PubMed Central after a 12-month moratorium (provided the appropriate funding acknowledgment has been supplied). Similarly, at this time, authors may post an electronic version of the article on their own personal websites, on their employer's website/repository, and/or on free public servers in the relevant subject area. Electronic versions of the accepted (or published) article must include a link to the published version of the article, together with the following text: "The definitive version is available at https://www3.interscience.wiley.com/journal/117957420/home." Authors can also choose to make their articles open access and available free for all readers through the payment of an author fee. This facility allows authors to fulfill the requirements for studies supported by agencies requiring open access before 12 months. For full details visit https://authorservices.wiley.com/author-resources/Journal-Authors/open-access/onlineopen.html

(7) Reprints

An order form for reprints will be included with the electronic transmission of initial proofs. For pricing of quantities in excess of 500 copies, please contact Helane Silverman (email: hsilverman@wiley.com).

SUPPLEMENT PUBLICATION

(1) Policy

A decision to publish a supplement is based on the topic, Guest Editor, proposed table of contents and contributing authors, and the availability of necessary funding. Supplement topics must be of importance to *Epilepsia* readers, and supplements will be published only if there is scientific or educational rationale for combining papers on a given theme within one publication. The number and quality of the articles must be sufficient to constitute a body of important information. Each supplement will have a Guest Editor who is an expert on the theme of the supplement. The Guest Editor is responsible for compiling articles and assisting with the editorial process and is responsible for the overall quality and integrity of the supplement. The publication of a supplement usually incurs charges, payable to Wiley Publishing.

(2) Publishing guidelines

Articles in a supplement are subject to the same copyright regulations and ethical publishing guidelines that apply to articles published in regular issues of *Epilepsia*. All supplement articles are peer-reviewed; the first level of review is carried out by the Guest Editor and his/her designates. The second level of review will include the articles being sent out for peer review.

(3) Online only and print supplements

Abstract supplements, from meetings or congresses sponsored by the ILAE or its chapters, will generally be published online only. Longer articles will be published in print supplements (these articles will also appear online). Print supplements may be generated from proceedings of symposia organized by an independent body of professionals in which the funding organization does not have a controlling voice on scientific content. The Guest Editor and/or organizers of such symposia should be members of ILAE chapters. Supplements from other sources including invited supplements initiated by the Editors-in-Chief will also be considered.

(4) Supplement content

The content of supplements must not be biased in the interest of any sponsor. *Epilepsia* does not permit presentations that extol a commercial product, and supplements should not be perceived as endorsing a particular product. Publication of supplements does not constitute product or sponsor endorsement by *Epilepsia* or the ILAE. In most cases, supplements should not focus on a single product; however, when a new product is introduced, a single product focus will be considered by the Editors-in-Chief. In all cases, the content of a supplement must be determined by a body of professionals working independently of the sponsor. The Guest Editor is charged with ensuring that the material presented in the supplement is not biased toward the interests of the product manufacturer.

(5) Supplement sponsorship

Most supplements require external sponsorship. When a supplement proposal is presented to the Editors-in-Chief, they will fix appropriate fees. Supplement costs may be negotiated with the Editors-in-Chief and the publisher's supplement representative. The Editors-in-Chief may choose to publish a supplement of particular academic and clinical value without external sponsorship.

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(7) Format of supplement articles

In general, articles should follow the format described above for Critical Review and Invited Commentary (in regular issues of the Journal). Contact the Editors-in-Chief for additional information and special instructions.

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(1) Authorship/Credit

Epilepsia follows the guidelines of the International Committee of Medical Journal Editors regarding criteria for authorship (http://www.icmje.org/). The author list should include those who have made substantial intellectual/conceptual contributions to the work. Such contributions should include participation in the following: (a) experimental design, data acquisition, and analysis and interpretation of data; (b) drafting and/or critically revising the article with respect to intellectual content; and (c) final approval of the manuscript version to be published. We strongly discourage the inclusion of "honorary" authors (individuals who are listed as authors but who have not contributed to the work/manuscript, for eg, heads of departments) and "ghost" authorship (individuals who have substantively contributed to the work and/or manuscript but are not listed as authors or contributors). In cases where writing support is necessary, the writer(s) should be acknowledged in the Acknowledgments section, and the source of funding for writing support should be provided under Disclosure of Conflicts of Interest. The corresponding/submitting author must, when submitting a manuscript, give assurance that all authors have read and approved the submitted manuscript. The corresponding/submitting author should also give assurance that all authors

Epilepsia's POSITION ON ISSUES INVOLVED IN ETHICAL PUBLICATION

have seen and approved the final (accepted) manuscript, and that the manuscript includes all conflict of interest declarations. All individuals who have contributed to the work but do not meet criteria for authorship should be cited in the Acknowledgment section.

(2) Funding

Sources of funding (for the research, data analysis, and manuscript generation) should always be disclosed in the Acknowledgments section. Sources may include government funding agencies, institutions and departments, private industry, and charitable organizations and foundations. Funding for all authors should be acknowledged. If no funding has been provided for the research, please include the following sentence: "This research did not receive any grant from the public, commercial, or not-for-profit sector funding agencies."

(3) Procedures involving Human and Animal Subjects

The authors should include within the manuscript an explicit statement indicating that the submitted study was approved by the relevant research ethics committee or institutional review board (IRB). When the study involves human participants (including material from human subjects), authors should also provide assurance that appropriate consent was obtained. When studies involve animal subjects, authors should provide methodologic details about steps taken to minimize pain/discomfort. Such papers must contain a statement that affirms that the experimental protocols were approved by the institutional animal care and use committee (IA-CUC).

(4) Confidentiality

In all cases, information and images derived from individual patients must be presented with assurance of appropriate consent and with details removed that might reveal the identity of the individual.

(5) Disclosure

All authors are required to disclose associations that might affect their ability to present and/or interpret data objectively, particularly financial ties to funding sources for the work under review (eg, membership on corporate scientific boards, stock ownership, consultant arrangements, patent ownership or application). Disclosure of such associations for the Editorial personnel of *Epilepsia* (Editors-in-Chief, Associate Editors, Editorial Board members) will be published each year. Reviewers will also be asked to affirm that they have no conflicts of interest when critiquing a manuscript.

(6) Research Misconduct (Data Fabrication/ Falsification)

Epilepsia will attempt to ensure that any allegations of misconduct are properly investigated. In the case of any allegations, authors will be given a right to respond. Although the Journal is limited in its ability to investigate misconduct, we will seek COPE's advice and alert the appropriate bodies and encourage them to investigate.

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Epilepsia requires that work submitted for publication is the authors' own work and has not been misappropriated. When previously published material is used, appropriate credit must be given, and written permission obtained (for use of copyrighted material). *Epilepsia* also explicitly discourages duplication of published material and redundant publication. All manuscripts submitted to *Epilepsia* are checked with the iThenticate plagiarism detection software to detect instances of overlapping and similar text. In the case of apparent or substantial overlap, authors will be asked to rewrite their article.

