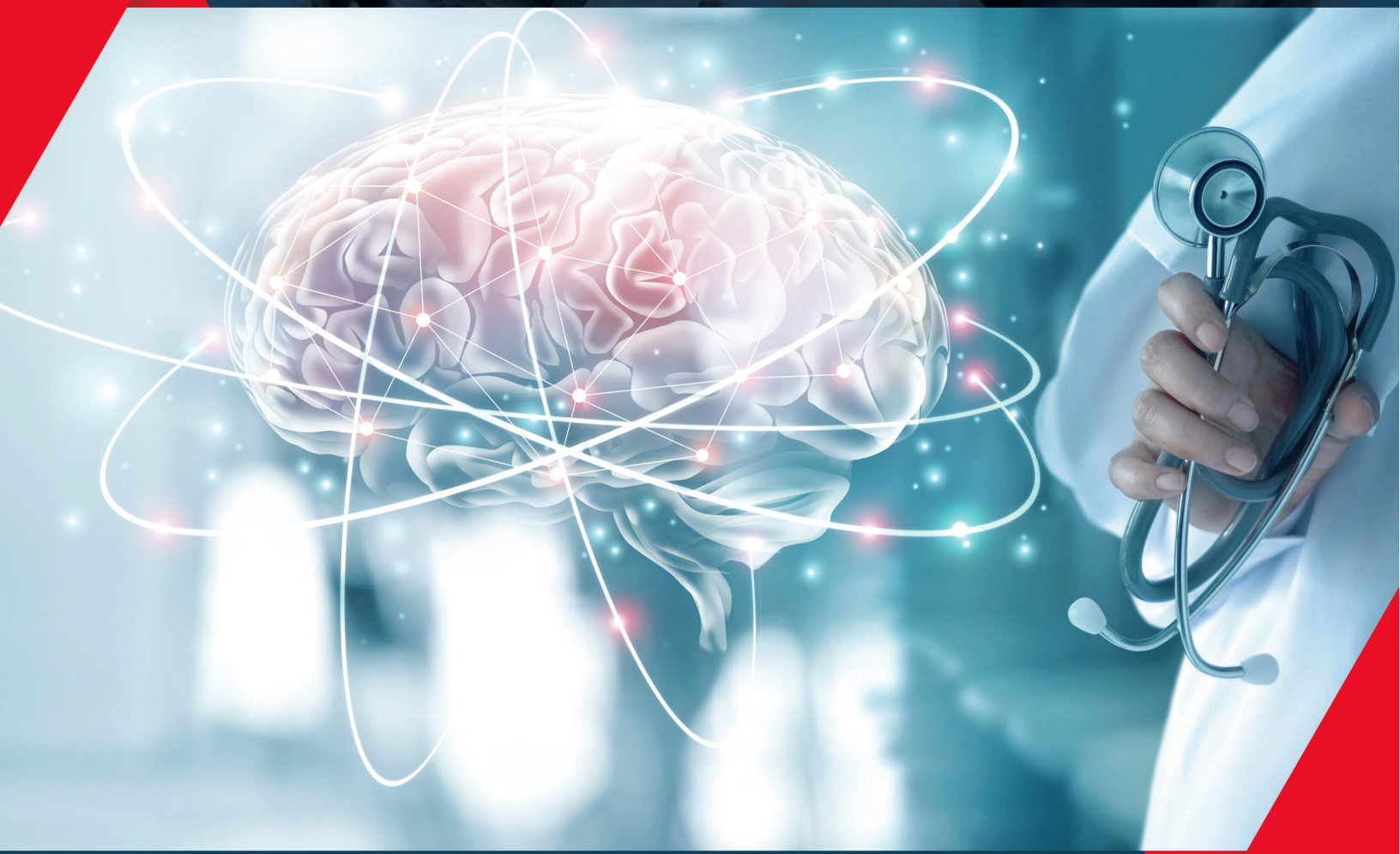
# FRONTIERS IN CLINICAL DRUG RESEARCH - DEMENTIA



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# Frontiers in Clinical Drug Research - Dementia

*(Volume 1)*

**Edited by**

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# Frontiers in Clinical Drug Research - Dementia

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# PREFACE

The book series ***Frontiers in Clinical Drug Research-Dementia*** presents cutting edge reviews written by the specialists in the field. The chapters in the 1st volume focus on drug research with special emphasis on clinical trials, and research on drugs in advanced stages of development for dementia and related disorders.

Khow & Yong, in chapter 1, discuss the challenges of bone and hip fractures in patients of Alzheimer's disease. Djordjevic *et al.*, in chapter 2, discuss the role of cholesterol in brain health and pathologies with special emphasis on Alzheimer's disease. Chapter 3 by Lake *et al.* reviews the advances in the treatment of Mild Cognitive Impairment (MCI) and dementia.

Chapter 4 by Uslu *et al.* gives an overview of analytical methods for the drugs used in the treatment of this disease. Kaushik and Jha, in chapter 5, present the nanotechnological advancements for the treatment of Alzheimer's disease. Chapter 6 by Mushtaq *et al.* presents the details of current challenges in Alzheimer's disease. The last chapter by Hani Nasser Abdelhamid, summarizes recent studies on the links between metals and Alzheimer's disease.

I am grateful to all the eminent scientists for their excellent contributions. The efforts of Ms. Fariya Zulfiqar (Manager Publications) and the leadership of Mr. Mahmood Alam (Director Publications) are greatly appreciated.

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# CHAPTER 1

# Meeting the Challenges of Falls and Hip Fractures in People with Alzheimer's Disease

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**Abstract:** Falls and hip fractures are common conditions among older people with Alzheimer's disease (AD) and are associated with high risk of morbidity and mortality. People with AD have up to an 8-fold increased risk of falling and 3-fold higher risk of hip fractures, compared with those who are cognitively intact. The increased risk of hip fractures among people with dementia may occur through a few pathways, including (a) risk factors that are common to both conditions, (b) the presence of dementia increasing incidence of hip fracture through intermediate risk factors such as falls and osteoporosis, and (c) side effects of treatment used in AD increasing hip fracture risk. A better understanding of these mechanisms and their effects on outcomes after hip fracture will assist in developing effective interventions and improving preventive strategies. Population aging heightens the need to recognize the interactions of these conditions in order to improve efforts to prevent hip fractures, improve outcomes through high-quality acute care and rehabilitation that returns patients to premorbid level of functioning, and provide evidence-based secondary prevention of falls or fragility fractures. Acute care of hip fractures focusing on orthogeriatric co-management has been shown to reduce length of hospital stay, perioperative complications including delirium, readmission rate and premature mortality. Secondary prevention of falls and further fractures is essential by ensuring risk factors for falling are addressed and osteoporosis is treated. New experimental approaches are being investigated to manage osteoporosis through surgical approaches in people with extremely high risk of recurrent hip fractures.

