Institution: Lancaster University

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

Title of case study: Research on biological effects of Galantamine underpins key change in NICE guidelines for early-stage sufferers of Alzheimer's disease

1. Summary of the impact (122 words)

Galantamine (Reminyl®) is one of the drugs recommended by NICE for treatment of Alzheimer's disease (AD). Until recently, it was approved only for the moderate stage of AD. In 2011, NICE guidance was changed to recommend that this drug could also be prescribed for early-stage AD. This has had a major impact on the lives of AD sufferers. In published research arising from an Alzheimer's Society Project Grant, Prof. Allsop at Lancaster demonstrated that Galantamine inhibits Aβ aggregation and so should be prescribed as early as possible during the course of AD due to its potential disease-modifying properties. This research underpinned arguments made by the Alzheimer's Society who were one of the key players in pressing for the change in NICE recommendations.

2. Underpinning research (519 words)

Alzheimer's disease (AD) is characterised neuropathologically by the formation of senile plaques and neurofibrillary tangles in the brain. The senile plaques contain a central deposit composed of a 39-43 amino acid peptide called β-amyloid (or Aβ), which accumulates in the form of numerous 'amyloid' protein fibrils. The accumulation of Aβ in the brain is widely thought to be an important step in the early stages of AD, and inhibiting the aggregation of Aβ, or blocking its neurotoxic effects, are possible approaches to treatment. Importantly, this type of therapy would be directed at a possible underlying cause of neurodegeneration in AD, and so would be expected to halt or slow the progression of the disease.

Prof. Allsop has a long-standing (>30 years) interest in Aβ aggregation and the development of inhibitors of this process. Since moving to Lancaster in 1998, he has looked at a wide range of inhibitors of Aβ aggregation, including benzofurans, nicotine, retro-inverso peptides, curcumin and curcumin-nanoparticles (see 3.2, 3.3, 3.4, 3.5, supported by grants 3.6, 3.7, 3.8, 3.9, 3.10). For the research directly underpinning this impact case, he investigated Galantamine and two other acetylcholinesterase inhibitors, Rivastigmine and Donepezil, for their ability to inhibit the aggregation and toxicity of Aβ. Galantamine in particular showed clear concentration-dependent inhibition of aggregation of Aβ *in vitro*, as determined by a variety of different experimental methods (3.1). Two different cell toxicity assays (MTT and lactate dehydrogenase) also showed that Galantamine reduced the cytotoxicity induced by Aβ (3.1). Further, nuclear magnetic resonance (NMR) spectroscopy studies were used to identify the locations and structures of all 16 of the proton sites in Galantamine, and difference NMR spectroscopy data demonstrated a solution-state interaction between Galantamine and Aβ. This indicates a specific binding interaction between Galantamine and Aβ, which would explain the effects of this drug on Aβ aggregation and toxicity.

The data generated by the Allsop group suggested that Galantamine may not act purely as a symptomatic treatment for AD, but could also have disease-modifying effects due to the neuroprotection afforded against Aβ aggregation and toxicity (3.1). **One conclusion from this research was that the drug should be prescribed** as **early** as possible during the course of the disease, so that its progression would be influenced when symptoms are not too advanced.

This research was carried out during the period 2001-2009, with **funds provided by two consecutive Project Grants from The Alzheimer's Society** to (PI) Prof. Allsop (see 3.6, 3.7) and supported by other underpinning grants (3.8, 3.9, 3.10). Other researchers at Lancaster were Dr. Thomas Huckerby (Reader in Spectroscopy, Department of Biological Sciences) who provided expertise in NMR spectroscopy, Dr. Susan Moore (Biological Sciences) employed as a Research Associate, Dr. Leanne Cooper (Research Associate working with Dr. Nigel Fullwood, Senior Lecturer, Biological Sciences), who provided expertise in electron microscopy, and Robert Millichamp (Masters student, Department of Biological Sciences) who carried out some of the NMR experiments under the guidance of Dr. Huckerby. Externally, research into the effects of Galantamine on apoptosis induced by Aβ in cell models were carried out by Prof. Brian Austen (St. George's Hospital Medical School, London) and his co-workers.