(8) Corrections of Erroneous Information

Authors are expected to proofread their articles carefully before returning page proofs for publication. They should make needed corrections at this time. We recognize that it is only human to err occasionally, and the Journal is committed to correcting mistakes when those errors affect the interpretation of data or information presented in an article. Such corrections will be published in the form of an Erratum and linked to the original article electronically. Errors that result from author oversight in the proofing process, and that do not affect data interpretation, will not be corrected.

(9) Peer Review

Epilepsia is committed to a peer-review system that is fair to the author and enhances the value of the articles published in the Journal. In order to encourage qualified reviewers to offer their time and efforts to the Journal, reviewer identity is kept confidential. Reviewers are chosen for their expertise in the field; conflicts of interest are avoided whenever the Editors are aware of such issues, and reviewers are asked to affirm that they have no conflicts of interest in reviewing a given *Epilepsia* manuscript. Authors are encouraged to identify specific individuals who, they believe, cannot provide unbiased review. Although the Editors-in-Chief reserve the right to make the final decision to accept or reject an article, appeals will be seriously considered. Address appeals to the Editors-in-Chief, who will examine the reviews and the author responses, consult the relevant Associate Editor, and seek additional reviewer input if deemed necessary.

Appendix B
Search strategy for systematic review

SEARCH BLOCK	CONCEPTS	MEDLINE via OVID	EMBASE via OVID	PSYCHINFO via OVID	CINAHL PLUS via EBSCO	Web of Science
IN-UTERO EXPOSURE	Pregnancy Prenatal Exposure Teratogen Fetal Toxicity	1. pregnancy/ 2. pregnancy complications/ 3. (fetal OR foetal OR fetus OR foetus OR prenatal).tw. 4. (infant$1 OR newborn$1 OR neonat$2).tw. 5. prenatal* drug expos*.tw. 6. fetal development/ 7. teratogens/ 8. teratogen*.tw. 9. prenatal* expos*.tw. 10. (fetotoxicity OR embryotoxicity OR reproductive toxicity).tw. 11. ((utero) OR (uterine)).tw. 12. or/1-15	1. pregnancy/ 2. pregnancy complication/ 3. "parameters concerning the fetus, newborn and pregnancy"/ 4. (fetal OR foetal OR fetus OR foetus OR prenatal).tw. 5. prenatal exposure/ 6. prenatal drug exposure/ 7. fetus development/ 8. teratogenic agent/ 9. teratogenicity/ 10. teratogen*.tw. 11. prenatal* expos*.tw. 12. fetotoxicity/ 13. embryotoxicity/ 14. reproductive toxicity/ 15. fetotoxicity OR embryotoxicity OR reproductive toxicity).tw. 16. ((utero) OR (uterine)).tw. 17. or/1-16	1. pregnancy/ 2. pregnancy complications.tw. 3. neonatal period/ 4. (fetal OR foetal OR fetus OR foetus OR prenatal).tw. 5. (infant$1 OR newborn$1 OR neonat$2).tw. 6. prenatal exposure/ 7. prenatal* drug expos*.tw. 8. fetus/ 9. embryo/ 10. teratogens/ 11. teratogen*.tw. 12. prenatal* expos*.tw. 13. fetotoxicity OR embryotoxicity OR reproductive toxicity).tw. 14. ((utero) OR (uterine)).tw. 15. or/1-14	1. (MH "Pregnancy") 2. TI "pregnancy complications" OR AB "pregnancy complications" 3. TI (fetal OR foetal OR fetus OR foetus OR prenatal) OR AB (fetal OR foetal OR fetus OR foetus OR prenatal) 4. TI (infant# OR newborn# OR neonat*) OR AB (infant# OR newborn# OR neonat*) 5. (MH "Fetal Development") 6. TI "prenatal* drug expos*" OR AB "prenatal* drug expos*" 7. (MH "Teratogens") 8. TI "teratogen*" OR AB "teratogen*" 9. (MH "drug toxicity") 10. TI ("fetotoxicity" OR "embryotoxicity" OR "reproductive toxicity") OR AB ("fetotoxicity" OR "embryotoxicity" OR "reproductive toxicity") 11. TI ("utero" OR "uterine") OR AB (" utero" OR "uterine")	1. TS=("Pregnancy") 2. TS=("Pregnancy complications") 3. TS=("fetal" OR "foetal" OR "fetus" OR "foetus" OR "prenatal") 4. TS=("prenatal* drug expos*" OR "prenatal* expos*") 5. TS=("fetotoxicity" OR "embryo toxicity" OR "reproductive toxicity") 6. TS=(teratogen*) 7. TS=("uterine" OR "utero")
				AND		
NEURO-DEVELOPMENT	Intellectual impairment Child development Neurodevelopment ASD ADHD Apraxia Dyspraxia IQ/GQ Cognitive function Memory Language Executive function Neuropsychology	13. Learning disorders/ 14. Intellectual disability/ 15. learning disab*.tw. 16. Developmental disabilities/ 17. neurodevelopment*.tw. 18. Neurodevelopmental disorders/ 19. Autism Spectrum Disorder/ 20. Autistic Disorder/ 21. Cognitive Dysfunction/ 22. IQ.tw. 23. autis*.tw. 24. mental* retard*.tw. 25. Child development/ 26. Neuropsycholog*.tw. 27. Neuropsychology/ 28. intellectual* impair*.tw. 29. intellectual* abilit*.tw. 30. cognitive function*.tw. 31. educational needs.tw.	18. Learning disorder/ 19. Intellectual* disab*.tw. 20. learning disab*.tw. 21. developmental disorder/ 22. developmental* disab*.tw. 23. neurodevelopment*.tw. 24. neurodevelopment* disorder.tw. 25. autism/ 26. Cognitive defect/ 27. cognitive development/ 28. intelligence quotient/ 29. IQ.tw. 30. autis*.tw. 31. mental* retard*.tw. 32. child development/ 33. neuropsycholog*.tw. 34. neurppsychology/	16. learning disability/ 17. learning disorders/ 18. intellectual development disorder/ 19. Intellectual* disab*.tw. 20. developmental disabilities/ 21. developmental* disab*.tw. 22. neurodevelopment*.tw. 23. neurodevelopmental disorders/ 24. Autism Spectrum Disorders/ 25. Social cognition/ 26. Cognitive ability/ 27. Cognitive impairment/ 28. intelligence quotient/ 29. IQ.tw. 30. autis*.tw. 31. mental* retard*.tw.	12. (MH "learning disorders") 13. (MH "intellectual disability") 14. (MH "developmental disabilities") 15. TI "learning disab*" OR AB "learning disab*" 16. TI ("developmental disab*" or "developmental disorder*") OR AB ("developmental disab*" or "developmental disorder*") 17. TI ("neurodevelopment*" or "neurodevelopmental disorder*") OR AB ("neurodevelopment*" or "neurodevelopmental disorder*") 18. (MH "Autistic Disorder") 19. TI "autis*" OR AB "autis*" 20. (MH "Cognition Disorders") 21. TI ("cognitive function*" OR "cognitive abil*" OR "cognitive impair*") OR AB ("cognitive function*" OR "cognitive abil*" OR "cognitive impair*")	8. TS=("learning disab*" OR "learning disorder*" OR "learning impair*" OR "intellectual* impair*" OR "intellectual* disab*") 9. TS=("developmental disorder*" OR "developmental disab*") 10. TS=("neurodevelopment*" OR "neurodevelopmental disab*" OR "neurodevelopmental disorder*") 11. TS=("autis*") 12. TS=("attention deficit" OR "attention deficit hyperactivity disorder" OR "ADHD") 13. TS=("cognitive function*" OR "cognitive abil*" OR

