Institution: University of Ulster

Unit of Assessment: 3A Allied Health Professions, Dentistry, Nursing and Pharmacy – Nursing and Health Science

Title of case study: Antiepileptic Drug (AED) Safety in Pregnancy - epidemiological surveillance of congenital anomalies (birth defects)

1. Summary of the impact

(1) Enhancing the awareness of (i) women of childbearing age suffering from epilepsy and prescribed new and/or older generation AEDs, and (ii) their healthcare professionals. Empowering both to make informed decisions through evidence-based practice that will reduce/prevent the risk of harm to unborn children potentially exposed to AEDs in early pregnancy.
(2) A change in the process by which GlaxoSmithKline (GSK) practices post-marketing epidemiological surveillance of the new generation AED 'lamotrigine' in pregnancy.
(3) Benefit to the methodological practice of other researchers in Europe involved with AEDs and epidemiological surveillance
(4) Contribution to building European system for reproductive safety evaluation

2. Underpinning research

The EU-funded European Surveillance of Congenital Anomalies network (EUROCAT), is coordinated and led by *Professor Dolk* since 2000. Surveillance to ensure early detection of new teratogens (i.e. birth defect causing exposures) originated following the thalidomide tragedy when thousands of children were born with limb defects due to a medication used in early pregnancy. EUROCAT population-based registries (42 in 23 European countries covering 1.7M births annually) annually transmit a dataset to a central database (Centre for Maternal, Fetal and Infant Research, Institute of Nursing and Health Research, University of Ulster) where quality validation, and epidemiologic surveillance and research are conducted relating to causes and prevention. This case study concentrates on AED safety in pregnancy. *Maria Loane* leads EUROCAT Central Database Management and Surveillance since 2002. *Professor Lolkje de Jong van den Berg*, led until recently the Medication Safety in Pregnancy Working Group, and collaborates closely on related research.

For newly licensed medications, safety information is limited to pre-marketing animal studies (with limited ability to predict harm in human pregnancy), since pregnant women are excluded from clinical trials. Post-marketing surveillance (pharmacovigilance) is essential for early detection of safety concerns, particularly difficult for birth defects due to the rarity of cases. Very large study populations are needed to provide sufficient statistical power. This research is relevant to regulatory decisions regarding medication safety and product safety information, and to clinical decision making regarding risk and benefit of treatment options.

The research output relates to case-control studies performed 2007-2009 using EUROCAT data to address hypotheses (or evaluate signals) from the literature regarding teratogenicity of AEDs (new -lamotrigine[1] and old - valproic acid[2]/carbamazepine[3])). An AED database was created for this referring to 3.9M births (19 registries, 1995-2005) including 98,075 livebirths, stillbirths or terminations with birth defects.
(i) The lamotrigine study[1] responded to a signal indicating an over 10-fold raised risk of orofacial clefts associated with lamotrigine, from the North American AED cohort. The study did not support the original signal, nor have subsequent updates[4].
(ii) Valproic acid was known to be teratogenic, but which birth defects were specifically associated was unknown as reports include chance associations. 7 of 14 birth defects suggested in the literature were confirmed as significantly associated with valproic acid exposure, with up to 13-fold risk. This is the first study to specifically identify types of birth defect caused, with implications beyond clinical practice to elucidating teratogenic mechanisms of action[2].
(iii) The carbamazepine study proceeded as for valproic acid, and in contrast confirmed only one significantly associated birth defect - spina bifida, with a much less raised risk than for valproic acid[3].

EUROCAT Guide 1.3: Instructions for the Registration of congenital anomalies[5], a methodological guide developed by a process of consultation and consensus for EUROCAT research and surveillance, includes standardised congenital anomaly inclusion/exclusion criteria and

classification and coding, used in the AED studies and all other EUROCAT studies, and available to other researchers in this field. This Guide also introduced the International Anatomic Therapeutic Classification coding of medication exposure for EUROCAT data, which, after a period of training and data source validation, has enabled the subsequent AED research.

Details of the Research Team

Professor Dolk (Professor of Epidemiology and Health Services Research) since 2000.
Maria Loane, Public Health Lecturer since 2002.
Visiting Professor of Pharmacoepidemiology, Lolkje de Jong van den Berg since 2010.

3. References to the research *Impact factors (IFs), citation reports, related funding, and google analytics have been included as quality indicators of the underpinning research.*

1. Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LTW and on behalf of the EUROCAT AED Working Group (2008), Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? *Neurology,*71, 714-722
Output: listed in REF2, IF: 8.312, Citations: 52 non-self citations in Scopus.
2. Jentink J, Loane M, Dolk H, Barisic I, Garne E, Morris J, de Jong-van den Berg L for the EUROCAT Antepileptic Study Working Group (2010), Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations, *The New England Journal of Medicine*, 362, 2185-2193
URL: http://www.nejm.org/doi/pdf/10.1056/NEJMoa0907328, IF: 53.298, Citations: 54 non-self citations in Scopus
3. Jentink J, Dolk H, Loane M, Morris JK, Wellesley D, Garne E, de Jong-van den Berg L for the EUROCAT Antiepileptic Study Working Group (2010), Intrauterine Exposure to Carbamazepine and Specific Congenital Malformations: Systematic Review and Case-Control Study, *British Medical Journal*, 341, c6581
URL: http://www.bmj.com/content/341/bmj.c6581.pdf%2Bhtml, IF: 14.093, Citations: 19 non-self citations in Scopus
4. Wang H, Garne E, Loane M, Dolk H, Morris JK, de Jong-van den Berg L (2012), Lamotrigine Use in Pregnancy and Risk of Orofacial Cleft, an Update. Poster presentation at The International Society of Pharmacoepidemiology's 28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 2012, Barcelona, Spain URL: http://onlinelibrary.wiley.com/doi/10.1002/pds.3324/pdf abstract 691 (page 321)
5. EUROCAT (2005). EUROCAT Guide 1.3. Instructions for the registration and surveillance of congenital anomalies [Online], available at: http://www.eurocat-network.eu/ABOUTUS/DataCollection/GuidelinesforRegistration/Guide1_3InstructionManual

Googleopen search: 103 results

Grant awarded to: Prof Helen Dolk, University of Ulster
Title: A case control study of isolated orofacial clefts and in utero exposure to lamotrigine
Sponsor: GSK Research and Development Ltd **Period:** Jan 2007–June 2007 **Value:** £252,745.00

Grant awarded to: Prof Helen Dolk, co-ordinating centre University of Ulster
Title: EUROCAT **Sponsor:** The EU Public Health Programme of the European Commission
Period: September 2007 to August 2010 **Value:** €1,469,480

GSK asked for continuation of the studies through updates – indicator of quality.
Grant awarded to: Prof Helen Dolk, University of Ulster
Title: A case control study of isolated orofacial clefts and in utero exposure to lamotrigine
Sponsor: GSK Research and Development Ltd **Period:** April 2009 to Dec 2013 **Value:** £451,250

This grant was awarded on the strength of our surveillance activities, including pharmacovigilance.
Grant awarded to: Prof Helen Dolk, co-ordinating centre University of Ulster
Title: EUROCAT Joint Action **Sponsor:** The European Commission's Public Health Programme
Period: Jan 2011 to Dec 2013 **Value:** €3,313,001 received by the co-ordinating centre and then distributed to be managed locally by associate partners (University of Ulster component €538,238).

Awarded on the strength of the AED pilot studies made possible through the above grants.
Who the grant was awarded to: Prof Helen Dolk, co-ordinating centre University of Ulster
Title: EUROmediCAT: Safety of Medication use in Pregnancy in Relation to Risk of Congenital Malformations **Sponsor:** European Union's 7th Framework Programme
Period: 1st March 2011 to 28th February 2015 **Value:** €2,996,100.00

4. Details of the impact

The WHO recognises "The Importance of Pharmacovigilance – Safety Monitoring of Medicinal

Products" for impacting drug regulation, clinical practice and international health (http://apps.who.int/medicinedocs/en/d/Js4893e/). Pharmacovigilance imparts an impact by empowerment and reassurance through knowledge. Negative results (results not supporting a signal regarding medication risk) are as important as positive results, but the impacts are less demonstrable, and do not attract media attention. In 2006, the European Medicines Agency adopted a guideline on "The exposure to medicinal products during pregnancy: Need for post-authorisation data". Within, EUROCAT is listed as a source of information for human pregnancy data collected post-authorisation (pg 9) (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf). Our research does not and should not stand alone. It is a component of the wider global pharmacovigilance agenda.

Evidence of impact described as:

1. Enhancing awareness of women of childbearing age suffering from epilepsy and prescribed AEDs, and their Healthcare Professionels (HCPs), empowering both to make informed decisions through evidence-based practice that will reduce/prevent the risk of teratogenic harm to unborn children potentially exposed to AEDs.

The valproic acid study[2] based on birth defect information of nearly 4M births had visibility in a high impact medical journal (NEJM) and in media (Source 1). The reemphasis and further clarification and quantification of the known teratogenicity, was an important part of changing awareness and practice. The lamotrigine study[1] which was largely negative was also important in helping women/HCPs make optimal medication choices based on updated patient information (Source 2).

Our research has been included in systematic reviews which inform evidence-based practice (Source 3) for women with epilepsy, but also with bipolar disorder, now a more common indication for use of some AEDs.

Contribution to Medscape, Motherisk and Patient.co.uk – authoritative, trusted, accessible online information for pregnant women/HCPs regarding the safety/risk to the developing foetus associated with maternal exposure to drugs. Rigorous literature reviewing allows rapid integration of new practice-changing evidence, such as our research on carbamazepine and lamotrigine (Source 4).

