Institution: University of Exeter

Unit of Assessment: UoA2, Public Health, Health Services and Primary Care

Title of case study: Supporting national policy making – "Extending the availability of drugs to combat Alzheimer's disease"

1. Summary of the impact (indicative maximum 100 words)

About 800,000 people are living with Alzheimer's disease in the UK today, at a cost of about £23 Billion/annum. Researchers in Exeter produced a report in 2010 about the effectiveness and cost-effectiveness of available drugs, which formed the basis for revised NICE guidelines (2011), recommending more widespread drug usage. 2012 NHS data showed a big increase in drug prescribing since 2010. We estimate that if the 110,000 people with untreated mild disease at the time of the report are now being treated, there would be an average delay in time to admission to care of 13,000 person years.

2. Underpinning research (indicative maximum 500 words)

In 2010, as part of its contract to support NICE, the University of Exeter's Peninsula Technology Group (PenTAG), led by Professor Hyde (appointed 2009) produced a health technology assessment (HTA) about the treatment of Alzheimer's disease with anticholinesterase (AChE) inhibitors. This HTA considered new evidence on the effectiveness and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine in the treatment of Alzheimer's disease, superseding the 2004 HTA report that had informed the previous NICE guidance. Although not formally published in the HTA Monograph series until 2012 (Bond et al)[1], the report was completed in June 2010 and considered by the Appraisal Committee of NICE in August 2010, who then issued their new guidance in March 2011. The report by PenTAG included systematic reviews, meta-analyses and mixed treatment comparisons of RCTs (both the new evidence alone and cumulatively with previous evidence), systematic reviews of cost-effectiveness evaluations, critical appraisals of three manufacturer submissions and a new cost-effectiveness model, subsequently published in peer review journals (Hyde et al, Peters et al) [2,3]. The findings showed a consolidation of evidence on the effectiveness of donepezil, rivastigmine, galantamine and slightly enhanced evidence on the effectiveness of memantine. For instance a statistically significant beneficial effect on measures of patient function and global impact emerged when randomised controlled trials comparing memantine with best-supportive care were formally meta-analysed in our report. This was not apparent previously. The most marked change was on the evidence on cost-effectiveness, which was greatly improved for donepezil, rivastigmine and galantamine and slightly improved for memantine relative to the assessment in 2004. The PenTAG model demonstrated that each of the AChE inhibitors was cost saving compared with best supportive care, and that for memantine the incremental cost-effectiveness ratio was £32,100/QALY gained. As well as including cutting edge analytical methods the report also included novel methods of presenting large volumes of research data of a complex nature (Pitt et al)[4].

Each piece of NICE guidance in the technology appraisal programme is supported by an independent academic report. In the multiple technology appraisal process a health technology assessment (HTA), generally comprising systematic reviews, meta-analyses and health economic modelling, is prepared by an academic group. The Exeter based Peninsula Technology Assessment Group (PenTAG) has been performing this role for 12 years and has conducted over 30 HTAs, all published in peer reviewed journals. The work is funded by DH through the NIHR HTA Programme. This is currently in its fourth period of renewal, which will run until 2016. The work was led by Professor Ken Stein until 2009 and subsequently by Professor Chris Hyde. The PenTAG group working on the Alzheimer's drug appraisal, while led by Hyde, was multidisciplinary, including economists (Anderson and Hoyle) as well as experts in systematic reviews (Hyde, Bond, Peters and others), and used new methodological approaches developed within the group (Pitt et al 2009) [4].

Grant:
Stein K. Technology Appraisal Reports (TARs). Dept of Health. April 2005 to March 2011. £2,430,000

3. References to the research (indicative maximum of six references)

Evidence of the quality of the research is clear from the following four publications in high quality peer-review journals:

1. Bond M, Rogers G, Peters J, Anderson R, Hoyle M, Miners A, Moxham T, Davis S, Thokala P, Wailoo A, Jeffreys M, Hyde, C.. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of NICE technology appraisal guidance 111): a systematic review and economic model. *Health Technol Assess* 2012;16(21):1-470.

2. Hyde C, Peters J, Bond M, Rogers G, Hoyle M, Anderson R, Jeffreys M, Davis S, Thokala P, Moxham T. Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease: systematic review and economic model. *Age and Ageing* 2013;42(1):14-20.

3. Peters J, Anderson R, Hoyle M, Hyde C. Evolution of a cost utility model of donepezil for Alzheimer's disease. *Int J Technol Assess Health Care* 2013;29:147-154. doi:10.1017/S026646231300007X.