**Keywords:** Alzheimer's disease, Cognitive impairment, Dementia, Falls, Hip fracture, Orthogeriatric, Prevention, Rehabilitation, Risk factors, Treatment.

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## INTRODUCTION

Alzheimer's disease (AD) is the most frequent form of dementia in many countries. Falls and hip fractures are common interrelated problems among older people with AD. The prevalence of AD increases with age, rising from 3.0% among those aged 65 to 74 years to 18.7% among the 75 to 84 years age group and even higher at 47.2% in people over 85 years [1]. Globally, the prevalence of dementia has been doubling every 20 years and is projected to affect 81 million by 2040, with many being affected by AD [2]. AD is a progressive condition that can interfere with self-care and social functioning.

Older people are more likely to fall resulting in catastrophic and life-threatening events. In addition, falls also have adverse consequences on their quality of life and that of their families or carers. It is estimated that 28-35% of community dwelling individuals older than 65 years fall each year and more than 50% of those living in residential care facilities [3]. In the United States, the absolute number of fall-related deaths has almost tripled from 8613 in 2000 to 25819 in 2016, according to the National Vital Statistics System [4]. The same study also reported that the age-adjusted fall-related mortality rate has doubled, rising from 46.3 to 105.9 per 100,000 women and from 60.7 to 116.4 per 100,000 men [4]. Falls also impose a heavy financial cost on the healthcare system. In 2015, the total medical costs attributable to fatal and non-fatal falls in the United States was nearly $50 billion [5].

About 85% of hip fractures happen in people over the age of 65 years [6]. With an aging population, the number of hip fractures worldwide is expected to rise from 1.7 million in 1990 to 6.3 million by 2050 [7]. In the first year after a hip fracture, only 50% regain their pre-fracture ambulation level and about 25% of people living in the community before the fracture would require care in a residential facility [8, 9]. Within three months after hip fracture, mortality is five to eight-fold higher than in age- and sex-matched controls and this excess mortality persists even after 10 years [10, 11].

This chapter will review the risk factors for falls and hip fractures in people with AD. This review will also describe the evidence for effective acute and post-acute care for hip fractures. In addition, effective strategies for primary and secondary prevention of falls and hip fractures in AD will also be examined.

## RISK FACTORS FOR FALLS IN ALZHEIMER'S DISEASE

Patients with dementia including those with AD experience an eight-fold higher risk of falls compared to those without dementia, and especially for sustaining recurrent falls [12]. In one case-control study of four-year duration, 36% of

patients with AD experienced a serious fall compared to 11% among those without the condition [13]. Several risk factors for falls are more prominent among people with AD (Table **1**).

**Table 1. Risk factors for falls in people with Alzheimer's disease.**

| |
|---|
| Changes in gait |
| • Shorter stride length |
| • Reduced gait speed |
| • Increased step-to-step variability |
| • Lower stepping frequency |
| • Increased double support ratio |
| • Increased sway path |
| Neurovascular instability |
| Delirium, especially acute hospital setting |
| Behavioural and psychological symptoms |
| Use of psychotropic medications |

The ability to walk without falling depends on an intact motor, sensory, balance, postural reflexes, and vision to maintain a steady upright position and to move safely. Moreover, cognitive abilities including attention, reaction time, executive function, visuospatial skills, and navigation are important for walking safely. Studies have found that people with AD have a shorter stride length, slower gait speed, greater step-to-step variability, lower stepping frequency, increased double support ratio (more time spent in stance phase), and larger sway path than those without the condition [14 - 16]. Stride length and gait speed have been found to be associated with the risk of falls [15]. About 40% of people with AD have a gait apraxia [17]. Impaired central integration of signals for maintaining gait and balance is thought to contribute to apraxia in AD [18]. People with AD can also be impulsive and take unnecessary risks due to impaired insight and lack of perception in relation to environmental hazards [19].

AD is associated with a high prevalence of autonomic dysfunction, leading to postural hypotension [20, 21]. This may lead to falls and hip fractures. In addition, a study of participants with AD found a prevalence of carotid sinus hypersensitivity in 28% [22].

In the acute hospital setting, delirium is common among people with AD and is a major risk factor for falls [23]. Delirium persisting after hospital admission is associated with a six-fold increase in the risk of falls [24].

**CHAPTER 2**

# Cholesterol in Brain Health and Pathologies: The Role in Alzheimer's Disease

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**Abstract:** Cholesterol is the molecule essential for life, but also with a possible detrimental role. Apart from being a vital structural constituent of the cells, cholesterol is a factor involved in many important cell processes. However, it has been known that high blood cholesterol is associated with many pathological conditions. An elevated level of cholesterol is linked with cardiovascular disease, diabetes and neurodegenerative disorders.

Almost quarter of the total cholesterol in the body resides in the brain. This vast pool is synthesized *in situ* and it is almost completely isolated and independent from the periphery due to the presence of blood-brain barrier. In the central nervous system, cholesterol plays important role in neural cells structure and functions, including synaptic transmission. Due to this, its content must be precisely maintained in order to keep brain function well. However, cholesterol is critically challenged in the aging brain and disturbed in several of pathological conditions, like Huntington's disease (HD), Parkinson's disease (PD), Niemann-Pick type C (NPC) disease and Smith-Lemli Opitz syndrome (SLOS), traumatic brain injury, multiple sclerosis (MS) and in Alzheimer's disease (AD).

Altered cholesterol metabolism has been extensively implicated in the pathogenesis of AD. A growing amount of evidence underscores the link between disturbed intracellular trafficking of cholesterol in the brain and the formation of amyloid plaques. The inheritance of the epsilon4 allele of the Apolipoprotein E (ApoE), the main transport protein for cholesterol in the brain represents the main risk factor for late onset form of Alzheimer's disease. Other genetic polymorphisms associated with critical points in cholesterol metabolism may also contribute to the AD pathogenesis. Hypercholesterolemia has been considered nowadays also as a risk factor, and all of these players are thought to promote the production of beta-amyloid and development of AD. Additional proof towards cholesterol involvement in the pathogenesis of AD gave epidemiological data of the cholesterol-lowering drugs, statins that have been shown to decrease the risk for AD.

