Institution:
UNIVERSITY OF LIVERPOOL

Unit of Assessment:
UOA2 - Public Health, Health Services and Primary Care

Title of case study:
Treatment Outcomes in Epilepsy

1. Summary of the impact

The epilepsy research group at the University of Liverpool (UoL) has undertaken a programme of work assessing treatment outcomes associated with antiepileptic drug treatment in patients with epilepsy. This includes two large pragmatic trials in patients with first seizures and newly diagnosed epilepsy, and cohort studies assessing malformations and cognitive development in children exposed to antiepileptic drugs in utero, and the work of the Cochrane Epilepsy Group. This work has influenced prescribing in the UK and worldwide through the following impacts:

- Triggered NICE guidelines update (2012), underpinning guidance on management of first seizures, new epilepsy, women with epilepsy
- Changes to drug labelling (SPC) for sodium valproate (2011)
- Informed guidance in other countries (e.g. German guidelines, International League Against Epilepsy Guidelines; US Medicine guidelines)
- Underpinned UK and EU policy on driving following first seizures and antiepileptic drug withdrawal

2. Underpinning research

The underpinning research was undertaken at the UoL between 1993 and 2013 and informs treatment decisions, guidelines and policy for people with epilepsy through randomized controlled trials, cohort studies, systematic review, prognostic modelling and statistical method development. It addresses the key clinical questions: when to start treatment and which is the appropriate treatment. These questions require assessment of both benefit and harm.

Key researchers from the UoL are Profs A Marson, G Baker, P Williamson, A Jacoby, D Chadwick (retired) and Dr C Tudur-Smith. The MRC Multicentre Study of Early Epilepsy and Single Seizures (MESS 1993-2000) recruited 1,400 patients and compared the policies of immediate and deferred treatment for patients presenting with single seizures and early epilepsy. This trial provides the best evidence worldwide to inform decisions about when to start treatment. Results showed that early treatment reduced the risk of a recurrence but had no effect on longer term seizure outcome or quality of life; and ends the long-standing debate that 'seizures beget seizures' in early epilepsy. Predictive modelling of data identified patients at low, medium and high risk of recurrence, informing risk prediction and thus clinical decisions. Data have also been modelled to underpin driving policy in the UK and EU following a process to harmonise legislation across the EU. Models identified time points at which it is appropriate to allow patients to return to driving and identified patients at higher risk.

The NIHR Health Technology Assessment Programme funded study of Standard and New Antiepileptic Drugs (SANAD 1998-2006) compared clinical, quality of life and cost effectiveness outcomes for standard and new antiepileptic drugs for patients with newly diagnosed epilepsy. This trial provides the best evidence worldwide to inform decisions about which is the drug of choice for particular patients. This trial identified lamotrigine, a new drug, as a first line treatment for newly diagnosed focal epilepsy, being as effective as the standard treatment, carbamazepine, but better tolerated, and cost effective. For generalised epilepsy patients, valproate, the standard treatment, was identified as the most effective treatment. This poses a significant challenge for the management of a particular patient subgroup, women of child bearing potential, for whom there is growing evidence that valproate is associated with a higher teratogenic risk.

This challenge is being addressed through the Liverpool group's collaboration with colleagues in Manchester and the US in a series of cohort studies assessing outcomes in children exposed to antiepileptic drugs in utero. In their large prospective study the Liverpool Manchester Neurodevelopment Group found a significant impact of sodium valproate exposure on cognitive development, particularly verbal IQ, in children assessed up to the age of 2 years. The NEAD study group (a UK/US NIH funded collaboration) found that in utero exposure to sodium valproate

had a significant and negative impact on the IQ of children when assessed at age 3 and 6 years in comparison to children exposed to other antiepileptic drugs (carbamazepine, lamotrigine, and phenytoin). Further, the UoL UK study demonstrated significant risks associated with in utero exposure to Sodium Valproate in comparison with control children across key areas of neuropsychological functioning, as well as an association with autism.

The Cochrane Epilepsy Group has its editorial base in Liverpool (NIHR funded, Marson Coordinating Editor, Tudur Smith Statistical Editor) has produced over 60 systematic reviews, focussing on drug treatments and other interventions for epilepsy. These reviews also underpin guidance provided by NICE in their 2012 epilepsy guidelines.

