Alzheimer's & Dementia 12 (2016) 60-64

Perspective

Why has therapy development for dementia failed in the last two decades?

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Abstract The success rate of the pharmaceutical research and development (R&D) for dementia drugs has been abysmally low, in the last two decades. Also low has been the number of pipeline drugs in development, compared to other therapy areas. However, the rationale of early terminations has not been reported in the majority of trials. These are key findings of the recently published pharmaceutical pipeline analysis by the UK-based Office of Health Economics (OHE). Our understanding of main challenges include (1) the significant gaps of knowledge in the nosology and complexity of the underpinning biological mechanisms of the commonest, not familial, forms of late onset dementias; (2) low signal-to-noise ratio, notwithstanding the lack of validated biomarkers as entry and/or end-point criteria; (3) recruitment and retention, particularly in the asymptomatic and early disease stages. A number of current and future strategies aimed at ameliorating drug development are outlined and discussed.

Keywords: Alzheimer's; Research & development; Clinical trials; Dementia; Attrition; Amyloid hypothesis

The recent report of the Office of Health Economics (OHE), on the pharmaceutical research & development (R&D) landscape for dementia drugs over the last two decades, confirms the previous findings of a nearly 100% attrition rate [1]. The report also highlights the very low numbers of pipeline drugs for dementia and their success rates across all phases, particularly in phase II, compared with other therapy areas. Indeed, only 3.8% of products in the discovery phase and 1.2% in phase III development had dementia as indication, compared with 31% and 24%, respectively, for cancer. The OHE report was commissioned by the present authors in our capacity as members of the Clinical and Technical Expert Group, appointed by the UK Department of Health during the period of September 2014–May 2015 to support the UK Government's Integrated Development initiative, following the first and second G8 global dementia London summits in December 2013 [2] and June 2014.

The OHE report provides a factual account of past and current R&D efforts, based on a pipeline analysis. By combining two clinical trial registers, the authors identified 2000 industry- and academia-sponsored registered trials during the past 20 years. One hundred twenty-nine trials were terminated, withdrawn, or suspended early. Nearly 900

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http://dx.doi.org/10.1016/j.jalz.2015.12.003
1552-5260/

products were identified for dementia indications from a commercial R&D product database, of which 197 were still in "active development" (in December 2014). The remaining products have, thus, been terminated/discontinued (216) or have been deemed "non-active."

Unfortunately, both sources provide limited information on the reasons for the discontinuations. For the 110 terminated trials, only 45% provided a reason, the most commonly quoted citing recruitment problems. For the products' database, the rationale for discontinuation was only reported in 26% of cases—the most common reason being a lack of efficacy or safety; yet this only applied to 11% of the 216 terminated products. This is another key message extracted from the report: information is either not reported or not available, for the vast majority of dementia drug early terminations and failures. Reporting must improve so that we can learn from failures and avoid needless exposure of trial participants to products of low probability of success and wastage of time, effort, and financial investment.

Marsden and Mestre-Ferrandiz [1] list 17 products marketed for dementia-related indications. The vast majority of these are diagnostic aids and symptom-modifying treatments; none of the trials for disease modification have been successful. Indeed, from our perspective, the only R&D therapeutic successes recorded over the last 20 years involved two classes of drugs for symptomatic relief: the cholinergic enhancing cholinesterase inhibitors (ChEIs) and the N-methyl-D-aspartate receptor antagonist memantine.

ChEIs are a transmitter replacement therapy similar to dopamine enhancement for Parkinson's disease, which have proved to be successful in randomized clinical trials (RCT) and in clinical practice, particularly for the cognitive symptoms of mild-to-severe stages of dementia due to Alzheimer's disease (AD), Parkinson's disease dementia (PDD), and dementia with Lewy bodies (DLB). Memantine was also shown to relieve some of the cognitive and behavioral symptoms in the moderate-to-severe stages of dementia. There is still controversy as to the added benefit of a combination of these two classes of drugs (ChEIs and memantine) possibly because an adequately powered factorial design was never used. These are the current "standard drugs" for AD, used as comparators in RCTs with new classes of drugs acting on nicotinic, serotoninergic, or histaminic receptors, looking for equivalent or additional symptomatic benefit.

Because ChEIs and memantine are now old enough to be generic, thus much cheaper, there are economic considerations to take into account in developing new symptomatic drugs with equivalent efficacy. In other words, companies have limited incentives to continue development of a safe and marginally effective new drug if it is not significantly more potent than a ChEI, such as donepezil.

The development of such drugs may, therefore, be abandoned because of fears that payers will be reluctant to accept a price premium over an already available, considerably less expensive, generic drug. Indeed, the OHE report noted that commercial reasons are becoming an increasingly important driver in the termination of projects. Moreover, payers and health technology assessment bodies will not grant price premiums to new drugs deemed as similar to existing drugs. A key issue, which is not unique to dementia, is, thus, how the "value" of new drugs is assessed relative to existing drugs (including generic versions of older drugs where available). Price in many countries is often linked to "value"—although the definitions of "value" across jurisdictions vary and is currently an important debate for medicines in general.

Despite significant investments over the last 20 years, attrition for disease-modifying products (i.e., therapies that can delay or arrest disease onset and progression) has been nearly 100%, as also highlighted by Schneider et al. [3] and Calcoen et al. [4], among others. It is, indeed, well known that the R&D costs for dementia are among the highest, mainly because of the very low success rate and considerably longer development times. However, the total cost of R&D failures for disease modification, over the last two decades, does not represent but a fraction of the annual worldwide societal costs for dementia care, estimated at $604 billion, in 2010 [5] and $818 billion in 2015 [6].

Various issues have delayed progress in the field of dementia. Our understanding of the key issues and potential strategies to ameliorate drug development are:

1. Late-onset dementias (LoD)

Late-onset dementias (LoD) are heterogeneous and, contrary to the familial AD forms, they are of complex and, as yet, poorly understood etiology. They are thought to result from complex interactions between a multitude of genetic "susceptibility" factors, expression and epigenetic phenomena, and the environment. In spite of considerable advances over the last two decades, we still lack clarity on disease nosology, extent and granularity of its heterogeneity, and complexity of the underpinning neurobiological processes [7]. This is a major knowledge gap for new paradigms in drug discovery for dementia therapies and a challenge for the scientific community and funding bodies. Moreover, the difficulty of precisely assessing disease stage with clinical measures adds to the heterogeneity that may further confound clinical trials. Yet, practically all trials have been targeting single pathways, with most disease-modifying trials targeting components of the amyloid cascade hypothesis.

Furthermore, it is well established that in most dementia patients aged >75 years, there are co-existing pathologies (amyloid, tau, large and/or small vessel pathology, Lewy bodies [LB]) associated with dementia, notwithstanding age-related pathologic findings that are also common in asymptomatic individuals and include accumulation of amyloid plaques, tangles, and LBs of increasing prevalence