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This chapter is aimed to summarize existing knowledge about the brain cholesterol metabolism, how the homeostasis is changed during aging and in various neurodegenerative diseases, with special emphasis on Alzheimer's disease. As a final point, we will try to give a full insight into the environmental influences (including dietary restriction and statins therapy) on brain cholesterol homeostasis.

**Keywords:** Aging, Alzheimer's disease, Brain injury, Central nervous system, Cholesterol homeostasis, Cholesterol metabolism, Dietary restriction, Neurodegenerative diseases, Oxysterols, Statins.

## INTRODUCTION

Nowadays, there is almost no molecule like cholesterol, surrounded by such a big debate. It has triggered so much attention since its discovery in the second half of the 18th century, and does not cease to provoke controversy among scientists, but also in the general population. It is indispensable for life in so many ways, but it can still be harmful and fatal for health. The fact that so far 13 Nobel Prizes were awarded for the achievements connected to the structure, function and metabolism of cholesterol, tells us a story about its significance. Cholesterol is often called the secret killer, but still, no cell membrane would exist without it. The cholesterol is "the one" that builds the membranes, keeps their integrity, permeability and cell viability. In contrast to a rigid cell wall that plants possess, animal cell's membranes rich in cholesterol are fluid. Its role does not stop here- cholesterol is a precursor in the biosynthesis of vitamin D, bile acids and all steroid hormones.

Representing double-edged sword cholesterol is still in the focus of a large number of studies that attempt to shed light on its role in physiological and pathological processes. French physician-chemist François Poulletier first isolated cholesterol from gallstones in 1784. It was named cholesterine by French chemist Michel E. Chevreul (Greek: chole for bile and stereos for solid). It took an entire century to get to exact molecular formula of cholesterol established by Austrian botanist Friedrich Reinitzer in 1888. Elucidating its structure was extremely difficult. Marvelous work of Heinrich O. Wieland and Adolf Windaus brought them the Nobel Prize in Chemistry in 1927 and 1928, respectively, for revealing tetracyclic cholesterol skeleton [for a review see 1]. Konrad Bloch (1964) won the Nobel Prize for the contribution to the clarification of cholesterol biosynthesis. Michael Brown and Joseph Goldstein, who received the Nobel Prize in 1985 for their work on cholesterol regulation, named cholesterol Janus, a molecule with two faces.

Every animal cell is capable of synthesizing cholesterol by a complex 37-step process and most of our cholesterol is indeed made in our own organism. However, cholesterol can be also absorbed directly from the food. The content of

cholesterol in our body is a result of a fine balance between the process of synthesis and the process of absorption. If cholesterol homeostasis is preserved, then the body compensates for any absorption of additional cholesterol by reducing cholesterol synthesis and on the contrary - it will synthetize additional cholesterol when we need it, in cases like pregnancy, or recovery from illnesses and injuries. To make things more complicated, our body recycles cholesterol whenever it is possible, rather than synthetizing it. Typically, about 50% of the cholesterol excreted by the liver is reabsorbed by the small intestine back into the bloodstream.

Cholesterol is essential for cell functioning. It is like the brick in the house wall, a structural component of each and every cell in our bodies, required for building and maintaining the integrity of animal cell membranes, thus providing a protective barrier. However, cholesterol is not only **mechanical constituent** of plasma membranes; it also **regulates the permeability and fluidity** of cell membrane over the range of temperatures. Tetracyclic ring structure (Fig. **1**) provides cholesterol capability to decrease membrane fluidity and makes membrane rigid.

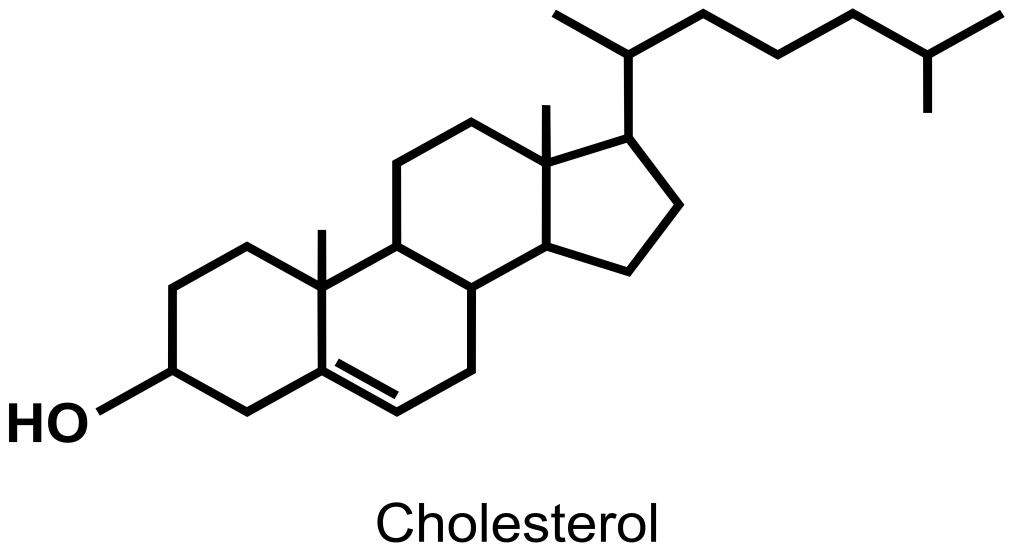


**Fig. (1).** Tetracyclic ring structure of cholesterol.

Cholesterol is a compelling modulator of the membrane proteins and also participates in numerous membrane trafficking and transmembrane signaling processes [2].

**CHAPTER 3**

# Advances in Treatment of Mild Cognitive Impairment (MCI) and Dementia: A Review of Promising Non-pharmaceutical Modalities

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**Abstract:** Currently, available mainstream approaches used to treat mild cognitive impairment (MCI) and dementia are limited. In view of the high prevalence rate of Alzheimer's disease (AD) and other forms of dementia and the enormous social and financial burden associated with dementia on a global scale, developing more effective and more cost-effective ways to treat MCI and dementia is an urgent priority. This chapter reviews research findings on promising non-pharmaceutical approaches being investigated for their potential clinical applications in treating symptoms of cognitive impairment and behavioral dysregulation associated with dementia, reducing the risk of developing dementia, and slowing rate of progression of cognitive decline in individuals with Mild Cognitive Impairment (MCI) or dementia. Non-pharmaceutical treatment approaches covered include diet, exercise, single and compound herbal formulas used in Asian medicine, herbals used in Western countries, select other natural products including dehydroepiandrosterone, idebenone, acetyl-L-carnitine, alpha lipoic acid, phosphatidylserine and phosphatidic acid, select vitamins, nPUFAs and probiotics. Other non-pharmaceutical modalities reviewed include chelating agents; non-invasive brain stimulation techniques employing weak electrical current, sound and light; music therapy; cognitive training; electroencephalography (EEG) biofeedback; multi-modal interventions; Wander gardens; sensory stimulation interventions; massage, mindfulness, and energetic therapies (Healing Touch, Therapeutic Touch, taichi and qigong). Although select natural products are supported by compelling research evidence, most modalities reviewed in this chapter are supported by limited findings. Large prospective placebo-controlled studies are needed to further elucidate mechanisms of action, verify the efficacy of the various non-pharmaceutical modalities, and identify safe and appropriate treatment protocols for MCI and dementia.

