Institution: Newcastle University

Unit of Assessment: UoA 4

Title of case study: Developing the first drug to treat the symptoms of Lewy body dementia and Parkinson's disease

1. Summary of the impact

Dementia is one of the greatest problems facing society today, both in financial terms and in terms of the quality of life of patients and caregivers. Newcastle research identified that cholinesterase inhibitors (CHEIs), originally licenced for use in Alzheimer's disease, would be of greater benefit in two other types of dementia; Lewy body dementia and Parkinson's disease. CHEIs are now recommended in national and international guidelines as a treatment for the cognitive and psychiatric symptoms associated with both of these conditions, which previously had no effective treatment. CHEIs are also licenced worldwide for use in Parkinson's dementia, and are used off-licence across the world as a first-line treatment for dementia with Lewy bodies.

2. Underpinning research

Key Newcastle researchers

- Professor Ian McKeith, Professor of Old Age Psychiatry (1994-2010, Strategic Research Advisor (2010-date)
- Professor Elaine Perry, Honorary Professor (1991-2009), Strategic Research Advisor (2009-2011, Emeritus Professor 2012-date)
- Professor Robert Perry, Clinical Reader/Consultant (1980-1999), Clinical Professor/Consultant (1999-2009), Emeritus Professor (2009-date).

Newcastle research into cholinesterase inhibitors

Cholinesterase inhibitors reduce the breakdown of the neurotransmitter acetylcholine, maintaining levels in the brain and therefore preserving communication between brain cells. CHEIs were first developed as a treatment for the symptoms of Alzheimer's disease (AD), including memory loss and anxiety, and were found to significantly improve cognition and activities of daily living (as measured using scales such as the Alzheimer's Disease Assessment Scale - Cognitive subscale).

In the early 1990s, Newcastle researchers identified that there was a greater deficiency of acetylcholine in post-mortem human brain tissue of patients with dementia with Lewy bodies (DLB) than in those with AD (R1). The Newcastle group therefore suggested that CHEIs might be especially effective in DLB. Prior to this, no effective treatments were available, since antipsychotic drugs (also known as neuroleptics) can cause severe, even fatal, adverse reactions in these patients (Rolinski *et al.* 2012 Cochrane review PMID: 22419314). The development of diagnostic criteria for DLB allowed the first therapeutic trials to be carried out, which led to the introduction of diagnostic criteria for DLB in 1996 (R2).

Following early feasibility studies in Newcastle (R3), McKeith led the first multi-centre trial, which demonstrated that CHEIs were indeed effective in DLB (R4). The results of this study showed that patients given the CHEI rivastigmine exhibited significantly fewer psychotic symptoms such as delusion and hallucination, and were significantly faster and better scoring at computerised cognitive tests than the placebo group. Following these results, CHEI treatment for DLB was taken up in clinical practice (see Section 4).

This work paved the way for similar treatment to be applied in Parkinson's disease dementia (PDD). The results of a preliminary trial by the same group of Newcastle investigators (R5) showed that patients given rivastigmine showed significant improvement over baseline scores in terms of hallucinations, sleep disturbance and cognitive scores, and that caregiver distress was also significantly reduced. A parallel study of the CHEI donepezil, in both DLB and PDD patients, confirmed these effects, and gave the first indication of clinical efficacy and acceptable side effects

in these two populations (R6). Based upon this evidence and using the methodology of the earlier Newcastle DLB study, the effects of rivastigmine in PDD were confirmed by a large multi-centre, placebo-controlled, randomised controlled trial (Emre *et al*. 2004, DOI: 10.1056/NEJMoa041470), which led to the licensing of CHEIs in PDD.

3. References to the research (Scopus citation data as at 31.7.13, Newcastle researchers in **bold**)

R1. **Perry EK**, Haroutunian V, Davis KL, Levy R, Lantos P, Eagger S, Honavar M, Dean A, Griffiths M, **McKeith IG** and **Perry RH** (1994) Neocortical cholinergic activities differentiate Lewy body dementia from classical Alzheimer's disease. *NeuroReport* 5, 747-749. DOI; 10.1097/00001756-199403000-00002. **Cited by 187.**

R2. **McKeith, IG**, Galasko, D, Kosaka, K, **Perry, EK**, Dickson, DW, Hansen, LA, Salmon, DP, Lowe, J, Mirra, SS, Byrne, EJ, Lennox, G, Quinn, NP, Edwardson, JA, Ince, PG, Bergeron, C, Burns, A, Miller, BL, Lovestone, S, Collerton, D, Jansen, ENH, Ballard, C, De Vos, RAI, Wilcock, GK, Jellinger, KA and **Perry, RH.** (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology* 47 (5): 1113-1124 DOI: 10.1212/WNL.47.5.1113. **2549 citations.**

