Institution: University of Oxford

Unit of Assessment: UOA5

Title of case study:

B vitamins can slow the disease process in early Alzheimer's disease

1. Summary of the impact

Research carried out by Professor David Smith of the University of Oxford established that B vitamins could slow the rate of Alzheimer-related brain atrophy and cognitive decline in people with mild cognitive impairment (MCI), an early stage of Alzheimer's disease which is common in the elderly. Since 2008 the impact on sales and marketing of B vitamins worldwide has been significant; **[text removed for publication]**, and over-the-counter and prescription B vitamin products marketed as helping to maintain memory function have achieved sales worth many millions of US dollars. Some doctors now prescribe B vitamins for the group of MCI patients identified by Smith as being most at risk.

2. Underpinning research

Dementia in all its forms affects 36 million people worldwide and is on the increase. Mild cognitive impairment (MCI) occurs in about one in six of those over 70 years old, affecting 5 million people in the USA and 14 million in Europe. About half of those with MCI will develop dementia within five years of being diagnosed, and there is an urgent need to identify ways of slowing cognitive decline in this population to delay or prevent the onset of dementias such as Alzheimer's disease (AD). The annual worldwide cost of AD has been estimated by Alzheimer's Disease International to be US $604 billion in 2010, about 1% of the world's GDP. The Health Economics Research Centre of the University of Oxford estimated the annual cost for the UK at £23 billion in 2008. Delaying dementia by five years would reduce these costs significantly, as well as halving the numbers of people dying from it, according to the UK charity the Alzheimer's Society.

In 1998 the Oxford Project to Investigate Memory and Ageing (OPTIMA), directed from Professor David Smith's base in the Department of Pharmacology at the University of Oxford, reported a case-control study of 164 patients over an eight-year period. The study showed that raised levels of plasma total homocysteine, low serum folate and low levels of vitamin B12, were strongly associated with pathologically-diagnosed AD[1]. A significant finding was that patients with elevated homocysteine levels at the first visit had more rapid atrophy of the medial temporal lobe (containing areas that are critical for new memory formation, including the hippocampus) during a 3-year follow up than those with lower homocysteine levels. The finding was subsequently confirmed worldwide by a meta-analysis which bore out the 'positive association between serum homocysteine and dementia' identified by Smith and colleagues[7]. The implication of this initial research – that treatment with vitamin B12 and folic acid could reduce homocysteine levels, and thus possibly slow or reverse the onset of dementia – was strong enough to lead Professor Smith to file a patent on behalf of the University for this method of treatment at the US Patent office in October 1997[2].

A second case-control study examining the influence of plasma homocysteine levels on global cognitive performance in 156 elderly community volunteers was reported on by Professor Smith and colleagues in 2000. The study confirmed that in normal elderly people the level of homocysteine was inversely related to cognitive function[3]. In 2008 it was shown in the same cohort that one of the main determinants of serum homocysteine, vitamin B12, was related inversely to the rate of atrophy of the whole brain in normal elderly people[4].

In 2005 Professor Smith and colleagues at OPTIMA began a two-year clinical trial in over 200 subjects (VITACOG) to test the hypothesis that lowering homocysteine levels by giving a mixture of B vitamins (folic acid, vitamins B12 and B6) would slow the accelerated rate of brain atrophy in people with mild cognitive impairment. The first results were reported in 2010; it was found that B vitamin treatment slowed the rate of atrophy of the whole brain by 30% on average. The treatment effect was greater the higher the baseline homocysteine, with a 53% slowing of atrophy in those

with the highest levels[5]. Although the trial was not powered for an effect on cognition, the second report from VITACOG showed that the B vitamin treatment slowed cognitive decline in four different domains and that it also improved the clinical status in two different tests. These cognitive and clinical effects were limited to those with high baseline homocysteine.

In 2011 OPTIMA began a much more sophisticated and in-depth analysis of the MRI scans of the brains of VITACOG participants to look for regional changes in grey matter. It was found that the B vitamin treatment slowed the rate of atrophy in exactly those brain regions that show marked atrophy in patients with AD. There was a seven-fold slowing of atrophy in these specific brain regions in participants who took B vitamins. The effect was dependent on the baseline homocysteine level. The study thus provided convincing evidence that high-dose B vitamin treatment could modify a key component of the disease process leading to AD: the atrophy of grey matter regions involved in the cognitive decline of the study participants[6]. The trial thus demonstrated for the first time that the disease process in AD is capable of being modified.