3. References to the research

References:

3.1 Matharu B., Gibson G., Parsons R., Huckerby T.N., Moore S.A., Cooper L.J., Millichamp R., Allsop D. and Austen B. (2009) Galantamine inhibits β-amyloid aggregation and cytotoxicity. *J. Neurol. Sci.* **280,** 49-58. doi: 10.1016/j.jns.2009.01.024

3.2 Twyman L. and Allsop D. (1999) A short synthesis of the β-amyloid (Aβ) aggregation inhibitor 3 p toluoyl-2-[4'-(3-diethylaminopropoxy)-phenyl]-benzofuran. *Tet. Lett.* **40,** 9383-9384. doi: 10.1016/S0040-4039(99)02030-4

3.3 Moore S.A., Huckerby T.N., Gibson G.L., Fullwood N.J., Turnbull S., Tabner B.J., El-Agnaf O.M.A. & Allsop D. (2004) Both the D-(+) and L-(-) enantiomers of nicotine inhibit Aβ aggregation and cytotoxicity. *Biochemistry* **43,** 819-826. doi: 10.1021/bi035728h

3.4 Taylor M., Moore S., Mayes J., Parkin E., Beeg M., Canovi M., Gobbi M., Mann D.M.A. and Allsop D. (2010) Development of a proteolytically stable retro-inverso peptide inhibitor of β-amyloid oligomerization as a potential novel treatment for Alzheimer's disease. *Biochemistry* **49,** 3261–3272. doi: 10.1021/bi100144m

3.5 Taylor M., Moore S., Mourtas S., Niarakis A., Re F., Zona C., Ferla B., Nicotra F., Masserini M., Antimisiaris S.G., Gregori M. and Allsop D. (2011) Effect of curcumin-associated and lipid ligand functionalised nanoliposomes on aggregation of the Alzheimer's Aβ peptide. *Nanomed: Nanotech. Biol. Med.* **7,** 541–550. doi: 10.1016/j.nano.2011.06.015 Submitted in REF2

Grants:

3.6 Alzheimer's Disease Society Project Grant, 2001-2004, PI Allsop, with L. Swanson and I. Soutar (Chemistry, Lancaster), A novel method for the study of amyloid β-peptide aggregation and its link with Alzheimer's disease, £100,809.

3.7 Alzheimer's Disease Society Project Grant, 2006-2009, PI Allsop, with N. Fullwood, T. Huckerby and F. Martin (Biological Sciences, Lancaster), "Effects of galantamine (Reminyl) and other acetylcholinesterase inhibitors on β-amyloid aggregation and toxicity", £122,000.

3.8 Wellcome Trust Project Grant, 1998-2000, PI Allsop, "Effects of benzofurans on amyloid fibrillisation and toxicity", £124,357.

3.9 Wellcome Trust Project Grant, 2002-2005, PI Allsop, "The role of hydrogen peroxide and hydroxyl radicals in amyloid-induced cytotoxicity", £241,786.

3.10 EU Framework 7, Specific Targeted Research Project, 2008-2013, 19 partners, co-

investigator Prof. David Allsop, Nanoparticles for the diagnosis and therapy of Alzheimer's disease (NAD), €11,110,000 (Lancaster €314,000).

Evidence of the quality of the research

All publications (3.1 to 3.5) are in peer-reviewed scientific journals, and all grants (total £854,000) were awarded through open competition nationally (3.6 to 3.9) or at a European level (3.10) following rigorous review by experts in the field. Allsop was PI on grants 3.6, 3.7, 3.8 and 3.9. The work published in 3.1 is the first to show that Galantamine binds to Aβ, and inhibits Aβ aggregation and toxicity *in vitro,* and has subsequently been confirmed by others. References 3.1, 3.2, 3.3, 3.4 and 3.5 have received a total of 166 literature citations (as of 24 Sept 2013).

4. Details of the impact (744 words)

An estimated **62,000 people in the UK develop Alzheimer's disease (AD) each year, of which the majority (50-64%) are in the early stages of the disease**, and the latter **are now eligible to receive the drugs** Reminyl (Galantamine), Aricept (Donepezil) or Exelon (Rivastigmine), **according to the revised (March 2011) NICE guidelines.** A fourth drug (Ebixa) is available for people in the late stages of the disease and in the moderate stages if they cannot tolerate the anticholinesterase drugs. The earlier rulings by NICE (November 2006) indicated that the acetylcholinesterase inhibitor drugs did not offer sufficient benefit to patients with early-stage disease (i.e. those with a Mini Mental State Examination (MMSE) Score of 21-26) to justify their use in these patients (5.1). However, NICE eventually reversed this decision (5.2) after much pressure from various patient groups, carer groups and clinicians, but most notably from The Alzheimer's Society, who were particularly vociferous in their support for change (5.3, 5.4, 5.5).

