

## **Should we move dementia research funding from a cure to its care?**

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### **1. Enduring challenges**

In a decade's time, by 2030, the global prevalence of dementia will reach 75 million, with a staggering cost of over US\$2 trillion worldwide.<sup>1</sup> The ambition to "identify a cure or a disease-modifying therapy for dementia by 2025" set in the 2013 G8 Dementia Summit called for significant increase in research funding to achieve that goal.<sup>2</sup> But the hope of finding a cure is not new, and dementia research has been focusing heavily on basic and applied biomedical science for that reason.

Figures compiled by the US National Institute for Aging are revealing: more than 30,000 projects are recorded in the International Alzheimer's Disease Research Portfolio database, 45% of which focused on molecular pathogenesis and physiology, drug discovery and development, but fewer than 5% on dementia care and impact of disease, and only 2% on nonpharmacological interventions.<sup>3</sup> In terms of research funding, data from the US showed that out of a total of US\$10,800 million, less than 4% was spent on care and impact research, and 3% on nonpharmacological interventions. The lion's shares went to pathogenesis and physiology (34%) and drug research (12%).<sup>3</sup>

With this long-standing tradition of research funding for cure over care, respective progress in these two areas is noteworthy. Alzheimer's disease, the most common type of dementia, was discovered over a century ago, with numerous studies conducted to understand its neuropathology. To date, only a handful of drugs have been approved for symptom control after diagnosis of Alzheimer's. A series of papers published by Cummings et al on the drug pipeline highlighted the high failure rate in drug development; a more positive outlook was suggested in their 2019 paper, making comparisons with the learning phase in drug discovery in other areas (e.g. cancer and HIV), although the arduousness of the task in dementia is highlighted, hardly surprising given that the brain is the most complex organ in the body.<sup>4-7</sup>

Meanwhile, nonpharmacological interventions such as cognitive stimulation therapy (CST) show consistent evidence in enhancing cognition plus benefits in quality of life,<sup>8</sup> while multicomponent programmes to support unpaid carers (caregivers) such as STRategies for Relatives (START) improve their mental health and wellbeing.<sup>9</sup> Both CST and START are cost-effective in both the short- and long-term.<sup>10</sup>

Since the G8 Dementia Summit, the World Health Organization (WHO) has involved a wider group of stakeholders in setting research priorities for 2025: these priorities go beyond the quest for a cure, and include prevention and care, with more funding going into tertiary prevention.<sup>11</sup> Similarly, to complement the G8 focus on finding a cure, the Alzheimer's Society in UK published a 'research roadmap' that emphasised prevention, diagnosis, intervention, and care – based on wide-ranging consultation with many different stakeholders.<sup>12</sup> While any priority-setting initiative inevitably sparks debate, much of the discussion has focused on methods to ensure representativeness of opinions and efficiency through coordination.<sup>13</sup> More could be said about what decision-makers need to consider when deciding where to invest in dementia research.

### **2. Is it economically justifiable and equitable?**

The aim of investing in health and care services research is, obviously, to improve population health and wellbeing. Resources are always scarce: decision-makers want to maximise gain in health and wellbeing from available resources, while also being cognizant of inequalities of risk, access, and affordability. Consequently, as well as understanding how treatment and care can improve outcomes, we also need to know what the economic consequences are, and how they are distributed. Unlike many other diseases, the major cost driver in dementia (nearly 85%) is related to family and social care rather than medical care.<sup>14</sup>

Care services can both directly improve quality of life, as well as indirectly through their effects on behavioural and psychological symptoms, whether in the community<sup>15</sup> or through personalising support in nursing homes.<sup>16</sup> Good care services are often not only cost-effective but sometimes also cost-saving (i.e. they more than pay for themselves<sup>10</sup>). In part this is because the costs of care appear to be driven strongly by needs associated with activities of daily living. On the other hand, “cognitive deficits in dementia are associated with costs only via their effect on the patients’ capacity for activities of daily living”.<sup>17</sup> Carer costs (associated with time spent caring, as well as any out-of-pocket expenditures) appear to be influenced by instrumental activities of daily living but not by cognition.<sup>18</sup> Of course, unpacking causality in relation to care pathways, outcomes and costs in a condition as complex as dementia is never going to be straightforward, but these and other studies point to the important roles that good care plays in improving wellbeing for people living with dementia and their carers, and in containing service-related and unpaid care costs.

Continuing the search for disease-modifying treatments is of paramount importance. The challenges of discovery and development are universally appreciated, but we should also not underestimate the associated challenges of implementation and adoption. Simulation modelling for Alzheimer’s Research UK showed that a range of (hypothetical) types of disease-modifying treatment will all be expensive to roll out, particularly if they slow rather than fully arrest disease progression, and/or if they lengthen life-spans, thereby increasing carer burden, with the inequality issues that would imply.<sup>19</sup> Moreover, unless there is some major breakthrough in biomarker discovery, the earlier in the disease pathway that any new treatment is administered, the larger the number of people that will need it and the higher the implementation cost. Yet companies must necessarily invest vast sums in basic and applied research in their quest for effective disease-modifying treatments, and their shareholders quite reasonably expect to recoup their (highly risky) investments through adequate pricing.

Whether any new ‘cures’ can prove as cost-effective as some available care arrangements is therefore still an open question. Anyway, high-quality care services are needed *now*: it may well take many years before an affordable ‘cure’ becomes widely available to the population. This is especially pertinent – indeed urgent – in low- and middle-income countries, where most families affected by dementia have very limited access to diagnosis, formal health or social care services, or carer support arrangements. Yet, these are precisely the regions of the world where dementia prevalence will grow most rapidly over the next few decades.

In a helpful paper on increasing value and reducing waste in research priority-setting,<sup>20</sup> Chalmers et al noted poor evidence for the value of basic research, because false positives are common in initially promising findings. This is particularly the case in dementia, with a track record of a 99.6% experimental drug failure rate (far lower than for cancer research, for example).<sup>7</sup> The problem lies in (a) difficulties in translating preclinical findings from trials in diseases that have a long-lasting pathogenesis, with the possibility that any treatment in symptomatic patients is too far ‘downstream’ for clinical benefits; and (b) the lack of reliable endpoints, with statistically significant changes in neuropsychological testing often having unknown relevance to clinically meaningful changes in daily functioning and quality of life. Thus, despite rigorous preclinical research, progress is undermined

when preclinical findings are being translated into clinical trials. Biogen's recent announcement of promising findings with aducanumab may, of course, signal a welcome change of fortune. Nevertheless, we continue to need a two-pronged response, investing in both care research and cure research, if we are to respond appropriately to the enormous personal, social and economic challenges of dementia.

### 3. Conclusions

Dementia is one of the most expensive public health problems of our time. Given the 50 million (and counting) people already affected by dementia, few of whom are likely to benefit from discovery of a cure, we must not lessen our efforts to ensure good quality care so as to maintain or improve the quality of their lives, as well as the lives of the family members and others who support them. Although this does not automatically make research investment in care more cost-effective, it does highlight the fact that any innovations in dementia – care or cure – that do not set out to maximise quality of life are less likely to find themselves economically justifiable. Funding for implementation research is urgently needed to facilitate universal coverage of basic care, simultaneously addressing inequality issues in this area.

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#### **Declaration of Interest**

The authors have no conflicts to declare.