Institution: The University of Manchester

Unit of Assessment: 4 (Psychology, Psychiatry and Neuroscience)

Title of case study: Worldwide reduction in the number of children exposed to harmful antiepileptic drugs in the womb

Period when the underpinning research was undertaken: January 2000 – August 2016

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Rebecca Bromley	Research Fellow	2013 - present
Jill Clayton-Smith	Honorary Professor in Medical Genetics	2007 - present
	Honorary Senior Lecturer	2000 - 2006

Period when the claimed impact occurred: August 2013 - December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Research undertaken at the University of Manchester (UoM) has been integral in reducing risks to fetal development from the treatment of epilepsy during pregnancy. The work of Bromley and Clayton-Smith demonstrated that sodium valproate taken in pregnancy can lead to increased rates of physical birth defects and lifelong cognitive, behavioural and social difficulties in the offspring. Their research has contributed to regulatory interventions and policy changes which have seen the prescribing of valproate become severely restricted in women and girls, resulting in tens of thousands fewer children being affected worldwide. Diagnostic guidelines and both genetic and neuropsychological clinical pathways have been developed to improve management for those affected.

2. Underpinning research

Treatment of chronic conditions such as epilepsy during the childbearing years requires a balance between optimising maternal health whilst reducing any risk to the development of their future child. Around the turn of the century it had been established that sodium valproate exposure in the womb led to an increased rate of physical birth defects. However, the substantial risk to the fetal brain and later child neurodevelopmental abilities remained limited to case reports and small retrospective studies with significant methodological shortfalls. A lack of rigorous evidence for the impact on the brain meant that women were only being counselled regarding the risk of physical malformations.

Funded by an Epilepsy Foundation grant, researchers at UoM began a prospective longitudinal study, which recruited hundreds of pregnant women with epilepsy who were taking antiepileptic drugs from the Merseyside and Greater Manchester regions. The children were followed up and assessed at <2,3, and 6 years of age. The assessments were blinded to whether or not the child was exposed to an antiepileptic medication. In 2003 the UoM cohort was combined with a similar cohort in the US and, with funding from the US National Institute for Health, led to the publication of the first prospective dataset regarding the significant delay to early development observed following exposure in utero to sodium valproate [1]. Data from the child follow up at 6 years of age demonstrated the substantial nature of the impact on child IQ and additionally highlighted wide-ranging impact on other key cognitive areas such as language, memory and attention [2]. The real life implication of such deficits was highlighted in the increased number of children with specialist educational needs provision (30% vs 2% of control children) [3] and a six-fold increase in the rate of autistic spectrum and other childhood development related diagnoses [4]. The level

of risk to child IQ associated with the exposure was observed to be halved for doses of valproate ≤800mg daily in comparison to those exposed above that level [3]. Determining that the risk to child development was associated with the dose or level of exposure was a highly relevant finding for clinical practice. The team's work also found that whilst the presence of physical malformations were indicative of additional impact on child brain functioning, neurodevelopmental difficulties, such as lowered IQ, autistic spectrum disorder and language delay, could also be present in the absence of these physical markers [3].

In collaboration with colleagues from around the UK, the team at UoM designed and implemented the collection of other cohorts of children exposed to antiepileptic medications from which the substantial and dose dependent cognitive risk associated with exposure in the womb to sodium valproate was replicated. Levetiracetam and lamotrigine, two alternatives to valproate, importantly showed no significant impact on child brain development after exposure in the womb in the team's work [2,3,5]. Two meta-analyses conducted by UoM researchers in collaboration with the Cochrane Epilepsy Group allowed for the combination of data on 900 and 15,000 children respectively and concluded that, unless necessary for maternal health, valproate should not be a first line treatment for women and girls [6].