3. References to the research

1. **Marson A**, **Jacoby A**, Johnson A, Kim L, **Gamble C**, and **Chadwick D**. Medical Research Council MESS Study Group. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet 2005. 365(9476):2007-13 Citations: 155 Impact Factor: 39.060

2. **Marson AG**, Al-Kharusi AM, Alwaidh M, Appleton R, **Baker GA**, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet 2007;369:1000-1015. Citations: 266 Impact Factor: 39.060

3. **Marson AG**, Al-Kharusi AM, Alwaidh M, Appleton R, **Baker GA**, et al. Valproate, lamotrigine or topiramate for generalized and unclassifiable epilepsy: results from the SANAD trial. Lancet 2007;369:1016-1026. Citations: 285 Impact Factor: 39.060

4. **Bonnet LJ**, **Tudur Smith C**, **Williamson PR**, **Marson AG**. Risk of recurrence after a first seizure and implications for driving. Further analysis of the MESS study. BMJ 2010;341:c6477 Citations: 10 Impact Factor: 17.215

5. Meador K, **Baker GA**, et al. 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 Citations: 258 Impact Factor: 51.658

6. Meador KJ, **Baker GA**, et al on behalf of the NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244-52. Citations: 13 Impact Factor: 23.917

Key Research Grants

1993-2002. **MRC**. Title, £1.3m, PIs **Chadwick** , **Jacoby**, Johnson

1998-2006. **NIHR Health Technology Assessment Programme**. Title, £1.3m, PIs **Chadwick**, **Jacoby**, Donaldson

2007-2013. **NIHR Programme Grant**. Title, £515k, PIs **Marson AG**, **Jacoby A**, **Baker GA**, **Williamson PR**, **Tudur Smith C**

2003 to 2013. **US NIH Grant**. Neurodevelopmental study of children exposed in utero £708,187. PI **Baker GA**

2009 to 2012 **Epilepsy Research Foundation** Cognitive consequences of in utero exposure to second generation antiepileptic drugs £100,000.00 PI **Baker GA**

2009 to2013. **Sanofi Sythelabo Educational Grant**. Support for the NEADS study: Antiepileptic Drugs exposure in utero £166,501.00 PI **Baker GA**

2011-2016. **NIHR.** Core support for the Cochrane Epilepsy Group. £500k. **A Marson**.

4. Details of the impact

The SANAD Trial identified lamotrigine as first line treatment for patients with focal epilepsy. This drug was demonstrated to be clinically and cost effective to the NHS. SANAD also identified valproate as the most effective treatment for patients with generalised epilepsy. A network meta-analysis of similar antiepileptic drug trials provides the best overview of currently available evidence. Prognostic modelling of these data allow the identification of patients at differing risk of seizure remission, allowing stratification for outcomes in patient consultations.

This work had the following impacts:

- SANAD triggered an update of the NICE epilepsy guideline which was published in 2012 [7]. This provides impact on the health and wellbeing of over 32,000 people per year who are newly diagnosed with epilepsy as well as over half of the 600,000 prevalent population that are treated with antiepileptic drug monotherapy.
- Data from SANAD and the network meta-analysis underpins the 2012 guidance provided by NICE. Lamotrigine is recommended as a first line treatment for focal epilepsy while gabapentin and topiramate are not. Valproate is recommended as a first line treatment for generalised epilepsy while topiramate is not. Identifying topiramate and gabapentin as poor choices for monotherapy has resulted in significant savings for the NHS.
- SANAD underpins guidance in other countries (e.g. German epilepsy guidelines [8], International League Against Epilepsy (ILAE guidelines) [9].
- SANAD allows better understanding of the impacts of taking antiepileptic drugs, including: that there are few important differences between drugs in quality of life outcomes; and that cognitive impairment associated with epilepsy is more likely related to underlying pathology than the drugs. This understanding will be important in devising future intervention programmes.

The MESS trial compared antiepileptic drug treatment versus no treatment following a first seizure and for early epilepsy and identified a subgroup of patients likely to benefit from treatment. Further prognostic modelling identifies patients at risk of recurrence to inform driving policy.

