Alzheimer disease (AD) is the commonest degenerative brain disease characterised by progressive cognitive decline, leading to impairment in self-care abilities. With the ageing of the Hong Kong population, the incidence of AD, which is age related, is expected to rise very significantly in the coming years. AD patients typically do not actively complain about dementia symptoms because of their insidious onset, the associated loss of insight and the common misconception that cognitive decline is normal in old age. On the other hand, the burden of the disease on families is severe, leading to physical and psychological morbidities and even increased mortality in family caregivers. AD is therefore a medical disease with major adverse social consequences.

The prevailing theory about the cause of AD is the amyloid cascade hypothesis. Abnormal metabolism of amyloid precursor protein leads to increased production of amyloid beta protein which precipitates into amyloid plaques. Amyloid beta protein somehow leads to hyperphosphorylation of Tau protein, which impairs the stability of microtubules in axons, leading to neurofibrillary tangles and eventually neuronal death. But whether amyloid plaques and neurofibrillary tangles are the causes or the effects of AD remains to be determined. An earlier phase one trial of an active vaccine of amyloid beta protein was abandoned because of the complication of meningoencephalitis. The vaccinated subjects continued to have progressive dementia, despite evidence of clearing of amyloid plaques on subsequent post-mortem examinations. Since then, more active and passive immunotherapies have been investigated. The more promising one is bapineuzumab, which is a humanised anti-amyloid beta monoclonal antibody. In its phase two trial, study "completers" and APOE epsilon4 noncarriers showed treatment effects in cognition and functional status. Vasogenic oedema of the brain on MRI was noted in 10% of subjects, but the subjects were not significantly symptomatic. Its phase three trial is on-going.

It has been well known for several decades that loss of cholinergic activity is an early and prominent feature of AD brain. Based on this important finding, several cholinesterase inhibitors (ChEI) were developed. Currently three of these drugs – Donepezil, Rivastigmine, Galantamine have been licensed for treatment in mild to moderate AD. They have been shown to have modest effects on cognition and behaviour in AD patients and are moderately well tolerated. There is no head to head to compare the efficacy or side effect incidence among the three drugs.

Before starting these drugs, patients and families should be warned that the effect is modest, but they may stabilise cognitive decline. The drug effect tends to be more noticeable in moderate AD.

Gastrointestinal side effects e.g. anorexia, abdominal pain, diarrhoea are quite common in Chinese patients, especially at high doses. These side effects may be avoided by stepping up the doses gradually and may lessen over time. The transdermal preparation of Rivastigmine has the advantage of having less GI side effects, but some patients complain of skin irritation from the patches. Apart from GI side effects, a meta-analysis of randomised trial data showed that syncope was more common with ChEI use. ChEI should therefore be used with caution in patients with cardiovascular disorders. Dizziness and frequency of urine may also be troublesome.

The other class of drug licensed for use in moderate to severe AD is memantine. It is believed to work by partially inhibiting the N-methyl-d-aspartate (NMDA) receptors. This may protect the NMDA receptors from the neurotoxic effect of over-stimulation by glutamate. Randomised placebo controlled trials have demonstrated modest cognitive benefits in moderate and severe AD. Post hoc analysis showed significant reduction in agitation and aggression, which was not consistently shown in randomised trials of ChEI. The effect of memantine in agitated AD patients has however not been specifically examined. Memantine is generally well tolerated, though it may potentiate the effects of anti-parkinsonian drugs and warfarin.

Memantine is therefore a good alternative of ChEI if there are GI side effects or when there is agitation or aggression in patients with moderate to severe AD. In a six-month randomised placebo controlled trial in moderate to severe AD patients, the addition of memantine to ChEI had a mild additive effect on cognition, behaviour and functional status and the combination was tolerated by patients. Whether this effect is sustained in the long term, and whether the ChEI and memantine combination is superior to memantine alone in moderate to severe AD warrants further investigation.
further investigations. Both memantine and ChEi’s confer fewer benefits in vascular dementia, but they seem to be efficacious in AD patients with concomitant cerebrovascular disease.

