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Dementia: An Overview

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Abstract: Dementia is a neurodegenerative disorder characterized by progressive and continuous loss of cognitive functions. The neuropsychiatric symptoms include apathy; agitation and depression. As the disorder progresses, the patient gradually becomes dependent on others to perform routine daily activities. Various underlying diseases or disorders are the root cause of the syndrome of dementia. Each of these disorder or disease is characterized by a specific signs and symptoms in combination with a presumed underlying neuropathology. Alzheimer's disease is the most prevalent cause of dementia. The second most prevalent cause is vascular dementia. In this review, the clinical types, pathophysiology and pharmacotherapy is summarized.

Keywords: Amnesia, Alzheimer's disease, Cognition, Dementia, Memory

1. INTRODUCTION

Learning and memory are two fundamental cognitive functions that confer us the ability to accumulate knowledge from our experiences (Liu *et al*., 2009). Learning refers to acquisition of any new information about the event in particular surroundings and subsequent retrieval of this information is referred to as memory (Okano *et al*., 2000). Memory, one of the most complex functions of the brain, comprises of multiple components such as perception/ sensation, registration, consolidation, storage, retrieval and decay/forgetting (Lindebooma and Weinstein, 2004; Parle *et al*., 2006). Memory may be sensory (registration), short-term memory and long-term memory (Nader, 2000). Consolidation refers to the process of conversion of short-term memory to long-term memory (Robbins and Murphy, 2006). Sensory memory (registration) is defined as a process of sensory perception and an ability to retain the perceived sensory signals in the sensory areas of the brain for relative short interval of time, following actual sensory experience. The incoming information first enters sensory memory, which holds an exact copy of what is seen or heard, for

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a few seconds or less. For instance, look at a flower and then close your eyes. An icon, of fleeting mental image of the flower will persist for about one-half second (Iconic memory). Similarly, information you hear is held in sensory memory as an echo (Echonic memory) for up to 2 seconds (Schweickert, 1993; Nader, 2000). In general, sensory memory holds information just long enough so that some of it can be transferred to the second memory system. Short-term memory (STM) holds small amounts of information for relatively brief periods; it is also called as working memory. It operates through central executive, visuo-spatial sketchpad and phonological loop. A central executive coordinates the material to focuss on reasoning and decision-making. The visuo-spatial sketchpad concentrates on visual and spatial information, while the phonological loop is responsible for holding and manipulating material related to speech, work and numbers (Ellis and Nathan, 2001). STM can be prolonged by rehearsal, the more time STM is rehearsed, the greater its chances of being stored in LTM. Long-term memory has the capacity to hold the information for months to years, it may be classified into declarative (explicit) and non-declarative (implicit) memory (Budsen and Price, 2005).

Declarative memory is a deliberate process to remember factual information such as names, faces and dates. It is stored in medial temporal lobe (mainly hippocampus) and diencephalons (Shaprine & Eichenbaum 2000; Budsen and Price, 2005). Non-declarative memory is unintentional recollection of earlier experiences (Nelson *et al*., 1992). It operates spontaneously without conscious efforts and it is stored in striatum, neocortex, amygdala and cerebellum. The CA1 (Deadwyler and Hampson, 1999) and CA3 neurons (Deadwyler and Hampson, 1999; Ramirez-Amaya *et al*., 1999) of hippocampus are responsible for spatial learning and memory (Gilbert, 2000). Declarative memory is divided into semantic memory and episodic memory. Semantic memory deals with general knowledge and facts about the world e.g. mathematical figures and historical dates (Budsen and Price, 2005) and episodic memory refers to biographical details of an individual such as accident and memorable events (Budsen and Price, 2005). Procedural memory is a form of non-declarative memory and it refers to skills and habits such as riding a bicycle (Budsen and Price, 2005). Priming and perceptual learning, simple classical conditioning and non-associative learning are other forms of non-declarative memory (Budsen and Price, 2005).

