

## Alzheimer's Dementia: An Update

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Alzheimer's disease is an age-related progressive neurodegenerative disorder and is the most common form of dementia seen in the world that has a challenging medical need. Currently it afflicts about 5% of the world's population with every indication that it is expected to grow dramatically in the future keeping in view our ageing society. The research into Alzheimer's has also grown rapidly with various diagnostic criteria and treatment guidelines. Currently available medications appear to be able to produce moderate symptomatic benefits but not to stop disease progression. In this review, the current understanding of the disorder, its management and currently available drugs as well as novel therapeutic strategies are discussed.

**Key words:** Alzheimer's dementia, current trends in management, dementia

**D**ementia is defined as a progressive impairment of cognitive functions occurring in clear consciousness (that is in the absence of delirium).<sup>48</sup> It is a progressive, degenerative disease characterized by cognitive decline, impaired memory, thinking and behaviour. Global impairment of intellect is the essential feature, manifested as difficulty with memory, attention, thinking, and comprehension. Other mental functions may often be affected, including change in mood, personality and social behavior. Nevertheless, the diagnosis of dementia should not be made without evidence of memory deficits and at least one other cognitive deficit (e.g., language or visual-spatial skills).

As more and more people live to advanced age, with the increasing life expectancy, prevalence of dementia will increase because it is primarily the illness of old age. World-wide estimates of the number of dementia sufferers vary from 15 to 18 million, and it is estimated that by 2025, 34 million people will have the disease, 71% of whom will live in developing countries.<sup>4</sup> The prevalence of dementia increases with age and doubles every 5 years starting from 1% at age 60 years to about 30-40% by 85 years.<sup>21</sup> The spread of HIV infection and the prolonged survival of patients with AIDS and other chronic diseases will further increase the number of cases of dementia.

### Diagnosis

The importance of early diagnosis is well recognized for:

- (i) Proper education and counseling for patients and their families,
- (ii) Initiation of medication,
- (iii) Planning of lifestyle and legal issues,
- (iv) Assessment of driving, and
- (v) Provision of early community support.<sup>12,18</sup>

Because dementia is a syndrome, several diagnostic criteria have been proposed, each emphasizing different aspects of the condition. However, the most commonly accepted definitions are the ones proposed by International Classification of Diseases 10 (ICD-10)<sup>32</sup> and Diagnostic and Statistical Manual for Mental Disorders 4th Edition-Text Revision (DSM IV TR).<sup>5</sup> Another commonly accepted definition is from the American Academy of Neurology (AAN) 2001 guideline which follows the DSM III-R that is equivalent to the DSM IV TR criteria.

The assessment and management of a person with dementia is complex and time consuming, and often requires the input of several health professionals. The assessment of a person's cognitive state is influenced by many factors, including cultural aspect and level of education. A screening tool such as the Mini Mental State Examination

Memory Parameters
One or more of language, praxis, gnosis and executive functioning.
Significant impairment and decline in social or occupational functioning.
Gradual onset and continuing cognitive decline.
Other central nervous system or substance induced conditions are excluded.
Deficits not exclusively during course of delirium and not better accounted for by depression.

Table 1. Diagnostic criteria for dementia (DSM IV TR).

is brief and simple to use, although other instruments are also available for use either singly or in combination.<sup>26,36</sup> Neuropsychological assessment provides a comprehensive profile of cognitive function that can help determine the presence, degree, and pattern of deficits, but is time consuming and expensive and is not uniformly available everywhere. Basic investigations including computed tomography (CT) scan and/or magnetic resonance imaging (MRI) of brain to exclude a structural abnormality are important to exclude any potentially reversible cause or coexisting condition which may not be clinically apparent.<sup>36,20</sup>

Brief cognitive assessment instruments that focus on limited aspects of cognitive function (i.e., Clock Drawing Test, Time and Change Test) may be considered when screening for dementia. Neuropsychiatric batteries (Neuropsychologic Battery, Mattis Rating Scale, Halifax Mental Status Scale, and Fuld Object Memory Test<sup>1</sup>), particularly those that emphasize memory function, should be considered in identifying patients with dementia when administered to a population at increased risk of cognitive impairment. Interview-based techniques (Blessed Roth Scale, Clinical Dementia Rating, and Informant Questionnaire on Cognitive Decline in the Elderly<sup>1</sup>) may also be considered.

