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Perspective

Current issues and future research priorities for health economic modelling across the full continuum of Alzheimer's disease

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Abstract Available data and models for the health-economic evaluation of treatment in Alzheimer's disease (AD) have limitations causing uncertainty to decision makers. Forthcoming treatment strategies in preclinical or early AD warrant an update on the challenges associated with their economic evaluation. The perspectives of the co-authors were complemented with a targeted review of literature discussing methodological issues and data gaps in AD health-economic modelling. The methods and data available to translate treatment efficacy in early disease into long-term outcomes of relevance to policy makers and payers are limited. Current long-term large-scale data accurately representing the continuous, multifaceted, and heterogeneous disease process are missing. The potential effect of disease-modifying treatment on key long-term outcomes such as institutionalization and death is uncertain but may have great effect on cost-effectiveness. Future research should give priority to collaborative efforts to access better data on the natural progression of AD and its association with key long-term outcomes.

Keywords: Alzheimer's disease; Dementia; Preclinical; Disease modification; Economic evaluation; Modelling; Disease progression; Health care decision making; Outcomes; Cost-effectiveness

1. Introduction

Dementia and its most common cause, Alzheimer's disease (AD) accounting for an estimated 60%–80% of cases [1], present one of the largest global challenges in health care today. Worldwide, 47 million people are estimated to have dementia with costs estimated at 818 billion US dollars in 2015 [2]. These numbers and costs are expected to increase dramatically over the coming decades, and new therapies are therefore urgently needed [2]. Drug development for AD over the last decade has been a disappointment. Only five drugs have been approved for the symptomatic

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treatment of AD (tacrine, donepezil, rivastigmine, galantamine, and memantine), and the magnitude of their effectiveness is generally considered to be modest although debated [3]. No new therapy has been approved since 2003, and a recent review identified more than 200 compounds failing in clinical development (phases 1 through 3) since then [4].

Yet, the pipeline for new AD drug treatments remains active and is today focused on treatments that may prevent, stop, or slow down disease progression, so-called disease-modifying treatments (DMTs). In parallel, there is a shift toward investigating treatment of subjects in earlier stages of the disease, for example, the A4 [5], TOMMORROW [6], and API [7] trials. The study subjects in these trials may either be cognitively normal individuals at risk for AD (often with genetic risk factors) or subjects in predementia stages of AD. The predementia stages include mild cognitive impairment (MCI) because of AD (also referred to as prodromal AD) and preclinical AD (i.e., subjects with pathologic evidence of AD but without the clinical phenotype of AD) [8].

Licensing/regulatory approval of future DMTs will not automatically translate into patient access with their availability depending on their incremental value from a health policy and payer perspective. Policy makers and payers will require evidence on how the clinical outcomes assessed in trial (e.g., cognitive function and conversion to dementia) translate across outcomes of greater relevance to patients, care providers, and society as a whole (e.g., quality of life, independence, mortality, and costs). Clinical trials are generally underpowered and too short to assess such outcomes [9], to which end health economic models combining trial data with real-world evidence are useful [10]. With the advancement of treatment in earlier stages of disease, including predementia and at risk populations, such models and modelling methodologies will be even more important because benefits are primarily expected to accrue in the long term, beyond the timeline of a clinical trial.

The available health economic models, and data they are commonly based on, have important limitations causing uncertainty in both the model outcomes and the conclusions drawn from model simulations [3,11,12]. Here, we identify and discuss the key issues in health economic modelling in AD with a particular focus on modelling the full continuum of the disease (from at-risk populations to late-stage dementia) and on setting out some suggestions for future research priorities.

2. Methods

This article is mainly based on the co-authors' perspectives of this topic. However, to complement and update our understanding and to reduce the risk of us missing important issues, a short review of the published literature was performed. This was not a comprehensive systematic review, and there may, therefore, be issues and opinions that others find important that we have not considered in this article.

We identified systematic review articles published in peer-reviewed scientific journals and health technology assessment reports and reviewed these to identify commonly discussed methodological issues and data gaps in AD health economic modelling. Bibliographic databases PubMed, EMBASE, and Cochrane library were searched using combinations of the following search terms including relevant permutations: Alzheimer's, dementia, modelling, cost-effectiveness, cost-utility, and economic evaluation. An additional search was performed in local databases on health technology assessments as identified through http://vortal.htai.org/. The search was performed in June 2015 and included publications published between January 2003 and May 2015.

Publications were included if they presented a review or discussion on methods or data in relation to the modelling of AD progression or methods on the economic evaluation or cost-effectiveness analysis of any intervention type (e.g., pharmacological, psychosocial support, and service delivery) in the diagnosis and/or treatment of AD and/or dementia. Publications only reporting individual outcomes (e.g., costs, utilities, and caregiver burden) in a population without putting them into the context of a decision-analytic model were excluded. Commentaries, letters, and non-English publications were also excluded. The identification of relevant articles was conducted by SL, and uncertain cases were discussed with AG.

Fig. 1 summarizes the review results. The search identified 14 relevant review articles [3,12–24] and 5 Health Technology Assessment reports [25–29]. Two additional review articles [11,30] were added after review of citations. A total of 21 publications form the basis of this analysis.

AG reviewed all identified articles and summarized issues and data gaps discussed in these. The material was shared and discussed with all co-authors who jointly and in consensus selected those they considered most important and categorized them into five key issues, each described under a separate heading in the subsequent Results section.

3. Results—key issues identified in systematic review articles

3.1. Currently available models oversimplify the natural progression of AD

The disease models underpinning the economic evaluation of symptomatic treatments in AD have generally been thought to oversimplify the natural progression of the disease [3]. Many models rely on single domains such as cognition, without consideration of other relevant symptoms including functional ability and behavior/mood. Models that include a broader range of symptoms have commonly not considered or described their interdependence