2 AMNESIA VS DEMENTIA

Amnesia is a condition in which memory is disturbed. Often this condition is reversible e.g. alcohol/wine-induced amnesia. Amnesia may develop either a an consequence of various neurological problems such as stroke, multiple cerebral

infarcts, head trauma and Alzheimer's disease or consumption of alcohol (Fama *et al*., 2004; McIntosh and Chick, 2004), chronic drug abuse (Vik *et al*., 2004) and certain chemical agents utilization (Chun, 2005). The memory impairment in amnesia is usually global, being both anterograde and retrograde (Cipolotti *et al*., 2001). Anterograde amnesia, is an inability to form new memories (Park *et al*., 2007), where as retrograde amnesia, is failure to retrieve old memories (Anand *et al*., 2007). Damage to the hippocampus, fornix, mamillary bodies, anterior and medial thalamic nuclei or basal forebrain can result in anterograde amnesia. Some authors have reported that severe anterograde amnesia is caused by bilateral lesions in medial temporal lobe structures (Di Gennaro *et al*., 2006), anteromedian thalamus (Carrera *et al*., 2004) or fornix (Poreh *et al*., 2006). Cases of anterograde amnesia were also developed by a unilateral lesion in mamillary body (Kupers *et al*., 2004), anterior medial thalamus (Summers, 2002), or hippocampus (Park *et al*., 2007).

Dementia refers to a syndrome that is characterized by progressive deterioration of cognitive functions. The neuropsychiatric symptoms include apathy; agitation and depression. As the disorder progresses, the patient gradually becomes dependent on others to perform routine daily activities. Various underlying diseases or disorders are the root cause of the syndrome of dementia. Each of these disorder or disease is characterized by a specific signs and symptoms in combination with a presumed underlying neuropathology. Alzheimer's disease is the most prevalent cause of dementia. The second most prevalent cause is vascular dementia (Chen *et al.*, 2009). It is often difficult to distinguish between subtypes of dementia. However, most dementias are progressive, irreversible and incurable. The risk factors and protective factors associated with dementia are listed in Table 1. The main risk factor for dementia is age. Prevalence is 2 % in those aged 65-69 years compared with 20% in those aged 85-89. The terms senile and pre-senile dementia have been used to differentiate between patients under or over 65 years but these are no longer in common use because the two types share some etiological features. Dementia is estimated to affect 24.3 million people worldwide. There are 4.6 million new cases of dementia every year and it is suggested that this figure will double every 20 years, reaching over 80 million by 2040 (Husband and Worsely, 2006).

3 CLINICAL TYPES AND PATHOPHYSIOLOGY OF DEMENTIAS

Dementia, according to the *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)*, is a syndrome that may be caused or characterized by multiple cognitive deficits, which include memory impairment and at least one of the following: aphasia, apraxia, agnosia or disturbance in executive functioning. Social or occupational function is also impaired. A diagnosis of

Table 1: Risk factors and protective factors of dementia

Risk factors		Protective factors	
Age	++	Apolipoprotein ε2 allele	++
Women	+	Low cholesterol level	+/-
Low education	+	Statins	+/-
First degree relative	+	Antihypertensive drug treatment	+
Down's syndrome	+	Moderate alcohol consumtion	+/-
Head trauma	+	Hormone replacement therapy (estrogen)	+/-
Apolipoprotein ε4 allele	++	Aspirin	-
Aluminum level	+/-	Nonsteroidal anti-inflammatory drugs	+/-
Hypertension	+	Dietary factors (vitamin E, antioxidants)	+/-
Depression	+	Lifestyle (active life, leisure activities, social support and network)	+/-
Mild cognitive impairment	++		
Heart disease/atrial fibrillation	+		
Cigarette smoking	++		
Diabetes mellitus	++		
Excessive alcohol consumption (3 drinks/day)	+		
Hyperlipidemia	+		
Hyperhomocysteinemia, low serum folate levels	+		
Previous mental decline	+/-		

Note: ++=confirmed; +=notable; +/-=controversial; -=negative. Adapted from Lobo and Saz, 2005

dementia should not be made during the course of a delirium. (A dementia and a delirium may both be diagnosed if the dementia is present at times when the delirium is not present.)

