

## TREATMENT OF DEMENTIA – AN OVERVIEW

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### ABSTRACT

The various treatment strategies in dementia target the 'ABC' domains of the disease: 'ADL-Activities of daily living (ADL)' or the functioning level, 'BPSD' (Behavioural and Psychological Symptoms of Dementia) and 'Cognitive' functions. The holistic treatment of dementia encompasses pharmacological and psychosocial interventions for the patients as well as supportive services for the caregivers. Specific pharmacological agents that can be used include cholinesterase inhibitors (ChEIs), NMDA-antagonist. Antipsychotics, antidepressants, and benzodiazepines may be used at times. Psychosocial management include environmental interventions, behavioural interventions, as well as recreational and adjunctive therapies such as reality orientation, validation therapy, reminiscence therapy and music therapy. Dementia related services include: dementia day centres, support group for carers, home care services, counselling services, nursing home for people with dementia, community hospitals and specialist services in acute hospitals. The services are provided by a plethora of health and social agencies and professionals. The integration of such services is a major challenge. Primary care practitioners can play a bigger role by participating in training and shared care programme.

### INTRODUCTION

It is a truism that the number of people with dementia in Singapore will increase substantially with the rapid ageing of the population. The challenges to the health and social services arise not just from the increase in number of patients, but also from the complexity of the needs of patients and their caregivers.

Despite advancement in pharmacological management of dementia in the last decade, 'treatment' in the context of dementia is not in the sense of cure. The treatment of dementia, in a broad and holistic sense, encompasses pharmacological and psychosocial interventions, usually delivered most effectively by a multi-disciplinary team from various healthcare and social facilities. Not all demented patients will be under the care of specialist health service and primary care can play a key role. The provision of an integrated, patient-centred, and seamless care is dependent upon effective working amongst the professionals involved. It also requires effective partnership with people with dementia and their caregivers.

The family plays a central role to enable patients with dementia to receive care at home for as long as possible. The lack of family support, on the other hand, often portends

premature institutionalisation. Caregivers need to be informed of the diagnosis and what to expect in the future. A realistic management plan needs to be formulated to address the care needs of the patient based on the patient's cognitive and functioning level as well as the presence of any BPSD. The plan should reflect the wishes of the patient and caregivers as much as possible. Care and services for caregivers of dementia is elaborated elsewhere and will not be discussed here.

### The 'ABC' of Dementia

The various treatment strategies usually target the 'ABC' domains of the disease: 'A' for 'ADL-Activities of daily living (ADL)' or the functioning level of the patient. 'B' refers to 'BPSD - Behavioural and Psychological Symptoms of Dementia', defined by Finkel and Burns as "Symptoms of disturbed perception, thought content, mood, or behaviour that frequently occur in patients with dementia", and 'C', the 'Cognitive' functions.

Caregivers are concerned, especially at the initial stage of the disease, about the declining cognitive functioning. However, studies have shown that it is the BPSD – which occur in up to 90% of patients – that are associated with increased caregiver distress, earlier nursing home admission, more rapid progression, exacerbation of functional and cognitive deficit, and increased cost of care.

### PHARMACOLOGICAL INTERVENTIONS

#### Cholinesterase Inhibitors (ChEIs)

Tacrine was the first ChEI to be approved for treatment of mild-to-moderate AD in 1995. Its use was curtailed by its potential hepatic toxicity and was gradually replaced by the safer 'second-generation' ChEIs that include donepezil, rivastigmine and galantamine.

Meta-analysis<sup>1</sup> has indicated that ChEIs confer a modest but significant therapeutic benefit in the treatment of AD. There is growing evidence to support their efficacy in treating moderate-to-severe AD. ChEIs are generally well tolerated, with side effects that tend to be dose-related and are most problematic during dose titration.