Dementia should be, however, differentiated from normal aging and mild cognitive impairment (MCI). There has been recent interest in MCI, with reports of annual conversion rates of MCI to AD of 6–25%,<sup>14</sup> and increasing with older age. A recent study indicated a conversion rate of 11% at 3 years.<sup>56</sup> MCI may be indicated by the presence of any of the parameters shown in **Table 2**.

Patients with mild cognitive impairment (MCI) should be recognized and monitored for cognitive and functional decline because of their increased risk for subsequent dementia. General cognitive screening instruments, which include the Mini-Mental State Examination, Kokmen Short Test of Mental Status, 7-Minute Screen, and Memory Impairment Screen, are useful for the detection of dementia when used in patient populations with increased prevalence of cognitive impairment.<sup>36</sup>

### Pathogenesis

AD accounts for about 60% of all dementia. The causes of AD are not fully understood. However risk factors may include:

- (i) Advancing age,
- (ii) Positive family history,
- (iii) Down's syndrome
- (iv) Recent or remote head injury
- (v) Lack of education
- (vi) Ethnicity,<sup>34</sup> and
- (vii) Presence of apolipoprotein E4<sup>72</sup>.

There is emerging evidence of an association of AD with depression, particularly in prodromal stages.<sup>35</sup>

Studies have, however, detailed certain protective factors which may include:

- (i) high levels of intellectual capacity
- (ii) Use of non-steroidal anti-inflammatory drugs
- (iii) prior estrogen exposure, and
- (iv) High Socioeconomic status.<sup>35</sup>

Alzheimer's dementia is an insidious and progressive dementia predominantly affecting memory function and language abilities and involving the temporo-parietal cortical areas of the brain. Memory loss is usually the first symptom. MRI (including functional MRI) may demonstrate evidence of hippocampal and mesial temporal changes<sup>49</sup> but is not diagnostic.

The underlying pathogenesis of AD is best described by the amyloid-cascade hypothesis. Genetic and environmental triggers influence the alteration of amyloid precursor protein (APP), which produces increased amounts of amyloid beta 42 contributing to plaque formation and consequent tau phosphorylation. Secretase activity is important in the initial process of APP metabolism. Pathologically, amyloid plaques, neurofibrillary tangles and reduction in cholinergic neuronal activity are the end result.<sup>45</sup>

Genetic abnormalities causative in early-onset AD (EOAD) are linked with chromosome 21 (APP gene),

chromosome 14 (presenilin 1) and chromosome 1 (presenilin 2), but account for a relatively small number (<1%) of all patients seen<sup>41</sup>. Genetic testing is available and recommended for those with a strong family history of EOAD. In late-onset AD, the association with apolipoprotein E4 (chromosome 19) has not been proven to be diagnostically useful for clinical practice.<sup>41</sup> Such testing is not recommended because at least one-third of individuals with AD do not have an E4 allele, and as many as 50% of those who are homozygous for E4 are cognitively normal at 80 years of age.<sup>35, 36</sup>

### Management

Current practice encourages open discussion of the diagnosis with patients and their families to allow management and treatment strategies to be implemented as early as possible and to allow to plan for the future. An integrated approach involving both psychosocial and pharmacological strategies is essential for better care and includes community and support services, professional groups (such as the Alzheimer's Association), memory-clinic services and geriatric services. The general practitioner plays a pivotal role in directing and managing care. Increasing community awareness of dementia, recent advances in research and the increasingly important role of medications have led to a more positive approach for the care of people with dementia and for their care givers.<sup>43</sup>

*Behavioural and psychological symptoms* of dementia (BPSD) are common, occurring in 90% of those with dementia at some point in their course. These include:

- (i) hallucinations,
- (ii) delusions,
- (iii) misidentifications
- (iv) agitation
- (v) depression
- (vi) anxiety
- (vii) aberrant motor behaviour
- (viii) Aggression.

