REVIEW ARTICLE

Dementia: A review

Alain Fymat

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According to the World Health Organization (WHO), dementia is "an umbrella term for several diseases affecting memory, other cognitive abilities and behavior that interfere significantly with a person's ability to maintain their daily living activities. It is not a normal part of aging". Many different diseases can cause dementia; these will be reviewed below. Not being a specific disease, these contributors do not reach to the primary cause of the disease. Unable to pinpoint the root cause of the disease, we are powerless in treating it. While drugs are available to alleviate some of the symptoms, they do not cure it. Indeed, there is presently no cure for dementia. The reason stems from our incomplete understanding of the deep biology of the contributing diseases and associated epigenetic/ ecogenetic influences. After a brief history of the disease, I will elaborate on the following factors: epidemiology, three phases of signs and symptoms (early, middle and late), risk factors, and four progressive stages (mild cognitive impairment, early, middle, and late dementia). I will also review the classification of the disease (both within the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders), the approach followed to reaching a diagnosis (preliminary and cognitive testings, imaging scans). I will further discuss the main contributors to dementia (Alzheimer disease; the various dementias: vascular, Lewy body, Parkinson, frontotemporal, and senility; normal pressure hydrocephalus; and Creutzfeldt-Jacobs disease) and other contributors. Still further, the various cognitive impairments (mild, fixed), neurodegenerative dementia as well as the variations of dementia with age of occurrence are succinctly described. Management of the disease and the associated psychopharmacotherapy are also detailed, although the medications used have little or no effect on the underlying disease process. Lastly complementary and preventive measures are outlined.

Key Words: Alzheimer disease; Delirium; Dementia; Frontotemporal dementia; Lewy body dementia; Precocious dementia; Senility (or Senile dementia); Syphilitic dementia; Stroke; Vascular dementia

INTRODUCTION

According to the definition provided by the World Health Organization (WHO, 2017), dementia is "an umbrella term for several diseases affecting memory, other cognitive abilities and behavior that interfere significantly with the ability to maintain daily living activities. Although age is its strongest known risk factor, dementia is not a normal part of aging". The associated brain diseases can cause a long-term, often gradual decrease in cognitive abilities, "emotional problems, language difficulties and decreased motivation". The definition provided by the U.S. National Institute of Neurological Disorders and Stroke (NINDS, 2018) is more detailed in stating that dementia is "a group of symptoms caused by disorders that affect the brain. It is not a specific disease" and "memory loss is a common symptom of dementia. However, memory loss by itself does not mean having dementia. People with dementia have serious problems with two or more brain functions, such as memory and language. Although dementia is common in very elderly people, it is not part of normal aging [1].

Many different diseases can cause dementia, including Alzheimer disease (AD), frontotemporal dementia (FTD), Lewy body dementia (LBD), vascular dementia (VD), syphilitic dementia (SD), mixed dementia (MD), senility dementia (SD), or the combined effect of two or more dementia types, and even stroke. About 10% of individuals present with MD, a usual combination of AD and another type of dementia such as FTD or VD. However, not being a specific disease, the above potential contributors do not reach to the primary cause of the disease. There lies our greatest shortcoming: unable to pinpoint the root cause of the disease, we are powerless in treating it. Sure, drugs are available to treat some of the symptoms of these contributing diseases but not the diseases themselves. Likewise, drugs available for dementia can also only alleviate its symptoms; they cannot cure it or repair brain damage. They may improve symptoms or at best slow down the disease. Indeed, there is no known cure for dementia [2-9]. This is a sad observation on the state of the situation. It stems from our incomplete understanding of the deep biology of the contributing diseases and associated epigenetic/ Eco genetic influences.

A BRIEF HISTORY

With decreasing risk factors and an elongating lifespan in the developed world, dementia has emerged as an increasing public health concern and will continue along this trajectory. Uncommon in pre-industrial times and relatively rare before the 20th century, dementia is becoming more common in the population as a whole. Among the top 10 causes of mortality in the world, the publication Global Health Estimates (2016) lists AD and other dementias as the fifth ranking one (Figure 1). Its annual cost is ~ $818 billion (the majority of which being provided by family careers). Since antiquity: Medical texts contain references to dementia.