#### Behavioural and Psychological Symptoms of Dementia (BPSD)

Evidence suggests that a cholinergic deficit resulting from a loss of cholinergic neurons is the biological basis of some BPSD in AD and related dementias. The review of the studies favors a benefit of the ChEIs in reducing BPSD. Of the three agents in current use, studies of all showed significant benefit in AD. Most studies showed a positive trend toward reduction of BPSD. In some studies, specific behavioral symptoms, particularly apathy and hallucinations, were reduced<sup>2</sup>.

### Long-term Efficacy and Safety of Cholinesterase Inhibitors

While available data for most of them are from trials of only 6 months' duration, long-term studies suggest that the benefits of ChEI treatment can endure for up to 4 years. A common pattern of response to treatment is initial improvement in cognition, followed by maintenance of cognitive gains above baseline for up to 1 year. This improvement is best detected by family and by objective cognitive tests such as the Mini Mental State Examination (MMSE). Generally, there is a decline in cognition to below baseline levels after approximately 1 year of treatment, but the level of cognition remains above that predicted for those not receiving pharmacologic treatment. Furthermore, long-term studies suggest that early diagnosis and treatment with ChEIs yield better long-term outcomes<sup>3</sup>.

Small et al<sup>4</sup> reported that projected mean scores in model-based untreated patients declined below 10 points on the MMSE at about 3 years, while the mean MMSE score of patients who remained on rivastigmine stayed above 10 points for 5 years.

### Vascular Dementia (VaD)

Cerebrovascular disease (CVD) frequently contributes to cognitive loss in patients with Alzheimer's disease (AD). Cholinergic deficits in vascular dementia (VaD) are due to ischemia of basal forebrain nuclei and of cholinergic pathways and can be treated with the use of the cholinesterase inhibitor used in AD. Controlled trials with donepezil, galantamine and rivastigmine in VaD, as well as in patients with AD plus CVD, have demonstrated improvements in cognition, behaviour and activities of daily living<sup>5-7</sup>.

### Parkinson's Disease Dementia (PDD)

Cholinesterase inhibitors have also been used in Parkinson disease dementia. A review by Maidment et al<sup>8</sup> concluded that ChEIs have a moderate effect against cognitive symptoms. There is no clear evidence of a noticeable clinical effect against neuropsychiatric symptoms. Tolerability including exacerbation of motor symptoms – in particular tremor – may limit the utility of cholinesterase inhibitors.

### Dementia with Lewy Bodies (DLB)

Rivastigmine has been shown to have a beneficial effect in DLB for visual hallucination delusions, anxiety and apathy<sup>9</sup>. The effect size is greater than that seen for a functional or global improvement in most trials of cholinesterase inhibitors in AD patients. In a case series of nine patients, donepezil appeared to improve hallucinations and overall function<sup>10</sup>.

### NMDA-antagonist

Memantine is currently the only available agent in this class and it represents a different neurochemical approach to the treatment of AD. It is a low-affinity antagonist to glutamate NMDA receptors and hence may prevent glutamate-induced excitatory neurotoxicity in dementia. It has also been reported to reduce tau phosphorylation in AD-like models in mice. Not only that, memantine has been approved for the treatment of moderate to severe AD based on two landmark studies<sup>11-12</sup>.

A review by Rossom et al<sup>13</sup> suggests that memantine seems to be promising and well tolerated in the treatment of moderate to severe VD or AD, either as monotherapy or in combination with donepezil. It appears to be particularly effective in improving cognitive, functional, and global outcomes in moderate to severe AD and in improving cognitive end points in mild to moderate VD.

A Cochrane review<sup>14</sup> suggests that for moderate to severe AD, memantine has a small beneficial effect at six months on cognition, activities of daily living and behaviour, supported by clinical impression of change. Whether memantine has any effect in mild to moderate AD is unknown. In mild to moderate vascular dementia, two 6-month studies reported that memantine improved cognition and behaviour but this was not supported by clinical global measures.

