Alzheimer's disease (AD)

- The most common neurodegenerative disease (causing progressive irreversible dementia) associated with old age.
- No cure for AD.

The cholinergic hypothesis

- The impairment of cognitive function and the behavioural disturbances that affect patients with Alzheimer's disease are mainly due to cortical deficiencies in cholinergic transmission.

Signs and symptoms

- Onset is usually late in life with increasing impairment of memory, developing gradually into a global impairment of cognition, orientation, linguistic ability and judgment.
- The clinical course is accompanied by growing disability and dependency on care.
- Personality changes (distrust, depression, anxiety, aggression etc).

The deficiency in cholinergic neurotransmission in Alzheimer's disease

- cholinesterase inhibitors are the first-line treatment for symptoms of this disease.

Classification of drugs used in Alzheimer's disease

- Reversible cholinesterase inhibitors: tacrine, donepezil and galantamine.
- Pseudo-reversible cholinesterase inhibitors: physostigmine, eptastigmine and rivastigmine.
- Irreversible cholinesterase inhibitors: metrifonate.

Tacrine:

- A cholinesterase inhibitor, was the first drug for the treatment of Alzheimer's disease.
- Tacrine is associated with hepatotoxicity
- For some cholinesterase inhibitors, such as rivastigmine, the cholinergic adverse effects such as nausea, vomiting, dizziness, diarrhoea and abdominal pain can be reduced by slowing the rate of dose.

- Donepezil and galantamine also significantly increase nicotinic receptor density, and increased receptor density may be associated with enhanced synaptic strengthening through long-term potentiation, which is related to cognitive function.

- Cholinesterase inhibitors have limited success because these drugs improve cognitive functions only in mild dementia and cannot stop the process of neurodegeneration. Moreover, drugs of this category show gastrointestinal side effects.

Markers for AD

- Beta-amyloid (690 amino acids) within the hippocampus (memory site) and the association cortex (language site) of AD patients.
- Also cerebrospinal fluid markers (including tau, phosphotau, and A beta 1-42) are probably important early biological markers that will provide an early diagnosis of AD.

Memantine

- A drug interfering with the glutaminergic brain transmitter system, the NMDA antagonist memantine, has recently been approved for the treatment of patients with severe AD.

- Memantine has been approved for moderate to severe dementia in United States of America recently. It is an uncompetitive, moderate affinity antagonist of NMDA receptors that inhibits the pathological functions of NMDA receptors while physiological processes in learning and memory are unaffected.
- Memantine is also reported to have beneficial effects in other CNS disorders viz., Parkinson's disease (PD), stroke, epilepsy, CNS trauma, drug dependence and chronic pain.

Other drugs in AD

- Epidemiological studies support the hypothesis that long-term treatment with the following, could protect against the development of AD:
- estrogen,
- antioxidants (vitamin E and selegiline),
- non-steroidal anti-inflammatory drugs,(ibuprofen, naproxen, indomethacin but not aspirin)
- cholesterol-lowering agents

Treatment with these drugs in manifest AD has been less promising.