Editorial

Alzheimer's Disease – Towards More Patient-centred and Meaningful Clinical Outcomes

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More than 100 years ago Alois Alzheimer first presented the clinical and pathological features of an unusual brain disease at his seminal lecture in Tübingen.[1] The patient, Auguste Deter, suffered memory loss, disorientation, hallucinations and died at an early age of 55. Post-mortem examination showed a brain with abnormally thin cerebral cortex, and microscopic features of senile plaques and neurofibrillary tangles. Alzheimer published his findings in 1907, and described another case in 1911.[2] In 1910, Emil Kraepelin named the condition 'Alzheimer's disease' (AD); and the eponym persists.

In the last few decades, the rapidly aging population has pushed dementia into the limelight, as both a devastating neurodegenerative disease, and a social and healthcare priority.[3] A steep rise in the prevalence of dementia, attributed mainly to AD, has caused significant physical and psychological morbidities, incurring heavy healthcare and social costs. In Singapore, the prevalence rate of dementia among those aged 65 years and above has risen in 20 years from 2.5%[4] to about 3.6%,[5] and is expected to escalate further as the population ages.

Although much progress has been made in our understanding of AD, the disease has thus far remained incurable, and largely unpreventable.[6] Hopes of arresting the AD scourge were placed on a drug that would not only arrest disease progression but also restore lost cognitive abilities. Drug trials over the last 10 to 12 years regularly showed that cholinesterase inhibitors and memantine produced statistically significant improvement in cognitive and global functional outcomes in AD. However, the treatment benefit of these 'anti-dementia' drugs on AD in clinical practice has been less consistent and homogenous, and is regarded generally as modest and marginal.[7]

Several possible factors may account for this frustrating discrepancy between the results of clinical studies and actual therapeutic experience.

One likely explanation may be traced to the differences between the carefully selected clinical trial cohort and the less restricted inclusion of patients in clinical practice. The standardising effects of the inclusion and exclusion criteria tend to recruit a homogenous cohort of patients into drug trials. The need to undergo cognitive testing may select those participants who are, on average, more literate than the general population of AD patients. This disparity is heightened by the complex and variable symptoms and presentations of the dementia syndrome. In multi-ethnic Singapore, the patients' cultural perception of AD, education level, and social environment may further confound the treatment outcomes within and outside trials.

A more significant contributing factor may be the predominant use of ability-based endpoints, whether purely cognitive or functional, to assess clinical drug efficacy in both dementia trials and clinical care. In dementia drug approval, the US Food and Drugs Administration mandates that 'dual efficacy' – cognitive abilities as measured by neuropsychological tests, and global function in terms of overall daily functional abilities – be used as primary outcome measures in landmark studies used to obtain approval for dementia drugs.[8]

While the rationale for using cognitive measures in a disease characterised by progressive cognitive and functional deterioration is obvious, it has become increasingly clear that a statistically significant improvement in neuropsychological test results does not necessarily translate into clinical changes that are both relevant and important to the patient, caregiver and physician.[7]

Such measures also suffer from a gradual loss of the power to reflect cognitive decline as the disease advances. For instance, the cognitive abilities tested in neuropsychological tests such as the cognitive subscale of the Alzheimer's disease Assessment Scale (ADAS-Cog)[9] may have little relevance to a patient whose activities are either simplified or taken over by caregivers. The power to detect any real cognitive benefits from a treatment is often diluted by the paucity of mentally challenging activities and environment. Further bias may also be introduced by

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behavioural problems in patients, and their family's capacity and resources for coping, all of which can be highly variable.

It may be argued that global function outcome measurements, such as the clinician-based impression of change (CIBIC)[10] and the clinician dementia rating (CDR),[11,12] are validated scales with strong psychometric properties, that can provide a comprehensive evaluation of patients.[13]

But these semi-structured scales are based largely on reported abilities in different functional domains, and may not distinguish between a loss of activity caused by cognitive decline and that caused by changes in social roles and family dynamics associated with ageing. In Singapore, patients are often 'relieved' of many daily tasks as an expression of the culture of filial piety. Respect for one's elderly parents is shown by freeing them from the burdens of personal activities of daily living (ADL), regardless of their residual or improved abilities. This action naturally decreases the sensitivity of psychometric scales that measure ADL-based and global function outcomes.