### Vitamin E

Vitamin E is a dietary compound that functions as an antioxidant scavenging toxic free radicals. Evidence that free radicals may contribute to the pathological processes in Alzheimer's disease has led to growing interest in the use of vitamin E in the treatment of this disorder.

Cochrane review found only one study which met the inclusion criteria (Sano 1996) which evaluated the effects of 10 mg of selegiline once daily and/or 1,000 IU of vitamin E twice daily as treatments for Alzheimer's disease. The reviewers concluded that there is insufficient evidence of efficacy of vitamin E in the treatment of people with Alzheimer's disease. There was a 3 folds excess of falls in the vitamin E group compared with placebo which requires further evaluation<sup>15</sup>.

### Ginkgo Biloba

A standardised extract is available for the treatment of a range of conditions including memory and concentration problems, dizziness, tinnitus and headache. The mechanisms of action include increasing blood supply by dilating blood vessels, reducing blood viscosity, modification of neurotransmitter systems, and reducing the density of oxygen free radicals.

One systematic review provided evidence that ginkgo biloba was superior to placebo in improving cognitive function<sup>16</sup>. But there have been several reports of serious side effects associated with commercially available ginkgo, including coma, bleeding, and seizures<sup>17-19</sup>.

A Cochrane review<sup>20</sup> concludes that Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Overall, there is promising evidence of improvement in cognition and function associated with Ginkgo. However, the three more modern trials show inconsistent results.

### Antipsychotics

Approximately 40% AD patients will experience psychotic symptoms at some stage during the course of cognitive decline. Presence of early psychotic symptoms may indicate more rapid deterioration, greater risk of behavioural disturbance and earlier need for institutionalisation.

Conventional antipsychotics have been shown to be superior

to placebo in controlling agitation & psychosis<sup>21-22</sup>. However, the effects are modest, about 18-26% improvement versus placebo in two meta analysis<sup>23-24</sup>. In addition, they are associated with treatment-emergent side effects, e.g. extrapyramidal symptoms (EPS) with high potency agent like haloperidol, postural hypotension and anticholinergic side effects with low potency agents such as chlorpromazine. Demented patients are also much more at risk of developing tardive dyskinesia. Hence, these agents should be used with extreme caution- with lowest possible dose, minimal duration and close review- and only when other options have failed. The use of anticholinergic agent such as benhexol to reverse the EPS of conventional antipsychotics should be avoided as they are likely to increase cognitive impairment.

Atypical antipsychotics such as risperidone, olanzapine, and quetiapine are at least as effective as conventional antipsychotics, are better tolerated, and have a lower propensity for EPS<sup>25-26</sup>.

In Apr 2005, FDA issued a Public Health Advisory of a total of seventeen placebo controlled trials performed with olanzapine (Zyprexa), aripiprazole (Abilify), risperidone (Risperdal), or quetiapine (Seroquel) in elderly demented patients with behavioural disorders; fifteen showed approximately 1.6-1.7 fold increase in mortality in the drug-treated group compared to the placebo-treated patients. Most causes of these deaths were either due to heart related events (e.g. heart failure, sudden death) or infections (mostly pneumonia). The rate of death in drug-treated patients was about 4.5% compared to a rate of about 2.6% in the placebo group.

In addition, cumulative findings of RCTs in which atypical antipsychotics (specifically risperidone and olanzapine) were compared to placebo, found that risperidone and olanzapine increased the risk of stroke by approximately 2 to 3 folds in elderly patients with dementia. The aetiology of this risk is not known, but may be related to metabolic effects and excess weight gain<sup>27-28</sup>.

Hence, antipsychotics should be regarded only as rescue medications for acute-onset (over hours or days) or for severe chronic BPSD, or used in patients who are aggressive and/or present a danger to themselves or others. If atypical antipsychotics are prescribed, physicians should screen for risk factors for both stroke and cardiovascular disease when initiating treatment. Regular monitoring should be undertaken if patients with chronic behavioural problems receive antipsychotic maintenance therapy.