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**Keywords:** Dementia, Healing Touch and Therapeutic Touch, Lifestyle Changes, Mild Cognitive Impairment (MCI), Multi-Modal Interventions, Natural Products, Non-Pharmaceutical Treatment, Taichi and Qigong.

## PROMISING NON-PHARMACEUTICAL TREATMENTS OF MCI AND DEMENTIA

- Limitations of conventional mainstream treatments
- Reviews of non-pharmaceutical treatments
  - Lifestyle changes: diet, exercise and sleep
  - Natural Products
    - Herbals
      - Herbals used in Asian systems of medicine (single herbs, complex herbal formulas)
      - Other herbals (*Rhodiola rosea, Melissa officinalis, Salvia officinalis*)
  - Non-herbal natural products: acetyl-l-carnitine, folate, B-12, B-6, thiamin, niacin, vitamin C, vitamin E, DHEA and testosterone, estrogen, n-PUFA (omega-3s), phosphatidylserine and phosphatidic acid, CDP-choline, essential oils, probiotics)
    - Other non-pharmaceutical treatment modalities
  - non-invasive brain stimulation (TMS, tDCS, gamma-band stimulation, photobiomodulation)
  - Music therapy
  - Cognitive training
  - Bright light
  - EEG biofeedback
  - Sensory stimulation interventions
  - Massage
  - Wander gardens
  - Mindfulness
  - Multi-modal interventions
  - Energetic therapies
- Healing Touch and Therapeutic Touch
- Taichi and Qigong

## LIMITATIONS OF CONVENTIONAL MAINSTREAM TREATMENTS

A systematic review found inconclusive evidence that non-steroidal anti-inflammatory agents (NSAID), antihypertensives, cholinesterase inhibitors, hormones and other medications are effective for preventing or reducing the risk of cognitive decline during healthy aging, developing mild cognitive impairment (MCI) or reducing the risk of developing Alzheimer's disease (AD) [1]. Current mainstream treatments of AD work by inhibiting the enzyme that breaks down

acetylcholine, thus increasing available levels of the neurotransmitter that is critical for learning and memory. Although available drugs sometimes lessen the severity of cognitive decline and behavioral disturbances that accompany AD, they do not address its root causes. Only five drugs have been approved by the U.S. Food and Drug Administration (FDA) to treat Alzheimer's disease (AD) [2]. Among these the cholinesterase inhibitors include tacrine, donepezil, galantamine and rivastigmine (Alzheimer's Association. FDA-Approved Treatment for Alzheimer's) [2]. Another drug, memantine, works by antagonizing glutamate receptors and is in a class by itself. Second-generation acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are no more effective than tacrine but require less frequent dosing.

All currently available pharmaceuticals have associated side effects that can be very distressing to individuals struggling with dementia, including vomiting, diarrhea and appetite loss. Tacrine, the first cholinesterase inhibitor, was removed from the market in 2013 because of concerns over hepatotoxicity.

Other drug classes that have been investigated for possible cognitive-enhancing benefits in AD include the monoamine oxidase inhibitors (MAOIs), estrogen replacement therapy (*i.e.*, in cognitively impaired postmenopausal women), naloxone, and different neuropeptides including vasopressin and somatostatin [3]. Promising novel treatments of Alzheimer's disease currently being investigated in clinical trials include a vaccine that may immunize individuals against formation of amyloid-beta, secretase inhibitors, anti-inflammatory agents, statins and a variety of nano-medicinal approaches [4 - 6]. Findings of studies on statins in dementia are inconsistent. However, a 2017 meta-analysis of 31 studies that met inclusion criteria for size and rigor found that regular statin use is associated with significant reduction of risk of developing dementia [7].

In addition to cognitive impairment, individuals struggling with MCI and dementia frequently experience depressed mood, anxiety, and psychosis. Conventional allopathic management of complex clinical presentations uses combinations of drugs that increase risk of unsafe interactions. Behavioral disturbances, including agitation and aggressive behavior toward caregivers, are commonly encountered in demented individuals. Although cholinesterase inhibitors result in only transient improvement in the early stages of dementia, they have become the standard conventional treatment of AD and other forms of dementia in industrialized countries because of findings of reduced agitation. In addition to pharmacological management, behavioral interventions, environmental enrichment, and social support may lessen the cognitive and behavioral symptoms of dementia.

CHAPTER 4

# Overview of Analytical Methods in Alzheimer's Disease Drugs: Optical, Chromatographic, and Electrochemical Methods

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**Abstract:** Alzheimer's disease is a neurodegenerative disorder that results in a loss of memory, cognitive problems, and personality change. The frequency of this disease is increasing rapidly due to the aging world population. Every year, more people are exposed to this age-related disorder. It is expected that the number of individuals diagnosed with Alzheimer's disease would increase to 100 million by 2050. The treatment of Alzheimer's disease costs more than $200 billion annually in the US and this cost will possibly grow to $1 trillion annually by 2050. There are two categories of drugs used for the treatment of Alzheimer's disease; while the first category attempts to treat the symptoms of the disease (such as rivastigmine, galantamine, and donepezil), the second category focuses on the specific site or physiological factor of the disease. Still, there are attempts to develop new therapies to prevent, defer, slow down the progress, or ameliorate the symptoms of this disease. Spectrophotometric, chromatographic, and electrochemical methods have proven to be sensitive and reliable for the determination of numerous compounds. In this chapter, recent advances in different analysis methods of various Alzheimer's disease drugs are summarized. Finally, this chapter aims to explore the advantages of methods as well as highlight the future perspectives of these methods in assaying Alzheimer drugs in pharmaceutical and biological samples.

**Keywords:** Alzheimer's disease, Amperometry, Analysis, Donepezil, Galantamine, Gas chromatography, Huperzine A, Liquid chromatography, Memantine, Potentiometry, Rivastigmine, Spectrophotometry, Spectrofluorimetry, Tacrine, Validation, Voltammetry.