2. A change in the process by which GSK practices post-marketing pharmacovigilance in relation to lamotrigine

In 2006, based on a signal from emerging data of the North American AED Pregnancy Registry, GSK alerted HCPs to a possible association of lamotrigine exposure with orofacial clefts. A US Federal Drugs Agency (FDA) warning followed (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126225.htm). GSK, FDA, UK Medicines and Health Regulatory Agency (MHRA) and European regulators (EMA) revised patient information, and agreed new research was needed to independently confirm this finding. GSK approached Prof. Dolk (2006) to establish the possibility of funding feasibility research by EUROCAT (Source 5). EUROCAT offered more appropriate and powerful observational research methods (Source 2, 6 and 7), than heretofore possible using the GSK run International Lamotrigine Pregnancy Registry (1992-2010)**.** The results of the EUROCAT research that ensued were disseminated by confidential report to GSK (Source 8) and scientific paper[1]. GSK shared the results with regulators who endorsed a revision to the core safety information provided in the Pregnancy and Lactation section of GSKs Global Data Sheet for lamotrigine, by insertion of - "*A case control study did not demonstrate an increased risk of oral clefts compared to other defects following exposure to lamotrigine*" (Source 2). Based on our data, the regulators expressed an interest in monitoring a potential signal for club foot and lamotrigine (Source 2), a study now underway (http://www.eurocat-network.eu/content/Poster-Lamotrigine-Mejnartowicz.pdf) within the GSK-funded research. Following closure of GSK's Registry, Prof. Harden, Director of Comprehensive Epilepsy Care Center, published a commentary explaining its replacement by further use of EUROCAT data (Source 9).

3. Benefit to the practice of other researchers in Europe.

EUROCAT guidelines[5] are utilised as the gold standard methodology by others when conducting research into birth defects and AEDs and are helping overcome non-comparability between studies (Source 10). Another important impact is strengthening the system of signal generation and signal evaluation in AED pharmacovigilance among research groups worldwide, such that signals generated by one research study are evaluated by one or more others, as our methodology clearly adheres to and has promoted this approach. An indirect impact of this research is that, in order to ensure scientific independence and transparency in industry-sponsored research, Prof Dolk chaired, for four years to 2012, the European Medicines Agency Working Group which developed a Code of Conduct for Scientific Independence and Transparency (http://www.encepp.eu/documents/encepp_studies/ENCePP%20Code%20of%20Conduct_20100507.pdf).

4. Sustainable Impact

These studies were the first to use EUROCAT data for investigation of specific drugs. Since then we have had many queries from pharmaceutical companies/researchers requesting data/information on other medications**.** A PhD student at the University has analysed the EUROCAT data in relation to antidepressant safety; an ongoing GSK funded study continues to study lamotrigine [4]. EUROmediCAT is looking further at newer generation AEDs, insulin analogs, antidepressants and antiasthmatic drugs, is testing new methodologies and has a wider aim of building a European system for reproductive safety evaluation.

5. Sources to corroborate the impact (listed in REF2, includes screen images for convenience)

Source 1a) – Text of the Valproic Acid Press Release. Available at http://www.eurocat-network.eu/content/Press-2010-Valproic.pdf

b) Details of 19 media articles

Source 2 – A statement from GSK (contact details listed in REF3b).

Source 3 A list of systematic reviews (of relevance to AEDs/epilepsy/bipolar disorder) in peer-reviewed journals that the listed research outputs have been included in.

Source 4 a) Articles on Medscape/Patient.co.uk that included the carbamazepine paper: Neurological Disease & Pregnancy, Seizure Disorders in Pregnancy, Neural Tube Defects, Spina Bifida **b)** Motherisk.org Is carbamazepine safe to take during pregnancy? Perinatal exposure to maternal lamotrigine – Clinical considerations for the mother and child

Source 5 – Copy of an Email

From: (Manager of Epidemiology at GlaxoSmithKline in 2006) Sent: 15 May 2006 10:08 To: Prof. Helen Dolk Cc: Prof. Lolkje de Jong van den Berg Subject: Use of EUROCAT for monitoring lamotrigine and specific defects

Source 6 - GlaxoSmithKline International (2010). The Lamotrigine Pregnancy Registry: Final Report - 1 September 1992 through 31 March 2010 (see pgs 4, 36, 37, 43 and 45). Available at: http://pregnancyregistry.gsk.com/documents/lam_spring_2010_final_report.pdf

Source 7 – Cunnington MC et al. (2011). Final results from 18 years of the International Lamotrigine Pregnancy Registry, Neurology, 76, 1817-1823 (see pg 1821)

DOI: 10.1212/WNL.0b013e31821ccd18.

Source 8 – EUROCAT 4th Report for GSK (CONFIDENTIAL)

Source 9 - Harden CL (2011). Complete the Following Statement: *Industry-Sponsored Antiepileptic Drug Pregnancy Registries Provide Information that is Beneficial to:* Patients, Doctors, The Sponsor, All of the Above, None of the Above, Cannot Respond Due to Risk of COI. Epilepsy Currents, 11,181–183. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3220421/pdf/i1535-7511-11-6-181.pdf

Source 10 – Publications citing EUROCAT Guide 1.3 in their methodology sections as basis for defining and classifying major birth defects **a)** Molgaard-Nielsen D and Hviid A (2011). Newer-generation AEDs and the risk of major birth defects. JAMA, 305, 1996-2002; **b)** Morrow J et al. (2006). Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register, J Neurol Neurosurg Psychiatry, 77, 193–198.

c) list of other known publications recovered from Google search.