Patients suffering from dementia with Lewy bodies (DLB) should not be prescribed conventional antipsychotics as severe and sometime fatal sensitivity to conventional antipsychotics and atypical antipsychotics have been reported<sup>29</sup>.

### Antidepressants

Depression is among the most frequent of the neuropsychiatric comorbidities in AD, affecting up to 50% of AD patients. Untreated depression is associated with severe negative consequences for patients and caregivers. Despite having a presentation in the context of AD that differs from typical

'geriatric' depression, it can be detected and quantified reliably in AD patients. The threshold for treatment of depression should be lower as newer anti-depressants are better tolerated by patients with dementia.

Both tricyclic antidepressants (TCA) and specific serotonin reuptake inhibitors (SSRI) have been shown to be moderately effective in treating depression in AD patients<sup>30-31</sup>. TCAs are often associated with side effects such as postural hypotension and those related to its anti-cholinergic properties. They should be avoided in general. If they were to be used, secondary (e.g. nortriptyline) rather than tertiary amines (e.g. amitriptyline, dothiepin) are preferred.

The first choice anti-depressant for treating depression in demented patients should be an SSRI or related anti-depressants.

There are suggestions that SSRI may also have a beneficial effect on anxiety, agitation<sup>32</sup> and psychotic symptoms<sup>30</sup> in dementia.

The side effects of SSRIs are generally mild and include:

- ✦ Gastrointestinal symptoms (e.g. nausea, vomiting)
- ✦ Restlessness
- ✦ Insomnia
- ✦ Weight loss

However, they can potentially cause SIADH resulting in hyponatremia. Some also have potentially clinically significant interaction with other drugs via the Cytochrome P450 enzymes in the liver, with the exception of Escitalopram and Sertraline.

Trazodone has also been shown to be effective for controlling agitation and sleep disturbance in patients with BPSD<sup>33-34</sup>.

In a double-blind RCT by Roth et al<sup>35</sup> Moclobemide, a reversible monoamine oxidase A inhibitor, was shown to be effective in treating depression in dementia.

Mirtazapine, a noradrenergic and selective serotonin antidepressant (NaSSA), has been reported in case series to have favourable effects on depression, anxiety, insomnia, anorexia and weight loss in patients with AD. Venlafaxine, a serotonin and noradrenaline reuptake inhibitor (SNRI), has also been shown to be efficacious in treating geriatric depression.

### Benzodiazepines

Benzodiazepines can be used for treating agitation, anxiety and insomnia in patients with dementia. But side effects are common and include excessive sedation, ataxia, amnesia and confusion. The risk of fall is increased especially with long-acting agents such as diazepam. Short-acting benzodiazepines such as lorazepam can be used for short periods. If patient requires long-term treatment for insomnia, an alternative agent with sleep-enhancing properties such as trazodone may be useful.

### PSYCHOSOCIAL INTERVENTIONS

Psychosocial interventions are an integral treatment component of the treatment of dementia. A number of psychomotor interventions have been demonstrated to benefit both patients with dementia<sup>36</sup> and caregivers<sup>37</sup>.

### Communication with Patients

Communication strategies have been shown to reduce professional and family carer stress<sup>38</sup>. Communication has to be pegged at patient's cognitive level. It can be an issue even in the early stage of dementia with receptive or expressive dysphasias.

Strategies to enhance communication include assuming a calm and supportive disposition in an environment free of noise or distraction, improving sensory input by maximizing vision and hearing, having face-to-face contact or appropriate touch during conversation, and simplifying content of discussion by focusing on one topic at a time. When talking to a dementia patient, speak slowly and distinctly using familiar words and short sentences. If the person seems frustrated and you don't know what he/she wants, try to ask simple questions that can be answered with a yes or no or one-word answer.