## INTRODUCTION

Dementia is a brain disorder resulting in significant deterioration of personal,

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social, and professional functions and it is defined as an acquired deficiency of memorial and cognitive processes. Other brain functions affected by this disease can be enumerated as orientation, calculation, learning abilities, cognition, language abilities, judgment, and reasoning. Dementia is not an outcome of normal aging processes; although there are some significant exceptions, dementia is a progressive disorder [1]. The behavioral changes emerged out of dementia are neither conscious nor are they the results of laziness or "letting go" [2].

Most dementias are categorized as neurodegenerative diseases because they emerged out of progressive degeneration and death of nerve cells [3]. Neurodegenerative disorders are the results of abnormal accumulation of non-dissolved proteins in the brain. These proteins are toxic and they have detrimental effects on selective nerve cells. They deteriorate the functions of these cells leading to the death of these cells at the end. Moreover, this abnormal protein accumulation affects synapses between nerve cells. The neural circuits can be cut because the chemical information between cells can not be transferred properly [4].

Alzheimer's disease (AD) is the most widely seen dementia type comprising almost 50-60% of all dementia cases [5, 6]. It has characteristic neuropathological and neurochemical properties. Generally, it is very insidious at the beginning and it advances slowly but consistently across years [2]. AD can also be defined as a heterogeneous disease which is a combination of environmental and genetic factors. The most significant risk factor for AD is age. The environmental risk factors are hypertension, estrogen supplements, smoking, stroke, cardiac diseases, depression, arthritis, and diabetes [6].

AD is characterized by the development of two main lesions, namely amyloid plaques and neurofibrillary tangles (NFTs) [7]. These two lesions resulted in progressive dementia that emerged out of neuronal dysfunction and death of cells at the hippocampus and medial, temporal, and parietal lobes of the brain. The defection at the hippocampus resulted in deterioration of short term memory and affects the daily routines of the patients. Later, the brain cortex and most importantly the areas responsible for linguistic and reasoning functions are influenced. In the end, other parts of the brain are eclipsed together with atrophy and functional losses [8].

The emergence of amyloid plaques is due to their pathological overproduction or as a result of β-amyloid peptide accumulation around neurons because of deteriorated clearance along the blood-brain barrier. The β-amyloid peptides accumulated at the brain are inclined to accumulate first towards soluble pathogenic β-amyloid oligomers and fibrils and then towards insoluble β-amyloid

plaques. The accumulation of β-amyloid plaques at brain arterial walls resulted in cerebral amyloid angiopathy [7]. According to the amyloid cascade hypothesis, which had been proposed at the beginning of the 1990s, the amyloid accumulations at AD resulting from a series of genetic and environmental factors and the neural cell degeneration emerging out of it ultimately leads to dementia [9].

The second significant lesion of AD is neurofibrillary tangles. The NFTs are composed of a protein called tau. Unlike plaques, the number of NFTs and their anatomical location in the brain is significantly related to the strength of dementia. Moreover, it is thought that the presence of NFTs within nerve cells is a strong indication of prospective cell death. Tau protein stabilizes the microtubules necessary for the rapid transfer of microscopic components at neurons from the nerve cell. The damaging microtubules resulted in functional losses of neurons. In AD, tau protein loses its ability to support microtubule stabilization and transforms into NFTs [10].

Since the definition of the AD at the beginning of the twentieth century, the discovery of amyloid plaques and NFTs at post-mortem brains of the patients became the basis for drug development studies for this disease; however, the discovery of drugs for the treatment of AD started with the discovery of the relationship between memory disorders and cholinergic pathways in 1984 [11]. It is understood that the neurons secreting acetylcholine for a long time are the neurons that are affected by AD the most. Acetylcholine (cholinergic) pathways are critically important for normal memory functions [12]. Since the discovery of the significance of acetylcholine for the treatment of AD, several treatments for overcoming the disease have been attempted. While earlier studies attempting to increase acetylcholine levels in the brain directly were not much promising, the methods developed for indirect boosting of acetylcholine levels by reducing its breakdown have some promising results [1]. Acetylcholinesterase (AChE), which is responsible for the hydrolysis of acetylcholine, was focused on to restore the cognitive impairment through rising neurotransmitter levels in the central nervous system [11]. The changes in neurotransmission in AD happens only after a significant level of cellular death. The lack of acetylcholine is not a reason but a result of the disease; therefore the treatments targeting for increasing the level of acetylcholine in the brain are not much effective to change the underlying causes of the disease [1]. In other words, the actual treatments of AD do not target underlying causes of AD but they attempt to cure the symptoms of the disease [1, 7, 12, 13]. Although numerous drugs are entering clinical monitoring processes, treatments curing the disease effectively can not be developed yet. That is why AD has been perceived as a priority for public health today [7].

CHAPTER 5

# Targeting Alzheimer's Disorders Through Nanomedicine

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**Abstract:** Neurodegenerative diseases have been known to exist in the human population for a long time, yet most of them do not have a cure even until now. With the recent surge of nanotechnology and its applications to physiology as nanomedicine, a new hope for a better future has been offered. Nanomedicine has opened up many areas of further research that can lead us to a probable cure for these diseases. This review particularly focuses on Alzheimer's disease (AD), which is a progressive neurodegenerative disorder. AD primarily affects the cerebral cortex in the forebrain and the hippocampus in the midbrain. According to the World Alzheimer's report, there are 46.8 million AD patients worldwide as of 2016 with a high probability of this statistic becoming double in the next two decades. For understanding this crucial situation, studying the pathology of AD, and recent advancements in the treatment of AD, specifically through nanomedicine becomes extremely important. Through this review, we intend to explore all the relevant aspects in relation to nanotechnological advancements for the treatment of Alzheimer's disease.

**Keywords:** Alzheimer's disease, Drug Delivery System, Lipid-based Nanoparticles, Neurodegenerative diseases, Nanoparticles, Nanomedicine, Neuroinflammation, Polymeric Nanoparticles.

## INTRODUCTION

Neurodegenerative diseases (NDs) are defined as a set of diseases that cause structural modifications to the neurons present in the human nervous system resulting in malfunctioning of the neuronal cells. This ultimately leads to a loss of cognitive, sensory and motor abilities. Though NDs have been prevalent in the human population for a long time, the drugs currently in clinical use are only for disease management and play a little-to-no role in disease cure.

