REVIEW ARTICLE

On Dementia and other Cognitive Disorders

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ABSTRACT

Dementia is an umbrella term for several diseases affecting memory, other cognitive abilities, and behavior that interfere significantly with the maintenance of daily living activities. It is not a normal part of aging. The author will review the many different diseases that can cause or contribute to dementia. However, not being a specific disease, these various contributors do not reach to the primary cause of the disease. Thus, unable to pinpoint the root cause of the disease, we are powerless in treating it, and 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 summary of the epidemiology of the disease, the author will cover the three phases (early, middle, and late) of its signs and symptoms, its risk factors, its four progressive stages (mild cognitive impairment and early, middle, and late dementia), and its classification (both within the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders). The study will also discuss the approach followed to reach a diagnosis (including preliminary and cognitive testings, and imaging scans). The main contributors to dementia (Alzheimer's disease; the various dementias: vascular, Lewy body, Parkinson, frontotemporal, and senility; normal pressure hydrocephalus; and Creutzfeldt-Jakob's disease) and other contributors are discussed. The various cognitive impairments (mild and fixed), neurodegenerative dementia as well as the variations of dementia with age of occurrence are succinctly described. Management of the disease and associated psychopharmacotherapy are also detailed, although the medications used have little or no effect on the underlying disease process. Finally, complementary and preventive measures are outlined.

Key words: Alzheimer's 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 (2017), 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 activities of daily living. Although age is the strongest known risk factor for dementia, it is not a normal part of aging". It is a broad category of brain diseases that cause a long-term and often gradual decrease in the ability to think and remember that is great enough to affect a persons' daily functioning. Other common symptoms include "emotional problems, language difficulties, and decreased motivation." The definition provided by the U.S. National Institute of Neurological Disorders and Stroke (2018) is more detailed in 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."

Many different diseases can cause dementia, including Alzheimer's disease (AD), fronto-temporal dementia (FTD); lewy body dementia, vascular dementia (VD), syphilitic dementia, mixed dementia (MD), senility dementia, or the combined effect of two or more types of dementia, and even stroke. About 10% of individuals present with MD, usually the 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.

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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. And, indeed, there is no known cure for dementia. 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/ecogenetic influences.[1-12]

EPIDEMIOLOGY OF THE DISEASE

With elongating lifespan in the developed world, dementia has emerged as an increasing public health concern. It was uncommon in pre-industrial times and relatively rare before the 20th century. As more people are living longer, and as risk factors are decreasing or better managed, dementia is becoming more common in the population as a whole. Alzheimer's disease (AD) and other dementias are fifth among the top 10 global causes of mortality [Figure 1].

Worldwide, dementia affected ~50 million people (2017), 46 million (2015), and 35.6 million (2010). with projections of 82 million (2030) and 152 million (2050), much of the increase located in low- and middle-income countries (nearly 60% of people affected). Table 1 shows the increasing percentage of dementia with age. In 2013, dementia resulted in about 1.7 million deaths up from 0.8 million in 1990.

Causes of dementia depend on the age when symptoms began. Thus, Table 2 illustrates the variations of dementia with age of occurrence.

SIGNS AND SYMPTOMS

Most dementia types are slow and progressive. In their early stages, the onset is gradual to the point of not being clearly noticeable. Symptoms vary across types and stages of the disease and vary with the individual. Signs and symptoms evolve along three phases (early, middle, and late) that have been loosely categorized in Table 3 as psychological, memory, cognition, behavioral, and motor. Behavioral and psychological symptoms almost always occur in all types of dementia.[13]

RISK FACTORS

While most dementias have several common risk factors, each dementia type has its own risk factors, but most forms have several risk factors. These are summarized in Table 4.

STAGING OF THE DISEASE

Dementia has four progressive and subsequent stages. Scores in the mini-mental state examination are provided in Table 5.

MENTAL DISORDER CLASSIFICATIONS

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 following classifications are presented in Table 6.