Due to the nature of this research, trials need to be very long term in order to demonstrate that B vitamins can not only slow cognitive decline, but delay or prevent the onset of AD. Hence there are plans for a new, longer and larger multicentre trial.

3. References to the research

1. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. (1998) Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol 55: 1449-1455. doi: 10.1001/archneur.55.11.1449 ***First report of raised homocysteine in confirmed Alzheimer's disease, and evidence that high homocysteine is associated with more rapid atrophy of the hippocampus; led to editorial in same issue on hyperhomocysteinemia as a new risk factor.***

2. Smith AD, Jobst KA. (1999) Method for treating Alzheimer's disease with folic acid. United States Patent 6008211. Granted December 1999. Available from: http://www.google.co.uk/patents/US6008221 ***Patent record describing the invention and its potential applications.***

3. Budge M, Johnston C, Hogervorst E, de Jager C, Milwain E, Iversen SD, Barnetson L, Budge M, King E, Smith AD. (2000) Plasma total homocysteine and cognitive performance in a volunteer elderly population. Ann New York Acad Sci 903: 407-410. doi: 10.1111/j.1749-6632.2000.tb06392.x ***First report of a relationship between homocysteine and global cognition in normal elderly people.***

4. Vogiatzoglou A, Refsum H, Johnston C, Smith SM, Bradley KM, de Jager C, Budge M, Smith AD. (2008) Vitamin B12 status and rate of brain volume loss in community-dwelling elderly. Neurology 71: 826-832. doi: 10.1212/01.wnl.0000325581.26991.f2 ***First report of association between low-normal B12 levels and increased rate of brain atrophy.***

5. Smith AD, Smith SM, de Jager CA, Whitbread P, Johnston C, Agacinski G, Oulhaj A, Bradley KM, Jacoby R, Refsum H. (2010) Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial. PLoS ONE 5: e12244. doi: 10.1371/journal.pone.0012244 ***First report from the VITACOG trial, demonstrating that B vitamin treatment slowed the rate of brain atrophy.***

6. Douaud G, Refsum H, de Jager CA, Jacoby R, Nichols T, Smith SM, Smith AD. (2013)Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci USA 110: 9523-9528. doi: 10.1073/pnas.1301816110 ***Third report from the VITACOG trial, showing that B vitamins markedly slowed the rate of atrophy in specific brain areas affected in AD in people with high homocysteine levels.***

Funding for research: Grants in excess of £3M since 1993 have been awarded from Bristol-

Myers Squibb, Alzheimer's Research Trust, Henry Smith Charity, Medical Research Council and Charles Wolfson Charitable Trust.

4. Details of the impact

No new drugs for memory loss conditions have appeared for at least the last decade, and many existing medications ease symptoms without slowing dementia. In this context, the results of Professor Smith's research are highly significant, since they confirm that a low-cost, easily available, treatment shows strong signs of being able to slow the onset of dementia in those with MCI. A recent meta-analysis estimates that the risk of developing dementia could be reduced by 20% by administering B vitamins in order to lower homocysteine levels[7]. Although people, including Smith himself, have stressed the need for longer-term studies to investigate these effects more deeply, many independent professionals have responded positively to the results of the VITACOG trial. It is clear that some doctors are already prescribing B vitamins to those with MCI and raised homocysteine. For example, since 2011, in line with the VITACOG findings, doctors in Sweden have been measuring homocysteine levels in people who report declining memory, and routinely prescribing folic acid and B vitamins to those with high homocysteine[8].

The major impact since 2008 has been on the sale of B vitamin products, both over-the-counter and on prescription, which make a claim to help improve or maintain memory function in those with MCI. Since Smith's 1999 patent covered this application of B vitamins, licence agreements based on the patent bring in substantial income to the University of Oxford. Interest from vitamin manufacturers began soon after the publication of Smith and colleagues' original findings and the publication of the US patent, and there are now a number of companies with licence agreements and royalty payments either in place or under negotiation. **[text removed for publication]**[11].