SEARCH BLOCK	CONCEPTS	MEDLINE via OVID	EMBASE via OVID	PSYCHINFO via OVID	CINAHL PLUS via EBSCO	Web of Science
		32. Memory/ 33. memory.tw. 34. Language/ 35. language.tw. 36. Language disorders/ 37. Executive function/ 38. (executive function* OR executive dysfunction*).tw. 39. attention deficit.tw. 40. DQ.tw. 41. (adaptive function* OR adaptive behavio?r).tw. 42. Apraxias/ 43. (apraxi* OR dyspraxi*).tw. 44. Attention Deficit Disorder with Hyperactivity/ 45. or/13-44	35. intellectual impairment/ 36. intellectual* impair*.tw. 37. intellectual* abilit*.tw. 38. cognitive function*.tw. 39. educational needs.tw. 40. Memory/ 41. memory.tw. 42. language/ 43. language.tw. 44. language disorder.tw. 45. executive function/ 46. (executive function* OR executive dysfunction*).tw. 47. attention deficit disorder/ 48. attention deficit.tw. 49. DQ.tw. 50. adaptive behavior/ 51. (adaptive function* OR adaptive behavio?r).tw. 52. apraxia/ 53. (apraxi* OR dyspraxi*).tw. 54. or/18-53	32. childhood development/ 33. neuropsycholog*.tw. 34. neuropsychology/ 35. intellectual* impair*.tw. 36. learning disab*.tw. 37. cognitive function*.tw. 38. educational needs.tw. 39. memory/ 40. memory.tw. 41. language/ 42. language disorders/ 43. language.tw. 44. executive function/ 45. (executive function* OR executive dysfunction*).tw. 46. attention deficit disorder with hyperactivity/ 47. attention deficit disorder/ 48. attention deficit.tw. 49. DQ.tw. 50. adaptive behavior/ 51. (adaptive function* OR adaptive behavio?r).tw. 52. apraxia/ 53. (apraxi* OR dyspraxi*).tw. 54. or/16-53	22. TI ("IQ" or "DQ") OR AB ("IQ" OR "DQ") 23. TI ("mental* retard*") OR AB ("mental* retard*") 24. (MH "Child Development") 25. (MH "Child Development Disorders, Pervasive") 26. (MH "Child Development Disorders") 27. (MH "Neuropsychology") 28. TI neuropsycholog* OR AB neuropsycholog* 29. TI "educational needs" OR AB "educational needs" 30. (MH "memory") 31. TI "memory" OR AB "memory" 32. (MH "language") 33. (MH "language disorders") 34. TI "language" OR AB "language" 35. (MH "Executive Function") 36. TI ("executive function*" OR "executive dysfunction*") OR AB ("executive function*" OR "executive dysfunction*") 37. (MH "attention deficit hyperactivity disorder") 38. TI "attention deficit" OR AB "attention deficit" 39. TI ("adaptive function*" OR "adaptive behavior" OR "adaptive behaviour") OR AB ("adaptive function*" OR "adaptive behavior" OR "adaptive behaviour") 40. (MH "Apraxia") 41. TI ("apraxi*" OR "dyspraxi*") OR AB ("apraxi*" OR "dyspraxi*")	"cognitive impair*" OR "cognitive disorder*") 14. TS=("intellect* abil*") 15. TS=("mental* retard*") 16. TS=("neuropsycholog*") 17. TS=("IQ" or "intelligence quotient" or "DQ" or "developmental quotient") 18. TS=("educational needs") 19. TS=("memory") 20. TS=("language") 21. TS=("executive function*" OR "executive dysfunction*") 22. ("adaptive function*" OR "adaptive behavior" OR "adaptive behaviour" 23. TS=("apraxi*" OR "dyspraxi*")
				AND		
AEDs	Epilepsy Anti-epileptic Anti-convulsant Seizure Lamotrigine Topiramate Levetiracetam	46. Epilepsy/ 47. Seizures/ 48. Anticonvulsants/ 49. (anticonvuls or convuls* or anti epilep* or epilep* or seizure*).tw. 50. Lamotrigine/ 51. Lamotrigin*.tw. 52. Topiramate/ 53. Topiramat*.tw.	55. epilepsy/ 56. seizure/ 57. anticonvulsive agent/ 58. (anticonvuls or convuls* or anti epilep* or epilep* or seizure*).tw. 59. Lamotrigine/ 60. Lamotrigin*.tw. 61. Topiramate/ 62. Topiramat*.tw.	55. epilepsy/ 56. epileptic seizures/ 57. anticonvulsive drugs/ 58. (anticonvuls or convuls* or anti epilep* or epilep* or seizure*).tw. 59. lamotrigin*.tw. 60. topirmat*.tw. 61. levetiracetam.tw. 62. Oxcarbazepin*.tw.	42. (MH "Epilepsy") 43. (MH "Seizures") 44. (MH "anticonvulsants") 45. TI ("anticonvuls*" or "convuls*" or "anti epilep*" or "epilep*" or "seizure*") OR AB ("anticonvuls*" or "convuls*" or "anti epilep*" or "epilep*" or "seizure*") 46. (MH "Lamotrigine")	24. TS=("epilep*" OR "anti epilep*" OR "anti-epilep*" OR "seizure*" OR "anticonvuls*" OR "anti-convuls*" OR "consuls*") 25. TS=("lamotrigin*") 26. TS=("topiramat*") 27. TS=("levetiracetam") 28. TS=("oxcarbazepin*") 29. TS=("eslicarbazepin*")