3. References to the research

1. Meador, K, Baker G, Browning N, **Clayton-Smith J**, Combs-Cantrell D, Cohen M, Kalayjian L, Kanner A, Liporace J, Pennell P, Privitera M, Loring D. On behalf of the NEAD Study Group. Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs. New England Journal of Medicine. 2009; 360 (16): 1597-1605. DOI:10.1056/NEJMoa0803531. *First output from prospective longitudinal study which was a collaboration between the US and UK and was the first to demonstrate reliably the impact of exposure to valproate as a fetus and later child cognitive difficulties.*
2. Meador, K., Baker, G.A., Browning, N., Cohen, M., Bromley, R.L., **Clayton-Smith J.**, Kalayjian L, Kanner A, Liporace J, Pennell P, Privitera M, Loring D. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurology, 2013; 12(3): 244-252. DOI:10.1016/S1474-4422(12)70323-X. *Demonstrated that the risk associated with valproate were significantly higher than other medications, that the impact remained at school age and that folate supplementation may have a protective effect.*
3. Baker GA, **Bromley RL**, Briggs M, Cheyne CP, Cohen MJ, Garcia-Finana M, Gummery A, Kneen R, Loring DW, Mawer G, Meador KJ, Shallcross R, **Clayton- Smith J**. IQ at 6 years following in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology, 2015; 84 (4): 382-390. DOI: 10.1212/wnl.0000000000001182 *Taken from UoM's UK prospective study this paper was the first to include an adequate sized control (no exposure) group. This allowed the magnitude of valproate risk to be documented clearly. Important dose relationships were also delineated.*
4. Bromley R.L., Mawer G., Briggs M, Cheyne C, **Clayton-Smith J**., Garcia-Finana M, Kneen R, Lucas SB, Shallcross R, Baker G.A., Dixon P, Fryer A, Gummery A, Kerr L. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. Journal of Neurology, Neurosurgery and Psychiatry, 2013; 84:637-643. DOI:10.1136/jnnp-2012-304270.*The first group level investigation in the relationship between prenatal exposure to valproate and increased risk of autistic spectrum disorder.*
5. **Bromley RL,** Calderbank R, Cheyne CP, Rooney C, Trayner P, **Clayton-Smith J.**, Garcia-Finana M, Irwin B, Morrow J, Shallcross R, Baker GA. Cognition in school-aged children exposed to levetiracetam, topiramate or sodium valproate. Neurology, 2016; 87 (18): 1943-1953. DOI:10.1212/WNL.0000000000003157.*The first data to directly compare the intellectual functioning of children exposed to alternatives to valproate in the womb vs children exposed to valproate.*
6. **Bromley R**, Weston J, Adab N, Greenhalgh J, Sannti A, McKay A, Tudur Smith, C, Marson, A. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the

child. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD010236. DOI:10.1002/14651858.CD010236.pub2. *Systematic review and meta-analysis of neurodevelopmental outcomes associated with prenatal exposure to valproate and other antiepileptic drugs. This was the first meta- analysis to contain prospectively ascertained data only and to compare directly at infancy through to adolescence the outcomes for valproate exposed children in comparison to children exposed to other antiepileptic drugs.*

4. Details of the impact

1. International impact on health of children born to women taking anti-seizure medications

1.1. The reduction of those harmed by valproate exposure: Valproate was once the treatment of choice internationally for epilepsy and bipolar disorder, reductions in its use have been observed around the world. As a result of research conducted at UoM, in 2014, the European Medicines Agency (EMA) issued guidance on the use of valproate in women of childbearing age [A], which led to a reduction in the number of children developing neurodevelopmental disorders as a consequence of having been exposed to the drug. Data from the Medicine and Health Product Regulatory Authority (MHRA) demonstrated a 40% decline (11.4 to 6.8 per 10,000 pregnancies) between 2010-2018 [B]. With up to 40% of exposed children expected to experience the associated neurodevelopmental difficulties, this reduction in prescribing translates into approximately *200 fewer children who will experience intellectual, language or autism related difficulties* per year in the UK alone. Similar reductions in the use of valproate have been seen across the world and cumulatively this translates into tens of thousands of children annually who are no longer at risk of the associated neurodevelopmental difficulties. More dramatic reductions in valproate use are expected over the next few years following the introduction in 2018 of new EMA measures to avoid valproate exposure in pregnancy [C] and the MHRA's Valproate Pregnancy Prevention Programme which was designed to ensure patients are fully aware of the risks and the need to avoid becoming pregnant whilst taking Valproate [D].