Dementia may occur due to both anatomical and biochemical changes in the brain. The behavioral and psychological symptoms of dementia include agitation/irritability/mood labiality, anxiety, apathy, delusion, depression symptoms, disinhibition, euphoria, hallucinations, loss of appetite and sleep disturbances (Tampi et al; 2011). Dementia has been etiologically associated with numerous heterogeneous conditions listed in Table 2 and is categorized in few subtypes according to its causes.

Table 2: Disorders that may produce dementia syndrome

DEGENERATIVE DISORDERS
Cortical
- Alzheimer's disease
- Frontotemporal dementia
- Dementia with Lewy bodies

Subcortical
- Parkinson's disease
- Huntington' s disease
- Wilson's disease
- Thalamic dementia

Others
- Multiple sclerosis

VASCULAR DEMENTIA
- Multi-infarct dementia
- Multiple large-vessel occlusions
- Strategic infarct dementia
- Lacunar state
- Binswanger's disease
- Chronic ischemia

HYDROCEPHALIC DEMENTIAS
- Communicating, normal pressure
- Non-communicating

CNS INFECTION-ASSOCIATED DEMENTIAS
- HIV-associated dementia
- Creutzfeldt- Jakob disease
- Neurosyphilis
- Chronic meningitis
- Viral encephalitis
- Progressive multifocal leukoencephalopathy
- Fungal meningitis (cryptococcal)

NEOPLASTIC DEMENTIAS
- Meningioma
- Glioblastoma
- Metastases
- Paraneoplastic syndromes

TRAUMATIC CONDITIONS
- Posttraumatic subdural hematoma
- Dementia pugilistica

CHRONIC INFLAMMATORY CONDITIONS
- Systemic lupus erythematous
- Other collegen-vascular disorders

PSYCHIATRIC DISORDERS
- Depression

METABOLIC DISORDERS
Anoxia
- Cardiac disease
- Pulmonary failure
- Anemia

Chronic renal failure
- Uremia encephalopathy
- Dialysis dementia

Hepatic failure
- Portosystemic encephalopathy
- Acquired hepatocerebral degeneration
- Endocrinopathies
- Thyroid, parathyroid disturbances
- Cushing's syndrome
- Recurrent hypo- or hyperglycemia

Porphyria

Vitamin deficiency states
- Thiamine (B_1), Cyanocobalamin (B_{12})
- Folate, Niacin

Other chronic metabolic abnormalities
- Hypo-or hyper-natremia
- Hematological conditions

TOXIC CONDITIONS
Alcohol related

Drugs
- Polydrug abuse
- Psychotropic agents
- Anticonvulsants
- Solvents and other inhalants
- Anticholinergic compounds
- Antineoplastic therapies
- Corticosteroids, NSAIDs
- Antihypertensives
- Cardiac medications

Metals
- Lead, mercury, arsenic
- Nickel, aluminum

Industrial agents and pollutants
- Carbon monoxide
- Organophosphate insecticides
- Organochlorine pesticides
- Perchloroethylene, toluene
- Trichloroethane, trichloroethylene
- Hydrocarbon inhalants

- Cortical dementia: dementias in which predominant involvement of dysfunction is in cortex region
- Subcortical dementia: dementias having predominant involvement of the white and grey matter structures such as basal ganglia, thalamus and frontal lobe projections.
- Mixed dementia: describes dementia involves both cortical and subcortical regions.