SEARCH BLOCK	CONCEPTS	MEDLINE via OVID	EMBASE via OVID	PSYCHINFO via OVID	CINAHL PLUS via EBSCO	Web of Science
	Oxcarbazepine Eslicarbazepine Zonisamide Perampanel Lacosamide Gabapentin	54. Levetiracetam/ 55. Levetiracetam.tw. 56. Oxcarbazepine/ 57. Oxcarbazepin*.tw. 58. Eslicarbazepin*.tw. 59. Zonisamide/ 60. Zonisamid*.tw. 61. Perampanel.tw. 62. Lacosamide/ 63. Lacosamid* 64. Gabapentin/ 65. gabapentin.tw. 66. or/46-65 67. and/12,45,66	63. Levetiracetam/ 64. Levetiracetam.tw. 65. Oxcarbazepine/ 66. Oxcarbazepin*.tw. 67. Eslicarbazepine/ 68. Eslicarbazepin*.tw. 69. Zonisamide/ 70. Zonisamid*.tw. 71. Perampanel/ 72. Perampanel.tw. 73. Lacosamide/ 74. Lacosamid*.tw. 75. Gabapentin/ 76. Gabapentin.tw. 77. or/55-76 78. and/17,54,77	63. Eslicarbazepin*.tw. 64. Zonisamid*.tw. 65. Perampanel.tw. 66. Lacosamid*.tw. 67. Gabapentin.tw. 68. or/55-67 69. and/15,54,68	47. TI "Lamotrigin*" OR AB "Lamotrigin*" 48. TI "topiramat*" OR AB "topiramat*" 49. (MH "Topiramate") 50. TI "levetiracetam" OR AB "levetiracetam" 51. TI "Oxcarbazepin*" OR AB "Oxcarbazepin*" 52. TI "Eslicarbazepin*" OR AB "Eslicarbazepin*" 53. TI "Zonisamid*" OR AB "Zonisamid*" 54. TI "Perampanel" OR AB "Perampanel" 55. TI "Lacosamid*" OR AB "Lacosamid*" 56. TI "Gabapentin" OR AB "Gabapentin" 57. (MH "Gabapentin") 58. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 59. S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 60. S42 OR S43 OR S44 S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 61. S58 AND S59 AND S60	30. TS=("zonisamid*") 31. TS=("perampanel") 32. TS=("lacosamid*") 33. TS=("gabapentin") 34. #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 35. #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 36. #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 37. #34 AND #35 AND #36
SEARCH RESULTS						
Database:		MEDLINE via OVID	EMBASE via OVID	PSYCINFO via OVID	CINAHL PLUS via EBSCO Host	Web of Science
Total results returned:		3620	3418	898	736	1369
Limits applied:		68. limit 67 to (english language and humans and yr="2000 -Current")	79. limit 78 to (english language and humans and yr="2000 -Current")	70. limit 69 to (english language and humans and yr="2000 -Current")	Limiters: human; English Language; >2000	Limiters: English; >2000 *Not possible to limit to human
Results returned after limits:		1790	2475	547	698	1122

Appendix C
Adapted Newcastle Ottawa Scale

Assessment of quality of a cohort study – Newcastle Ottawa Scale (adapted using Bromley et al. 2014).	
Selection (tick one box in each section)	
1. Representativeness of the exposed cohort a) truly representative (e.g., population dataset) ★ b) somewhat representative (e.g., disease specific registers; recruitment from >2 hospitals) ★ c) selected group of patients (e.g., recruited from highly specialsed centre, <2 sites) d) no description of the derivation of the cohort	☐ ☐ ☐ ☐
2. Selection of the unexposed cohort a) drawn from the same community as the intervention cohort ★ b) drawn from a different source c) no description of the derivation of the non intervention cohort	☐ ☐ ☐
3. Ascertainment of exposure a) secure record (e.g., medical or phamarcy record) ★ b) structured interview ★ c) other / no description	☐ ☐ ☐ ☐
4. Dose investigated a) ascertainment via individual medical record ★★ b) structured interview ★ c) retrospective structured interview d) other / no description	☐ ☐ ☐
5. Demonstration that outcome of interest was not present at start of study a) yes (e.g., truly prospective cohorts, recruited into study before/during pregnancy) ★ b) no	☐ ☐
Comparability (tick one box in each section)	
1. Comparability of cohorts on the basis of the design or analysis a) study controls for key confounds (child age, sex, SES, maternal outcome, GA). ★ b) study controls for other important factors (e.g., parental age at birth, nicotine exposure, alcohol exposure, maternal disease factors, breastfeeding, folate, parity, cocomittant medication use) ★ c) study controls for key confounds plus other factors ★★ d) cohorts are not comparable on the basis of design or analysis	☐ ☐ ☐ ☐
Outcome (tick one box in each section)	
1. Assessment of outcome a) blind direct assessment of child ★★ b) routine medical/education review (non-blinded at point of assessment) ★ c) parental report (non-blinded) d) other / no description	☐ ☐ ☐ ☐
2. Was follow up long enough for outcomes to occur a) yes ★ b) no	☐ ☐
3. Adequacy of follow up of cohorts a) complete follow up: all subjects accounted for ★ b) incomplete follow up but description of those lost is provided AND no implication for outcome is suspected ★	☐ ☐ ☐

c) incomplete follow up and/or no description of those lost, with significant impact on outcome likely d) no statement/unclear	☐

NOS – CODING MANUAL FOR COHORT STUDIES

SELECTION

1) Representativeness of the Exposed Cohort (NB exposure = intervention)

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the study sample from some general population. For example, subjects derived from groups likely to contain exposed people are likely to be representative of exposed individuals, while they are not representative of all people the community.

Allocation of stars as per rating sheet

2) Selection of the Non-Exposed Cohort

Allocation of stars as per rating sheet

3) Ascertainment of Exposure

Allocation of stars as per rating sheet

4) Demonstration That Outcome of Interest Was Not Present at Start of Study

In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

COMPARABILITY

1) Comparability of Cohorts on the Basis of the Design or Analysis

Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

OUTCOME

2) Assessment of Outcome

For some outcomes, reference to the medical record is sufficient to satisfy the requirement for confirmation. This may not be adequate for other outcomes where reference to specific tests or measures would be required.

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (health records, etc.) ☆
b) Record linkage (e.g. identified through ICD codes on database records) ☆
c) Self-report (i.e. no reference to original health records or documented source to confirm the outcome)
d) No description.

3) Was Follow-Up Long Enough for Outcomes to Occur

An acceptable length of time should be decided before quality assessment begins.

4) Adequacy of Follow Up of Cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

Allocation of stars as per rating sheet

Quality Rating Guidelines UPDATED TOOL	
Good Quality	5 or 6 stars in selection AND 1 or 2 stars in comparability AND 3 or 4 stars in outcome (requires 1 star per item)
Fair Quality	4 stars in selection AND 1 or 2 stars in comparability AND ≥2 stars in outcome (does not require 1 star per item)
Poor Quality	1 - 3 stars in selection AND 0 stars in comparability AND 0 or 1 stars in outcome

Appendix D
UK Epilepsy and Pregnancy Register letter of support

Department of Neurology (Ward 4E)
Royal Victoria Hospital
Belfast BT12 6BA

Level 6
Out Patients department
Royal Victoria Hospital
Grosvenor road
Belfast
BT12 6BA

3rd September 2018

Dear Dr Bromley

Re: Neurodevelopmental Outcomes in Children exposed to Topiramate in the Womb.

On behalf of the UK and Ireland Epilepsy and Pregnancy Register Committee I am pleased to inform you that we agree to recruitment for Rebecca Knight's project through our register.

We look forward to working with you on this.