In the 7th century BC: The human lifespan was divided into six phases by Pythagoras (the Greek philosopher). The last two phases denoted as "old age" (63-79 years old) and "advanced age" (80 to death) were described as the "senium", "a period of mental and physical decay". The "final phase" was "the scene of mortal existence closing after a great length of time that very fortunately, few of the human species arrive at, where the mind is reduced to the imbecility of the first epoch of infancy". In 550 BC: Solon (a Greek Athenian statesman and poet) argued that "the terms of a man's will might be invalidated if he exhibited loss of judgment due to advanced age". In the 6th century BC: Chinese medical texts described a demented person as a "foolish old person". In the 5th century BC: Plato (the ancient Greek philosopher) stated that "the elderly were unsuited for any position of responsibility because their judgment, imagination, power of reasoning and memory had gradually been blunted by deterioration". In the 1st century BC: Cicero (a Consul of the Roman Republic) considered that "the loss of mental function was not inevitable in the elderly" and " affected those old men who were weak-willed" Notwithstanding its precociousness, this view is in line with modern-day medical opinion although, for centuries past, it was largely ignored in favor of Aristotle's thoughts. In the 2nd century AD: Celsius (the Greek philosopher) simply

International Institute of Medicine and Science, California, USA

Correspondence: Alain Fymat, International Institute of Medicine and Science, California, USA. Telephone (760) 507-6862, e-mail alain.fymat@fiimas.org

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echoed Aristotle's beliefs. In the 3rd century AD: Galen (the physician and father of modern day medicine), like Celsius before him, merely repeated Aristotle's beliefs. From 330 AD-1453 AD: During the Ottoman Empire, Byzantine physicians wrote of dementia because seven of the Byzantine Emperors displayed signs of cognitive decline. In the 13th century AD: The friar Roger Bacon asserted that "the brain, not the heart, was the center of memory". From the 13th century until the end of the 19th century: Dementia encompassed mental illness and any type of psychosocial incapacity. During the 19th century until the first half of the 20th century: Dementia in the elderly was considered as the result of cerebral atherosclerosis. By the 1960s: Neurodegenerative diseases and age-related cognitive decline were linked. In 1907: Alzheimer described the disease bearing his name, associating it with certain microscopic changes in the brain, but still associating it with a rare middle age disease. In 1913-1920: Schizophrenia (including paranoia and decreased cognitive capacity) and dementia praecox (precocious dementia, PD) are used interchangeably. By the 1970s: The medical community maintained that Alzheimer disease was the cause of the vast majority of mental impairments rather than vascular dementia, which is rarer than previously thought. In 1976: Robert Katzmann (a neurologist) suggested that senile dementia and Alzheimer disease are linked. By the end of the 20th century: The medical community believed that dementia is a mixture of both Alzheimer disease and vascular dementia. In the 21st century: Other types of dementia, distinct from Alzheimer and vascular dementia were identified but their causal etiology remains unclear and many hypotheses (theories) have been advanced but these are largely based on risk factors[11-16]. In 2018: Fymat (this author) posited that the root cause (not a risk factor) of Alzheimer (and other neurodegenerative diseases) is but an autoimmune disease having gone rogue.

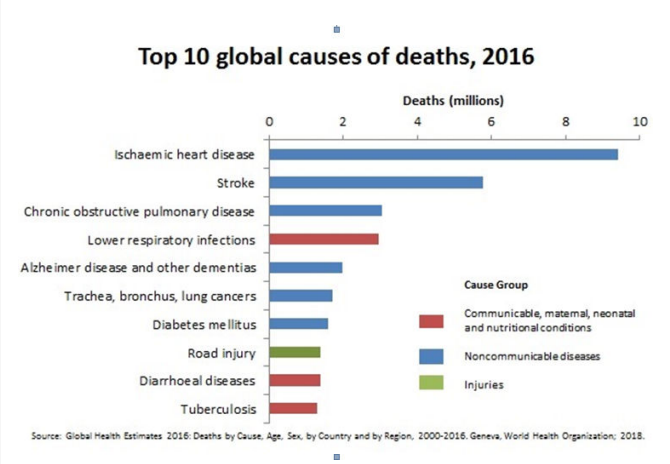

Figure 1: Source: Global Health Estimates 2016. Cause groups: red (communicable maternal disease, neonatal and nutritional conditions); blue (non-communicable diseases); green (injuries).

EPIDEMIOLOGY OF THE DISEASE

Worldwide, cases of dementia have increased from 35.6 million in 2010 to 46 million in 2015, around 50 million in 2017, with projections to 82 million in 2030 and 152 million in 2050. At the same time, the rate of occurrence increases significantly with age. This is being attributed to the rising numbers of people with dementia who live in low- and middle-income countries (~60% of people affected), where the sharpest increases in numbers is affected. Table 1 summarizes the estimated proportion of the general population aged 60 and over with dementia. It shows that dementia caused ~1.7 million deaths in 2013, up from 0.8 million in 1990.

Table 1: Percentage of Dementia Cases as a Function of Age.

Age* ==> % for different populations	65-74	75-84	Over 85
Low-to-middle income	3%	19%	~50%
Developed countries	5%	5%	20-40%

*Slightly higher in women than men at ages 65 and older.

