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Review

Slowing the progression of Alzheimer's disease; what works?

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ABSTRACT

Alzheimer's disease (AD) is an age-related progressive dementia, which is increasing in prevalence worldwide. Typically affecting short-term memory at onset, this devastating illness advances to impair all aspects of cognition, as well as non-cognitive domains. Although much effort has been made in recent years to develop disease-modifying treatments, medications which provided promising results in pre-clinical research have so far faltered in human clinical trials. Attention has recently shifted into trying to identify preventative measures that may delay the onset of the illness. Preventative factors include physical activity, proper diet, cognitive stimulation and the management of conditions such as hypertension, diabetes and obesity. However, it remains imperative to identify approaches that may help patients already diagnosed with the illness. Alongside pharmacological research, much work has been done on uncovering strategies which may slow down the progression of AD. This review aims to summarize evidence supporting or refuting methods impacting on the progression of the disease. AD remains a chronic and serious condition, therefore any intervention delaying the onset of moderate/severe symptoms will have a significant impact on patients and their families.

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1. The natural progression of Alzheimer's disease; evidence from pre-medication studies

Alzheimer's disease (AD) is an age-related clinical syndrome, which causes a progressive dementia in the elderly. It is characterized by a slow, hidden onset, and there must be evidence of decline from normal functioning for a clinical diagnosis to be made (APA, 2014). The progression of the condition is divided into three stages of mild, moderate or severe, as determined by results of global cognitive test scores (McKhann et al., 2011). The relationship between cognitive symptoms and the multiple observed pathologies in AD is not yet fully understood. For instance, the presence of amyloid-β (Aβ) plaques first used to identify AD as a distinct disorder, does not clearly correlate with AD symptoms (Giannakopoulos et al., 2003; Hardy and Selkoe 2002) and they can be found in healthy elderly with no cognitive impairment (Aizenstein et al., 2008). The number of neurofibrillary tangles (NFT) has been found to correlate with cognitive status, but this is not specific to AD (Takashima, 2013). Clinical cognitive tests have been validated by use in multiple dementia and healthy populations; the Mini Mental State Examination (MMSE) for instance has been shown to decline by an average of four points in one year in non-treated AD patients (See Table 1).

By reviewing pre-medication studies, the natural progression of AD can be assessed. Early observational studies before dementia medication became widely prescribed show a significant cognitive and functional decline in AD patients compared to healthy age-matched populations. For instance, Berg et al. (1988) found a 30% mortality rate in AD patients compared to <10% in age-matched controls after five years. Also, 73% of those with AD had been admitted into a nursing home, whereas this occurred for <5% of the controls. The average rate of decline in patients with mild AD in cognitive tests is shown in Table 1.

Findings from the historical literature are difficult to compare and contrast due to different cognitive testing methods used. Some studies have focused on particular cognitive domains known to be associated with mild AD (e.g., Piccini et al., 1995) whereas others have used various measures of global cognition (e.g., Burns et al., 1991; McCleary et al., 1996). It has now been established that typically presenting AD does not affect all areas of cognition at once, but is a cascade of different cognitive domains being affected at different stages (McKhann et al., 2011). Therefore, global measures may not be fully useful by themselves as they may miss patterns of cognitive decline. According to clinical guidelines, initial presentation of AD involves short-term memory loss and orientation problems; however it must be appreciated that when a patient presents to healthcare services they may have been living with the condition for some time.

To elucidate which areas of cognition and other factors are affected at different stages of AD, Overall et al. (1990) identified symptoms associated with six distinct stages of severity (three pre-morbid and three disease stages of AD). Interestingly, symptoms presented in the pre-morbid stages involved social withdrawal, anxiety, personality and sleep disturbances, whereas specifically cognitive issues occurred in the third and fourth stages; suggesting that cognitive performance in itself may not be the best indicator of developing dementia. Caregivers and relatives are in a unique and perhaps under-appreciated position to observe such personal changes which may be missed by traditional dementia screening practices.

1.1. Individual rates of decline

Individual heterogeneity in the pattern and rate of decline in patients has been observed. Piccini et al. (1995) followed thirty-one mild AD patients for three years, assessing cognition every six months. Nineteen participants remained classified as mild for at least two years and therefore were considered by the authors to have 'plateaued' at an early stage of the condition. Compared to a group of twelve patients who did not experience a plateau, the 'plateaued' group took significantly longer to reach the study end-points of incontinence, severe cognitive decline and death. The ability to predict subsequent decline is useful for development of treatment strategies and healthcare planning for the patient. Observational studies in medication-naive patients have identified several factors that can increase the rate of cognitive and functional decline in AD. However, this field has sometimes found contradictory results as shown in Table 2.

A factor which seems to clearly increase the rate of disease progression is a family history of AD. Sporadic AD is distinguished from familial AD which has known genetic causes, however, appreciation of genetic links to sporadic AD is increasing. For instance up to 91% of those homogenous for the $\epsilon 4$ allele of the APOE gene are likely to develop AD, and presence of the $\epsilon 4$ allele lowers the age at which AD develops (Corder et al., 1993). Other genetic variations identified by genome-wide association studies have been found to influence the risk of developing AD through their interaction with protein degradation and transport, immune activity, lipid transport and metabolism, and mitochondrial function (Tosto and Reitz, 2013). Their influence upon rate of progression of AD is now beginning to be explored (Wang et al., 2014).

Most findings concur that an earlier age of onset leads to a poorer prognosis in cognitive decline (Lucca et al., 1993; Stern and