Best wishes

Beth Irwin
Epilepsy Nurse Specialist
Co-ordinator UK Epilepsy & Pregnancy Register

Principal investigator: Dr J Craig, Consultant Neurologist

Co-investigators: Dr J Morrow, Dr H Smithson General Practitioner, Dr P Morrison Genetics
Dr L Parsons Neurology, Dr A Russell Neurophysiology,
Dr Lucy MacKillop Obstetric Physician

Appendix E
Participant information sheet

Neurodevelopmental Outcomes in Children Exposed to Topiramate in the Womb (NOCT) Study

Participant Information Sheet (PIS)

This information sheet should be read alongside the University of Manchester's privacy notice, accessible at http://documents.manchester.ac.uk/display.aspx?DocID=37095

You are being invited to take part in a research study as part of a Clinical Psychology Doctorate. The study aims to find out whether exposure to a certain type of epilepsy medication impacts upon the development of babies. Before you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please read the following information carefully and discuss it with others if you wish. Please ask 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. Thank you for reading this.

Who will conduct the research?

The research will be supervised by Dr Rebecca Bromley (Research Fellow) and Dr Anja Wittkowski (Clinical Psychologist) and carried out by Rebecca Knight (Trainee Clinical Psychologist). The study is being conducted in collaboration with the UK Epilepsy and Pregnancy Register.

What is the purpose of the research?

Epilepsy is a brain condition that causes seizures. It can often be treated with medicine. Most women with epilepsy will need to carry on taking epilepsy medicine while they are pregnant. Certain older types of epilepsy medicines are linked with higher rates of developmental problems in children exposed to them in the womb. These can include problems with thinking skills and behaviour. Women who are pregnant or are of childbearing age are offered newer medicines instead, like topiramate.

There is not enough research yet investigating the risks to child development associated with topiramate exposure in the womb for us to provide clear advice to women with epilepsy on topiramate. This study will aim to understand whether exposure to topiramate in the womb has any influence on how the child develops. It will look at whether children exposed to topiramate in the womb have different levels of developmental skills (such as in communicating) than children who have not been exposed to the medicine (a control group).

Why have I been contacted?

We are looking for 102 people to take part in this research. As you are aware, your details are registered on the UK Epilepsy and Pregnancy Register. These details tell us that:

- You are a woman with epilepsy
- You have a child between the ages of 3-16 years.
- You took topiramate during your pregnancy *OR* took no epilepsy medicine during pregnancy.

If this information is correct then you may be able to take part in the study, if you would like to. This is why you have been contacted.

What would I be asked to do if I took part?

If you wish to take part in this study then a member of the research team will telephone you to ask some questions about your child's medical history. This is to make sure that you are suitable to take part in the study. You will be able to ask the researcher any questions you have about the study to help you decide if you wish to take part. If you are happy to go ahead, then you and the researcher will agree on a suitable date and time for you to take part in a telephone interview. You will be asked to complete a consent form and post this back to the research team free of charge before the day of the interview.

Your telephone interview will be with a member of the research team and may take up to 40 minutes to complete. The first part of the interview will involve finding out about the history of your child's development. The researcher will ask you some questions about your own and the father's health and background. The second part of the interview will involve questions about your child's current communication skills, social skills and daily living skills. If you are unsure of your answers, or if you do not wish to answer a question, just let the researcher know.

How often would I be contacted if I took part?

If you choose to take part in the study, then the research team will contact you by letter/email to confirm the telephone interview appointment and provide consent forms to complete. You can choose to receive an appointment reminder by text or email closer to the time of the interview. If you opt into receiving a summary of the study's findings after it has ended, then a newsletter will be posted or emailed to you. The only other times the research team may contact you is if we have not received your consent form, if you miss the appointment for the telephone interview.

What are the possible benefits of taking part?

There may be no direct benefits to you personally, but in the longer term the findings of this study will be of benefit to both women with epilepsy and their doctors by providing information about how exposure to topiramate in the womb may or may not influence the child's development. This may be relevant to you if you are planning another pregnancy in the future.

What are the possible disadvantages and risks of taking part?

Although it is uncommon, it is possible that thinking about your child's development may be upsetting, especially if you have existing concerns about this. The research team will be able to talk through your concerns and signpost you towards the most suitable professional for you to seek advice from in your local area.

What will happen to my personal information?

In order to undertake the research project we will need to collect the following personal data:

- **Your contact details**, including your name, postal or email address and telephone number.
- **Your health information,** including details about your epilepsy and pregnancy with your child.

- **Parental information**, including age, ethnicity and information about any developmental problems that have run in the family.
- **Your child's information**, including their date of birth and information about the history of your child's development since birth.

Some of this information will be collected from you directly. Other information will be collected from information that is held on the UK Epilepsy and Pregnancy Register. Only the research team will have access to this information.

We are collecting and storing this personal information in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 which legislate to protect your personal information. The legal basis upon which we are using your personal information is "public interest task" and "for research purposes" if sensitive information is collected. For more information about the way we process your personal information and comply with data protection law please see our Privacy Notice for Research Participants (http://documents.manchester.ac.uk/display.aspx?DocID=37095).

The University of Manchester, as Data Controller for this project, takes responsibility for the protection of the personal information that this study is collecting about you. In order to comply with the legal obligations to protect your personal data the University has safeguards in place such as policies and procedures. All researchers are appropriately trained and your data will be looked after in the following way:

The study team at the University of Manchester will have access to your personal identifiable information (data which could identify you). This will be stored separately from the research data (the interviews you complete), which will be made anonymous by allocating you a study ID. All personally identifiable information will be kept confidentially and securely; information that is in paper format will be kept in a locked filing cabinet in a locked office on NHS premises until the study closes. After this time, paper data will be securely stored by the University of Manchester.

Personally identifiable information that is in electronic format will be stored on computers accessed only through the NHS. Unless you provide consent for to be contacted about future research (optional), your contact details will be destroyed after the study closes. Your consent form and anonymised research data will be retained for up to 15 years. All transmission and storage of participant identifying data complies with current relevant NHS security standards.

You have a number of rights under data protection law regarding your personal information. For example you can request a copy of the information we hold about you. This is known as a Subject Access Request. If you would like to know more about your different rights, please consult our privacy notice for research (http://documents.manchester.ac.uk/display.aspx?DocID=37095) and if you wish to contact us about your data protection rights, please email dataprotection@manchester.ac.uk or write to The Information Governance Office, Christie Building, University of Manchester, Oxford Road, M13 9PL. at the University and we will guide you through the process of exercising your rights.

You also have a right to complain to the Information Commissioner's Office by visiting

https://ico.org.uk/concerns or by telephoning 0303 123 1113.

Will my participation in the study be confidential?

Your participation in the study will be kept confidential to the study team and those with access to your personal information as listed above. Your research data will be anonymised by removing any of your personal data and using a participant ID number instead.

Under certain circumstances, we might need to disclose information about you to individuals outside of the research team:

- Information may be shared with individuals from regulatory authorities for auditing and monitoring purposes.
- In the event of concerns about your safety or the safety of others, information may be shared with your GP or your family.
- In the event of you reporting current/future illegal activities your information may be shared with relevant authorities.