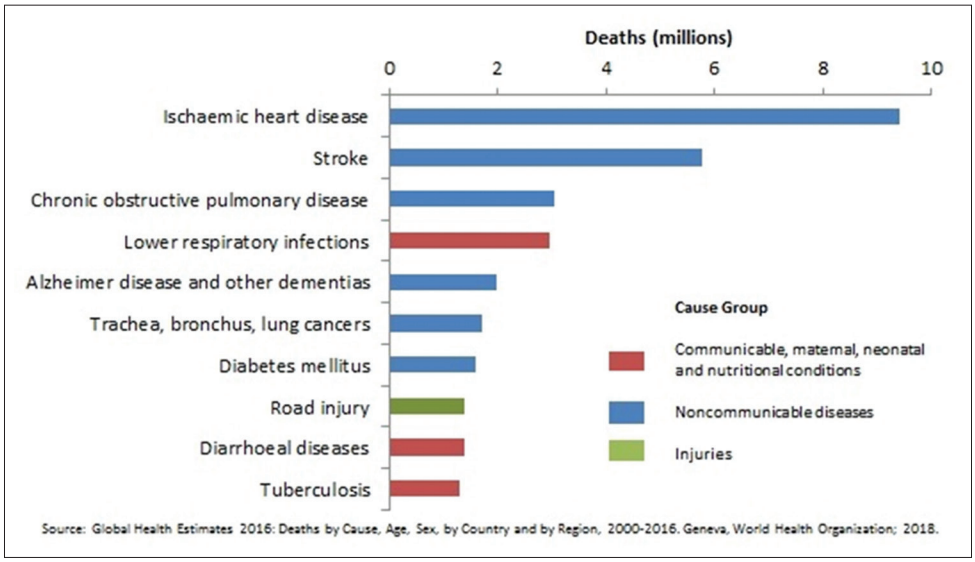

Figure 1: Top 10 global causes of deaths, 2016. Source: Global Health Estimates 2016. Cause groups: Red (communicable maternal disease, neonatal, and nutritional conditions); blue (non-communicable diseases); green (injuries)

APPROACHES TO DIAGNOSIS

A diagnosis requires a change from a persons' usual mental functioning and a greater decline than one would expect due to aging. Being very similar in all types of dementia, symptoms cannot by themselves help to reach the correct diagnosis of dementia type(s). Diagnosis usually proceeds along the following lines (Table 7). Screening the general population for dementia is not recommended.[14-31]

Table 8 provides the sensitivity and specificity of common tests for dementia.

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		20–40

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

REVERSIBLE DISEASES

Hypothyroidism, Vitamin B12 deficiency, Lyme disease, and neurosyphilis are reversible diseases. All people with memory

Table 2: Dementia variations with age of occurrence

Age	Contributor (s)	Treatment effects
<40	Rare without other neurological disease Genetic disorders can cause true NDD: AD, SCA 17 (dominant inheritance), X-linked ADL, GD type 3, MCLD, NPD, PKAN, WD	Treatment of underlying psychiatric illness, alcohol or drug abuse or metabolic disturbance WD is particularly important since cognition can improve with treatment
<65	AD is most frequent Inherited forms account for higher proportion FTLD and HD account for the rest VD in cases of repeated brain traumas CTE	
> 65	Alzheimer's dementia (AD), VD, or both and DLB occurring alongside either AD or VD or both Hypothyroidism NPH	Fully reversible with treatment Treatment may prevent progression and improve other symptoms

NDD: Neurodegenerative Dementia, AD: Alzheimer's Disease, SCA: Spinocerebellar Ataxia, MCLD: Metachromatic Leukodystrophy, NPD: Niemann–Pick Disease, PKAN: Pantothenate Kinase-Associated Neurodegeneration, WD: Wilson Disease, CTE: Chronic Traumatic Encephalopathy, DLB: Dementia with Lewy Bodies, AD: Alzheimer's Dementia, WD: Whipple disease, FTLD: Frontotemporal lobar degeneration, GD: Gaucher disease, HD: Huntington disease, NPH: Normal pressure hydrocephalus, TSD: Tay–Sachs disease, VD: Vascular disease

Table 3: Signs and symptoms of dementia

Phase	Psychological	Memory	Cognition	Behavioral	Motor
Early (gradual onset)	Lost in time and space	Forgetfulness	Speech and language difficulties		
Middle (progressing disease)	Communication difficulties Attention deficit Problem solving	Lost at home Forgetfulness Memory distortions Confusion	Increased speech and language difficulties (anomia)	Wandering Restlessness Repeated questioning Agitation Anxiety Apathy	Help personal care Balance problems Tremors Trouble eating and swallowing
Late (advanced disease)	Unaware of time and space Delusions Hallucinations Depression Disinhibition Impulsivity Psychosis	Serious memory disturbances Difficulty recognizing relatives and friends		Agitation Aggression Crying Anger	Total dependence and inactivity Difficulty walking

Table 4: Principal risk factors for dementia

Age	Family History (ApoE ϵ4)	Other factors
Biggest risk factor: <60: Rare>80: Common 80–85: 1 in 6>85: 1 in 3>90: 1 in 2	Increased risk of AD if First degree relative with AD Relative developed AD<70 Decreased risk if: Relative got AD late in life Half of people with ApoE ϵ4 develop AD by age 90	Hypertension Diabetes Lifestyle factors (including lack of social connections and mental engagement)