Medications such as antipsychotics (including atypical ones) and mood stabilisers are used for these symptoms<sup>18</sup> although the evidence for their use is not strong. Ongoing assessment is essential because the need for medication is likely to vary throughout the course of the disease. There is an increasing evidence for the efficacy of atypical antipsychotics in those with BPSD<sup>18</sup> and cholinesterase inhibitors have shown positive outcomes with regards to these symptoms.<sup>18, 11</sup>

*Cognitive and intellectual problems* of AD include disturbances in the areas of memory, language, visual spatial problems and higher executive dysfunctions. Non-cognitive behavioral manifestations may include changes in personality, deterioration in judgment, wandering, psychosis, mood disturbances, agitation or sleep-wake cycle abnormalities.

Numerous neurochemical abnormalities have been demonstrated on autopsy and with functional neuroimaging in Alzheimer's disease. These include acetylcholine (Ach), norepinephrine, serotonin, dopamine, GABA, glutamate, corticotrophin releasing hormone, and

somatostatin. These findings are significant particularly as they relate to the development of potential pharmacological interventions for AD.<sup>62</sup>

The most robustly described neurochemical deficits are in the cholinergic system. The activity of choline acetyltransferases, the enzyme responsible for the final step of acetylcholine synthesis, is substantially reduced in patients with AD. This is particularly evident in the nucleus basalis of Meynert and several neocortical regions.<sup>9</sup>

Norepinephrine deficits have also been the target for research for potential replacement strategies. GABA is a widely distributed inhibitory neurotransmitter. The activity of GABAergic neurons is reflected by glutamic acid decarboxylase (GAD). In AD, abnormalities of GAD have been described, as have deficits in GABA, particularly in the temporal cortex.<sup>62</sup> Glutamate, an excitatory amino acid, also has been implicated in AD. Changes in N-methyl-D-Aspartate (NMDA), a glutamate receptor, have been described. NMDA receptor activation plays a crucial role in learning and memory, and, thus, it seems counterintuitive that an NMDA antagonist would improve the symptoms of AD.<sup>48</sup>

### Treatment Strategies

1. Cholinesterase Inhibitors (ChE-Is): Drugs under this category include Tacrine, Donepezil, Rivastigmine and Galantamine. Metrifonate, another drug in this category has fallen out of favour.
2. Acetylcholine Precursors: The only drug in this category is CDP-Choline or Citicoline.
3. NMDA Receptor Antagonist: This is a relatively new category and includes only one drug, Memantine.

Name of the various drugs, their pharmaco-dynamics and pharmacokinetics along with adverse reactions are detailed below:

#### Tacrine

A variety of early clinical studies showed that tacrine had potential benefits for AD patient but were not well controlled. Meta-analysis of the multi-center Well absorbed orally but with low bioavailability. Tacrine clinical trials has shown that 80 mg/day was effective and that lower doses of 40 mg/day and 20 mg/day were not effective.<sup>33</sup> Gastrointestinal problems- e.g., nausea, diarrhea, vomiting, appetite loss, increased gastric acid secretion, dyspepsia, weight loss.

#### Donepezil

Donepezil has been compared with placebo in 6 randomized controlled trials.<sup>24, 60</sup> Both 5-mg and 10-mg doses of the drug were found to be effective in improving cognitive and global functioning after 6 months of treatment. When data were pooled across the studies, the higher dose appeared to be more effective.<sup>75</sup> One of the trials in which donepezil was given for 12 months showed sustained improvement in MMSE scores above baseline for 9 months, after which the scores declined steadily to below the starting point, parallel to the

Parameters
Memory complaint, preferably corroborated by an informant.
Objective memory impairment.
Normal general cognitive function.
Intact activities of daily living.
Not fulfilling criteria for dementia.