ADL-based measures can also be confounded by an "all or nothing" approach by families in helping patients with cognitive impairment. More often than not, a patient's cognitive improvement translates only into a partial improvement in an ADL item, say cooking or managing daily medications. Many cautious caregivers will take over the task completely, usually out of concern for the patient's safety, or because it requires more effort to help or supervise a patient. In such situations, informants are generally unable to discern any fractional change in functional status, thereby reducing the discriminant power of the scale.

There may therefore be a need for a radical change in treatment approach, based on conceptual and practical issues, to account for the natural history of AD and how the illness is experienced by patients as well as caregivers. AD is a relentlessly progressing illness, albeit at a low pace. As the disease enters its moderately severe and advanced stages, most patients forget their past, are unable to plan for the future, and can only enjoy or suffer 'the present'. Treatment, and its outcome measures, must evolve with disease severity to address newly emerging issues.[14]

Such a model anchors patient evaluation primarily on the contemporaneous quality of life and psychosocial well-being. These domains have more meaning for patients and caregivers than numerical scores obtained in neuro-psychological tests, global function assessment, and rating of abilities in ADL. Instead of testing the patient or getting the informant to report on residual abilities in cognitive and ADL tasks, the clinician should ask about positive features such as enjoyment of meals and activities, restful sleep, pleasurable recognition of relatives, and check the absence of negatives such as pain, itch, low mood, anxiety, and fear.[15-18]

Greater emphasis should therefore be placed on the individual's needs, quality of life, and comfort than on observable abilities, both when setting goals of care and in assessing treatment efficacy. For instance, a patient who no longer observes the rules when playing a card game but nevertheless shows overt signs of enjoying the experience is seen as having a desirable quality of life despite his cognitive decline. Conversely, any improvement in cognition and ADL status should be judged according to whether it enhances the patient's quality of life. If it merely leads to distress and agitation, then the value of such benefits from the vantage point of patients and their caregivers should be critically appraised.[19]

One other outcome measure important in guiding treatment decisions is caregiver stress. Alzheimer's typifies diseases whose clinical outcomes depend strongly on caregivers' well-being, morale, and their capacity to cope with the physical and psychosocial demands of caregiving.[20] Local studies have echoed the consistent finding that caregiver stress closely correlates with the patient's behavioural status, and that providing both practical and emotional support to caregivers is pivotal.[21,22] Managing any AD patient while neglecting the quality of life of caregiver will often lead to premature institutionalisation or crisis hospitalisation of the patient.[23] There is also evidence suggesting that treatment with cholinesterase inhibitor may reduce caregiver stress via their behaviour-modifying effect,[24-26] suggesting therefore that caregiver stress could be a useful surrogate marker for assessing treatment utility in AD.

In recent years, major drug trials have increasingly included quality of life measures and caregiver stress levels, but only as secondary or supplementary outcome measures. Application in clinical practice is also not routine. To promote their importance may seem counter-intuitive, counter-reductionism, and inconsistent with current research and clinical frameworks. But it is essential firstly to select care goals based on an appropriate disease model and then to use outcome measures tailored to these goals. Some trials failed to do so.

At a recent meeting on selecting outcome measures for Alzheimer clinical trials, dementia researchers reaffirmed this perspective by reiterating the need for better models of illness change, scales that are more responsive to improvement, and easily interpreted outcome measures, in deciding whether a clinically meaningful change has occurred.[27]

It is not the writer's intent here to advocate abolishing

ability-based outcomes in the management of AD. These are well standardised and validated and will remain useful, specifically in research and treatment involving patients with early dementia. But until a cure is found, we will need to refocus on AD as a disease that progressively alters personhood, relationships, and life experiences of both patients and family caregivers. Especially with disease progression, we should now shift from a model demonstrating cognitive and functional abilities to one incorporating quality of life and well being.

Such an approach enables an accurate description of patient's values and needs, and facilitates a more patient-centred and respectful system of care delivery.[28] Regardless of their ADAS-Cog and CDR scores, what ultimately matters to AD patients and their caregivers at every stage of the illness is dignity, comfort and an optimal quality of life.

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