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Some of the most popular NDs include Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease (PD) and Frontotemporal dementia (FTD). Most of the NDs are caused due to misfolding of essential messenger proteins such as amyloid plaques, transactive response DNA-binding protein 43 (TDP-43), dopamine neurotransmitters and serotonin. AD is caused by an irreversible neuronal loss and vascular toxicity resulting due to extracellular deposition of Aβ peptide, in the form of senile plaques, and neurofibrillary tangles of phosphorylated tau protein. In PD, there is loss of neurons involved in the dopaminergic pathway and proteinaceous Lewy bodies, which are α-synuclein aggregates present in the central nervous systems (CNS) and peripheral nervous system (PNS) [1, 2]. Both AD and PD are characterized by progressive memory loss, depleting decision -making ability and, degradation of cognitive and sensory perceptions [3 - 6]. A group of disorders showing rigidity, tremors and stature instability are categorized under a clinical syndrome termed as Parkinsonism [7], including PD as one such kind of disorder. ALS is a type of motor neuron degenerative disorder, where there is damage to motor neurons of both the CNS and the PNS. Here, the nervous connections between both cortex-brainstem and spinal cord-muscles are severely affected [8]. Although, aggregation of TDP-43 is thought to be a major cause of ALS, yet the disease pathway has not been clearly understood until now [8]. FTD is another type of neurodegenerative disorder, which is often linked to ALS due to their genetic and neuropathological common links [9]. A patient of FTD shows signs of forgetfulness and altered social behaviour. Language dysfunctionality is also observed in some kinds of dementia [9].

The recent surge in nanomedicine has given new hope as a prospective cure for NDs. The field of nanomedicine involves the use of nanotechnology for designing particles, with sizes ranging in the order of $10^{-9}$ m (nanometer), which can potentially be used as drugs and in drug delivery systems to inhibit such misfolding and agglomeration. Most diseases occur due to malfunctioning of some biological aspect involved, at a nanoscale [10]. Through nanoparticle-based drugs and delivery systems, there is an attempt to utilise the similarity in size shared between the nanoparticle and the biological molecules, and target the factors that are ultimately resulting in the disease. Due to their small size, nanomaterials display a high surface area to volume ratio. This translates to higher reactivity as the particles offer more surface area for the ligand to interact with, making it a favourable option for transporting drugs to their targets [11]. It is the dynamic and versatile nature of nanoparticle-based drug designing that gives it an edge over traditional medicine. Still, the extent of nanotoxicity caused and the unknown long-term effects of nanoparticle therapy can pose as disadvantages of this approach. Thus, clinical application of nanotechnology as medicine in NDs require exhaustive studies in appropriate models [12].

Major types of nanoparticles (NPs) commonly associated with biomedical research include liposomes, albumin-based, polymeric NPs, microemulsions, metallic NPs like gold, nano-emulsions, iron oxide and quantum dots [13]. Amongst these, polymeric NPs, lipid NPs, micro- and nano-emulsions are majorly involved in designing nanomedical therapies.

This review particularly focuses on AD, which is a progressive neurodegenerative disorder, primarily affecting the cerebral cortex in the forebrain and the Hippocampus in the midbrain [14, 15]. 46.8 million AD patients were reported worldwide in 2016 by world Alzheimer's report, with an expected double in number in the next two decades [16]. AD can be sporadic or familial in nature. The cases of familial AD are far lower than patients of acquired AD (measured 11.3% in the Asian population in 2016) [17]. The genes that are majorly observed as carriers of mutation leading to AD are *APP, PSEN1 and PSEN2* [5, 18]. Although AD is the most common of all the NDs, researchers do not yet completely understand its complex pathophysiology. Through this review, we attempt to explore the major pathways of the disease, the current treatment used for it and the prospective solutions that nanomedicine-directed research has to offer in future.

## AD PATHOLOGY AND CURRENT TREATMENT TRENDS

There are many factors that need to be considered in order to find a cure for a disease. A detailed understanding of the disease pathway can serve as a starting point for exploring potential treatments. Understanding AD and its pathology have provided an insightful approach towards designing treatments and drugs for it. AD results majorly due to inter-cell neurofibrillary tangles and intracellular neuritic plaques [19 - 21]. Paired helical filaments (PHF) form the tangles and amyloid aggregation results in these plaques. Two major pathways (Fig. **1**) have been suggested as probable disease pathologies for AD: Beta-amyloid (Aβ) cascade and Tau pathology. Both Aβ and Tau protein are associated with normal neuronal metabolism. Aβ is processed through a complex enzyme using amyloid precursor protein (APP) and is cleaved into peptides of various sizes [22, 23]. Modification in the proteolytic processing by APP results in aggregation of Aβ in the neuronal synapses, leading to a decline in the signaling efficiency. Even though inter-neuron Aβ deposition is identified as a crucial factor in AD, yet Aβ accumulation may not be the stand-alone cause of AD. It has been reported that even with the presence of Aβ deposits, the subject still did not suffer from AD.

Tau is a major microtubule-associated protein (MAP) present in six molecular isoforms in a mature neuronal cell in the human nervous system. It is majorly responsible for stabilizing the microtubular network in the neuronal cell.

# CHAPTER 6

# Current Challenges in Alzheimer's Disease

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**Abstract:** Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disease, the manifestation of which primarily leads to progressive dementia and ultimately results in death. Currently, 5.5 million people are afflicted with this disease in the USA alone while 50 million are suffering from this disease across the world. The disease is recognised by two pathological markers *viz*. senile plaques and neurofibrillary tangles (NFT). About 50% of the population beyond the age group of over 85 years exhibit symptoms of AD since the majority of cases of AD are sporadic or idiopathic and only 5-10 percent cases are genetic. At present, there is no effective treatment for this disease and most of the drug trials used to control or stop the disease have failed as they are directed to target symptoms and not the cause of the disease. The therapeutic agents that are most commonly used for AD include cholinesterase inhibitors (CI), which enhance cholinergic neurotransmission. Diagnosis of AD still poses a significant challenge regarding the lack of information about the manifestation as well as the status *viz*. progression of this disease. However, there is enough optimism to believe that we will soon be able to develop biomarkers which would help us to accurately detect the progression of the disease. Therefore, the present chapter will provide an extensive overview of the disease and focus on possible ways to develop and formulate effective strategies to control this dreadful disease. The purpose of this citation is to guide researchers and personnel associated with pharmaceutical sciences into a new domain of investigations. This paper depicts the present scenario and projects the future challenges posed by Alzheimer's disease.

**Keywords:** Alzheimer's disease, Alpha Secretase, Amyloid precursor protein, Beta amyloid, Beta Secretase Biomarkers, cholinesterase, Gamma Secretase, INNOTEST, Neurofibrillary tangle, Neurogranin, Tau.