SIGNS AND SYMPTOMS

Most dementia types are slow and progressive with variable symptoms across type and stage of the disease and vary with the affected individual. The diagnosis is a differential one from previous mental functioning with a greater differential than would have been expected due to aging. The signs and symptoms evolve along the following three phases:

Early phase: Gradual, often overlooked with common symptoms (forgetfulness, space and time confusion).

Middle phase: Clear and more restricting symptoms as the disease progresses, including need for greater help, having balance problems; tremors; trouble eating and swallowing; speech and language difficulties; behavioral changes (wandering, restlessness, repeated questioning); forgetfulness (of recent events, peoples' names); other difficulties (communication, attention, problem-solving); and memory distortions (sequence of events, combination of memories, confusion of people, etc.) [17-23].

Late phase: Marked by serious memory disturbances (including not recognizing relatives and friends), greater physical difficulties, near total dependence and inactivity, behavioral changes (including aggressiveness, crying, anger), unawareness of time and space.

In all types of dementia, behavioral and psychological symptoms (BPSD) almost always occur such as: abnormal motor behavior; agitation; aggression; anxiety; apathy; sleep changes; delusions; depression; disinhibition and impulsivity; elated mood; irritability; and psychosis.

RISK FACTORS

Each dementia form has its own risk factors but most dementia types have certain common risk factors. These are:

Age: The biggest risk factor for people aged 60 years or more, especially over 80 years of age (80-85: ~1 in 6 persons; above 85: ~1 in 3 persons; above 90: ~1 in 2 persons). This is a less frequent risk for people younger than 60.

Family history: There is an increased risk for people with a first-degree relative having AD, and more so if that relative developed AD at a younger age (less than ~70). There is also a heritable genetic component, apoE4 [24-26], although in this case only about one-half develop AD by age 90 because of other causative factors.

Other factors: These include: diabetes, hypertension and attendant risks, and lifestyle factors (sedentary lifestyle, lack of social connections and mental engagement, etc.).

STAGING OF THE DISEASE

Dementia has four progressive and successive stages. The corresponding scores in the Mini-Mental State Examination (MMSE) are provided in Table 2 below:

Mild cognitive impairment (MCI): Signs and symptoms (memory problems, trouble finding words) are subtle and not severe enough to affect daily life function. However, 70% of persons affected will go on to develop dementia at some later point in their life.

Early stage dementia (ESD): Symptoms (memory difficulties, anomia, executive function problems, personality change, social withdrawal, etc.) are more noticeable.

Middle stage dementia (MSD): Symptoms (problem-solving difficulties, impaired social judgment, preclusion of outside-of-the-home functioning, needed assistance for personal care and hygiene) generally worsen.

Late stage dementia (LSD): Symptoms (required assistance for personal care and hygiene, needed supervision for personal safety, changes in diet and sleep patterns, etc.) change significantly.

Table 2: Mini-Mental State Examination and Dementia Stages.

Dementia Stage	MMSE Score
Mild cognitive impairment (MCI)	27-30 (normal)
Early stage dementia (ESD)	20-25
Middle stage dementia (MSD)	06-17
Late stage dementia (LSD)	<< 6

MENTAL DISORDER CLASSIFICATION

The classification of mental disorders (also known as psychiatric nosology or taxonomy) is a key aspect of psychiatry and other mental health professions, and an important issue for people who may be diagnosed. The two established classification systems are: Chapter 5 of the International Classification of Diseases (ICD-10) and Version V of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the latter having been produced by the American Psychiatric Association (APA). The codes in both classifications have been converged, however, significant differences remain. Other classification schemes include, for example, the Chinese Classification of Mental Disorders (CCMD) and the Psychodynamic Diagnostic Manual (PDM). Chapter 5 of the ICD-10 focuses on "mental and behavioral disorders". It consists of 10 main groups with specific subcategories in each group. Unlike DSM-V, it includes personality disorders on the same domain as other mental disorders. It further states that a mental disorder is "not an exact term" although it is generally used to imply the existence of a clinically recognizable set of symptoms or behaviors associated in most cases with distress and with interference with personal functions." As part of its development of ICD-10, the World Health Organization (WHO) has revised its classifications. On the other hand, the DSM organizes each psychiatric diagnosis into five dimensions (or axes, or domains) related to different aspects of disorder or disability. Dementia (axis 1, group 2) was reclassified as a neurocognitive disorder with various degrees of severity.

APPROACH TO DIAGNOSIS

Since symptoms can be very similar in all types of dementia, they cannot by themselves help in reaching the correct diagnosis of demential type(s). Diagnosis is usually based on the history of the illness, preliminary tests, and cognitive testing with medical imaging, and blood tests used to rule out other possible causes or conditions. The MMSE is one commonly used cognitive test (Table 2).