In any other circumstances where it is felt we might need to share information about you to individuals outside of the research team, we will ask for your consent to do this.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether or not to take part. If you do decide to take part then you will be asked to sign a consent form. Once we have received this, we will let your GP know that you are taking part in the study. If you decide to take part you are still free to withdraw at any time without giving a reason and without detriment to yourself or any impact on your NHS care. However, it will not be possible to remove your data from the project once it has been anonymised and forms part of the dataset as we will not be able to identify your specific data. This does not affect your data protection rights.

Will my data be used for future research?

When you agree to take part in a research study, the information about you may be provided to researchers running other research studies in this organisation. The future research should not be incompatible with this research project and will concern the development of children born to women with epilepsy. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/).

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you regarding any other matter or to affect your care. It will not be used to make decisions about future services available to you.

Will taking part in the research cost me anything?

No. The study will only involve your time. However, as a thank you for taking part, we would like to enter you into a prize draw to win one of four £20 vouchers.

What is the duration of the research?

Although this study will be running for several months, the duration of your participation will a maximum of one hour. This will include time to complete the initial screening telephone interview, followed by the data collection interview.

Where will the research be conducted?

The research will be collected by telephone interview. We would ask that you make sure you are sitting somewhere that is comfortable and private, such as your home.

Will the outcomes of the research be published?

After the study is completed, we will analyse the results and submit them for publication in a scientific journal. We will send you a newsletter summarising what we have found and information on where to find the full scientific paper from, should you wish to read this also. Presentations may also be given at scientific conferences and at conferences about epilepsy. Results will be used to improve understanding about topiramate, so women with epilepsy have more information about their medication choices. You will not be identified in any publication or presentation.

Who has reviewed the research project?

The project has been reviewed by the University of Manchester Research Ethics Sub-Committee, the NHS Research Ethics Committee and the Health Research Authority.

What if it goes wrong?

If you have a concern or complaint about any aspect of this study, you should ask to speak to the researchers:

Rebecca Knight, Trainee Clinical Psychologist
Tel: 0161 701 4514
rebecca.knight-4@postgrad.manchester.ac.uk

Dr Rebecca Bromley, Research Fellow
Tel: 0161 276 6602/4542
Rebecca.Bromley@manchester.ac.uk

Dr Anja Wittkowski, Clinical Psychologist
Tel: 0161 306 0401
Anja.Wittkowski@manchester.ac.uk

If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact:

The Research Governance and Integrity Manager, Research Office, Christie Building, University of Manchester, Oxford Road, Manchester, M13 9PL, by emailing: research.complaints@manchester.ac.uk or by telephoning 0161 275 2674.

What Do I Do Now?

If you have any queries about the study or if you are interested in taking part then please return the enclosed slip or give us a call:

Rebecca Knight, Trainee Clinical Psychologist
Tel: 0161 701 4514
rebecca.knight-4@postgrad.manchester.ac.uk

This project has been approved by the NHS Research Ethics Committee

Appendix F
Participant invite follow-up letter

xxxxxxxxxxxxxx

NOCT RESEARCH TEAM
c/o Genetic Medicine Research Office
6th Floor, St Mary's Hospital
Oxford Road
Manchester
M13 9WL
0161 276 4542

Dear xxxxxxxxx,

Re: Neurodevelopmental Outcomes in Children Exposed to Topiramate in the Womb (NOCT) Study

We recently wrote to you about a new study looking at whether certain epilepsy medications have an impact on the development of babies in the womb.

In case you did not receive this letter, we have enclosed a Participant Information Sheet (PIS) for you to read. This will tell you what the study is about and what participating would involve. We would be very grateful if you would consider taking part.

If you are interested in hearing more about this study or have any questions, please **complete the reply slip with your contact details and return it back to us using the prepaid envelope provided.** Alternatively, you can give the research team a call using the number at the top of this letter. If we don't hear from you within the next month, we will assume that you do not wish to participate in the study and we will not contact you again.

Thank you for reading this letter.

Best wishes,

Rebecca Knight
Trainee Clinical Psychologist *working under supervision of*

Dr Rebecca Bromley ClinPsyD, PhD
NIHR Research Fellow & Clinical Psychologist

Appendix G
Health Research Authority ethical approval

NHS
Health Research Authority

London - Central Research Ethics Committee
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 1048 007

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

08 August 2019

Dr Anja Wittkowski
University of Manchester
2nd Floor Zochonis Building
Brunswick Street
Manchester
M13 9PL

Dear Dr Wittkowski

Study title:	**Neurodevelopmental Outcomes in Children exposed to Topiramate in the Womb**
REC reference:	**19/NW/0299**
Protocol number:	**NHS001504**
IRAS project ID:	**256953**

Thank you for your response to the Committee's request for further information on the above research. The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study:

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise). Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

It is a condition of the REC favourable opinion that all clinical trials are registered on a publicly accessible database. For this purpose, clinical trials are defined as the first four project categories in IRAS project filter question 2. For clinical trials of investigational medicinal products (CTIMPs), other than adult phase I trials, registration is a legal requirement.

Registration should take place as early as possible and within six weeks of recruiting the first research participant at the latest. Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

As set out in the UK Policy Framework, research sponsors are responsible for making information about research publicly available before it starts e.g. by registering the research project on a publicly accessible register. Further guidance on registration is available at: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

You should notify the REC of the registration details. We will audit these as part of the annual progress reporting process.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites listed in the application subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

The favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [NOCT Study Cover Letter]		02 February 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of Sponsor Insurance I]		13 March 2019
GP/consultant information sheets or letters [NOCT Study GP Letter]	1	10 December 2018
Interview schedules or topic guides for participants [NOCT Study Brief Health and Background Interview]	2	26 May 2019
IRAS Application Form [IRAS_Form_18042019]		18 April 2019
IRAS Checklist XML [Checklist_12062019]		12 June 2019
Letter from sponsor [Letter from Sponsor (University of Manchester)]		13 March 2019
Letters of invitation to participant [NOCT Study Consent to Contact]	2	02 February 2019
Other [NOCT Study Appointment Letter]	1	02 February 2019
Other [NOCT Study Consent Follow-up]	1	10 December 2018
Other [NOCT Study Distress Protocol]	1	10 December 2018
Other [NOCT Study DNA Letter]	1	10 December 2018
Other [NOCT Study Invite Follow-up]	2	02 February 2019
Other [NOCT Study No Contact Letter]	2	02 February 2019
Other [NOCT Study UKEPR letter of support]		03 September 2018
Other [NOCT Study Risk Assessment Form]	1	19 February 2019
Other [UKEPR Registration Form]	3	01 April 2013
Other [Evidence of Sponsor Insurance II]		
Other [Evidence of Sponsor Insurance III]		
Other [Combined Liability Confirmation Letter]		
Other [NHS REC Cover Letter and Response]		12 June 2019