3.1. Cortical Dementias

3.1.1 Alzheimer's disease

Alzheimer's disease (AD) accounts for around 60 per cent of all cases of dementia (Fratiglioni et al., 2007). AD is a progressive neurodegenerative condition that may be of presenile or senile onset depending on whether the occurrence of disease is before or after the age of 65 years. Clinically, the patient presents itself as a progressive dementia of insidious onset with subtle personality alterations eventually resulting in complete anomia, agnosia and apraxia. The disease is occasionally accompanied by steep disturbance, anxiety, aggression and agitation (Cummings, 2004). Histopathological evidence of senile plaques and neurofibrillary tangels, either at autopsy or under rare circumstances, when biopsy is obtained, constitutes the most reliable diagnosis. Senile plaques are the clusters of degenerative nerve endings containing extracellular deposits of β-amyloid. Neurofibrillary tangles are microscopic paired helical filaments mainly made up of phosphorylated tau proteins (Kamphuis and Wurtman, 2009). Neocortex and hippocampus are the major regions characterized by these abnormalities. In fact, severity of cognitive impairment in AD correlates with the density of these plaques in neocortex. Biochemically, AD affects some of the selective neurotransmitters and neuromodulators. There has been a considerable deficiency of acetylcholine in brain of virtually all the patients of AD, who have been studied (Shah *et al.*, 2008). The serotonergic and noradrenergic systems also seem to be affected particularly when the onset of the disease is before the age of 75 years. Putative pathogenic mechanisms include glutamate neurotoxicity, free radical production, aluminum accumulation, apoptosis and inflammation (Silvestrelli *et al.*, 2006).

3.1.2. Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) accounts for 15 to 20 per cent of dementia cases. The disease seems to lie somewhere between AD and Parkinson's disease. DLB has distinct microscopic features: patients present with Lewy bodies and amyloid plaques in the subcortical and cortical regions of the brain.

Neurofibrillary tangles are less commonly seen. Lewy bodies are eosinophilic cytoplasmic inclusions that are distinct from neurofibrillary tangles. They contain a protein called alpha-synuclein, which is normally responsible for synaptic plasticity. Alpha- synuclein also appears to regulate the size of presynaptic vesicular pools of neurotransmitters and, therefore, influences neurotransmission. In DLB, heavily phosphorylated alpha-synuclein becomes cross linked to form the insoluble complexes that are Lewy bodies. Lewy bodies also contain a variety of inflammatory markers (eg. interleukins), proteases, BA and lipids. Lewy body development is accompanied by neuronal loss with specific deficits in cholinergic and dopaminergic neurotransmission (Husband and Worsley 2006).

3.1.2. Fronto-temporal dementia

FTD, sometimes also referred to as fronto-temporal lobar degeneration (FTLD), is the second commonest cause of dementia in younger people (< 65 years) (Ratnavalli, 2002), and produces focal atrophy of the frontal and/or anterior temporal lobes, with concomitant cognitive features (Neary *et al.*, 2005). Two major presentations are recognized:

(i) A behavioural variant (bvFTD)- bvFTD is characterised by a prominent change in personality and social behaviour, with apathy and/or disinhibition, emotional blunting, stereotyped or ritualised behaviours, loss of empathy alterations in appetite and food preference with limited or no insight. These changes reflect involvement of orbital and mesial frontal lobes (Sjogren and Andersen, 2006).
(ii) A language variant, which in turn is divided in two different patterns: semantic dementia (SD) and progressive non-fluent aphasia (PNFA). In SD, there is a profound loss in conceptual knowledge (or semantic memory) causing anomia and impaired comprehension of words, objects, or faces. In PNFA, by contrast, there is a gradual loss of expressive language abilities with impairments in phonological (sound-based) and grammatical aspects of language production. Repetition of multisyllabic words and phrases is impaired but, in contrast to SD, word comprehension and object recognition are well preserved (Lillo and Hodges, 2009).

3.2 Subcortical dementias

***3.2.1** Parkinson's disease*

The one-third patients with Parkinson's disease are prone to subcortical and progressive dementia. The neurodegeneration is not only confined to substantia nigra but spread to other subcortical nuclei including the limbic system and the

cerebral cortex. Furthermore, the underlying neurochemical deficits associated may be losses of cholinergic, dopaminergic and noradrenergic innervations (Kulisevsky and Pagonabarraga, 2009; Hindle, 2010).