R3. **McKeith, IG**; Grace, JB; Walker, Z; Byrne, EJ; Wilkinson, D; Stevens, T and **Perry, EK.** (2000) Rivastigmine in the treatment of dementia with Lewy bodies: Preliminary findings from an open trial. *International Journal of Geriatric Psychiatry.* 15: 5, 387-392. DOI: 10.1002/(SICI)1099-1166(200005)15:5<387::AID-GPS131>3.0.CO;2-9. **115 citations.**

R4. **McKeith IG**, Del Ser T, Spano PF, Emre M, Wesnes K, Anand R, Cicin-Sain A, Ferrara R and Spiegel R (2000). Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 356, 2031-2036. DOI: 10.1016/S0140-6736(00)03399-7. **719 citations.**

R5. Reading PJ, Luce AK and **McKeith IG** (2001). Rivastigmine in the treatment of parkinsonian psychosis and cognitive impairment: Preliminary findings from an open trial. *Movement Disorders* 16(6), 1171-1174. DOI: 10.1002/mds.1204. **180 citations.**

R6. Thomas AJ, Burn DJ, Rowan EN, Littlewood E, Newby J, Cousins D, Pakrasi S, Richardson J, Sanders J and **McKeith IG** (2005). A comparison of the efficacy of donepezil in Parkinson's disease with Dementia and Dementia with Lewy bodies. *International Journal of Geriatric Psychiatry* 20 (10): 938-944. DOI: 10.1002/gps.1381. **57 citations.**

Relevant funding awards

1994-1995 Mental Health Foundation North East £1,000. Which patients with Lewy body dementia are at risk of severe side effects from major tranquilisers.

1998-2001 Novartis Pharmaceuticals £239,972. Prospective, multicentre, randomised double blind placebo-controlled exploratory study to evaluate the safety tolerability.

1999-2004 Medical Research Council (MRC) £1,130,524. Dementia with Lewy bodies: Diagnosis and Treatment.

2001-2002 Pfizer Limited £50,000. A pilot study into the effects of donepezil on cognitive impairment and neuropsychiatric features in patients with dementia with Lewy bodies and Parkinson's disease.

2005-2009 MRC £955,675.00 BH041206 - Support for Newcastle Brain Tissue Bank.

4. Details of the impact

The challenge of dementia

Dementia is one of the largest issues facing society today, with 35.6 million people affected worldwide – a prevalence of nearly 5% in those aged over 65. The 2009 World Alzheimer's report (EV a) estimates that dementia has an annual global cost of $315 billion, and contributes nearly 1% of all Disability Adjusted Life Years (DALYs). However, since dementia is largely a disease of older people, in the over 60s it accounts for 4.1% of DALYs and 11.3% of Years Lived with Disability worldwide.

The most common type of dementia after Alzheimer's disease is dementia with Lewy bodies (DLB) which, together with the related disorder Parkinson's disease dementia (PDD), comprise 15–20% of all dementias in older people (EV b, c, d). DLB and PDD are characterised by persistent and disabling psychiatric symptoms, which cannot be managed using standard anti-psychotic (neuroleptic) treatments because of increased morbidity specific to DLB, such as deterioration of cognition and increased parkinsonism. European guidelines from 2012 state: "[patients with DLB] *show a propensity to have exaggerated adverse reactions to neuroleptic drugs, with a significantly increased morbidity and mortality."* (EV e). This specific sensitivity was originally recognised by Newcastle researchers (McKeith *et al.* 1992 *BMJ*, PMID: 1356550).

The impact of Newcastle research on guidelines

Newcastle work found that CHEIs significantly reduce psychiatric symptoms and improve cognition, without substantial risk of side effects. As a consequence, CHEIs are now widely recommended for use in both DLB and PDD. This is the first time treatment has been available to manage the symptoms of these conditions. NICE clinical guideline 42, updated in March 2011, (EV f, p 36) recommends that people with DLB should be offered a CHEI under certain conditions: "*People with DLB who have non-cognitive symptoms causing significant distress to the individual, or leading to behaviour that challenges, should be offered an acetylcholinesterase inhibitor*." The guidelines include R4 as the only trial to compare the CHEI rivastigime to placebo in DLB.

These guidelines also report that "*Overall, the results of the economic analysis indicate that acetylcholinesterase inhibitors are likely to be a cost-effective treatment option for people with DLB experiencing non-cognitive symptoms*" (EV f, pg 257), drawing on R4 as the sole source of effectiveness data.