Participant consent form [NOCT Study Consent Form]	2	02 February 2019
Participant information sheet (PIS) [NOCT Study Participant Information Sheet]	3	26 May 2019
Research protocol or project proposal [NOCT Study Protocol]	2	02 February 2019
Summary CV for Chief Investigator (CI) [Anja Wittkowski CV]	1	
Summary CV for student [Rebecca Knight CV]		
Summary CV for supervisor (student research) [Dr Rebecca Bromley CV]		
Validated questionnaire [Vineland Adaptive Behaviour Scale Third Edition]		

Statement of compliance

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

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

19/NW/0299	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp
Dr George Gkimpas
Chair Email: nrescommittee.northwest-gmcentral@nhs.net

Enclosures: "After ethical review – guidance for researchers"
Copy to: Ms Lynne Macrae, University of Manchester

Appendix H
Blank consent form

Neurodevelopmental Outcomes in Children Exposed to Topiramate in the Womb (NOCT) Study

CONSENT FORM – PLEASE POST BACK TO THE RESEARCH TEAM

If you are happy to participate, please complete and sign the consent form below. Please **initial each box** to indicate you consent to take part. Once completed, please **return this copy to the research team** using the prepaid envelope provided.

	Activities	Initials
1.	I confirm that I have read and understand the attached information sheet (Version 3, 26.05.2019) for the above study and have had the opportunity to consider the information and ask questions and had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without detriment to myself. I understand that it will not be possible to remove my data from the project once it has been anonymised and forms part of the data set. I agree to take part on this basis.	
3.	I agree that any data collected may be published in anonymous form in academic books, reports or journals. I understand that my identity will not be revealed in any publication.	
4.	I give permission for information that is held on the UK Epilepsy and Pregnancy Register about me/my child to be shared with the research team for the purposes of collecting information for this study.	
5.	I consent to completing the telephone interview about parental factors and my child's development.	
6.	I consent to my GP being informed about my participation in this study.	
7.	I understand that there are certain circumstances under which the research team would be obliged to break confidentiality. I confirm that this has been explained in more detail in the participant information sheet.	
8.	(Optional) I agree to my contact details being retained for up to three years so that researchers may contact me in the future about participating in ethically approved research.	
9.	I agree that the researchers may retain my contact details in order to provide me with a summary of the findings for this study.	
10.	I understand that relevant sections of data collected during the study may be looked at by responsible individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in the research. I give permission for these individuals to have access to this data.	
11.	I agree to take part in this study.	

Data Protection

The personal information we collect and use to conduct this research will be processed in accordance with data protection law as explained in the Participant Information Sheet and the Privacy Notice for Research Participants (http://documents.manchester.ac.uk/display.aspx?DocID=37095)

Name of Participant:

Signature: Date:

Name of Researcher:

Signature: Date:

Neurodevelopmental Outcomes in Children Exposed to Topiramate in the Womb (NOCT) Study

CONSENT FORM – YOUR COPY TO KEEP

If you are happy to participate, please complete and sign the consent form below. Please **initial each box** to indicate you consent to take part. Once completed, please **keep this copy for your own records.**

	Activities	Initials
1.	I confirm that I have read and understand the attached information sheet (Version 3, 26.05.2019) for the above study and have had the opportunity to consider the information and ask questions and had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without detriment to myself. I understand that it will not be possible to remove my data from the project once it has been anonymised and forms part of the data set. I agree to take part on this basis.	
3.	I agree that any data collected may be published in anonymous form in academic books, reports or journals. I understand that my identity will not be revealed in any publication.	
4.	I give permission for information that is held on the UK Epilepsy and Pregnancy Register about me/my child to be shared with the research team for the purposes of collecting information for this study.	
5.	I consent to completing the telephone interview about parental factors and my child's development.	
6.	I consent to my GP being informed about my participation in this study.	
7.	I understand that there are certain circumstances under which the research team would be obliged to break confidentiality. I confirm that this has been explained in more detail in the participant information sheet.	
8.	(Optional) I agree to my contact details being retained for up to three years so that researchers may contact me in the future about participating in ethically approved research.	
9.	I agree that the researchers may retain my contact details in order to provide me with a summary of the findings for this study.	
10.	I understand that relevant sections of data collected during the study may be looked at by responsible individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in the research. I give permission for these individuals to have access to this data.	
11.	I agree to take part in this study.	

Data Protection

The personal information we collect and use to conduct this research will be processed in accordance with data protection law as explained in the Participant Information Sheet and the Privacy Notice for Research Participants (http://documents.manchester.ac.uk/display.aspx?DocID=37095)

Name of Participant:

Signature: Date:

Name of Researcher:

Signature: Date:

Appendix I
Brief health and background interview proforma

Study ID	Interview Date (DD MM YY)
NOCT_	

Eligibility Screen

Has the participant received enough information and do they wish to participate?	Yes	No	
Date consent form posted/emailed			Comments:
Date completed consent received			

Child current age in years and months:	

Has the child had an acquired brain injury?	Yes	No
If Yes, please give details:		

Does the child have any health difficulties?	Yes	No
If Yes, please give details:		

Does the child have a diagnosis of a neurodevelopmental disorder?	Yes	No
If yes please give details:		

Study ID	Interview Date (DD MM YY)
NOCT_	

Demographic Information

Maternal Health

Epilepsy. Age at onset:

1 <5 years of age	2 6-12 years of age	3 13-18 years of age	4 >19 years

Epilepsy. Type (tick one):

1 Generalised Epilepsy (grand mal)	2 Focal Epilepsy (partial, petit mal)	3 Juvenile Myoclonic	4 Partial with Secondary Generalisation
5 Childhood Absence Epilepsy	6 Symptomatic Epilepsy	7 Not sure	8 Other (please record)

Does anyone else in your family have epilepsy?

1 Yes	2 No

If yes, please tick all that apply:

1 Mother	2 Father	3 Sister	4 Brother
5 Grandmother	6 Grandfather	7 Aunty	8 Uncle

What time of the day or night do/did you experience seizures (tick all that apply)?

