TITLE: DOCTORING DEMENTIA: AUGMENTATION VS MONOTHERAPY

Authors: Mohd Zikrullah Najmuddin¹ and Rafidah Bahari¹*

Affiliation: Faculty of Medicine, University of Cyberjaya, Persiaran Bestari, Cyber 11, 63000 Cyberjaya, Selangor, MALAYSIA.

Corresponding author: Rafidah Bahari (rafidahbahari@cyberjaya.edu.my)

Abstract
Dementia is a common condition seen in the older population. Two most commonly used medications are acetylcholinesterase inhibitors (AChE inhibitors) and N-methyl-D-aspartate (NMDA) receptor antagonist. They are frequently used alone, but evidence for a combination therapy is emerging. This review discusses the use of augmentation therapy for dementia patients.

Keywords: dementia; pharmacotherapy; augmentation strategy

Introduction
Advancement in medical sciences results in people living longer. In some countries, the number of the elderly population is rising faster than the rate of birth. With older population, more morbidities are seen. One of the most common condition afflicting this population is dementia, in particular Alzheimer’s Disease.

In most cases, dementia is incurable. However, treatment which slows down the progression of the disease have already been in use for decades with varying degrees of success. Medications are usually the mainstay of treatment in dementia patients. The most common medications are Acetylcholinesterase Inhibitors (AChE inhibitors or anti-cholinesterases) and N-methyl-D-aspartate (NMDA) receptor antagonist. However, if either of them is effective, would a combination therapy work better? This review examines the effect of combining the two most commonly used medications for dementia.

Case Study
Mr. A. is a 65-years-old retired married teacher who initially presented with worsening forgetfulness in the past 4 months. The forgetfulness came on gradually about 4 years ago. It started off with him losing his things and family members were frequently asked to search for them. Lately, the frequency has increased. It then progressed that he started to forget recent activities and events. He was also having difficulty remembering conversations he had and would repeat the same topic again and again.

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Recently, the patient has started to become suspicious of others. When he could not find his belongings, he would accuse family members of stealing them. This was associated with irritability and increased verbal aggression. At this time, he also started to withdraw socially, remaining in bed most of the time and not taking interest in household activities.

In the past 4 months, the patient has begun to lose control over his bladder, became confused over the time of day and got lost in familiar surroundings. He became dependent for activities of daily living and was unable to wash, dress or feed himself due to his confusion.

During examination, he appeared appropriate to his age, well groomed, maintained good eye contact and was cooperative. When assessing his cognition, his orientation, calculation, abstract thinking and memory were significantly impaired. He also had poor judgement and no insight to his condition.

**Discussion**

Dementia is not uncommon in the older age groups. It is characterized as an impairment in cognitive, behavioral and also emotional functioning. According to Royal College of Physicians of London, dementia is defined as an impairment in the higher cortical functions such as solving problems, emotional control, language and communication, and the most important one is the memory.

As mentioned above, the most commonly used drugs in treating dementia are Acetylcholinesterase Inhibitors (AChE inhibitors or anti-cholinesterases) and N-methyl-D-aspartate (NMDA) receptor antagonist. Acetylcholine (AChE) is a neurotransmitter in the brain and functions as a messenger, conveying information from one synaptic cleft to another. Acetylcholine is broken down by an enzyme cholinesterase. In dementia patient, AChE inhibitor is used to inhibit the breakdown of the acetylcholine by the cholinesterase enzyme. This will increase the level of acetylcholine in the synaptic cleft, improving symptoms. On the other hand, the NMDA receptor antagonist exerts its function differently. In dementia, especially Alzheimer’s Disease, overproduction of glutamate causes neurotoxicity to the brain cells. NMDA receptor antagonist blocks the current flowing through the NMDA receptors which normalizes the glutaminergic system. This in turn reduces brain damage and slows down progression of the condition.

A study done by Geerts & Grossberg in 2006 utilized the use of Galantamine (AChE inhibitor) and Memantine (partial NMDA receptor antagonist) combined to work on both the cholinergic and glutamatergic system at the same time. They found that this combination showed better response in patient with Alzheimer’s Disease. The combination of these drugs also modulates the nicotinic and glutamatergic activities leading to improvement the patient’s cognitive function and delays progression of Alzheimer’s Disease.

According to Farrimond et al (2012), there is a significant advantage for a combination of Memantine and acetylcholinesterase inhibitors compared to using acetylcholinesterase inhibitor
alone. Substantial improvement is seen in patient’s cognition, global outcome, activity of daily living and behaviour. Prior to that, a study by Winblad et al (2007) also demonstrated that there is considerable benefit in using a combination of Memantine and acetylcholinesterase inhibitor compared with the acetylcholinesterase inhibitor alone in term of cognition, global improvement and behaviour in these patients.

A systemic review and meta-analysis study was done by Dania (2014) to assess the efficacy of having combination therapy compared to the monotherapy in patients with dementia. Surprisingly, only two studies by Tariot (2004) and Grossberg (2013) shows that there is statistically significant benefit of having combination therapy rather than monotherapy in term of patient’s cognition and functioning. Other studies by Posteinsson (2008), Howard (2012), Farlow (2010) and Choi (2011), showing that there is no statistically significant difference between usage of combination therapy compared to monotherapy in patients with Alzheimer’s Disease.

Hence, although in theory there may be an argument for the combination of AChE inhibitors and NMDA receptor antagonist, the results are not always advantageous. The hazards of combination therapy may not be ignored. As usually the case, medications take together may interact and sometimes in harmful ways. Also, the practice of polypharmacy reduces patient’s compliance to medications and raises the cost of healthcare.

The practice of combining medication and psychosocial therapy is beyond the scope of this review. However, it may be a better option for some patients, especially if their dementia is at an early stage.

In conclusion, although there may be some benefit to the use of AChE inhibitors and NMDA receptor antagonists combined, the disadvantages may not be overlooked. At present, recommendation from most guidelines is that the combination therapy using AChE inhibitors and NMDA Receptor antagonist may be beneficial in dementia of moderate to severe condition. Furthermore, a combination of acetylcholinesterase inhibitor with a non-pharmacological intervention might be more helpful in patient with dementia rather than using a monotherapy alone.

**References**


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