This work had the following impacts:

- MESS data underpin NICE guidance (2012) for patients with first seizures [7]. The guidance highlights the prognostic modelling to inform risk stratification and decision making. This informs the management, impacting on the health and wellbeing, of over 60,000 people who experience a first unprovoked seizure per annum in the UK.

- Prognostic modelling of data from MESS informed UK and EU driving policy (2012) [9,10]. Regulations changed for patients with a first seizure who are allowed to drive once 6 months seizure free rather than 12 months, unless in a high risk group. Designation of 'high risk' was informed by prognostic modelling of MESS.

The aforementioned cohort studies assessing outcomes associated with in utero exposure to antiepileptic drugs treatment inform treatment decisions by providing reliable and valid information about the risks to the unborn children. These studies have quantified risk to cognitive development associated with a number of antiepileptic drugs and identify sodium valproate as the drug with the greatest risk. Data allow better informed decision making and have informed guidelines, and regulators.

This work has had the following impacts:

- Altered prescribing practices in the UK and US: There has been a substantial reduction in the prescribing of valproate to women with epilepsy of child bearing age and a subsequent increase in alternative drugs including lamotrigine and levitaricatem [5,6,15].
- The recommendations of the Federal Drugs Administration [13] "*The U.S. Food and Drug Administration (FDA) is informing the public that children born to mothers who take the anti-*

seizure medication valproate sodium or related products (valproic acid and divalproex sodium) during pregnancy have an increased risk of lower cognitive test scores than children exposed to other anti-seizure medications during pregnancy. This conclusion is based on the results of epidemiologic studies that show that children born to mothers who took valproate sodium or related products throughout their pregnancy tend to score lower on cognitive tests (IQ and other tests) than children born to mothers who took other anti-seizure medications during pregnancy."

- Updating of patient information leaflet for the drug Epilim (sodium valproate), warning of the risks associated following feotal exposures [15].
- The publication of guidelines for preconceptual counselling for WWE both in the UK and US [12,13,14].

Beneficiaries of this work include

- People with new onset first seizures (60,000 per annum) and epilepsy (32,000 per annum). The work has identified treatment options with the best outcomes and has identified benefit harm trade-offs, leading to better informed treatment choices and a focus on outcomes of importance and relevance to them.
- The NHS and other health systems caring for people with epilepsy, through providing effective and cost effective care. Topiramate and gabapentin were found to be both less effective and more costly and are rarely used a monotherapy in epilepsy.
- Guideline developers including NICE.
- DVLA and similar EU bodies currently harmonising regulations across EU member states.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

7. NICE Guidelines. The diagnosis and management of the epilepsies in adults and children in primary and secondary care. Clinical Guideline 137, NICE 2012. http://guidance.nice.org.uk/CG137

8. German guidelines. Elger CE, Beyenburg S, Dengg D et al. Erster epileptischer Anfall und Epilepsien im Erwachsenenalter. In: Diener HC, Putzki N (eds) Leitlinien für Diagnostik und Therapie im der Neurologie. Stuttgart: Georg Thieme Verlag, 2008.

9. ILAE Guidelines http://www.ilae.org/Visitors/Documents/Guidelines-epilepsia-12074-2013.pdf

10. DVLA decision to adopt EU recommendations for single seizures. DfT advisory panel minutes and at a glance guidance: http://webarchive.nationalarchives.gov.uk/20130411225420/http://dft.gov.uk/dvla/medical/medical_advisory_information/medicaladvisory_meetings/minutes/~/media/pdf/medical/mins_10032011%20Neuro.ashx

11. American Academy of Neurology and American Epilepsy Society guidelines Management Issues for Women with Epilepsy Neurology 2009

12. Royal Society of Medicine Primary Care Guidelines [Managing epilepsy in women: new guidelines 2004, 2011].

13. FDA alert June 2011, http://www.fda.gov/Drugs/DrugSafety/ucm261543.htm

14. Updating of patient information leaflet for the drug Epilim [Sodium Valproate], warning of the risks associated following feotal exposures. http://www.medicines.org.uk/emc/medicine/10913/PIL/Epilim+100mg+crushable+tablets/

15. Ackers R, Besag FM, Wade A, Murray ML, Wong IC Changing trends in antiepileptic drug prescribing in girls of child-bearing potential. Arch Dis Child. 2009 Jun;94(6):443-7.