Preliminary testings

Usually employed to rule out confounding deficiencies/illnesses. They consist of:

Niacin, Folate, or Vitamin B12 deficiency (of which pernicious anemia is a type): Vitamin B12 is important for growth, cell production, and, importantly, nerve function. However, it does not improve outcomes in those with cognitive problems. (Likewise, statins have no benefit in dementia).

Delirium [also known as "acute confusional state (ACS)"]: An organically-caused decline from a previous baseline level of mental function, delirium includes attentional deficit behavior and disorganization. It is a set of symptoms that involve other cognitive deficits, changes in arousal (hyperactive, hypoactive, or mixed), perceptual deficits, altered sleep-wake cycle, and psychotic features such as hallucinations and delusions. It may be caused by a disease process outside the brain that nonetheless affects the brain, such as infection or drug effects (particularly anti-cholinergics or other CNS depressants such as benzodiazepines and opioids). It manifests a new organic brain dysfunction. It can easily be confused with a number of psychiatric disorders or long term organic brain syndromes, because many of the signs and symptoms are conditions also present in dementia, depression, and psychosis.

Mental illnesses (depression and psychosis) testing: Using the Neuropsychiatric Inventory (NPI) or the Geriatric Depression Scale (GDS) tests.

Paralytic dementia (also known as general paresis, general paralysis of the insane): It is a severe neuropsychiatric disorder that has been classified as an organic mental disorder, which is caused by chronic meningoencephalitis that leads to cerebral atrophy in late-stage syphilis.

Infective conditions: These include cryptococcal meningitis, AIDS, Lyme disease, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis, syphilis, and Whipple disease.

Cognitive testing

Usual tests (memory, executive function, processing speed, attention, language skills, emotional and psychological adjustment) are used to rule out other etiologies and determining relative cognitive decline over time or from estimates of prior cognitive abilities. Several, reasonably reliable tests have been employed and studied; it is recommended to administer them to people over age 65 (including demented patients) with memory complaints:

The Mini Mental State Examination (MMSE): A useful tool if accompanied by an assessment of a person's personality to perform activities of daily living and behavior.

The Montreal Cognitive Assessment Test (MOCA): A very reliable screen test, it is somewhat better than the MMSE for detecting mild cognitive impairment (MCI). It can be completed on-line.[50]

The Self-Administered Questionnaire (SAQ): It asks about the person's everyday cognitive functioning to complement the information obtained from brief cognitive tests.

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): It is not known how accurate this questionnaire is for diagnosing or predicting dementia;

The Alzheimer Disease Caregiver Questionnaire (ADCQ): It is about 90% accurate. It can be completed online or in the office by a caregiver; and

The General Practitioner Assessment of Cognition (GPAC): It was designed for use in the primary care setting.

Table 3 provides the sensitivity and specificity of common tests for dementia. (Note: Screening the general population for dementia is not recommended):

Table 3: Sensitivity and Specificity of Common Tests for Dementia.

Test	Sensitivity (%)	Specificity (%)
MMSE	71-92	56-96
3MS	83-93.5	85-90
AMTS	73-100	71-100

Laboratory tests

Routine blood tests are usually performed to rule out treatable causes. These tests include:

- Vitamin B12 (as seen earlier);
- Folic acid (FA, as seen earlier);
- Thyroid-stimulating Hormone (TSH);
- C-reactive protein (CRP) (a measure of inflammation); and

- Full blood count, including electrolytes, calcium, renal function, and liver enzymes.

Abnormalities may suggest vitamin deficiency, infection, or other problems that commonly cause confusion or disorientation in the elderly.

Imaging Scans: Brain scanning may help in the diagnosis or even provide an accurate one. However, only a brain biopsy (not recommended, but can be performed at autopsy) can lead to an absolutely accurate diagnosis.

- Computed Tomography (CT) or Magnetic Resonance Imaging (MRI): Either of these two scans-is commonly performed, although neither one evidences the diffuse metabolic changes of dementia in a person that shows no gross neurological problems (such as paralysis or weakness) on neurological exam. Either test may suggest normal pressure hydrocephalus (NPH) (a potentially reversible cause of dementia), other types of dementia, and infarction (stroke).
- Functional Neuroimaging Modalities of Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET): These tests are similar in their ability in detecting dementia and are more useful than either CT or magnetic resonance imaging (MRI). Further, being able to differentiate the vascular cause (i.e., multi-infarct dementia) from AD dementia, SPECT is superior to differentiation by clinical exam.

Recent research has established the value of PET imaging using carbon-11 Pittsburgh Compound B(PIB-PET) or carbon-aa dihydrotetrabenazine (DTBZ) as a radiotracer has shown that persons with MCI will develop AD within two years [27-30].

CONTRIBUTING DISEASES

The main contributors to dementia are summarized in Table 4. Other minor contributors are also mentioned later in this section.

More than one type of dementia (one of the factors listed in Table 4) may exist in the same person, as noted earlier. Also, a small proportion of cases run in families.