Table 5: Staging of dementia and mini-mental state examination scores

Dementia stage	Signs and symptoms	MMSE score
MCI	Subtle (apparent in retrospect) Not severe enough 70% progress to dementia Mostly memory difficulties	27–30 (normal)
ESD	Interfere with daily activities Difficulties: Memory, anomia, executive functions, psychological, cognition, behavioral, and motor	20–25
MSD	Worsen Executive/social judgment impaired Assistance required (hygiene, care)	6–17
LSD	24 h assistance/supervision Changes in diet Significant changes in sleeping habits	<6

MCI: Mild cognitive impairment, ESD: Early stage dementia, MSD: Middle stage dementia, LSD: Late stage dementia, MMSE: Mini-mental state examination

Table 6: Classification of mental disorders

ICD-10 or later	DSM-V*	Others
Similar categories than DSM-V: 10 groups with subcategories Includes personality disorders	Similar categories than UCD-10 5 dimensions (axes and domains) Dementia is a neurocognitive disorder with various degrees of severity (axis 1 and Group 2)	CCMD PDM

*Produced by the American Psychiatric Association, ICD: International Classification of Diseases, DSM: Diagnostic and Statistical Manual of Mental Disorder, CCMD: Chinese Classification of Mental Disorders, PDM: Psychodynamic Diagnostic Manual

difficulty should be checked for hypothyroidism and B12 deficiency. For Lyme and neurosyphilis, testing should be done if there are risk factors for those diseases. As 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.

CONTRIBUTING DISEASES

The main contributors to dementia are summarized in Table 9 with other (unlisted) minor contributors, including senilitic dementia (SD) or senility, normal pressure hydrocephalus, and syphilis.

TYPES OF COGNITIVE IMPAIRMENT

The following instances of cognitive impairment must be differentiated [Table 10].[32-51,27]

ON NEURODEGENERATIVE DEMENTIA

Dementia that begins gradually and worsens progressively over several years is usually caused by a neurodegenerative disease - that is, by conditions that affect only or primarily the neurons of the brain and cause gradual but irreversible loss of function of these cells. Less commonly, a non-degenerative condition may have secondary effects on brain cells, which may or may not be reversible if the condition is treated.

Table 7: Approaches to a dementia diagnosis

Type	Approach	Outcome/Characteristic
History	History of the illness	
Preliminary tests	To rule out confounding diseases/disorders: Niacin, folate or Vitamin B12 deficiency, and statins ACS: Deficits in cognition, perception, sleep-wake cycle, psychosis (hallucinations, delusions). May be caused by infection or drugs (anticholinergics, benzodiazepines, and opioids) Mental illnesses (depression and psychosis) Paralytic dementia (aka general paresis; general paralysis of the insane): Caused by chronic meningoencephalitis; leads to cerebral atrophy in late-stage syphilis. Infective conditions: Cryptococcal meningitis; AIDS; Lyme disease, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis, syphilis, and WD	No solid evidence of benefit Not a disease. Varies in severity over time. Sudden change in mentation. Not to be confused with depression, dementia, psychosis. May appear on background of mental illness or dementia Use NPI or GDS tests Severe neuropsychiatric disorders (classified as an organic mental disorder)
Cognitive tests	Tests of memory, executive function, processing speed, attention, language skills, and emotional and psychological adjustment	To rule out other etiologies To determine relative cognitive decline over time: MMSE, AMTS, 3MS, TMT, CDT, MOCA, SAQ, IQCODE, ADCQ, GPAC
Laboratory tests	To rule out other treatable causes	Vitamin B12, FA, TSH, CRP, full blood count (electrolytes, calcium, renal function, and liver enzymes)
Imaging scans	CT, MRI Functional neuroimaging (SPECT, PET. PIB-PET)	No evidence of diffuse metabolic changes. May suggest NPH (a potentially reversible cause of dementia). Can yield information on VD For long-standing cognitive dysfunction. To differentiate VD from AD

GDS: Geriatric Depression Scale, NPI: Neuropsychiatric Inventory, SPECT: Single-photon emission tomography, CT: Computed tomography, PET: Positron-emission tomography, MMSE: Mini-mental state examination, 3MS: Modified mini-mental state examination, AMTS: Abbreviated mental test score, TMT: Trail Making Test, CDT: Clock Drawing Test, MOCA: Montreal Cognitive Assessment Test, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, ADCQ: Alzheimer's Disease Caregiver Questionnaire, GPAC: General Practitioner Assessment of Cognition, CRP: C-reactive protein, PIB-PET: (Carbon-11) Pittsburgh Compound B (a radiotracer), NPH: Normal pressure hydrocephalus, TSH: Thyroid-stimulating hormone, WD: Whipple disease, ACS: Acute Confusional State (or Delirium), FA: Folic acid, VD: Vascular disease

Table 8: 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

MMSE: Mini-mental state examination, 3MS: Modified mini-mental state examination, AMTS: Abbreviated mental test score

DISEASE MANAGEMENT

Except for the treatable types of dementia listed above and in the absence of a thorough understanding of its deep biology, there is currently no cure for the disease. Medical interventions remain, therefore, palliative with the aim to alleviate pain and suffering. They include:[52-61]

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

Other management approaches are as follows

Psychological and reminiscence therapies

While benefits are small, these therapies can improve the quality of life, communication, and possibly mood in some circumstances. Areas covered include:

- Quality of life, cognition, communication, mood, and cognitive reframing for caretakers;
- Validation therapy; and
- Mental exercises: Such as cognitive stimulation programs (for people with mild-to-moderate cognitive impairment).