Most AD patients are older people with multiple comorbidities and polypharmacy. The risk and benefits of the ChEi or memantine should be considered carefully in each patient. If side effects are suspected, trial of dose reduction or stoppage should reverse the symptoms. But one has to bear in mind that stoppage of ChEi’s may lead to significant cognitive decline within a couple of weeks. The use of AD drugs in late AD is controversial, even though some benefits in cognition have been demonstrated. In the later stage of AD, cognition may not be the primary concern for family caregivers or the quality of life of the patients.

AD is very commonly associated with neuropsychiatric symptoms e.g. delusion, agitation, aggression, depression and behavioural problems e.g. wandering, day night reversal. These problems cause more stress to caregivers than cognitive decline, and significantly impair the patients’ quality of life. Anti-psychotic drugs are commonly prescribed for these neuropsychiatric and behavioural problems. Although they invariably cause sedation, there is scant evidence that they improve neuropsychiatric symptoms and none for behavioural problems like wandering, care refusal, shouting, inappropriate urination. There are short-term randomised trials which showed reductions in agitation and aggression with atypical anti-psychotic drugs. The long-term effects are however uncertain. Prospective studies, on the other hand, strongly suggest that long-term use of anti-psychotic drugs (typical or atypical) is associated with greater risks of sudden death, stroke, falls and mortality. Anti-psychotic drugs should therefore be limited to short term use if at all. When compared with the typical anti-psychotic drugs, the newer atypical anti-psychotic drugs have less severe side effects particularly in Parkinsonism, but some AD patients may remain very sensitive to them.

Anxiety depression is common in AD patients. Tricyclic anti-depressants should be avoided because of their anti-cholinergic side effects. Selective serotonin re-uptake inhibitors (SSRI’s) work just as well as they do in cognitively normal people. Even in the absence of clinical depression, Citalopram (a SSRI) has been shown to be as efficacious as risperidone in reducing agitation and aggression, though SSRI’s generally take a few weeks to achieve their full effects. When faced with severe agitation and aggression, atypical anti-psychotic drugs may therefore still have a role in the short term. When one intends to stop SSRI’s, one should do so gradually as sudden withdrawal can lead to severe anxiety.

Sleep is often disturbed in AD. Apart from ensuring good sleep hygiene, zopiclone may help. Benzodiazepines should be used with caution because of risks of falls and day time somnolence. SSRI’s do not improve sleep per se and may even impair it. More sedating anti-depressants like trazodone and mirtazapine may be useful in promoting sleep and reducing anxiety at the same time. Both drugs do not have anti-cholinergic side effects. Mirtazapine increases appetite which may be helpful in those AD with weight loss. The efficacy of these two drugs in reducing neuropsychiatric symptoms in AD is however unproven. Anticonvulsants e.g. sodium valproate and carbamazepine have shown some benefits in controlling agitation and irritability.

All in all, although there is as yet no disease-modifying drug for AD, there are effective drugs to slow cognitive decline and to control the neuropsychiatric symptoms. But most of these drugs have significant side effects which have to be actively looked out for. Anti-psychotic drugs are harmful. With the availability of alternative drugs, their use should be confined to the short term.

Behavioural problems of AD do not respond well to drugs. Psychosocial interventions may be more important in their management. Structured caregiver training programmes have been consistently shown to be effective in reducing caregiver stress and in improving their self efficacy in caring. Staff training in nursing homes can reduce the frequency of behavioural problems of in-residents with AD. In addition, cognitive-stimulating activities and physical exercises have proven benefits in slowing cognitive decline in AD. In the home setting, AD elders usually have low motivation in sticking to these “healthy” activities. Day care is an excellent setting to engage AD elders in these activities, while providing some respite to the family caregivers at the same time. There is every hope that these non-pharmacological interventions when combined with judicial use of drugs can minimise the devastating effects of AD on the quality of life of the patients and their families.

References