Reversible diseases: There are four main causes of easily reversible dementia:

- Hypothyroidism;
- Vitamin B12 deficiency;
- Lyme disease; and
- Neurosyphilis.

All people with memory difficulty should be checked for hypothyroidism and B12 deficiency. For Lyme disease and neurosyphilis, testing should be done if there are risk factors for those diseases. Because risk factors are often difficult to determine, testing for neurosyphillis and Lyme disease, as well as other unmentioned factors, may be undertaken as a matter of course in cases where dementia is suspected.

Alzheimer disease (AD): This is the first most common contributing factor to dementia (Table 4). For a recent review of this disease and recent research developments, refer to Fymat [31-34].

Vascular dementia (VD): This second most important contributing factor to dementia is due to reduced blood flow to the brain either as a result of clogged blood vessels or fatty deposits within (Table 4). It is more common among people who have had strokes or are at risk for strokes, especially those with longstanding high blood pressure and diabetes. It typically involves a series of minor strokes.

Dementia with Lewy bodies (DLB): Caused by abnormal proteins (the Lewy bodies) within brain cells, this form of dementia shows symptoms similar to those in Parkinson disease (PD). The primary symptoms are visual hallucinations, attention disorganization, executive functions difficulties,"Parkinsonism", etc. Imaging is not always necessary and may not be diagnostic although there are particular signs in SPECT images (occipital hypoperfusion) and PET images (occipital hypometabolism). Diagnosis is generally straightforward for the practicing neurologist.

Parkinson disease dementia: It can occur in the course of PD with very similar symptoms to DLB [For a recent review of PD and Parkinsonism [34-37].

Frontotemporal dementia (FTD): As its name implies, frontotemporal dementia (FTD) targets two specific brain areas, the frontal and temporal lobes. It is caused by nerve cell loss in the brain and may precede the onset of AD. It manifests itself in three forms: speech impairment and eventually loss, language difficulty, and drastic personality change but memory problems are not its main feature. The three main types are: Behavioral variant FTD: The most common with major personality and behavior symptoms. Temporal variant (or semantic) dementia: Loss of meanings (words, objects, etc.) Progressive nonfluent aphasia (PNFA): A speech problem (use of one-syllable words leading eventually to becoming mute)[38].

Mixed Dementia (MD): Among persons at more advanced age (especially 85 and greater), there can be more than one cause of dementia, often both AD and vascular damage.

Progressive supranuclear palsy (PSP): A form of dementia characterized by eye movement problems, balance problems, rigid muscles, irritability, apathy, social withdrawal, depression. It is sometimes misdiagnosed as PD. On brain scans, there are no common visible brain abnormalities except an atrophied midbrain [39].

Corticobasal degeneration (CBD): A rare form of dementia with the following signs: difficulty using only one limb (named "alien limb") over which there seems to be no brain control, asymmetric movement symptoms (myoclonus, dystonia, tingling of the limbs), speech difficulty (inability to coordinate mouth muscles). The affected brain areas are the posterior frontal and parietal lobes, although many other brain parts can be affected. Creutzfeldt-Jacob disease (CFD): Caused by prions, CFD is a slowly progressive dementia.

Encephalopathy: Resembles dementia, with possible causes including:

- Brain infection: Viral encephalitis (VE); sub-acute sclerosing encephalitis (SASE); Whipple disease (WD).
- Brain inflammation: Limbic encephalitis (LE); Hashimoto encephalopathy (HE); cerebral vasculitis (CV); tumors (lymphoma, glioma); drug toxicity (e.g., anticonvulsant drugs); metabolic failures (liver, kidneys); and chronic subdural hematoma (CSH).

Immunologically mediated inflammatory conditions: Behcet disease (BD); multiple sclerosis (MS); sarcoidosis; Sjogren syndrome (SS); systemic lupus errhythematosus (SLE); and celiac disease (CD). Early treatment includes immunomodulators or steroids.

Other medical and neurological conditions: They can be caused by cumulative damage to the brain from chronic alcoholism, repeated head injuries (e.g., among former professional boxers or football players) [40-46].

Inherited conditions: These include: Alexandre disease (AD); cerebrotendinous xanthomatosis (CX); dentatorubal pallidoluysian atrophy (DPA); Epilepsy; Fatal familial insomnia (FFI); Fragile associated tremor/ataxia syndome (FXTAS); Glutaric aciduria type 1 (GA); Krabbe disease (KD); Maple syrup urine doisease (MSUD); Niemann-Pick disease type C (NPD); Neuronal ceroid lipofuscinosis (NCL); Neuroacanthocytosis; Organic acidemias; Pelizaeus-Merzbache disease (PMD); San Filippo syndrome type B (SFS); Spinocerebellar ataxia type 2 (SCA); and Urea cycle disorders [47-51].