Written prompts and reminders may be helpful. Gesturing may remain relatively intact for some and can be useful. Try to talk about feelings rather than arguing over facts and keep things positive. Offer positive choices like "Let's go out now," or "Would you like to wear your shoes now?"

### Disclosure of Diagnosis

Many healthcare professionals remain hesitant in disclosing the diagnosis of dementia to patient. Family may also object to the discussion of diagnosis with patient or they would euphemistically attribute it to as a 'natural phenomenon of old age'.

Although some patients may find such approach acceptable, many patients do wish to be told about the diagnosis<sup>39</sup>. Disclosure is not a one-off event. It has to be patient-led, be adapted to patients' cognitive level, and transpire in the context of a supportive doctor-patient relationship.

### Environmental Interventions

In general, an ideal environment is one that is non-stressful, constant, familiar and secure. It should preferably have space for safe walking, visual barriers to preventing exiting, adequate lighting, low noise levels and adequate safety features (such as bath rails, bath mats, toilet railings) especially for those with unsteady gait.

### Behavioural Interventions

While some behavioural disturbances are due to physical discomfort (e.g. constipation) and require appropriate medical interventions, many behavioural disturbances result from the *interaction* between specific behaviour exhibited by patients and the responses of the caregivers. Working with families and other carers has been shown to reduce carer stress<sup>40</sup>. This may involve reassessing the behaviour disturbance, the possible antecedents, and the consequences of the behaviour. Having identified the ABCs (Antecedents, Behaviours, and Consequence), an intervention can be designed to either remove the antecedents or to change the carers' response. Sometimes, just teaching the carers how to make sense of the patient's behaviour, e.g. understanding apathy as the reason for the patient's apparent

'laziness', can provide some relief to the carers and mitigate its negative impact on the carers.

Many a time, carers can be taught that a simple strategy like distracting the patient from the problems, rather than reasoning/arguing with the patient or simply backing off from the situation can be more effective.

An activity planning approach has been advocated for patients who are cared for in the community. This involves engaging the patients in pleasurable activities for the purpose of stimulating the mind, enhancing physical health and reducing behavioural disturbances. The activities that the patient enjoyed in the past are identified and then modified to the patient's current level of functioning.

### Reality Orientation (RO)

Reality orientation helps to make the milieu as rational and knowable as possible by reminding the patients of the 'who, where, what, and why' of what is going on in a friendly, firm and dignified way. This could possibly result in improved sense of control and self esteem. But there has been criticism of RO in clinical practice, with some fear that it has been applied in a mechanical fashion and has been insensitive to the needs of the individual. There is also a suggestion that constant re-learning of material can actually contribute to mood and self-esteem problems.

A Cochrane review<sup>41</sup> concluded that there is some evidence that RO has benefits on both cognition and behaviour for dementia sufferers. And it appears that a continued programme may be needed to sustain potential benefits.

### Validation Therapy

Validation techniques provide a modified form of reality orientation to more impaired individuals who do not respond well to reality orientation. It posits that each expression or action put forward by the demented individual reflects a compromised but meaningful effort at communication.

### Reminiscence Therapy (RT)

Reminiscence Therapy (RT) involves the discussion of past activities, events and experiences with another person or group of people, usually with the aid of tangible prompts such as photographs, music and archive sound recordings, household and other familiar items from the past. It restores feeling of worth and competence through articulation of past successes. It also helps to soothe the fear of facing the unknown future through reminiscing about past challenges that have been overcome.

Reminiscence therapy is one of the most popular psychosocial interventions in dementia care and is highly rated by staff and participants.

A Cochrane review<sup>42</sup> on RT reported that the results were statistically significant for cognition (at follow-up), mood (at follow-up) and on a measure of general behavioural function (at the end of the intervention period). The improvement on cognition was evident in comparison with both no treatment and social contact control conditions. Caregiver strain showed

a significant decrease for caregivers participating in groups with their relative with dementia, and staff knowledge of group members' backgrounds improved significantly. No harmful effects were identified on the outcome measures reported.