Table 9: Contributors to dementia

Disease	Contribution (%)	Characteristics and symptoms
AD	50–70	Cause: Death of nerve cells (neurons) in important parts of the brain Symptoms: Repetition, getting lost, difficulties keeping track of bills, forgetting to take medication, short-term memory loss, word-finding difficulties, trouble with visual-spatial areas, reasoning, judgment, insight Signs: Hippocampus, shrinkage of frontotemporal parts
VD	25	Cause: Stroke (s); blood vessels diseases, hypertension, CVDs (particularly previous heart attack, angina), diabetes Symptoms: Minor strokes Signs: Lost or damaged ischemic brain areas
LBD	15	Cause: Abnormal protein structures within brain cells. Treatable with medication Symptoms: PD (trembling, stiffness, and slowness), visual hallucinations, difficulty with visual-spatial function, problems with attention, organization, executive functions, "Parkinsonism" (tremor, rigid muscles, stiffness, slowness, and emotionless face). Signs: Vivid, long-lasting hallucinations; "act out of dreams," occipital hypoperfusion hypometabolism
PDD		Cause: During the course of PD Symptoms: Very similar to DLB
FTD		Symptoms: Personality changes, abnormal social behavior, language difficulties (memory problems are not a main feature) Signs: Nerve cell loss in frontal and temporal lobes. Arises at earlier age than AD. 3 types: Behavioral, temporal (or semantic), and progressive non-fluent aphasia
MD		Cause: More than one (often AD and vascular) Signs: Over 80 years of age
PSP		Symptoms: Eye movement problems, falling backward, balance problems, slow movements, rigid muscles, irritability, apathy, social withdrawal, depression, progressive difficulty eating and swallowing, eventually talking. Misdiagnosed as PD Signs: Atrophied midbrain
CBD		Symptoms: Many different types of neurological problems, get worse over time Signs: Affected frontotemporal lobes; difficulty using only one limb ("alien limb"), asymmetric symptoms (myoclonus or jerky movements of one or more limbs), strange repetitive movements (dystonia), speech difficulty (inability to move mouth muscles in coordinated way), numbness and tingling of limbs, neglect one side of vision or senses
CJD		Cause: Prions Symptoms: Slow (at times rapid) progression
Encephalopathy		Causes: Brain infection (viral or sclerosing encephalitis) and WD Brain inflammation: LE; HE; CV; tumors (lymphoma, glioma); drug toxicity (e.g., anticonvulsants) Metabolic causes: Liver or kidney failure, CSH
Immunologically mediated		Causes: Chronic inflammatory conditions, BD, MS, sarcoidosis; SS, SLE, CD, and non-celiac gluten sensitivity Signs: Can rapidly progress. Good response to early treatment (immunomodulators and steroids)
Inherited conditions		Causes: AD, CX, DPA, epilepsy, FFI, FXTAS, type 1 GA, KD, MSUD, type C NPD, NCL, neuroacanthocytosis, organic acidemias, PMD, type B SFS, type 2 SCA, urea cycle disorders

(Contd...)

Table 9: Continued

Disease	Contribution (%)	Characteristics and symptoms
Other conditions		Causes: Cumulative damage in the brain (e.g., in chronic alcoholism and repeated head in juries)

AD: Alzheimer's disease, VD: Vascular dementia, LBD: Lewy body dementia, PDD: Parkinson's disease dementia, FTD: Frontotemporal dementia, MD: Mixed dementia, PSP: Progressive supranuclear palsy, CBD: Corticobasal degeneration, CJD: Creutzfeldt-Jakob's disease, SCA: Spinocerebellar ataxia, NPD: Niemann–Pick disease, DLB: Dementia with Lewy bodies, PD: Parkinson disease, LE: Limbic encephalitis, HE: Hashimoto encephalopathy, CV: Cerebral vasculitis, CSH: Chronic subdural hematoma, BD: Behcet disease, MS: Multiple sclerosis, SS: Sjogren's syndrome, SLE: Systemic lupus errhythematosus, CD: Celiac disease, CX: Cerebrotendinous xanthomatosis, DPA: Dentatorubal pallidoluysian atrophy, FFI: Fatal familial insomnia, FXTAS: Fragile, X-associated tremor/ataxia syndome, GA: Glutaric aciduria type 1, KD: Krabbe disease, MSUD: Maple syrup urine disease, NCL: Neuronal ceroid lipofuscinosis, PMD: Pelizaeus-Merzbacher disease, SFS: Sanfilippo syndrome, WD: Whipple disease, VD: Vascular disease, CVDs: Cardiovascular diseases