Table 4: Contributors to Dementia.

Disease	Contribution (%)
Alzheimer disease (AD)	50-70
Vascular dementia (VD)	25
Lewy body dementia (LBD)	15

Parkinson disease dementia (PDD)	
Frontotemporal dementia (FTD)	
Mixed dementia (MD)	
Senilitic dementia or senility (SD)	
Normal pressure hydrocephalus (NPH)	
Parkinson disease (PD)	
Syphilis	Unspecified
Creutzfeldt-Jacobs disease (CJD)	

ON COGNITIVE IMPAIRMENT

The following instances of cognitive impairment must be differentiated:

Mild cognitive impairment (MCI): Often difficult to diagnose (MMSE scores ~25-50), about 70% of people with MCI develop some form of dementia in one of the following two categories:

- Amnestic MCI: Primarily memory loss. People with amnestic MCI may develop AD;
- Non-amnestic MCI: Not primarily memory difficulties. People with non-amnestic MCI may develop other types of dementia [52].
- Often difficult, the MCI diagnosis requires Peterson criteria (memory or other cognitive complaint thought-processing; memory or other cognitive problem). The problem must not affect the person's daily functioning and the person must not have dementia.

Fixed cognitive impairment (FCI): Long-term effects on cognition such as may result from:

- Various types of brain injury: including traumatic brain injury: These may cause diffuse axonal injury (damage to the brain's white matter), whether generalized or local (as also may neurosurgery) [53-56].
- Temporary brain hypoxia: May lead to hypoxic-ischemic injury. Strokes (ischemic stroke, or intracerebral, subarachnoid, subdural or extradural hemorrhage) or infections (meningitis or encephalitis) affecting the brain, prolonged epileptic seizures, and acute hydrocephalus may also have long-term effects on cognition.
- Excessive alcohol use: May cause alcohol dementia (AD); Wernicke encephalopathy (WE) or Korskoff psychosis (KP) [57-59].

ON NEURODEGENERATIVE DEMENTIA

Dementia that begins gradually and worsens progressively over several years is usually caused by neurodegenerative disease (NDD). A non-degenerative condition may have secondary, possibly reversible effects, if treated.

DEMENTIA VARIATIONS WITH AGE OF OCCURENCE

Causes of dementia depend on the age when symptoms begin:

Over 65 years of age: The main contributor in a large number of cases is AD, VD, or both, DLB that may occur alongside either or both AD and VD, and hypothyroidism (fully reversible with treatment). Though relatively rare, it is important to recognize normal pressure hydrocephalus (NPH) since treatment may prevent progression and improve other symptoms of the condition.

Under 65 years of age: While much less common, AD is still the most frequent contributor, and even more so if inherited. Frontotemporal lobar degeneration (FTLD) and Huntington disease (HD) make up for the remainder of cases. VD also occurs and, subsequent to repeated head trauma, leads to chronic traumatic encephalopathy (CTE).

Up to 40 years of age: Rare and caused by psychiatric illness, alcohol or drug abuse. Other causes may be metabolic disturbances and genetic disorders that may provoke neurodegenerative dementia, including: AD, SCA17 (dominant inheritance); X-linked adenoleukodystrophy (ADL); Gaucher disease (GD) type 3; metachromatic leukodystrophy (MCLD); Niemann-Pick disease (NPD); pantothenate kinase-associated neurodegeneration (PKAN); Tay-Sachs disease and Wilson disease (WD), which are all recessive. In WD, cognition can improve with treatment [60-65].

MANAGEMENT

Except for the treatable types listed above, and in the absence of a thorough understanding of the deep biology of dementia, there is currently no cure for the disease. As previously emphasized, medical interventions remain therefore palliative with aim to alleviate pain and suffering. They include:

- Cognitive and behavioral interventions.
- Education and support for the patient and the patient's family and caregiver(s).
- Activity and exercise programs.

Psychological and reminiscence therapies: While benefits are small, the areas covered include: Quality of life, cognition, communication, mood, and cognitive reframing for caretakers; Validation therapy; and Mental exercises: such as cognitive stimulation programs.

Adult daycare centers, special care units in nursing homes, and home care: These institutions provide specialized care and one-on-one care in the home.

Psychiatric nursing: Can make a distinct contribution to patients' mental health [49].

PSYCHOPHARMACOTHERAPY FOR ALZHEIMER DISEASE AND OTHER DEMENTIA

Treatment of memory problems (optional): Several medicines are presently available for treating AD. The trial lasts about 8-weeks with monitoring for side effects and response.

Cholinesterase inhibitors: These drugs allow the chemical acetylcholine to be active, making up for its AD-related drops: Donepezil (Aricept®); Rivastigmine (Exelon®); and Galantamine (Razadyne®) (Figure 2).