Within two hours of waking	Only when asleep	Any time of the day or night	Not sure

Study ID

NOCT_ | | | |

Interview Date (DD MM YY)

Seizure types (tick all that apply):	**1. Generalised seizure (generalised tonic-clonic, grand mal attack).** Unconsciousness with the body becoming stiff with rhythmic jerking of all the limbs and possibly 'frothing' at the mouth, difficulty breathing and loss of bladder and bowl control. If you were standing you'd fall down. Followed by a period of tiredness.	
	2. Focal Seizure (partial seizure, petite mal attack). During a focal seizure symptoms differ across individuals but may include: - Movement or stiffening in one part of the body - One part of the body going limp or floppy - Brief irregular jerks in one part of the body - Lip smacking - Turning of the head and eyes to one side - Changes in hearing, vision or taste - Sudden feelings of anxiety or fear - Hearing things which aren't there Awareness may be impaired or the individual may still be aware of their surrounding.	
	3. Absence Seizures (attacks with a trance like state). A brief episode of no more than a few seconds with blankness without falling and possibly flickering of the eyelids. There may or may not be loss of consciousness.	
	4. Brief jerks of the arms and body. Brief jerks which occur usually within a couple of hours of waking.	
	5. Any other information or type of attacks?	
	If others, please describe:	

Study ID	Interview Date (DD MM YY)
NOCT_	

Did you have any seizures during your pregnancy with the study child?	Yes	No	Unsure
If yes please give details, including frequency:			

Were these tonic clonic seizures?	Yes	No	Unsure
If yes please give details, including frequency:			

In addition to your epilepsy do you have any other health conditions?	1 No	2 Yes	If yes, please describe
Do you suffer from any mental health or psychiatric conditions?	1 No	2 yes	If yes, please describe

Study ID

NOCT_ | | | |

Interview Date (DD MM YY)

Maternal medication *** to be completed after the VABS interview***

	Tick	Dose (Total daily mg)	Date started (DD MM YYYY)	If applicable, date stopped using during this pregnancy (DD MM YYYY).
Topiramate (Topamax)				
Was baby breastfed?	**NO**			
	YES	Details (for how many months; dose during breastfeeding):		

Other medications during the pregnancy:

NAME	Dose (Total daily)	Date started (DD MM YYYY)	If applicable, date stopped using this pregnancy (DD MM YYYY).

Study ID

NOCT_			

Interview Date (DD MM YY)

Did you drink alcohol during this pregnancy?

No- nothing	Yes- occasional drink	Yes- some (2 or more drinks per week)
Details (types of drink/units and frequency):		

Did you smoke during this pregnancy?

No- nothing	Yes- occasional cigarette	Yes- frequent
Details:		

Were there any stressors or complications during your pregnancy/labour with study child?

No	Yes

If yes, give details:

Maternal Family History

Is there a family history of birth defects?

No	Yes	
If yes, describe		

Study ID	Interview Date (DD MM YY)
NOCT_	

Is there a family history of requiring specialist education?	No	Yes	
	If yes, describe		

Do any of the children in your family have illnesses or developmental problems?	No	Yes	
	If yes, describe		

Maternal demographics

Current age:

Ethnicity (tick one):

1 White British	2 White-Other	3 Asian-British	4 Asian-Other	5 Black-British	6 Black-Other
Other:					

Age they left <u>full time</u> education? (tick one):

1 < 16 years	2 16-17 years	3 18 years	4 19-21 years	5 > 21 years	6 Still in f/t school

Did they complete any qualifications? (tick all that apply):

1 None	2 CSE'S or GCSE's	3 HND, Diploma	4 O levels, A levels	5 Degree	6 Post-grad Degree

Study ID	Interview Date (DD MM YY)
NOCT_	

Occupation:	(Please list. If not currently working what was previous position):

Do they have supervisory or managerial responsibilities?	Yes	No	If Yes, for how many people:

Paternal Family History

Is there a family history on the father's side of birth defects?	No	Yes	
	If yes, describe		

Is there a family history on the fathers side of requiring specialist education?	No	Yes	
	If yes, describe		

Do any of the father's family have illnesses or developmental problems?	No	Yes	
	If yes, describe		

Study ID

NOCT_			

Interview Date (DD MM YY)

Paternal Demographics

Fathers current age:

Ethnicity (tick one):

1 White British	2 White-Other	3 Asian-British	4 Asian-Other	5 Black-British	6 Black-Other
Other:					

What age did they leave <u>full time</u> education? (tick one):

1 < 16 years	2 16-17 years	3 18 years	4 19-21 years	5 Over 21 years	6 Still in f/t school

Did they complete any qualifications? (tick all that apply):

1 None	2 CSE'S or GCSE's	3 HND, Diploma	4 O levels, A levels	5 Degree	6 Post grad Degree

Occupation:

(Please list. If not currently working what was previous position):

Do they have supervisory or managerial responsibilities?

Yes	No	If Yes, for how many people:

Study ID	Interview Date (DD MM YY)
NOCT_	

Child Demographics

Gestation age at birth	weeks	Weight at birth	kg
Height at birth	cm	OFC at birth	cm

Did they have any health problems at birth?

No	Yes	Did they need an admission to SCBU?

If yes, describe

Child gender assigned at birth

M	F

In your opinion was your child on time for their early developmental milestones?

No	Yes

Describe

Study ID

NOCT_ | | | |

Interview Date (DD MM YY)

In your opinion has your child ever had difficulties with social skills?

No	Yes

If yes, describe

Do they or have they experienced any difficulties with learning at school?

No	Yes	Do they have a statement or EHCP?

If yes, describe

Does your child have any difficulties with hearing or eyesight?

No	Yes

If yes, describe

Study ID

NOCT_			

Interview Date (DD MM YY)

Does your child have any other difficulties?

No	Yes

If yes, describe

Has your child ever had involvement from a specialist healthcare profession such as (tick all that apply):

1 SLT	2 OT	3 Physio	4 CAMHS	5 Other

Further details:

Regular medications taken by child

NAME	Dose (total daily)	Date started (DD MM YYYY)	Reason for medication

Notes

Study ID

NOCT_ | | | |

Interview Date (DD MM YY)

Signature of Research Personnel

Date form completed (DD MM YYYY)

Appendix J
VABS-III scoring classifications

Qualitative Descriptors

Sometimes test scores are grouped into bands, with qualitative descriptors assigned to the score bands. Although qualitative descriptors can help in communicating test results to individuals who are unfamiliar with quantitative test scores, they have serious limitations (e.g., semi-arbitrary cutoffs that do not account for measurement error), as described in the Manual. Because of these limitations, qualitative descriptors are not included in the presentation of results on the previous pages. They are also not included in the narrative description of results below. However, for situations where they might serve a purpose, the following qualitative descriptors may be used:

Adaptive Level	Subdomain *v*-Scale Scores	Domain and ABC Standard Scores
High	21 to 24	130 to 140
Moderately High	18 to 20	115 to 129
Average	13 to 17	86 to 114
Moderately Low	10 to 12	71 to 85
Low	1 to 9	20 to 70

Appendix K
VABS-III outcomes for children excluded from analysis

Supplementary Table. Unadjusted means, standard deviations and rates of below average performance for children excluded from the analysis due to existing conditions known to effect neurodevelopment.

Excluded children (*n* = 4)		
VABS-III	**Mean (SD)**	**No. (%) ≤85**
ABC	80.50 (19.05)	3 (75.00%)
Communication	78.50 (19.16)	3 (75.00%)
Daily Living Skills	81.75 (18.67)	3 (75.00%)
Socialisation	83.00 (15.95)	3 (75.00%)

Abbreviations: VABS-III = Vineland Adaptive Behaviour Scale, Third Edition; ABC = Adaptive Behaviour Composite.

The VABS-III normative sample mean is 100 with SD of 15 points. A score ≤85 would therefore be classified as below average adaptive levels.