***3.2.2** Huntington's disease*

Huntington's disease (HD) is an autosomal dominant disorder with an average course of 15 to 20 years. It typically affects patients between 30 and 50 years of age and has a prevalence of between four and seven per 100,000 worldwide (Roze *et al.*, 2010). The main and initial symptom of HD is "fidgety" movements (chorea) but cognitive decline, attention deficit and depression follow. Development of bipolar disease and schizophrenia is common in patients with HD. The gene mutation responsible has been identified as a polymorphic trinucleotide repeat in chromosome 4p. This is responsible for producing mutant forms of the Huntington protein. This is normally found in cell cytoplasm but, in HD, it is seen in nuclei. The mechanism of neurodegeneration as a result of this genetic mutation is unclear and the net result is a deficit in GABAeric and increased dopaminergic activity (Krobitsch and Kazantsev, 2011).

3.2.3. Wilson's disease

The characteristic extrapyramidal signs are seen in the patients with Wilson's disease. The symptoms of depression, disinhibition, personality changes and reduced impulse control are common; however the cognitive deficits are usually mild. The psychopathological features observed here are by virtue of abnormal and destructive deposition of copper in the basal nuclei; due to an inherited defect in the copper-carrying serum protein ceruloplasmin (Shimizu, 2004).

3.2.4. Normal pressure hydrocephalus

The characteristic triad of clinical symptoms of this neuropsychiaric syndrome includes motoric and psychopathological features i.e. an early abnormal gait (resembling the steps of spastic paraparesis); subcortical dementia with particularly severe apathetic features and urinary incontinence (that may not appear until late in the course. The cognitive difficulties appear with the onset of the incident. The neuropsychiatric deficits are due to the tissue destruction by stretching as a result the chronic hydrocephalus (Kazui, 2008).

3.3 Mixed dementias and dementia in disseminated brain diseases

***3.3.1** Vascular dementia*

Vascular dementia (VaD) remains the second most common form of dementia (upto 20% of all cases) in the elderly after AD (Roman, 2002). It is the result

of brain injury produced by cerebrovascular disease, either hemorrhagic or ischemic, or by hypoperfusive lesions resulting from cardiac disease or circulatory failure (Roman, 2005). The high prevalence of VaD in the aging population is a reflection of the fact that stroke and ischemic heart disease (IHD) are the two leading causes of morbidity and mortality in the elderly. The small brain infarcts leads to cognitive deterioration when they have enough cumulative effects on critical areas of the brain, results VaD. Depending upon the nature, extent and site of neuropathological lesion, the VaD may be categorized into several subtypes such as-

(i) Large vessel vascular dementia
   (a) Multi-infarct dementia:- Multiple large complete infarcts localized in cortico–subcortical area, mainly in white mater, are responsible for dementia.
   (b) Strategic infarct dementia:- Single brain infarct, often lacunar in size, damages functionally critical areas of the brain (e.g. angular gyrus, thalamus, basal forebrain, posterior cerebral artery, and anterior cerebral artery territories).

(ii) Small-vessel vascular dementia:-
   (a) Subcortical: It is involved in Binswanger disease, CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), and characterized by multiple lacunes with extensive perifocal incomplete infarctions.
   (b) Cortical and subcortical: It is involved in hypertensive, arteriolosclerotic angiopathy, amyloid angiopathies and collagen-vascular disease.

(iii) Hypoperfusive vascular dementia:-

   Ischemic-hypoxic dementia is a characteristic of diffuse anoxic-ischemic encephalopathy, and characterized by restricted injury due to selective vulnerability i.e. mesial temporal lobe sclerosis, incomplete white-matter infarction and border-zone infarction.

(iv) Hemorrhagic vascular dementia:

   Hemorrhagic dementia, occur mainly in traumatic subdural hematoma, subarachnoid hemorrhage, cerebral hematoma and venous thrombosis.

3.3.2 *Infection associated dementia*

HIV dementia: HIV dementia (HIVD) is likely to become more common, considering the rise in HIV infection. It is estimated that up to 30 percent of patients with HIV will develop HIVD. HIVD is a subcortical dementia where patients present with poor cognitive flexibility, reduced response times,

apathy and emotional lability. The pathological mechanism involved in HIVD appears to be apoptosis in neuronal cells as a result of various neurotoxic chemicals (proteases, cytokines etc) shed from infected macrophages and glial cells within the CNS. There is some evidence to suggest that treatment with antiretroviral agents could reduce the incidence of HIVD and, in patients who have developed the dementia, possibly stop or slow progression (Sharma and Bhattacharya, 2009).