Cognitive Impairment Type	Subtypes	Characteristics	Diagnosis
Mild (MCI) MMSE=25–30	Amnestic	Memory loss develop Alzheimer's disease	Difficult. Requires Petersen criteria: Memory or other cognitive Problem not severe enough Person must not have dementia
70% of people with MCI develop some form of dementia	Non-amnestic	Memory loss not primary Develop other dementias	
Fixed (FCI) long-term effects	Various types of brain injury	Irreversible cognitive impairment	Diffuse axonal injury Localized damage due to neurosurgery
	Temporary reduction in brain's blood or oxygen supply	Hypoxic/ischemic injury Strokes (ischemic stroke, intracerebral, subarachnoid, subdural or extradural hemorrhage) Infections (meningitis, encephalitis) Epileptic seizures Acute hydrocephalus	Long-term effects on cognition
	Excessive alcohol use	AD WE KP	

AD: Alcohol dementia, WE: Wernicke encephalopathy, KP: Korsakoff psychosis, FCI: Fixed cognitive impairment, MCI: Mild cognitive impairment, MMSE: Mini-mental state examination

Care in adult centers and special units in nursing homes and in the home

These institutions provide specialized care (supervision, recreation, meals, limited health care, music therapy..., as well as providing respite for caregivers). Home care can provide one-on-one support and allow for the more individualized attention that is needed as the disorder progresses.[24,10,62]

Psychiatric nursing

Can make a distinctive contribution to patients' mental health.

PSYCHOPHARMACOTHERAPY FOR AD AND OTHER DEMENTIAS

Changes in medication management

The Medications Appropriateness Tool for CoMorbid Health - Dementia criteria can help to identify the ways that a diagnosis of dementia changes medication management for other health conditions.[63]

Alternative therapies

- Aromatherapy and massag: Unclear benefits.
- Cannabinoids: Can relieve behavioral and psychological symptoms of dementia.

Table 10: Types of cognitive impairment

Pathology	Drugs	Precautions	Side Effects
Memory problems Monitored 8-week course	Provide no cure: Cholinesterase inhibitors*: Donepezil (Aricept®), Rivastigmine (Exelon®), Galantamine (Razadyne®) Memantine (Namenda®): Used in combination with anti-cholinesterase NMDA receptor blockers Folate or Vitamin B12 Statins Blood pressure medications	Symptoms may worsen if the treatment is stopped or after treatment Periodic evaluation of the treatment required May cause increase in cardiovascular-related events	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 problem Dizziness, aggression, and hallucinations No improved outcomes No benefit No clear link with dementia
Behavioral symptoms	Environment change, physical exercise, avoiding triggers that cause sadness, socializing with others, engaging in pleasant activities Antipsychotics		Agitation, anxiety, irritability Not usually recommended due to little benefits, side effects, increased risk of death
Depression	Behavioral therapy and/or medications SSRI: Fluoxetine (Prozac®), Sertraline** (Zoloft®), Paroxetine (Paxil®), Citalopram** (Celexa®), Escitalopram (Lexapro®)		
Anxiety and aggression	Medications		Can be caused by several factors: confusion, misunderstanding, disorientation, frightening, paranoid delusions, hallucinations, depression, sleep disorders, reduced sleep or altered sleep/wake cycles, medical conditions (such as difficulty urinating or severe constipation, other causes of physical pain or discomfort)
Sleep problems	Medications or/and behavior changes benzodiazepines (diazepam) and non-benzodiazepine hypnotics: To be avoided Melatonin, Ramelteon, Trazodone		Worsened confusion, increased risk of falls, increased cognitive impairment Little evidence to improve sleep in dementia patients
Pain	Medications		Decreased ambulation, depressed mood, sleep disturbances, impaired appetite, falls, and exacerbation of cognitive impairment, profound functional, psychosocial, and quality of life implications

(Contd...)

Table 10: *Continued*

Pathology	Drugs	Precautions	Side Effects
Eating difficulties	Assisted feeding, gastrostomy, feeding tube		Worsening pressure ulcers, fluid overload, diarrhea, abdominal pain, local complications, risk of aspiration

*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. **Sertraline and Citalopram do not reduce symptoms of agitation compared to placebo and do not affect outcomes, NMDA: N-Methyl D-Aspartate receptor blckers, SSRI: Selective serotonin reuptake inhibitors

- Omega-3 fatty acid supplements from plants or fish sources: Do not appear to benefit or harm people with mild-to-moderate AD or improve other types of dementia.