Table 2. Criteria for diagnosing mild cognitive impairment (MCI).

scores of patients given placebo.<sup>77</sup> One study investigated the effects of treatment over 24 weeks in patients with moderate to severe Alzheimer's disease (Mini-Mental Status Examination (MMSE) scores of 5 to 17), in which all outcomes measures improved.<sup>24</sup>

Regarding adverse effects in randomized clinical trials in which the doses of donepezil were increased from 5 to 10 mg after 2 weeks, the proportion of patients with gastrointestinal side effects such as nausea ranged from 17% to 24%, and dropout rates related to adverse events such as autonomic side effects ranged from 8% to 18%.<sup>13</sup>

### Rivastigmine

The most recently published clinical trial of rivastigmine for AD was a 26-week randomized, double-blind placebo-controlled study in which high dose (6-12 mg/day, n = 243) and low dose (1-4 mg/day, n = 243) were compared with placebo (n = 239). By week 26, cognitive deterioration occurred in the placebo group. High dose of rivastigmine was superior to placebo on the ADAS-cog ( $p < 0.05$ ) subscale. Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) measures showed improvement in the high dose group compared to placebo ( $p < 0.001$ ). Improvement in function, as measured with the PDS (Progressive Deterioration Scale), demonstrated improvement in the high dose group and deterioration in the low dose group ( $p < 0.05$ ).<sup>61</sup>

### Galantamine

In a prospective study of 978 patients randomized to placebo, 8, 16, or 24 mg of galantamine per day in two divided doses were given; the difference in mean change in ADAS-Cog scores between the placebo and 24 mg treatment groups was 3.6 in the observed case analysis after 21 weeks of treatment ( $p < 0.001$ ). Change in CIBIC-Plus ( $p < 0.001$ ) and total Neuropsychiatric Inventory (NPI) scores ( $p < 0.05$ ) were also significantly better than placebo in the 24 mg galantamine group in this study and this group did not differ from the 18 mg/day group on these measures. Dosing changes in this study were made every 4 weeks and rates of nausea were 13% and 17% in the 16 and 24 mg/day galantamine group compared to the placebo rate of 5%.<sup>73</sup>

### Metrifonate<sup>71</sup>

In terms of cognitive improvement pooled data in American studies showed an effect size of 3.8 ADAS-cog points with an improvement over baseline of 1.8 points, the latter comparable with the best in its class.<sup>17</sup> The European MALT study<sup>19</sup> showed similar efficacy on cognition, significant changes in behaviour and function and for the first time in a placebo-controlled study significant improvements in career burden.<sup>69</sup>

### cdp- choline (Citicoline)

One of the first strategies was an attempt to increase acetylcholine production by precursor loading. However, there is really no storage of choline or lecithin in the brain and repeated studies have failed to produce positive results.<sup>10</sup>

### Memantine

Reisberg, et al.,<sup>55</sup> conducted a 28-week, multicenter, randomized, double-blind, placebo-controlled, parallel arm trial on the efficacy of memantine in patients with moderate to severe AD. Patient eligibility criteria included a diagnosis of AD with NINCDS-ADRDA criteria, Global Deterioration Scale (GDS) stage five or six, Functional Assessment stage (FAST) greater or equal to 6a, and a MMSE score of three to 14. Patients receiving memantine had a better outcome than those receiving placebo on primary and secondary endpoints. Memantine treatment was safe and well tolerated.

Pomara, et al.,<sup>54</sup> have performed a multicenter, randomized, double-blind, parallel-arm, placebo-controlled, phase III trial in the United States to study the efficacy and safety of memantine in patients affected with mild to moderate AD. They enrolled 403 patients more than 50 years of age with clinical diagnosis of probable AD (NINCDS-ADRDA criteria) and an MMSE score of 10 to 22. Memantine-treated patients for 24 weeks performed significantly better than placebo-treated patients on the Assessment Scale ADAS-cog, the CIBIC-plus, and NPI, although they exhibited similar functional performance measured by the ADCS-ADL. Furthermore, memantine was safe and well tolerated.

Rive, et al.,<sup>57</sup> evaluated the autonomy in patients affected with moderate to severe AD. They included 252 patients who scored between three and 14 on the MMSE in a randomized, double-blind clinical trial that studied the efficacy of 20 mg memantine daily versus placebo for a period of 28 weeks. Activities of daily living were assessed using the ADCS-ADL severity. They concluded that a patient treated with memantine was more than three times as likely to be autonomous after six months and therefore may reduce costs and decrease the overall burden of care.