1.2. Regulatory impact

The reduction in valproate prescribing was implemented by a growing body of evidence regarding fetal harm and by formal regulatory intervention. The UoM team's work has been utilised by regulatory agencies in their recommendations on the use of valproate in women and girls. In 2014, EMA reviewed evidence regarding the risks associated with valproate exposure in utero [A]. As well as including the team's published work, Bromley contributed to the review meetings as a 'Topic Expert'. Following this, in 2018 the EMA issued further restrictions and requirements to strengthen previous recommendations. Measures included banning use for migraine/bipolar disorder in pregnancy and not allowing use in any woman able to have children unless conditions of the new pregnancy prevention programme were met [C]. Seven out of the nine documented references came from the UoM team's collaborative prospective study with its US colleagues or its additional UK based studies, highlighting that the impact on the developing brain was central to their decision making.

Bromley has continued to work with the MHRA as a member of the Steering Group of the MHRA Valproate Register and as a 'Topic Expert' for the Commission on Human Medications.

The regulatory impact is wider than the UK and EU however, and a Patient Campaigner in New Zealand wrote: *"We can see the positive impact that this research has made, particularly with the acceptance of neurodevelopmental and cognitive impacts of valproate exposure during pregnancy on the foetus. Medsafe (our regulatory body for medicines) now has a section on "Learning and behavioural problems (neurodevelopmental disorders)" in alerts on their website".* Executive Officer of FACS NZ (Foetal Anti-Convulsant Syndrome New Zealand) [E].

1.3. Product information impact

Bromley and Clayton-Smith's work has directly influenced the data now contained in the Summary of Product Characteristics and the Patient Information Sheets for valproate. The Head

of Regions for Global Pharmacovigilance for the manufacturer Sanofi wrote: "*The findings contributed to understanding the disorders associated with prenatal exposure to valproate, were cited whenever relevant in documents submitted to the regulatory authorities and have supported updates of product information as well as measures to minimize the risks (such as educational materials for health care professionals and patients*)" [F].

1.4. Professional guidance impact

In order to make prescribing safer for women and their children, evidence-based guidelines are needed and the teams' work has been used frequently in both national and international guidance papers across both neurology and obstetric practice. Examples include the Royal College of Obstetricians and Gynaecologists Green Top Guidance (2016) [Gi] and the International League Against Epilepsy's International Task Force publication (2019) on the management of pregnancy in women with epilepsy [Gii]. The International League Against Epilepsy is the world's leading association of health professionals and scientists and has a newly established Women and Pregnancy Task Force, to which Bromley has been admitted as a member.

2. Impact on the health care of individuals affected by exposure to valproate

In 2018 an international multidisciplinary consensus document (Diagnosis and management of individuals with Fetal Valproate Spectrum Disorder; a consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability [H]) regarding the diagnosis and care pathway for individuals with Fetal Valproate Spectrum Disorder was led by Clayton-Smith. Within a year this document brought about improvements for people affected, with many families downloading this freely accessible document and sharing it with their doctors. To date the guidelines have been accessed 6,184 times according to the hosting website. Further, Clayton-Smith and Bromley used the guidelines to establish the first multidisciplinary pathway for individuals with Fetal Valproate Spectrum Disorder at Manchester University Hospital NHS Foundation Trust.