They have been conditionally recommended by the U.K. National Institute for Clinical Excellence (NICE) as an option in the management of mild-to-moderate AD and by the U.S. Food and Drug Administration (FDA) for mild, moderate and severe dementia.[7,42,53]

Common adverse effects: They include: nausea, vomiting, gastrointestinal upset, diarrhea, weight loss, fainting; spells, difficulty sleeping with very vivid dreams (when taken at bedtime), muscle cramping, slow heart rate and fainting in people with heart problems.

Precautions: Donepezil should be used with caution in people with (a) cardiac problems: heart disease, cardiac conduction disturbances, chronic obstructive pulmonary disease (COPD), severe cardiac arrhythmias; (b) asthma; (c) sick sinus syndrome (SSD); (d) peptic ulcer disease (PUD) or taking non-steroidal anti-inflammatory drugs (NSAID); and (e) in case of predisposition to seizures.

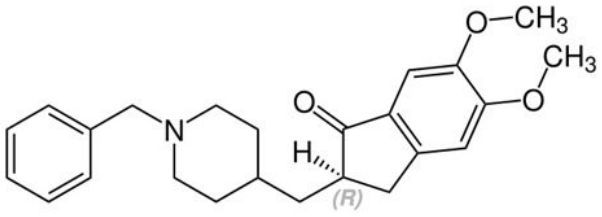

Figure 2: Chemical Formula for the Cholinesterase Inhibitor Donepezil.

Memantine (Namenda®): Usually employed along anti-cholinesterase but works differently x a protector from further damage. Possible side effects incklude: Dizziness, aggression and hallucinations.

N-Methyl D-Aspartate (NMDA) receptor blockers: Memantine may be beneficial but less conclusively than for acetylcholinesterase inhibitor (AchEI) or anti-cholinesterase. These two drugs may be used in combination thanks to their differing mechanisms of action. Still, the benefit of these combined drugs remains slight. Folate or Vitamin B12: Show no improved outcomes in cognitive problems. Statins: Show no benefit. Blood pressure medications: There is no clear link with dementia.

Precaution: People may experience an increase in cardiovascular-related events if these medications are withdrawn. Possible side effects: Dizziness, aggression and hallucinations.

Treatment of behavioral symptoms including depression: Antipsychotics are commonly employed; they have little benefit but present side effects (confusion, depression). For depression, selective serotonin reuptake inhibitors (SSRI) are preferred. Widely used forms of SSRIs include:

- Antipsychotics: Not routinely recommended (due to their small benefit and risky side effects, including stroke and possibly death) but used only if non-drug therapies have not worked, and the person's actions threaten themselves or others [20-23].
- Selective serotonin reuptake inhibitors (SSRI): Preferred over other choices in patients with dementia. Widely used SSRIs include: Fluoxetine (Prozac®); Sertraline (Zoloft®); Paroxetine (Paxil®); Citalopram (Celexa®); and Escitalopram (Lexapro®).

Note: Sertraline and Citalopram do not reduce symptoms of agitation compared to placebo and do not affect outcomes.

Anxiety and aggression: Caused by a number of factors, including: confusion, disorientation, paranoid delusions, hallucinations, etc.

Sleep problems: Can be treated with either medicine or behavior changes, or both.

Changes in medication management: The Medications Appropriateness Tool for Co-Morbid Health – Dementia (MATCH-D) criteria can help changes in medication management. Alternative therapies: Aromatherapy, cannabinoids, omega-3 fatty acid supplements do not offer notable benefits.

COMPLEMENTARY TREATMENTS

Pain: Aging is accompanied with a substantial, at times persistent, burden of pain, which must be addressed.

Eating difficulties: Options available are: assisted feeding; gastrostomy feeding tube (aside from complicated operational procedures and, albeit very small, risk of fatality), may cause agitation; worsening pressure ulcers; fluid overload; diarrhea; abdominal pain; local complications; and risk of aspiration. Palliative care: Recommended.

PREVENTION

No medications or supplements have shown good preventative evidence, including blood pressure medications. Efforts to prevent dementia include: Early education; decrease of risk factors (hypertension, diabetes and obesity, hearing loss, depression, social isolation; lifestyle changes that incorporate physical exercise and social activities; and computerized cognitive training that may improve memory.

CONCLUSIONS

While much is known about dementia and the underlying and contributing factors, and much has been published on the subject, we still do not understand the deep biology of the disease. Lacking this understanding, we have so far failed to find a cure and continue to be limited to symptomatic treatments that have limited or no benefit. In the case of Alzheimer dementia, the main contributor, there is a ray of hope in the recent suggestion [28] that the root cause of Alzheimer may be but an autoimmune disease gone rogue, and that deposits (or plaques) of beta-amyloid (a protein) and the neurofibrillary tangles (disorganized masses of protein fibers within the brain cells) may only be the signs of a brain homeostasis that had broken down under an avalanche of brain insults [17-19]. Similar innovative ideas and suggestions should be pursued for the other contributors to dementia.