### Music Therapy

Music has been suggested as a feasible and less costly intervention to manage agitated behaviours in older people with dementia: Music tailored to the patient's individual tastes is more effective in reducing agitation<sup>43</sup>.

A review<sup>44</sup> of eight research-based articles showed that preferred music intervention demonstrated positive outcomes in reducing the occurrence of some types of agitated behaviours in older people with dementia. The small sample sizes and some variations in the application of the preferred music intervention mean that caution is needed in drawing conclusions from these studies. Separately, the Cochrane reviewers<sup>45</sup> also concluded that the methodological quality and the reporting of the five studies reviewed were too poor to draw any useful conclusions.

## DEMENTIA-RELATED SERVICES

The majority of people with dementia remains in their own homes for most of the duration of the illness, and hence are cared for by family members. Some families employ domestic helpers to provide the care. However, the family still has to be informed about available support services and how to access them. The family physician may play an instrumental role in liaising with such services and coordinating them.

### Dementia Day Centres (DCC)

There are currently eight DCCs with a total capacity for about 240 clients. These facilities offer a safe and secure environment as well as structured therapeutic activities in the day for the patient. It also allows the family to have time to take a break or perform other tasks/chores.

### Support Group for Carers

Alzheimer's Disease Association (ADA), O'Joy Care services and Shan You Counselling Centre have support groups for families. Tsao Foundation and ADA also conduct training sessions for carers.

### Home Care Services

These comprise home medical, home nursing, and home help services, which provide services to homebound elderly. Home medical services are provided by about 11 organisations that include dedicated home medical service providers such as Code 4, Hua Mei Mobile Clinic, and Touch as well as community hospitals and nursing homes. Home Nursing Foundation, community hospitals and some nursing homes are the providers of home nursing services. IMH provides psychogeriatric domiciliary outreach services through its pilot project called 'Aged Psychiatry Community Assessment and Treatment Service' (APCATS).

### Counselling Services

Counselling services for elderly is currently provided by SAGE Counselling Centre, various Family Service Centres (FSC) and the Department of Psychological Medicine, NUS. Apart from providing face-to-face counselling and referral assistance to the elderly and their family, SAGE Counselling Centre also has a centralized toll-free number for telephone counselling.

### Nursing Home with Dementia – Specific Facilities

Nursing home placement may be necessary for some dementia patients who have significant functional decline and are no longer able to care for themselves. Although an integral component of the continuum of services, it should be the choice when other options are not feasible. Demented-specific nursing homes are preferred in order to deal with the behavioural challenges some patients with dementia may present. At present, only six such facilities run by Voluntary Welfare Organisations (VWOs), are available and they have a total capacity of about 500 beds.

### Community Hospitals

These provide a variety of step-down care services and respite care. Geriatric and psychogeriatric consultations are also available.

### Specialist Services in Acute Hospitals

These services are provided by specialists such as geriatricians, neurologists, geriatric psychiatrists and other healthcare professionals, and comprise inpatient services, outpatient services, and Geriatric Day Hospital (AH, CGH). IMH also runs two satellite psychogeriatric clinics at Geylang Polyclinic and Alexandra Behavioural Medicine Clinic at Viking Road. Geriatric and psychogeriatric services are available to approved providers (community hospitals and nursing homes) based on the 'Framework for Integrated Health Services for the Elderly' established in 2002.

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## TAKE HOME MESSAGES

- o The various treatment strategies in dementia target the 'ABC' domains of the disease: 'ADL-Activities of daily living (ADL)', 'BPSD' (Behavioral and Psychological Symptoms of Dementia) and 'Cognitive' functions.
  - o They encompass pharmacological and psychosocial interventions for the patients, and supportive services for the caregivers.
  - o The services are provided by a plethora of health and social agencies and professionals and the integration of such services is a major challenge.
  - o Primary care practitioners can play a bigger role by participating in training and shared care programme.
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