Dental hygiene

There is limited evidence linking poor oral health to cognitive decline. Poor oral hygiene can have an adverse effect on speech and nutrition causing general and cognitive health decline. Oral bacteria (*Porphyromonas gingivalis, Fusobacterium nucleatum, Prevotella intermedia, Tannerella forsythia*, and Treponema spirochetes) and oral viruses have been observed in the brains of Alzheimer's patients.

Note on spirochetes

These are neurotrophic in nature, meaning that they act to destroy nerve tissue and create inflammation. Inflammatory pathogens are an indicator of AD. Bacteria related to gum disease have been found in the brains of AD individuals. They invade nerve tissue in the brain, increasing the permeability of the blood–brain barrier and promoting the onset of AD among the elderly population.[41]

Note on herpes simplex virus (HSV)

It was found in over 70% of the 50 and older population, and it persists in the peripheral nervous system and can be triggered by stress, illness, or fatigue. High proportions of viral-associated proteins in amyloid-containing plaques or neurofibrillary tangles (NFTs) highly confirm the involvement of HSV-1 in AD pathology. HSV-1 produces the main components of NFTs, the primary marker of AD.

Palliative care

Recommended before the late stages of dementia. Given the progressive and terminal nature of the disease, palliative care can be helpful to patients and their caregivers by helping both people with the disorder and their caregivers understand what to expect, deal with loss of physical and mental abilities, plan out a patient's wishes and goals including surrogate decision-making, and discuss wishes for or against cardiopulmonary resuscitation and life support.

PREVENTION

No medications or supplements have shown good preventative evidence, including blood pressure medications. Efforts to prevent dementia include:

- Early education;
- Decrease in risk factors: High blood pressure, smoking, diabetes and obesity, hearing loss, depression, and social isolation;
- Lifestyle changes: Physical exercise and social activities; and
- Computerized cognitive training: May improve memory.[64]

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 effect. In the case of Alzheimer's dementia, the main contributor, there is a ray of hope in the recent suggestion[21-40] that the root cause of Alzheimer may be an autoimmune disease gone rogue and that deposits (or plaques) of beta-amyloid (a protein) and the NFTs (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. Similar innovative ideas and suggestions should be pursued for the other contributors to dementia.

Abbreviations: AChEI: Acetyl Choline Esterase Inhibitor; ACS: Acute Confusional State (or 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: Behavioral 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; CX: Cerebrotendinous Xanthomatosis; DPA: Dentatorubal Pallidoluysian Atrophy; DSM: Diagnostic and Statistical Manual of Mental Disorders; DTBZ: (carbon-11) dihydrotetrabenazine (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: Fronto-Temporal 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: Huntingron Disease; HE: Hashimoto encephalopathy; HXV: Herpes Simplex Virus; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; KD: Krabbe Disease; KP: Korskoff 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 Ceroid Lipofuscinosis; NICE: (U.K.) National Institute for Clinical Excellence; NIDDS: National Institute of Neurological Disorders and Stroke; NDD: Neuro Degenerative Disease; NFD: Neuro Fibrillary Tangles; NMDA: N-Methyl D-Aspartate receptor blckers; NPD: Niemann-Pick Disease; NPH: Normal Pressure Hydrocephalus; NPI: Neuropsychiatric Inventory; Antipsychotics: 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; SSD: Sick Sinus Syndrome; SSRI: Selective Serotonin Reuptake Inhibitors; TMT: Trail-Making Test; TSD: Tay-Sachs Disease; TSH: Thyroid Stimulating Hormone; VD: Vascular dementia; VE: Viral encephalitis (VE); WD: Whipple Disease; WD: Wilson Disease; WE: Wernicke Encephalopathy; World Health Organization (WHO).