Creutzfeldt-Jakob Disease: It is a dementia with an extremely rapid course, caused by transmissible infectious agent, the prion. Cognitive deterioration is progressive, widespread and accompanied by pyramidal and extrapyramidal signs i.e myoclonic jerks, ataxia and muscle rigidity. Death generally occurs in 6-12 months. The pathological changes are widespread in the cortex and the subcortical structures. Spongiform change in neurons is characteristic and neuronal loss and astrocytic proliferation occur (Dupiereux *et al.*, 2009).

Neurosyphilis: It may evolve into different types of dementia if left untreated. The most severe form is general paresis, often evident 15-20 years after the original infection. The dementia may be easily recognized in the advanced state by characteristic signs, such as pupillary abnormalities, dysarthria, tremor of the tongue and hypotonia (Nagano and Abe, 2004).

Chronic meningitis caused by chronic bacterial or fungal infections, can eventually cause progressive dementia, with fluctuations in arousal and cognitive performance, apathy, lethargy, disorientation and cranial nerve abnormalities (Herta *et al.*, 2005).

Herpes simplex encephalitis may cause major neurological and cognitive sequelae (Cyngiser, 2008).

3.3.3 *Metabolic and toxic dementias*

Metabolic and toxic dementias form a heterogenous group of diseases of special interest to the psychiatrist because they are potentially reversible and relatively frequent in medical settings (Craft, 2009). Dementia in these conditions has predominantly subcortical features but may have mixed characteristics. Progression of dementia is usually dependent on the chronicity of the metabolic or toxic condition, and the further course tends to be disease-specific. Hippocampal neurons are probably most vulnerable to anoxic injury but are also vulnerable to severe hypercholesterolemia and to repeated or severe episodes of hypoglycemia (Yaffe *et al.*, 2004). Hypothyroidism can produce subcortical damage through a mechanism of relative cerebral hypoxia. Vitamin B_{12} deficiency has been associated with disseminated degeneration in areas of

cortical white matter, the optic tracts and the cerebeller peduncles (Osimani *et al.*, 2005). In pellagra, nicotinic acid and probably other vitamin B deficiencies may lead to neuronal destruction (Hillborn and Marttila, 2010). Alcoholic dementia is one possible complication of chronic alcoholism (Hulse *et al.*, 2005). This situation may be a result of associated malnutrition, especially of B vitamins and particularly thiamine. Thiamine (vitamin B_1) deficiency causes Wernicke's encephalopathy. Prolonged untreated thiamine deficiency can result in an irreversible dementia/amnestic syndrome (Korsakoff's psychosis) (Phaf *et al.*, 2000). Dementing syndromes may also occur in chronic intoxication with medications (prescribed or abused by patients). The onset is accidental, and physicians should be alert to the possibility of this reversible dementia. Elderly patients are more vulnerable to developing the dementing syndrome (Bassil & Morley, 2010).

3.3.4 *Neoplastic-associated dementia:*

Neoplastic diseases (depending upon tumor location, extent as well as rapidity of tumor growth) essentially may produce any kind of neuropsychiatric symptoms. *Meningioma* tumor present in frontal lobe is associated with symptoms like cognitive loss with apathy, negativism and akinesia. *Limbic encephalopathy* is a complication of small cell lung carcinoma and may manifest with dramatic, sudden onset of memory loss. A full dementia syndrome may eventually develop (Staropoli, 2008).

3.3.5 *Dementia following traumatic brain injury:*

Traumatic brain injury may cause variety of cognitive difficulties. The severe trauma with loss of consciousness is called as *post-traumatic amnesia*. *Dementia pugilistica* called as dementia of boxers, commonly starts with signs of ataxia, dysarthria and Parkinson's like extrapyramidal signs before cognitive effects are appreciated (Dekosky *et al.*, 2010).