## INTRODUCTION

Alzheimer's disease (AD) is the most common neurological disorder in which the

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death of neuronal cells leads to dementia and eventually results in fatality [1]. The disease was first described by a German psychiatrist, Alois Alzheimer, in 1906, when he carried out the autopsy of the brain of a patient named Auguste Deter. He found two prominent pathological markers, which were later named as neurofibrillary tangles and neurotic plaques. Neurofibrillary tangles are composed of hyperphosphorylated tau protein and neurotic plaques are composed of beta amyloid peptides [2, 3]. AD as the leading cause of dementia is now reaching an epidemic level in which 5.5 million people in the USA and 50 million people all around the world are suffering from this disease [4]. AD starts in the midbrain with mild cognitive impairment and damages the formation of new memory [5, 6]. The disease then progresses to other parts of the brain which results in problems with speech, mood swings, personality disorders, decision making, and emotions. At later stages of the disease, old memories are also destroyed and the patient becomes completely dependent on care and remains bed-ridden [5, 7, 8]. At present, there is not a single drug, which could cure or stop the progression of this disease [9]. The reason being the pathology of the disease, which starts 20-30 years prior to the appearance of symptoms in the patients and most of the drug trials are used to target symptoms and not the cause of this disease. To stop the progression of the disease at an early stage, researchers in Colombia are targeting the people prone to the early onset of AD due to rare genetic mutations. If researchers are able to develop a drug that could prevent cognitive decline in these individuals, it could revolutionize the drug therapy for this disease. To decrease the symptoms of AD, few drugs are approved by FDA, which target cholinesterase [10, 11] and N-methyl-D-Aspartate (NMDA) glutamate receptor [12]. This is not the only hurdle in the way to find a cure for this disease. AD cannot be diagnosed by a single test. INNOTEST assay, which detects total tau, phosphorylated tau, and beta amyloid 1-42 in cerebrospinal fluid (CSF) was developed 10-15 years ago [13 - 15]. Since then there have been many modifications and advances in the diagnosis of this disease. Novel Ultrasensitive Immunoassay and Mass Spectrometry are holding great promises for early diagnosis of this disease. Efforts are being made for better biomarkers which could detect the exact progression of this disease. One of the recent additions to this group is neurogranin, this protein specifically detects cognitive deterioration in AD [16]. For neurological disorders, including AD, CSF acts as an efficient matrix for biomarkers as compared to the blood. It has an advantage, which is in close proximity to the brain and the brain secretes proteins into it.

## PATHOLOGY

In order to develop effective therapeutic drugs to control or stop the progression of this threatening disease, it is imperative to obtain a better understanding of this disease. The disease is caused by abnormal folding and processing of proteins.

AD is recognised by beta amyloid plaques (Aβ), neurofibrillary tangles, dystrophic neuritis, and neuropil threads [2, 3]. Aβ plaques are composites of 39 to 43-amino acid peptides generated by sequentially proteolytic cleavage of 110-130 kDa amyloid precursor protein (APP) by beta-secretase (β-secretase) and gamma-secretase (γ-secretase) via the amyloidogenic pathway. In fact, APP is processed *via* two distinct pathways: the amyloidogenic and the non-amyloidogenic pathway. In the non-amyloidogenic pathway, alpha-secretase (α-secretase) cleaves APP, twelve amino acids from the transmembrane domain at the N-terminal, releasing a large soluble fragment known as soluble amyloid precursor protein alpha (sAPPα). The remaining membrane-bound C-terminal fragment of 83 amino-acids called C-terminal fragment alpha (CTFα) is then processed by γ-secretase to liberate the short p3 fragment and the APP intracellular domain (AICD). The amyloidogenic pathway starts with the cleavage of 16 amino acids by β-secretase upstream from the α-secretase cleavage site, generating a soluble amino terminal APP derivative called soluble amyloid precursor protein beta (sAPPβ) and a membrane inserted C-terminal fragment beta (CTFβ) which is 99 amino acids long. This is followed by further cleavage of CTFβ fragment in a progressive manner by γ-secretase, giving rise to Aβ peptides of different lengths from 38–43 amino acids and an additional ACID fragment [17]. Fig. (**1**) Amyloid plaques which are spherical protein aggregates can be divided into two types: neuritic and diffuse plaques. Neuritic plaques consist of microscopic foci of extracellular filamentous Aβ protein that exhibit a cross-sectional diameter ranging from 10 μm to 120μm. Dystrophic neurites contain enlarged lysosomes, degenerating mitochondria, and paired helical filaments in the vicinity of the plaques along with microglia and astrocytes [18]. The most common isoforms of Aβ are Aβ40 and Aβ42; the shorter form is typically produced by cleavage that occurs in the endoplasmic reticulum, while the longer form is produced by cleavage in the trans-Golgi network [19]. The biological functions of APP and the factor(s) that trigger the APP proteolytic cascade remain unclear. The importance of APP in the pathogenesis of Alzheimer's disease is suggested by several findings. Notably, mutations in APP or presenilin; two proteins that are implicated in familial forms of Alzheimer's disease leading to an increase in the amyloidogenic form of Aβ [3]. γ-secretase is an enzyme complex consisting of at least four subunits: presenilin (PS, PS1, or PS2), presenilin enhancer-2 (PEN-2), nicastrin, and anterior pharynx-defective-1 (APH-1). Presenilins 1 and 2 (PS1 and PS2) are highly homologous polytopic membrane proteins of mammals principally localized to the ER and Golgi apparatus [20]. It is the presenilin subunit that possesses the γ-secretase active site responsible for executing the intra-membrane sequential processing of APP [21]. More than 50 miss sense mutations in PS1 and PS2 have been found in families with early-onset Alzheimer's disease and cellular and transgenic modelling of such mutations

CHAPTER 7

# Metals Linked to Alzheimer's Disease

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**Abstract:** Exposure to metals including copper, zinc, aluminum, and iron ions occurs inevitably. Any disturbance in metal homeostasis develops diseases and abnormalities. Metal ions undergo an electric charge balance *via* gaining or losing electrons from surrounded biomolecules. They bind to amyloid fibrils or tau proteins in the brain in a way that links to the development of neurodegenerative diseases including Alzheimer's disease (AD). For several decades, scientists have been exploring possible links between metals imbalance and AD. However, very little is known about the exact mechanisms governing the links of metals to AD. This book chapter summarizes recent thoughts in the research studies that focus on the links between metals and AD. Most of the current results suggested that metal binding to amyloid binds affects the architecture of the protein fibrils and rate of propagation.