Diseases/Disorders Cited: Acute Confusional State (or Delirium); Alzheimer Disease; Alexandre Disease:Alcohol Dementia; Adenoleukodystrophy; Behcet Disease; Cortico Basal Degeneration; Celiac Disease; Chronic Obstructive Pulmonary Disease; Chronic Subdural Hematoma; Chronic Traumatic Encephalopathy; Cerebral Vasculitis; Cerebrotendinous Xanthomatosis;Dentatorubal Pallidoluysian Atrophy; Early Stage Dementia; Fixed Cognitive Impairment; Fatal Familial Insomnia; Fronto-Temporal Dementia; Fronto Temporal Lobar Degeneration; Fragile X-Associated Tremor/Ataxia Syndrome; Gaucher Disease; Huntingron Disease; Hashimoto Encephalopathy; Herpes Simplex; Krabbe Disease; Korskoff psychosis; Lewy body dementia; Limbic encephalitis; Late Stage Dementia; Mild Cognitive Impairment; Metachromatic Leukodystrophy; Mixed dementia; Multiple Sclerosis; Middle Stage Dementia; Maple Syrup Urine Disease; Neuronal Ceroid Lipofuscinosis; Neuro Degenerative Disease; Niemann-Pick Disease; Precocious Dementia; Parkinson Disease; Parkinson Disease Dementia; Pantothenate Kinase-Associated Neurodegeneration; Pelizaeus-Merzbache Disease; Progressive Non-Fluent Aphasia; Progressive Supra Nuclear Palsy; Peptic Ulcer Disease; Sub-Acute Sclerosing Encephalitis; Spino Cerebellar Ataxia;Syphilitic Dementia; San Filippo Syndrome; Systemic Lupus Errhythematosus;Sjogren Syndrome; Sick Sinus Syndrome; Tay-Sachs Disease; Vascular dementia; Viral encephalitis; Whipple Disease; Wilson Disease; Wernicke Encephalopathy.

Drugs Listed: Anticholinergics; Antipsychotics; Benzodiazepines (central nervous system depressants); Blood pressure medications; Cholinesterase inhibitors: Donepezil (Aricept®), Rivastigmine (Exelon®), Galantamine (Razadyne®); Folates; Hypnotics (benzodiazepines: diazepam; non-benzodiazepine); Memantine (Namenda®); N-Methyl D-Aspartate receptor blockers; Memantine; Niacin; Opioids; Selective Serotonin Reuptake Inhibitors: Fluoxetine (Prozac®), Sertraline (Zoloft®), Paroxetine (Paxil®), Citalopram (Celexa®), Escitalopram (Lexapro®); Sleep aids (melatonin; ramelteon); Statins; Vitamin B12.

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APPENDIX 1

The top 10 causes of death

(World Health Organization, 24 May 2018)

Of the 56.9 million deaths worldwide in 2016, more than half (54%) were due to the top 10 causes. Ischemic heart disease and stroke are the world's biggest killers, accounting for a combined 15.2 million deaths in 2016. These diseases have remained the leading causes of death globally in the past 15 years.

Chronic obstructive pulmonary disease claimed 3.0 million lives in 2016, while lung cancer (along with trachea and bronchus cancers) caused 1.7 million deaths. Diabetes killed 1.6 million people in 2016, up from <1 million in 2000. Deaths due to dementias more than doubled between 2000 and 2016 make it the fifth leading cause of global deaths in 2016 compared to fourteenth in 2000.

Lower respiratory infections remained the most deadly communicable disease, causing 3.0 million deaths worldwide in 2016. The death rate from diarrheal diseases decreased by almost 1 million between 2000 and 2016 but still caused 1.4 million deaths in 2016. Similarly, the number of deaths by tuberculosis decreased during the same period but is still among the top 10 causes with a death toll of 1.3 million. HIV/AIDS is no longer among the world's top 10 causes of death, having killed 1.0 million people in 2016 compared with 1.5 million in 2000.

Road injuries killed 1.4 million people in 2016, about three-quarters (74%) of whom were men and boys.

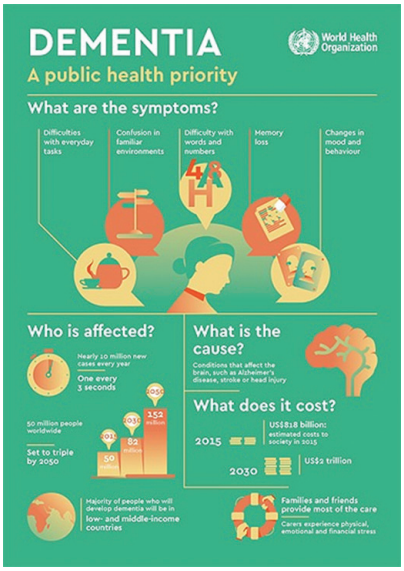
APPENDIX 2

The World Health Organization Dementia Fact Sheet # 362

(April 2012).[65]

Infographic on dementia

(This infographic includes information about the symptoms of dementia, cause, number of people affected, and cost)



Facts

Symptoms	Decreased ability to think and remember, emotional problems, problems with language, decreased motivation
Usual onset	Gradual
Duration	Long term
Causes	Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia
Diagnostic method	Cognitive testing (mini-mental state examination)
Differential diagnosis	Delirium
Prevention	Early education, prevent high blood pressure, prevent obesity, no smoking, exercise, social engagement
Treatment	Supportive care
Medication	Cholinesterase inhibitors (small benefit)
Frequency	46 million (2015)
Deaths	1.9 million (2015)

Signs and symptoms

Dementia affects each person in a different way, depending on the impact of the disease and the person's personality before becoming ill. The signs and symptoms linked to dementia can be understood in three stages.