The 2011 Consensus statement from the British Association of Psychopharmacology (EV b) gives a category A (strongest) recommendation of the use of CHEIs in both DLB and PDD: "*There is type I evidence* [strongest] *to support treatment with cholinesterase inhibitors in … both dementia with Lewy bodies and Parkinson's disease dementia and that both cognitive and neuropsychiatric symptoms improve*" (pg. 1004). Within these guidelines, R4 forms part of the evidence that "[randomised controlled trials] *of cholinesterase inhibitors have demonstrated benefit in cognitive and non-cognitive symptoms in DLB and PDD*" (pg. 1003). These guidelines also state that CHEIs improve patient quality of life, for example alleviating symptoms such as hallucinations, apathy, anxiety and sleep disorders (pg. 1003).

Recent guidelines from the European Federation of Neurological Societies (2012, EV e) also recognise the benefit of CHEIs in DLB patients, stating that "*patients with DLB respond to cholinesterase inhibitors with improvement in cognitive and psychiatric symptoms"* (pg. 1176). In terms of patient quality of life, these guidelines state that "*Cholinesterase inhibitors… also may decrease or prevent psychotic symptoms, particularly hallucinations… and DLB*" (pg. 1177). These guidelines draw on the 2012 Cochrane review by Rolinski *et al*., in which the only paper to support use of CHEIs in DLB is R4.

The impact of Newcastle research on drug prescribing in clinical practice

Newcastle work has revolutionised the drug management of patients with DLB and PDD, allowing the disabling symptoms to be managed for the first time. Using the results and methodology of Newcastle research into CHEI use in DLB, a later study (Emre *et al.*) showed that rivastigmine was

effective in PDD. This provided evidence for the Medicines and Healthcare products Regulatory Agency (MHRA) granting the first UK licence to use CHEIs in PDD in November 2009 (licence number PL 10622/0450, EV g). Since then, six further licences have been granted to companies worldwide, including the US and UK (EV g). Trials to support similar licensing for DLB remain ongoing, although practice guidelines (EV b, e, f) support the widespread off-licence use of CHEIs in DLB.

The Professor of Biological Psychiatry at the University of Southampton (EV h), states: "*As a university researcher in dementia I can state that cholinesterase inhibitors … are widely prescribed across the UK and the world for the condition of dementia with Lewy bodies… The evidence produced by Prof McKeith was sufficient for the prescribing of these drugs to gain a drug licence and was sufficiently compelling for inclusion in the 2011 British Association of Psychopharmacology treatment guidelines… It is common practice* [to prescribe] *these drugs which have resulted in much patient benefit for both the patient's cognition and other associated psychopathology.*"

The National Clinical Director for Dementia, NHS England (EV i), has stated: "*The recognition of Lewy bodies as a cause of dementia and its unique clinical characteristics have been made possible by the work and descriptions of the Newcastle group … the basic science and cutting edge translational research which highlighted the benefits of the cholinesterase drugs … has had a significant influence on clinical practice*."

Summary
Newcastle work showed that CHEIs were effective in patients with DLB and PDD, whose symptoms could not be managed using existing drugs. This allowed an extension of the use of CHEIs, demonstrated by their recommendation in national and European guidelines, and MHRA licensing since 2009. CHEIs are now widely used to treat the disabling symptoms of DLB and PDD, improving patient quality of life.

5. Sources to corroborate the impact

EV a. The 2009 World Alzheimer's report: http://www.alz.co.uk/research/files/WorldAlzheimerReport.pdf

EV b. O'Brien, J and Burns, A. (2011) Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. *Journal of Psychopharmacology.* 25(8) 997–1019.

EV c. Rahkonen *et al*. (2003). Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. *Journal of Neurology, Neurosurgery and Psychiatry*; 74:720–724

EV d. The Alzheimer's Society factsheet: rarer causes of dementia http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=135

EV e. Sorbi, S., *et al.* (2012). EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. *European Journal of Neurology*. 19: 1159-1179.

EV f. NICE Clinical Guideline 42, updated March 2011: http://www.nice.org.uk/nicemedia/live/10998/30320/30320.pdf

EV g. Licence numbers PL 35574/0018, PL 00037/0654-7, PL 35533/0014, PL 17277/0060-63 (also PL 17277/0120-0127), PL 24668/0117-20 and PL 18157/0240. Full information can be found by entering the licence numbers at www.mhra.gov.uk .

EV h. The Professor of Biological Psychiatry at the University of Southampton. Contact details available on request.

EV i. The Consultant Old Age Psychiatrist, Manchester Mental Health and Social Care Trust, also the National Clinical Director for Dementia, NHS England. Contact details available on request.