3.3.6 *Psychiatric disorders associated dementia:*

The relationship between dementia and depression is complex. *Pseudodementia* is a term used to describe the condition of depressed patients who perform poorly on cognitive tasks because of lack of interest and motivation. However, *dementia syndrome of depression* (DSD) occurs during episodes of severe mood disorders (Korczyn and Halperin, 2009).

A wide variety of medications have been proposed to treat different types of dementia. Table 3 enlists the common pharmacotherapeutic options to delay symptom progression and to improve quality of life for the patient of dementia.

Table 3: Pharmacotherapy of Dementia

Drug	Mode of action	Evaluation/Comments	Reference
Precursors to Acetylcholine (ACh): Choline, Lecithin, glycerophosphorylholine	Increase amount of ACh	Not effective alone/high dose difficult to tolerate by the patient	Shah *et al.*,2008; Scarpini *et al.*, 2003
Acetylcholinesterase inhibitors: Tacrine, donepezil, physostigmine, metrifonate, galanthamine, rivastigmine	Prevent the breakdown of ACh	Clinical modest effects on isolated cognitive measures. May decrease negative behaviors.	Summer, 2006; Trinh *et al.*, 2003
Cholinergic agonists: Bethanecol	Muscarinic agonist	Some subjective improvement.	Caccamo *et al.*, 2009
ACh release modulators: Fampridine, Linopridine Ondensetron Captopril	K^+-channel blockers Serotonin receptor antagonist ACE inhibitor	Effective in animal model of cognitive impairment	Solntseva *et al.*, 2003; Esbenshade *et al.*, 2008
Memantine	NMDA-receptor partial antagonist	Safe; may be useful in AD, VaD and mixed dementia. However, additional data is needed.	Thomas and Grossberg, 2009
Other therapeutic agents			
Ergoloid mesylates: Nicergoline, hydergine	Metabolic enhancement	Modest clinical effect, possibly due to mood elevation.	Olin *et al.*, 2001
Estrogen	Increase blood flow to brain, affect nerve growth factor, Prevent atrophy of cholinergic neuron, reduce oxidative stress	Some clinical trials have shown improvement in cognition function	Pike *et al.*, 2009
Nonsteroidal anti-inflammatory drugs (NSAIDs)	May prevent degeneration if immune/inflammatory effects cause plaque and tangle formation	Reduced prevalence of AD in rheumatoid groups vs. control and some groups taking anti-inflammatory medication.	Wyass, 2006; Stewart, 1997
Nerve growth factor	May attenuate rate of degeneration of remaining ACh neurons	Based on animal studies, NIA workgroup concluded strong rationale for clinical trials	Tuszynski, 2007
Nimodipine	Inhibits calcium influx that occurs with cellular changes, may slow progression of disease	Less deterioration on some memory tests, minimal cognitive benefits.	Tomassoni *et al.*, 2008
Selegiline (L-deprenyl)	Irreversible MAO-B inhibitor, acts as asn antioxidant and increases adrenergic stimulation	Improvements in sone cognitive testing, was comparable to vitamin E in delaying disease progression.	Shah *et al.*, 2008

Drug	Mode of action	Evaluation/Comments	Reference
Vitamin E	Antioxidant, traps free radicals, may inhibit lipid peroxidation	Delayed Alzheimer's progression.	Zandi *et al.*, 2004; Parigi *et al.*, 2006
Acetyl-l-cartnitine	Neuroprotective/ promotes ACh synthesis	Some minimal benefits on cognitive tests.	Nalecz, 2004
Nootropic agents: piracetam, oxiracetam, aniracetam	Enhances brain metabolism, possibly neuroprotective	Many studies show increases cognitive tests and some symptoms, minimal benefits.	Farlow, 2009; Winnicka *et al.*, 2005
Statins	HMG-CoA reductase inhibitor, antioxidant, anti-inflammatory, improve endothelial dysfunction	Mechanism of affecting learning and memory not known	Schreurs, 2010

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