**Keywords:** Alzheimer's disease, Bioinorganic, Metals, Neurodegenerative diseases.

## INTRODUCTION

Dementia, including Alzheimer's disease (AD), is a syndrome in which there is deterioration in memory, learning functions, and performance of normal activities [1, 2]. Alzheimer's disease (AD) is a progressive, and chronic neurodegenerative disorder of the brain [1]. According to WHO, it is considered as the most common (60–70%) cause of dementia in elderly people age over 65 years old [1]. It was estimated that 5.3 million people were living with AD, and the patient's number will rise to 13.8 million by 2050. In 2019, the direct costs of caring for people with AD and other dementias are estimated to be $233.9 billion [3]. Patient of AD at the early stage of dementia suffer from forgetfulness, losing track of the time, and becoming lost in familiar places. These symptoms are progressed to becoming unaware of the time and place, and having difficulty recognizing relatives and friends. Several factors such as mutations in the β-amyloid (Aβ) rel-

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ated genes amyloid protein precursor (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) (<1% of total AD cases), diabetes, hypertension, sleep disorder, and psychological stress may increase the risk of AD [4].

Despite decades of research, scientists still don't fully understand what causes the neurodegenerative disease, although metals are expected to play a significant role in dementia [5]. Metals are ubiquities and can be found in our daily nutrition [6]. Modern fields such as metallobiology are punctuated by diseases that have specific abnormalities in metals or metal transport proteins, such as acrodermatitis enteropathica (failure of zinc absorption across the intestine) [7], amyotrophic lateral sclerosis (ALS, where Cu/Zn superoxide dismutase 1 plays a role) [8], and Wilson's disease (mutations in the copper transport gene, adenosine triphosphatase ATPase, *ATP7B*) [9]. The links between metals imbalance and neurodegenerative disorders including AD are unknown. Several endogenous proteins are involved in metal transportation on body [10]. The interactions of metal ions with amyloid precursor protein (APP), and Aβ enhance reactive oxygen species (ROS) formation, leading to Aβ over-production, aggregation, and enhanced neurotoxicity [11].

This book chapter summarizes the links between metals and Alzheimer's disease [12 - 14]. Different metals such as copper, iron, zinc, magnesium, calcium [15], aluminum [15], magnesium [16], and selenium [17], showed a link to AD [18]. These metals can be essential biometals (*e.g.*, iron, zinc, copper, manganese, magnesium, and calcium), or neurotoxic metals (*e.g.*, aluminum, lead, cadmium, and mercury) [11, 19].

## KEY PROTEINS IN THE BRAIN

Aβ and tau are two key proteins in the brain. Misfolding and aggregation of Aβ or tau proteins leading to the formation of plaques, and neurofibrillary tangles (NFTs), respectively.

The predominant Aβ peptide isoforms comprise 40–42 amino acids chains (sequence: AEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA) [20, 21]. Amyloid is misfolding, and aggregation of amyloid monomers with ordered and stabled structures [22]. Amyloids are typically hard, and waxy deposits consisting of protein. Normally, these folded proteins are cleared from the brain. In contrast, those who suffer from Alzheimer's disease have an unusual amount of sticky amyloid fibrils in their brains. Due to ageing, these fibrils accumulate instead of decomposition, and increasingly hamper functions of the brain.

Tau proteins (τ-proteins) are abundant proteins in neurons of the central nervous

system. The defect in tau proteins prevents stabilization of microtubules properly causing neurodegenerative diseases such as Alzheimer's disease.

## LINKS BETWEEN METALS AND AD

The exposure of human to metals occurs daily. Metals are present naturally in the body and can be provided *via* external sources. They can be classified to biological and non-biological metals (Fig. **1**). The links between metals and AD for both metals are summarized in Fig. (**1**), and discussed in the following sections.

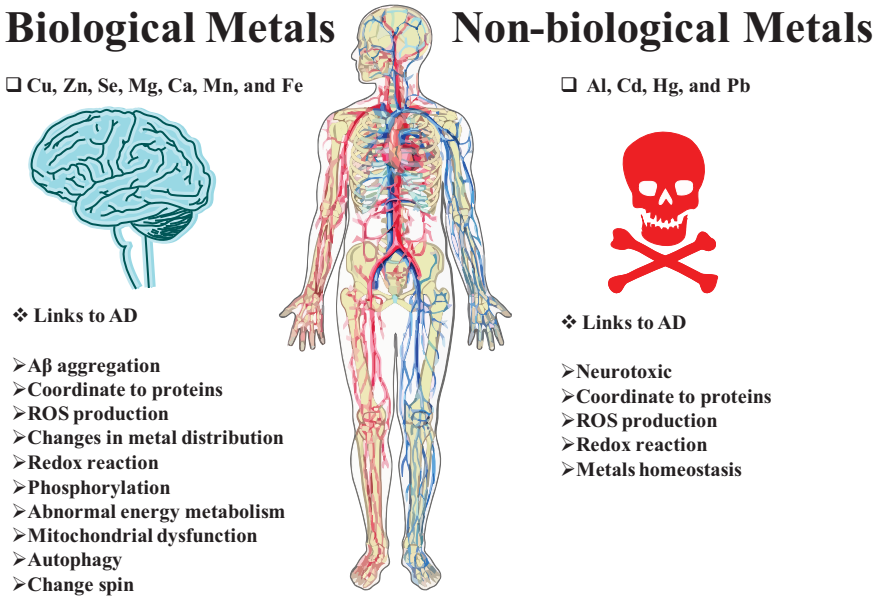


**Fig. (1).** Overview of human exposure to metals causing AD and their links.

## BIOMETALS LINK TO ALZHEIMER'S DISEASE

### Calcium and Magnesium

Calcium (Ca), and magnesium (Mg) ions serve as messengers and display role in controlling cellular function, neuronal growth, and signal transmission [23].

Excessive $Ca^{2+}$ in the endoplasmic reticulum (ER) is released *via* type 2 ryanodine receptors (RyanR2) in AD spines due to increase in expression and function of RyanR2 [15]. Store-operated $Ca^{2+}$ entry (nSOC) pathway is disrupted in AD spines due to down regulation of stromal interaction molecule 2 (STIM2) proteins. Because of these $Ca^{2+}$ signaling abnormalities, imbalance in activities of $Ca^{2+}$-calmodulin dependent kinase II (CaMKII), and $Ca^{2+}$-dependent phosphatase

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## PROF. DR. ATTA-UR-RAHMAN, *FRS*

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.