

Final report from the MAGDR Subgroup 1 on Priority Topics in Dementia Research, February 2011

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1. Summary

The Subgroup brought together leading researchers, funding organisation representatives and policy makers to identify the priority topics in dementia research that should be addressed in the near and longer-term, with a view to delivering new and more effective treatments, improved care, and preventive strategies. The conclusions of the group were informed by previous work undertaken through the 2008 MRC Strategic Review of Neurodegeneration Research, the 2009 National Dementia Strategy, and outputs from the 2009 Ministerial Dementia Summit and 2011 National Institute for Health Research (NIHR) Dementia Research Workshop.

Key areas to emerge where future action should be targeted were:

- Further preclinical research to understand disease mechanisms and progression to identify new targets and approaches for therapeutic development.
- The exploitation of longitudinal population studies to identify the risk and protective factors relating to dementia.
- Wider recruitment of research participants, both to study the 'prodromal' phase in advance of clinical presentation with dementia and to allow demarcation of the various dementia subtypes for more effective targeting and evaluation of interventions.
- The refinement and promotion of public health strategies for the prevention of dementia.

- Further research into behavioural and psychological symptoms in order to provide more effective management of challenging behaviour and improved quality of life.
- The promotion of research in general hospitals and care homes to improve the management of co-morbidities and the physical health of patients with dementia, and provide an evidence-base for more effective care delivery.

3. Research priorities

The Group reconsidered and elaborated upon the issues and priorities identified at the 2009 Ministerial Dementia Research Summit, according to the thematic categories of cause, cure and care. These were considered in terms of the scientific opportunities provided through advances in the knowledge-base and technology, with a view to identifying the most pressing priorities, and whether these would be deliverable in the shorter or longer term. The following themes emerged as areas where future research activity should be focussed:

i) Understanding disease mechanisms and progression

More research is needed into disease mechanisms to promote the development of new therapeutic strategies since current approaches are not effective and new drug targets are needed.

Near term

- Mechanistic research in dementia should draw on research in other neurodegenerative disorders as it becoming increasingly apparent that these share common genetic and molecular pathways.
- Current effort in research in Alzheimer's disease is focussed on the amyloid cascade hypothesis, although current pharmacological treatments targeting this have to date proved disappointing. Evaluation of alternative hypotheses – for example tau pathology, inflammatory components and lipid processing - should be pursued in the search for new drug entities and combinatorial approaches that might be effective in treating dementia. In all cases, there should be an emphasis on understanding the most beneficial time-window for treatment efficacy.
- The development of more predictive animal and cellular models and validated biomarkers of disease development and progression will be critical to this, an area that can be progressed through industry partnership.
- Induced pluripotent stem cells, typically derived from the skin cells of patients, will provide a new generation of neuronal cell models to help elucidate disease pathways and provide the basis of high throughput platforms for drug screening.
- Increased donation of brain tissue is needed to provide researchers with data to better understand the disease processes underlying dementias. However, such brain collections must be tied to detailed clinical data to be useful. Validated normal controls are also needed, which should have adequate longitudinal assessments.
- Consideration should be given to the more routine use of cerebrospinal fluid (CSF) sampling in UK patients, with biobanking where possible, which may offer some advantages for biomarker research and early diagnosis.

Longer term

- We need to elucidate how genetic risk factors interact with environmental determinants, either to promote or protect against the development of dementia.
- Increased understanding of the interplay of disease pathologies across the various forms of dementia is needed to provide a deeper insight into changes in brain pathology during clinical progression of the disease. The role of vascular factors, including in mid-life, may be particularly important. .

- New animal models should be developed to better represent aspects of chronic disease, coupled to emerging technologies such as bioluminescent cell-reporters that will allow the real time monitoring of disease progression.
- Stem cell research offers the long term promise of providing routes to repair and regenerate damaged brain tissue.

ii) Longitudinal population studies

Longitudinal population studies are key to increasing our understanding of the ageing process, and to identify the risk and protective factors relating to dementia.

Near term

- Opportunities exist to better utilise existing population studies, for example general birth cohorts such as those commenced in 1948 and 58, or large cross-sectional studies such as UK Biobank and Generation Scotland. Such cohorts could be provided with enhancements to allow studies/assessments in dementia, while datasets should be made as accessible as possible for external groups to undertake secondary analysis.

Longer term

- New prospective studies will also be needed, which should be undertaken as part of a long-term strategy in order to maximise the opportunity provided through the NHS and to engage the necessary stakeholders across the biomedical and social spectrum. Such studies should especially include early and pre-dementia subjects as this will eventually be the focus of therapeutic strategies to slow or prevent disease progression. The promotion of brain donation at the end of life from study participants, which could be linked to clinical and brain imaging data, would further provide researchers with a rich data set data to better understand the disease processes underlying dementias.

iii) Recruitment of research participants and clinical studies

Near term

- The creation of a national register of patients, possibly linked to the emerging network of NHS memory clinics, would allow early identification of patients for research and provide potential participants for clinical trials.
- A significant boost to the research agenda could be provided through routinely providing the patient with the opportunity to be asked to participate in research at the point of diagnosis, as is already happening in some centres.
- There is a need for more clinical studies of people with mild cognitive impairment, which would be facilitated by a reduction in the limitations imposed by regulatory bodies in this context. This relates to both study participation, where multi-centre studies are particularly challenging, and clarity on the perspectives of the regulatory agencies regarding the use of surrogate markers to define prodromal disease.
- Stratification of study participants, through improved diagnosis as well as genetic screening to separate out the various dementia sub-types, offers opportunities to better target and evaluate intervention studies.
- Common methodologies and platforms are needed, for example in brain imaging and cognitive assessment, to facilitate the analysis and exchange of data between study centres.
- There is a need to improve and standardise outcome measures, whether using biomarker or patient related outcomes. An opportunity exists to build on the consensus criteria that have emerged from several international consensus meetings, eg. for clinical trial outcome evaluation.