ABBREVIATIONS

AChEI: Acetyl Choline Esterase Inhibitor

ACS: Acute Confusional State (Delirium)

AD: Alzheimer Disease

AD: Alexandre Disease

AD: Alcohol Dementia

ADCQ: Alzheimer Disease Caregiver Questionnaire

ALD: Adeno Leuko Dystrophy

AMTS: Abbreviated Mental Test Score

APS: American Psychiatric Association

BD: Behcet Disease

BPSD: Behavior and Psychological Symptoms of Dementia

CASI: Cognitive Abilities Screening Instrument

CBD: Cortico Basal Degeneration

CCMD: Chinese Classification of Mental Disorders

CD: Celiac Disease

CDT: Clock-Drawing Test

COPD: Chronic Obstructive Pulmonary Disease

CPR: Cardio Pulmonary Resuscitation

CRP: C-Reactive Protein

CSH: Chronic Subdural Hematoma

CT: Computed Tomography

CTE: Chronic Traumatic Encephalopathy

CV: Cerebral Vasculitis

CTX: Cerebro Tendinous Xanthomatosis

DPA: Dentatorubal Pallidoluysian Atrophy

DSM: Diagnostic and Statistical Manual of Mental Disorders

DTBZ: (carbon-11) Dihydro Tetra Benazine (a radiotracer)

ESD: Early Stage Dementia

FA: Folic Acid

FCI: Fixed Cognitive Impairment

FDA: (U.S.) Food and Drug Administration

FFI: Fatal Familial Insomnia

FTD: Frontotemporal Dementia

FTLD: Fronto Temporal Lobar Degeneration

FXTAS: Fragile X-Associated Tremor/Ataxia Syndrome

GD: Gaucher Disease

GDS: Geriatric Depression Scale

GPAC: General Practitioner Assessment of Cognition

HD: Huntington Disease

HE: Hashimoto Encephalopathy

HXV: Herpes Simplex Virus

IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly

KD: Krabbe Disease

KP: Knockoff Psychosis

LBD: Lewy Body Dementia

LE: Limbic Encephalitis

ICD: International Classification of Diseases

LSD: Late Stage Dementia

MATCH-D: Medications Appropriateness Tool for Co-morbid Health – Dementia

MCI: Mild Cognitive Impairment

MCLD: Meta Chromatic Leuko Dystrophy

MD: Mixed dementia

MS: Multiple Sclerosis

3MS: Modified Mini-Mental State Examination

MMSE: Mini-Mental State Examination

MOCA: Montreal Cognitive Assessment Test

MRI: Magnetic Resonance Imaging

MSD: Middle Stage Dementia

MSUD: Maple Syrup Urine Disease

NCL: Neuronal Steroid Liposuction

NICE: (U.K.) National Institute for Clinical Excellence

NIDDS: National Institute of Neurological Disorders and Stroke

NDD: Neuro Degenerative Disease

NFD: Nero Fibrillary Tangles

NMDA: N-Methyl D-Aspartate receptor blockers

NPD: Niemann-Pick Disease

NPH: Normal Pressure Hydrocephalus

NPI: Neuropsychiatric Inventory

NSAID: Non-Steroidal Anti-Inflammatory Drugs

PD: Precocious Dementia

PD: Parkinson Disease

PDD: Parkinson Disease Dementia

PDM: Psychodynamic Diagnostic Manual

PET: Positron Emission Tomography

PIB-PET: (carbon-11) Pittsburgh Compound B (a radiotracer)

PKAN: Pantothenate Kinase-Associated Neurodegeneration

PMD: Pelizaeus-Merzbache Disease

PNFA: Progressive Non-Fluent Aphasia

PNS: Peripheral Nervous System

PSNP: Progressive Supra Nuclear Palsy

PUD: Peptic Ulcer Disease

SASE: Sub-Acute Sclerosing Encephalitis

SAT: Self-Administered Test

SCA: Spino Cerebellar Ataxia

SD: Syphilitic Dementia

SFS: San Filippo Syndrome

SLE: Systemic Lupus Errhythematosus

SPECT: Single Photon Emission Tomography

SS: Sjogren Syndrome

SSRI: Selective Serotonin Reuptake Inhibitors

SSS: Sick Sinus Syndrome

TMT: Trail-Making Test

TSD: Tay - Sachs disease

TSH: Thyroid Stimulating Hormone

VD: Vascular Dementia

VE: Viral Encephalitis

WD: Whipple Disease

WD: Wilson Disease

WE: Wernicke Encephalopathy

WHO: World Health Organization

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