Early stage: The early stage of dementia is often overlooked because the onset is gradual. Common symptoms include:

- Forgetfulness
- Losing track of the time
- Becoming lost in familiar places.

Middle stage: As dementia progresses to the middle stage, the signs and symptoms become clearer and more restricting. These include:

- Becoming forgetful of recent events and people's names
- Becoming lost at home
- Having increasing difficulty with communication
- Needing help with personal care
- Experiencing behavior changes, including wandering and repeated questioning.

Late stage: The late stage of dementia is one of near total dependence and inactivity. Memory disturbances are serious and the physical signs and symptoms become more obvious. Symptoms include:

- Becoming unaware of the time and place
- Having difficulty recognizing relatives and friends
- Having an increasing need for assisted self-care
- Having difficulty walking
- Experiencing behavior changes that may escalate and include aggression.

Common forms of dementia

There are many different forms of dementia. Alzheimer's disease is the most common form of dementia and may contribute to 60–70% of cases. Other major forms include vascular dementia, dementia with Lewy bodies (abnormal aggregates of protein that develop inside nerve cells), and a group of diseases that contribute to frontotemporal dementia (degeneration of the frontal lobe of the brain). The boundaries between different forms of dementia are indistinct and mixed forms often coexist.

Rates of dementia

Worldwide, around 50 million people have dementia, with nearly 60% living in low- and middle-income countries. Every year, there are nearly 10 million new cases.

The estimated proportion of the general population aged 60 and over with dementia at a given time is between 5 and 8 per 100 people.

The total number of people with dementia is projected to reach 82 million in 2030 and 152 in 2050. Much of this increase is attributable to the rising numbers of people with dementia living in low- and middle-income countries.

Treatment and care

There is no treatment currently available to cure dementia or to alter its progressive course. Numerous new treatments are being investigated in various stages of clinical trials.

However, much can be offered to support and improve the lives of people with dementia and their carers and families. The principal goals for dementia care are as follows:

- Early diagnosis to promote early and optimal management
- Optimizing physical health, cognition, activity, and well-being
- Identifying and treating accompanying physical illness
- Detecting and treating challenging behavioral and psychological symptoms
- Providing information and long-term support to carers.

Risk factors and prevention

Although age is the strongest known risk factor for dementia, it is not an inevitable consequence of aging. Further, dementia does not exclusively affect older people - young-onset dementia (defined as the onset of symptoms before the age of 65 years) accounts for up to 9% of cases. Some research has shown a relationship between the development of cognitive impairment and lifestyle-related risk factors that are shared with other non-communicable diseases. These risk factors include physical inactivity, obesity, unhealthy diets, tobacco use and harmful use of alcohol, diabetes, and midlife hypertension. Additional potentially modifiable risk factors include depression, low educational attainment, social isolation, and cognitive inactivity.

Social and economic impacts

Dementia has significant social and economic implications in terms of direct medical and social care costs and the costs of informal care. In 2015, the total global societal cost of dementia was estimated to be US$ 818 billion, equivalent to 1.1% of global gross domestic product (GDP). The total cost as a proportion of GDP varied from 0.2% in low- and middle-income countries to 1. 4% in high-income countries.

Impact on families and carers

Dementia is overwhelming for the families of affected people and for their carers. Physical, emotional, and economic pressures can cause great stress to families and carers, and the support is required from the health, social, financial, and legal systems.

Human rights

People with dementia are frequently denied the basic rights and freedoms available to others. In many countries, physical and chemical restraints are used extensively in care homes for older people and, in acute-care settings, even when regulations are in place to uphold the rights of people to freedom and choice.

An appropriate and supportive legislative environment based on internationally accepted human rights standards is required to ensure the highest quality of service provision to people with dementia and their carers.

The World Health Organization (WHO) Response

The WHO recognizes dementia as a public health priority. In May 2017, the World Health Assembly endorsed the Global action plan on the public health response to dementia 2017-2025. The Plan provides a comprehensive blueprint for action - for policy-makers, international, regional, and national partners, and WHO - in areas such as increasing awareness of dementia and establishing dementia-friendly initiatives; reducing the risk of dementia; diagnosis, treatment and care; research and innovation; and support for dementia carers.

An international surveillance platform, the Global Dementia Observatory, has been established for policymakers and researchers to facilitate monitoring and sharing of information on dementia policies, service delivery, epidemiology, and research.

The WHO has developed iSupport and an e-health solution that provides information and skills training for carers of people living with dementia. The first study of the usability and effectiveness of iSupport is taking place in India.

Dementia is also one of the priority conditions in the WHO Mental Health Gap Action Program (mhGAP), which aims to scale-up care for mental, neurological, and substance use disorders, particularly in low- and middle-income countries.