### Other Drugs

Physostigmine on initial trial was poorly tolerated and is not yet licensed for use.<sup>76</sup> Eptastigmine was withdrawn from market due to development of Neutropenia.<sup>76</sup> Linopirdine, an Ach releaser, was developed by Dupont; showed no advantage over placebo and was later found to have a releasing affect on Ach only in the presence of high potassium concentrations suggesting limited use in vitro.

Besipirdine, a similar drug, developed by Hoechst, was a selective M-channel blocker (a potassium channel inactivated by muscarinic agonist) and was found not to be an effective Ach releaser and trials have been unremarkable.<sup>76</sup> Xanomeline, an Ach Agonist stopped because of unacceptable S/Es.<sup>37</sup> Sabcomeline is a partial agonist of M<sub>1</sub> receptors. A significant improvement on ADAS-cog was seen in a randomized placebo-controlled trial in 364 patients over 14 weeks.<sup>37</sup> Antioxidants target the prevention of dementia and its progression by reducing oxidative injury. Part of the injury from amyloid- $\beta$  deposition in AD is through free radicals and the resultant oxidative cellular damage.<sup>50</sup>

Studies have shown that Vitamin E in large daily dose of 2000 IU (1000 IU twice daily) is an effective antioxidant for delaying the rate and progression of AD.<sup>3,36,64</sup> An alternative to supplementation is a high intake of foods containing vitamin E. A diet rich in this vitamin (nuts (almonds, hazelnuts, and peanut butter), sunflower seeds, shrimp, plain wheat grain, and fortified cereals) can reduce the rate of cognitive decline in the elderly.<sup>46</sup> Selegiline, a selective MAO-B inhibitor was found to be superior to placebo in delaying time to death, and decline in activities of daily living. However, there was no benefit in regards to cognition, rate of institutionalization.<sup>64</sup>

Anti-inflammatory drugs may slow the process of AD and provide a degree of neuronal protection.<sup>59</sup> A six month trial of Diclofenac for treatment of AD reported a slightly slower, but not statistically significant, decline in cognition.<sup>65</sup> Treatment with corticosteroids has failed to show improvement in cognition or behavior.<sup>2</sup> Trials with Rofecoxib and other selective COX-2 inhibitors, however, have not yet seen promising.

Some clinical trials suggest that patients receiving estrogen replacement therapy may respond better to ChE-Is.<sup>67</sup> Estrogen also demonstrates effects on oxidation by stimulating the peroxidase reaction. It is converted to the catechol estrogen which is an antioxidant. Estrogen affects genes that inhibit the production of pathological proteins.<sup>47</sup> Additionally, estrogen appears to promote the non-amyloidogenic processing of amyloid precursor protei.<sup>31</sup> But long term use of estrogen has been limited due to some concern about the development of breast, uterine or ovarian cancer. The guidelines state that estrogen should not be prescribed to treat AD.<sup>36</sup>

Retrospective epidemiological studies show a decreased risk of developing AD and dementia among those taking 'statin' drugs to lower blood lipids, particularly in those less than 80 years of age.<sup>29,58</sup> The cholesterol lowering agent simvastatin and lovastatin reduce intracellular and extracellular levels of A $\beta$ 42 and A $\beta$ 40 peptides in primary cultures of hippocampal neurons and mixed cortical neurons,<sup>23</sup> and simvastatin reduces cholesterol turnover in the brain.<sup>42</sup> More studies are needed to determine whether lowering serum cholesterol with statins may retard the pathogenesis of AD or other dementias.<sup>68</sup>

Glycogen synthase kinase- 3 beta (GSK-3 beta) is involved with the phosphorylation of tau, an event in the pathway leading to tangle formation through presumed cytoskeletal changes in microtubules.<sup>25,63</sup> Valproate is an

inhibitor of GSK-3 beta<sup>15</sup> and may be a therapeutic target in AD. Additionally, other GSK-3 beta inhibitors are being developed.<sup>44</sup>