4. Pitt M, Stahl-Timmins W, Anderson R, Stein K. Using information graphics in health technology assessment. Toward a structured approach. *Int J Technol Assess Heath Care* 2009;25(4):555-563. DOI: 10.1017/S0266462309990286

4. Details of the impact (indicative maximum 750 words)

The NICE appraisal process depends on evaluations of efficacy and cost-effectiveness in various circumstances, and these appraisals are always based in the multiple technology appraisal process on the work of independent academic centres such as PenTAG[1,2]. The reports are HTAs which generally consist of systematic reviews, meta-analyses and health economic models combined. The impact NICE has made since its inauguration is acknowledged to be partly attributable to the high quality of the independent academic reports delivered in tight timescales. NICE guidelines are now recognised to be of importance throughout the developed world[3] The Exeter based PenTAG group has contributed greatly to this process through its many reports for NICE and its methodological research.

The specific project (HTA 09/87/01) was commissioned by the NETSCC HTA programme on behalf of NICE in November 2009 with the title 'The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Review of TA111)'. The project was to review and update the evidence presented to NICE in 2004 of how good a number of drugs were for treating Alzheimer's disease. The assessment would also assess whether the reviewed drugs were likely to be considered good value for money for the NHS. The final technology appraisal report, consisting of systematic reviews, meta-analyses and mixed treatment comparisons of RCTs (both the new evidence alone and cumulatively with previous evidence), systematic reviews of cost-effectiveness evaluations, critical appraisals of three manufacturer submissions and a de novo cost-effectiveness model was submitted in June 2010 and considered by the NICE Appraisal Committee in August 2010[3].

In the previous guidance NICE in 2004 had recommended that donepezil, galantamine and rivastigmine could be used for people with moderate Alzheimer's disease but memantine could only be used in clinical trials.

The report from PenTAG[4] was the key piece of evidence that informed the decision by NICE's

Appraisal Committee to provide its 2011 guidance, which extended the availability of donepezil, galantamine and rivastigmine to people with mild Alzheimer's disease, and allowed memantine to be used with those with severe forms of the disease for the first time[5]. This guidance was released in March 2011. It is mandatory for NHS commissioners to adhere to any technology appraisal guidance released. Data for prescribing in England published on the NHS Health and Social Care website indicates that there has been a massive increase in use of these drugs between 2010, the year before the 2011 NICE guidance was released, and 2012, the first complete year after (although arguably the full extent of the effect on prescribing may not be seen until the 2013, the data for which are not yet available). Between 2010 and 2012 donepezil use increased by 41%, rivastigmine by 51% and memantine by 278%, with 3% decrease in use of galantamine[6,7]. Based on the results of the economic model in our HTA we estimate that there were 110,000 persons with "untreated" mild Alzheimer's disease in England and Wales at the time of the change in guidance and if these individuals are now prescribed either donepezil or galantamine or rivastigmine we can expect on average cognition to be improved by 4% (absolute increase) in this population and there to be a cumulative delay in time to admission to long term care of 13,000 person/years. Similarly we estimate that there were 103,000 persons with "untreated" severe Alzheimer's disease in England and Wales at the time of the change in guidance and if these individuals are now prescribed memantine we can expect on average cognition to be improved by 3% (absolute increase) in this population and there to be a cumulative delay in time to admission to long term care of 8,000 person/years, with consequential large financial savings.

The change in decision about recommended drugs was directly attributed by NICE to change in the evidence, the key source of which was PenTAG's independent academic report[8,9,10]. The NICE decision on drugs for Alzheimer's disease thus provides a clear example of how PenTAG's research makes an impact on national policy making, and the important influence of the independent academic report is always reflected in the NICE appraisal process. In addition, NICE does have great worldwide influence[3], so we expect that this work has had beneficial impacts on the treatment on patients with Alzheimer's disease throughout the world.

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

To support the central role of independent academic reports in the NICE appraisal process:

1. http://www.nice.org.uk/aboutnice/howwework/devnicetech/developing_nice_multiple_technology_appraisals.jsp
   and
2. http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

To support the worldwide importance of NICE:

3. http://www.nytimes.com/2008/12/03/health/03nice.html?pagewanted=all

PenTAG report to NICE:

4. http://www.nice.org.uk/nicemedia/live/12248/49789/49789.pdf

NICE's guidance on drugs for Alzheimer's disease:

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

To support changes in drug prescribing:

6. https://catalogue.ic.nhs.uk/publications/prescribing/primary/pres-cost-anal-eng-2012/pres-cost-anal-eng-2012a-rep.pdf
   and
7. https://catalogue.ic.nhs.uk/publications/prescribing/primary/pres-cost-anal-eng-2010/pres-cost-anal-eng-2010-rep.pdf

To support NICE attributing change in guidance to change in evidence:

8. http://www.bbc.co.uk/news/health-11486367
   and
9. http://www.telegraph.co.uk/health/healthnews/8045775/Alzheimers-u-turn-by-Nice-to-allow-drugs-for-mild-cases.html
   and
10. http://www.channel4.com/news/alzheimers-drug-u-turn-welcomed