Some of the arguments for this change centred around criticism of the economic model used by NICE to calculate whether the drugs offered value for money, because this model did not accurately reflect the hidden economic costs of care for dementia patients outside of hospital. However, the publication of further studies into the potential clinical benefits of these drugs to patients with "mild" AD in the five years leading up to the NICE reappraisal also contributed to the arguments for change. During this period, research-based evidence for disease-modifying effects of the acetylcholinesterase inhibitor drugs started to appear, suggesting that they may not be purely symptomatic treatments, and that early intervention should be recommended to gain the most benefit to patients from these drugs.

The research of Allsop and collaborators into the disease-modifying effects of Galantamine was directly funded by The Alzheimer's Society (3.6, 3.7) and the results and potential significance of this research, in terms of the recommended early treatment for people with AD, were well known to the Society and were widely publicised through their printed literature and also *via* their website for a few years prior to their final publication in 2009 (5.6, 5.7, 5.8).

The following two quotations refer directly to the work of Prof. Allsop, and are taken from The Alzheimer's Society Newsletter 'The Journal of Quality Research in Dementia' (5.6):

"**There is an exciting piece of research from David Allsop's group in Lancaster**, looking at the potential therapeutic properties of existing acetylcholinesterase inhibitors. These drugs are used currently for treating symptoms of dementia, but there is lack of substantial evidence to show whether or not they may be of therapeutic value in treating disease progression. **The results of this current study will highlight important evidence in putting forward an argument in using these drugs in a therapeutic context.**"

"The current investigations into the potential therapeutic applications of the existing cholinesterase

inhibitor drugs could be groundbreaking if they are found to have disease-modifying effects on Alzheimer's disease progression. This would mean that **there would be a case for prescribing these drugs at earlier stages of disease and for longer**, rather than just to treat symptoms at the later stages as is the current state of affairs."

This impact case is supported by a letter (5.9) from the former Head of Research (2003-2011) of The Alzheimer's Society, and the following passage is taken directly from this letter:

"Alzheimer's Society fought a hard campaign during several years to have the recommended prescription window widened. As part of the campaign, the organisation sought to build the evidence base through commissioning critical reviews of existing clinical research literature and providing research grants to scientists seeking to better understand the underlying mechanisms of the active pharmaceuticals' biochemical and cellular activities.

The Amyloid β aggregation starts in the brain many years before symptoms of dementia appear in Alzheimer's disease and the search is still on for drugs that can prevent the aggregation early. **Prof Allsop's research demonstrating that Galantamine had an additional biochemical activity of inhibiting this aggregation was an important supporting argument at the time of the campaign.** It seemed to promise that the drug would likely be efficacious in the early stages of disease. Although not evidenced at the time, this result made it more likely that some of the other cholinesterase inhibitors might also have biochemical effects in addition to the inhibition of acetylcholine degradation….Together with the critical reviews of existing clinical research **it helped win the case for people with dementia** and their carers."

5. Sources to corroborate the impact (indicative maximum of 10 references)

Documentation on the new NICE guidelines for AD (March 2011)

5.1 http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11600

5.2 http://www.nice.org.uk/guidance/index.jsp?action=byID&o=13419

Alzheimer's Society Challenges to NICE recommendations

5.3 http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=461

5.4 http://www.publications.parliament.uk/pa/cm200607/cmselect/cmhealth/503/503we05.htm

5.5 http://www.alzheimers.org.uk/site/scripts/news_article.php?newsID=11

Documented Reference to Prof. Allsop's Research on Galantamine by The Alzheimer's Society

5.6 Alzheimer's Society Quality Research in Dementia, Issue 4, September 2007

5.7 Alzheimer's Society Quality Research in Dementia Annual Roundup, 2008-2009

5.8 Alzheimer's Society Quality Research in Dementia, Issue 95, February 2010

Letter of Support from The Alzheimer's Society

5.9 Former Head of Research in Alzheimer's Society