Since 2008 other companies have shown considerable interest. In 2011 the pharmaceutical company Recip (part of the Swedish company Meda) gained approval in Sweden for marketing a B vitamin product containing B12 and folic acid. The Swedish authorities allow the claim to be made that the product 'maintains memory function and mental performance', reflecting the positive view of medical professionals in Sweden reported above. The product is available over-the-counter in pharmacy shops throughout Sweden with the trade name TriBvit Plus. In July 2012 Recip/Meda introduced the tablet in the UK (called here TrioBe Plus) for sale online[12]. Also in 2012, Cobalz, a UK company, began to market a product (Betrinac) in the UK containing the same B vitamins, 'to maintain brain performance and memory as you get older'. **[text removed for publication]**, the product is targeted at elderly people with high homocysteine levels and thus clearly based on the Oxford research[13]. Isis Innovation (a wholly-owned subsidiary of the University of Oxford, which helps Oxford University researchers to commercialise intellectual property arising from their research) has filed a second international patent[14] **[text removed for publication]**.

Upon publication of the first paper from the VITACOG trial in September 2010, and again in May 2013 after publication of the third paper, there was extensive media coverage around the world of the findings[15]. This has promoted worldwide and ongoing discussion about the potential benefits of B vitamins in delaying or preventing dementias. It has also helped to raise the profile of MCI and encourage more attention to be given to the earlier stages of dementia. More recently, the Quality and Outcomes Framework (QOF), a voluntary annual reward and incentive programme for all GP surgeries in England, set a target for patients with a new diagnosis of dementia to have tests including serum vitamin B12 and folate levels (NICE recommendation 1.4.2.1) [16].

5. Sources to corroborate the impact

7. Wald DS, Kasturiratne A, Simmonds M. (2011) Serum homocysteine and dementia: Meta-analysis of eight cohort studies including 8669 participants. Alzheimer's Dementia 7: 412-417. doi: 10.1016/j.jalz.2010.08.234 ***Refers to 'an approximate 20% reduction in risk of dementia' from B vitamin treatment.***

8. Gerlin, A. Vitamins That Cost Pennies a Day Seen Delaying Dementia. Washington Post, May

2013. Available from: http://washpost.bloomberg.com/Story?docId=1376-MMJY6G6K50YP01-6AP7P4U53HS4OM5BR4MD5H1O5F ***Article from the Washington Post confirming that, in Sweden, B vitamins are routinely prescribed to those with high homocysteine levels.***

9. **[text removed for publication]**.

10. **[text removed for publication]**.

11. Income, royalty information and licence discussions can be confirmed by Isis Innovation.

12. Meda AB. TriBvitPlus: http://www.leveminnet.se/om-tribvit-plus/ ***Manufacturer's webpage (in Swedish) for TriBvitPlus*.** Meda Pharmaceuticals.TrioBe Plus:.http://www.triobeplus.co.uk/ ***Manufacturer's webpage for TrioBe Plus*.**

13. Cobalz Ltd. Betrinac: http://www.cobalz.co.uk/ ***Manufacturer's webpage for Betrinac, making explicit the link with high homocysteine levels.***

14. Smith AD, Refsum HM. (2010) Treatment of Cognitive Disorders. International Patent application PCT/GB2010/051557: http://www.google.com/patents/WO2012001336A1?cl=en ***Patent record describing the invention and its potential applications*.**

15. A detailed list of all the news reports from 2010-13 is held by the University's Press Office, who can be contacted at press.office@admin.ox.ac.uk. Two example reports are:
    - Hughes, J. Vitamin B 'puts off Alzheimer's', study suggests. BBC News. 2010 Sep 8. Available from: http://www.bbc.co.uk/news/health-11239437 ***Report on the VITACOG trial from the BBC's 10 O'Clock News, including an interview with a patient who confirmed the positive benefits of taking B vitamins as part of the trial.***
    - Burne, J. Should you be taking vitamin B to protect against Alzheimer's? Daily Mail, 20 May 2013. Available from: http://www.dailymail.co.uk/health/article-2327993/Should-taking-vitamin-B-protect-Alzheimers.html ***Report on phase 3 of the VITACOG trial from the Daily Mail.***

16. National Institute for Health and Care Excellence. Quality and Outcomes Framework Indicator NM09 QOF ID: DEM003. Aug. 2010. Available from: http://www.nice.org.uk/aboutnice/qof/indicators_detail.jsp?summary=13076 ***QOF indicator for patients with a new diagnosis of dementia.***