2.1. Contribution to the Government commissioned First Do No Harm Review

In July 2020 the First Do No Harm Review, led by Baroness Cumberledge, was published. It highlighted multiple levels of failure which allowed the prescribing of valproate to continue without adequate warnings regarding its impact on fetal development. The research work, oral and written testimonies of the UoM researchers, was directly referenced on eight occasions in the review's publication. On page 13, Bromley's direct response regarding the delays in detecting the neurodevelopmental effects of valproate is referred to in full [I].

It was lobbying by patient groups which brought about the First Do No Harm Review and they write: *"Throughout our Parliamentary Campaign for those affected by Valproate, the lobbying process has required proof that exposure in the womb to valproate causes significant harms, and this could not have been achieved without the work of Professor Clayton-Smith and Dr Bromley".* Member of INFACT (Independent Fetal Anti-Convulsant Trust) patient group in the UK [J].

3. Increased public knowledge regarding the risks of valproate

Over the last seven years there have been a number of opportunities for Bromley and Clayton-Smith to increase public knowledge surrounding the risks of valproate in pregnancy. These have included appearances on BBC Breakfast's 'red sofa' to discuss the EMA's contraindication of valproate in pregnancy and a specific BBC Inside Out programme focused on valproate in pregnancy. The research team worked with the BBC researchers to develop the Inside Out documentary and Bromley featured on the programme. The average viewing figures for each of these programmes are 7,000,000 and 3,000,000 respectively. Following the airing of these programmes both the research team and patient support groups experienced numerous enquires from families who suspected that they may have an affected child.

5. Sources to corroborate the impact

A. Clinical Practice Research Datalink study monitoring the use of valproate in girls and women in the UK: January 2010 to June 2019. MHRA, 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/844070/CPRD_valproate_usage_report-3rd-revision-Nov-19.pdf. This document demonstrates the reduction in valproate prescribing since 2010.

B. MHRA's Guidance for Healthcare Professionals - Information on the risks of valproate. A risk minimisation measure, part of the valproate pregnancy prevention programme. November 2019 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/860761/Booklet-for-healthcare-professionals.pdf. This document outlines the risk posed to the fetus by valproate and makes direct reference to the work from Manchester-based researchers.

C. New measures to avoid valproate exposure in pregnancy endorsed. EMA, May 2018. https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-new-measures-avoid-valproate-exposure-pregnancy-endorsed_en-0.pdf. This document highlights the restrictions now placed on valproate due to the harm it poses to the developing fetus.

D. Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) review valproate and related substances. EMA, 2014. https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances . This document summaries the EMA's decision to strengthen its warnings regarding valproate and references UoM's work directly.

E. Letter from the Executive Officer of FACS NZ (dated 27 January 2020) which highlights the impact of Manchester researchers on the area and on the literature provided by the New Zealand Health Authority.

F. Letter from the Head of Regions, Sanofi Pharmacovigilance (dated 17 February 2020) which outlines how Sanofi as the Market Authorisation Holder for valproate in Europe utilised the research from Manchester.

G. National and international guidance papers which have used UoM research to inform neurology and obstetric practice.

   i. Royal College of Obstetricians and Gynaecologists Epilepsy in Pregnancy Green-top Guideline No. 68 June 2018.

   ii. International League against Epilepsy Task Force on Women and Pregnancy report on the management of epilepsy in pregnancy 2019.

H. Consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability regarding diagnosis and care pathway for individuals with Fetal Valproate Spectrum Disorder. Clayton-Smith et al. *Orphanet Journal of Rare Diseases* (2019) 14:180. Statement led to improvements for individuals affected by exposure to valproate.

I. First Do No Harm. The Independent Medicine and Medical Devices Safety Review: https://www.immdsreview.org.uk/Report.html which references the oral and written testimony of Bromley and Clayton-Smith.

J. Letter from INFACT, UK (dated 09 January 2020) which highlights how the Manchester based work has assisted them in their political lobbying activities as they sought increased restrictions and a government review.