iv) Prevention strategies

Near term

- The key preventative factors for developing dementia include a healthy diet, promoting physical and cognitive activity and controlling cardiovascular risk factors such as diabetes, high cholesterol and hypertension. The prevention of dementia could therefore be promoted through public health interventions focused on 'healthy body, healthy mind', with clear opportunities to link with other public health strategies addressing heart disease, obesity etc. This should also emphasise that intervention is important in mid-life if not earlier.

Longer term

- A key public health research question in this area will be how to effect behavioural change, while effort will also be needed to target the message to the younger generation to empower them to act before mid-life.
- The analysis of combined epidemiological datasets should be promoted to help tease out the effects of comorbidities and the relationships between environmental and genetic factors.

v) Behavioural and psychological symptoms and interventions

Near term

- There is a need for an increased focus on research into behavioural and psychological symptoms for people with dementia, particularly with regard to managing challenging behaviour and improving their quality of life.
- Behaviour disturbance is highly heterogeneous and the evidence base for interventions is poor. This includes the current widespread use of antipsychotics, where there are emerging concerns over their long-term detrimental effects, as well as the evaluation and better use of non-drug interventions, including improved training in care homes and service implementation.

Longer term

- Current evidence on implementing psychological and non-drug interventions is largely derived from intensive, short-term studies, and a challenge remains to make these pragmatic and translatable to real-world settings. Impact assessments on carers are also needed.

vi) Promoting research in care homes and the community

Near term

- More research is needed to address comorbidity, especially in relation to vascular disease, and to improve the physical health of patients with dementia. Further research is also needed to better understand the connection between the cognitive and physical aspects of dementia.
- Research into falls prevention is also an important issue, while there is also a broader need for more research into the quality and impact of care received by people with dementia in general hospitals, especially on acute wards.
- Assessments are needed as to the effectiveness of interventions undertaken by carers, especially in relation to quality of life. An evaluation of different models of community-based care is needed, e.g. re-ablement and personalisation, as are improved patient-related outcome measures.

- There are significant gaps in terms of research on end of life and palliative care for people with dementia. Current hospice care models need to be developed for transfer to social care settings.

Longer term

- The development of research networks in this sector would assist access to research populations and encourage care homes to share expertise and information that would improve standards of care. An important issue in this context is that care homes do not come under the NHS and therefore each home needs to be registered separately as a research site and staff trained in good clinical practice which presents a barrier to research. The issue of service support cost provision in this sector also needs attention.
- There is a need for systematic reviews of qualitative studies on care and improved dissemination of results in this domain.
- Research should evaluate the use of assistive technology to promote mobility and/or prevent dependency. Activity is needed to assess the impact and design of the built environment (for example, in terms of the patient's own home, care homes and end-of-life facilities).

vii) Broader issues to address

- Regulatory hurdles:
 - while it is acknowledged there needs to be a balance between regulation and safety, the regulatory framework surrounding animal and human tissue research and in experimental medicine can be particularly difficult to negotiate. This issue has been considered in some depth by the recent review by the Academy of Medical Science.
- Research culture:
 - this needs to be cultivated from the point of diagnosis onwards, including care homes/general hospital. There is poor education and recognition of dementia amongst non-specialist healthcare workers. In hospitals this interface would be helped if clinical research staff contributed to NHS memory clinic assessments.
 - the training and awareness of GPs in particular is seen to be a significant issue, not only in respect of providing a diagnosis, but as a gateway for treatment and care. GPs need more support and training in dementia, and benefit could be gained through having a GP dementia specialist in all big practice groups (as for diabetes in some places).
 - in addition, more effort is needed in persuading clinicians /practitioners to take-up existing evidence-based interventions.
 - in the longer term research will be facilitated through developing better data systems to allow more systematic recording and tracking of an individual's care pathway.
- Developing capacity:
 - this remains weaker than in many other areas of biomedical research and there is a need to engage young researchers and attract those from conjoint disciplines. A window of opportunity exists in this regard since improvements in our understanding of the disease process coupled to advances in technology mean that tractable questions are now emerging. One way to address this could be through specific workshops and initiatives. In addition, recent 'restructuring' within the UK Pharma industry means there may be opportunities for academia to engage skilled, experienced scientists from this sector which could positively contribute to its translational effort.

- efforts are needed to address the increasing shortage of neuropathologists in the UK, although this is a long-term and worldwide problem.
- Collaborative research:
 - increased international collaboration, with standardisation of approaches and pooling of expertise and resources, should be promoted. This would increase the power of studies and may facilitate the involvement of more individuals with dementia in clinical trials.
 - new collaborations with industry, both in the biopharma sector and beyond, should also be encouraged to promote the translational agenda. A concerted stimulus for commercial Research and Development would be beneficial to all.
 - a near-term opportunity in this regard is the developing *EU Joint Programming in Neurodegeneration (JPND)*, through which a broad European 'strategic research agenda' will be produced by the end of 2011 as a basis for future co-operation between national funding agencies and stakeholder groups over the coming decade.