Ginseng is the most widely used of all herbal remedies. People have used ginseng for thousands of years as an ergogenic for the restoration of strength, mental work capacity, and resistance to stress. Studies, however, have not found any significant ergogenic effects on work performance or differences with placebo in concentration, memory, and cognition.<sup>22</sup>

Huperzine A, derived from the moss *Huperzia serrate*, is a Chinese herbal remedy for the treatment of dementia. Its effect on cognition may be comparable to that of the AChE-Is.<sup>8</sup> It is a reversible AChE-I and should not be taken if the patient is on AChE-I drug. Compared to tacrine and donepezil, huperzine A has longer duration of action and a higher therapeutic index.<sup>8</sup> In addition, huperzine A may improve working memory via an adrenergic mechanism and protect against glutamate-induced toxicity.<sup>51</sup> The side effects of this herbal remedy are generally mild and similar to other AChE-Is.<sup>53</sup>

## Novel Disease Modifying Approaches for the Treatment of AD

### Immunization Therapy

#### *A $\beta$ Vaccination*

Schenk, et al.,<sup>66</sup> first reported that immunization of transgenic mice with synthetic, pre-aggregated Amyloid  $\beta$ -42 resulted in reduction of the extent and progression of AD pathology. This approach appeared to achieve behavioral benefit in the animals as well.<sup>7</sup> Since then much progress has been made in designing a vaccine appropriate for human use. After promising preclinical results in several species, clinical trials using A $\beta$ -42 (AN-1792) in conjunction with the T helper (Th) 1 adjuvant QS-21 were initiated in humans.

Gelinas, et al.,<sup>28</sup> in their review showed that patients who generate antibodies exhibit slower rates of cognitive decline; however, increased incidence of micro hemorrhages in mice after passive A $\beta$  immunotherapy was reported. Despite numerous adverse events associated with clinical trials of AN-1792, preliminary data demonstrate that vaccination can reduce AD pathology and mitigate progressive cognitive decline associated with the disease.

Knowledge gained from studies on A $\beta$  immunotherapy will allow optimization of the vaccine to avoid side effects, while generating a highly specific and effective new generation vaccines.

### Processing of App to Generate A $\beta$ Peptides

One of the targets of disease modifying therapeutic intervention is the soluble pool of A $\beta$  itself. Strategies to reduce soluble A $\beta$  postulated mechanisms include the activation of membrane receptors and the permeabilization of membranes by the binding of A $\beta$  to the cell surface. Other strategies include the use of selective antibiotics and metal chelators.

### Decreasing A $\beta$ Peptide Production By Blocking $\gamma$ -Secretase

Another novel approach, based on intracellular expression of single chain antibodies (intrabodies) specific to  $\gamma$ -site is of therapeutic significance if appropriate delivery mechanisms such as by intranasal administration of phage expressing anti- $\gamma$  site directed antibodies are shown to be safe in humans.<sup>6, 52</sup>

### Decreasing A $\beta$ Peptide Production by Blocking Gamma-Secretase

$\gamma$ -Secretase is now known to be a hetero-oligomer containing at least 4 protein components, ps-1/ps-2, nicastrin, anterior pharynx defective-1 (APH-1) and presenilin enhancer-2 (PEN-2) in a high molecular weight complex of unknown stoichiometry. It is likely that each of the subunits may be a target for therapeutic intervention.<sup>70</sup>

### Enhancing $\beta$ -Secretase

The predominant pathway by which APP is processed that does not give rise to A $\beta$  fragments is referred to as the non amyloidogenic pathway. The initial APP processing involves the cleavage of APP by  $\beta$ -secretase. Preliminary data suggests that members of the sortin nexin family of proteins can reduce the rate of APP endocytoses and increases APP production, possibly by exposing the APP substrate to ADAM-10 [a disintegrin and metalloproteinase (ADAM)] for an extended period of time. Also Li, et al.,<sup>39</sup> identified analogous mechanism by brain derived cDNA sequencing that can decrease  $\beta$ -secretase cleavage and elevated  $\alpha$ -cleavage. (e.g.: small ubiquitin related modifier (SUMO-2) which decreases A $\beta$  secretion by 80%). Biological implications of sumoylation include alterations in protein stability or sub cellular location. Hence the activation of SUMO-2 is a potential therapeutic target for a disease modifying strategy in AD.<sup>40, 74</sup>

### Chelation Therapies

The apparently critical involvement of metals, particularly iron and copper, in both oxidative stress and protein aggregation processes renders chelation therapy a sensible strategy towards the treatment of neurodegeneration.

#### Hexadentate chelators

Two hexadentate ligands have been investigated for the treatment of neurodegenerative disease, desferrioxamine (DFO) and a synthetic amino-carboxylate ligand, DP-109.<sup>16</sup> DFO treatment led to a significant reduction in the rate of decline of daily living activities, leading to the conclusion that sustained administration of DFO might slow the clinical progression of dementia associated with AD. DP-109 has been demonstrated to possess a strong inhibition activity on plaque formation and deposition in female hAbPP-transgenic Tg 2576 mice.<sup>30, 38</sup>

#### Tridentate chelators

Aroyl hydrazone ligands are currently under investigation for their ability to penetrate the CNS. The neutral class typified by isonicotinoyl picolinoyl hydrazine (IPH) would appear to be promising.

#### Bidentate chelators

To date, a range of 8-hydroxyquinoline analogues have demonstrated the greatest potential for the treatment of neurodegeneration and one compound, clioquinol (CQ) has entered clinical trial.

Chelation therapy may be considered as a valuable strategy both for the treatment and for the investigation of neurodegeneration.

### Omega-3 Fatty Acids

Deficiencies in omega-3 FA and/or an imbalance in the ratio of omega-6 FA to omega-3 FA have been implicated in a variety of disorders affecting the CNS, including AD. A positive association between intake of omega-3 FA and reduction of cardiovascular risk and adverse outcomes (dementia) was reported<sup>27</sup>. Epidemiological studies have suggested that groups of people who consume diets high in omega-3 FAs may experience a lower prevalence of certain neurological conditions, particularly cognitive impairment and dementia disorders and thus hold promise in the treatment of dementia.

Although all the above strategies are being evaluated, none of them are recommended as there is insufficient evidence to support the use either of other antioxidants, anti-inflammatories, or other putative disease-modifying agents specifically to treat AD because of the risk of significant side-effects in the absence of demonstrated benefits.<sup>36</sup>

### Summary of Pharmacotherapy for Mild to Moderate 'AD'

#### 1. ChE-I:

- First line- Donepezil (5 mg once daily to 10 mg in four weeks).
- Alternative first line- Galantamine (4 mg twice daily to 8 – 12 mg twice daily in four week increments).
- Second line- Rivastigmine (1.5 mg twice daily to 6 mg twice daily in four week increments).
- Monitor potential S/Es: nausea, vomiting, cramps, diarrhea, and bradycardia.
- Treat until MMSE scores fall to 10 or less.

#### 2. Antioxidant therapy:

- First line- Vitamin E at 2000 IU/day.
- Second line- Selegiline 10 mg daily.
- Monitor potential S/Es: bleeding problems.

#### 3. Memantine can be recommended (5 mg once daily to 20 mg/day in two divided doses in four weeks).

#### 4. Herbal remedies do not contribute sufficiently in patients already on medications.

#### 5. Promising treatments under investigations: NSAIDs, statins, amyloid vaccine.

#### 6. Psychoactive medicines for target behavioral symptoms.

### Conclusions

Medications for the treatment of Alzheimer's disease that are available today include cholinesterase inhibitors and the NMDA-receptor antagonist, memantine. These drugs are safe and in several large and independent studies, they were reported to produce moderate symptomatic benefits. At present, however, there is no treatment available

that can stop the progressive deterioration of cognitive functions in the Alzheimer's disease patients. The development of novel drugs with strong disease-modifying properties therefore represents one of the biggest unmet medical needs today.

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