GENERAL INTRODUCTION
The nervous system is an organ system containing a network of specialized cells called neurons that coordinate the actions of an animal and transmit signals between different parts of its body. In majority of animals, the nervous system consists of two parts, central and peripheral. The central nervous system (CNS) is the part of the nervous system that integrates the information that it receives from, and coordinates the activity of all parts of the body of animals—that is, all multicellular animals except sponges and radially symmetric animals such as jellyfish. Some classifications also include the retina and the cranial nerves in the CNS. Together with the peripheral nervous system, it has a fundamental role in the control of overall behavior. The CNS is contained within the dorsal cavity, with the brain in the cranial cavity and the spinal cord in the spinal cavity. In vertebrates, the brain is protected by the skull, while the spinal cord is protected by the vertebrae, and both are enclosed in the meninges (Maton et al., 1993).

BRAIN

Brain is the most complex and delicate organ of the body. This part of the nervous system in vertebrates, enclosed within the skull, is connected with the spinal cord, and is composed of gray matter and white matter. It is the control center of the central nervous system, receiving sensory impulses from the rest of the body and transmitting motor impulses for the regulation of voluntary movement. The brain also contains the centers of consciousness, thought, language, memory, and emotion.
The brain is made of three main parts: the forebrain, midbrain, and hindbrain

- The forebrain consists of the cerebrum, thalamus, and hypothalamus (part of the limbic system).
- The midbrain consists of the tectum and tegmentum.
- The hindbrain is made of the cerebellum, pons and medulla. Often the midbrain, pons, and medulla are referred to together as the brainstem.

Olfactory lobe: Either member of a pair of lobes in the forebrain, at the anterior end of the cerebrum. They contain the endings of the olfactory nerves (the first pair of cranial nerves) and are concerned with the sense of smell, being prominent in the dogfish and other animals that depend on this sense.

Cerebral Cortex: The cerebrum or cortex is the largest part of the brain, associated with higher brain function such as thought and action. The cerebral cortex is divided into four sections, called "lobes": the frontal lobe, parietal lobe, occipital lobe, and temporal lobe. Here is a visual representation of the cortex:

Frontal lobe: Associated with reasoning, movement, emotions and problem solving.
Occipital lobe: Associated with visual processing.
Parietal lobe: Associated with orientation, recognition and perception of stimuli.
Temporal lobe: Associated with perception, recognition of auditory stimuli, memory and speech.

Hippocampus: Hippocampus is one of the major brain structures, that is part of the limbic system, which is responsible for functions like, emotion, behavior, long-term memory and olfaction. Hippocampus is located in the medial temporal lobe, beneath the cortex.

Cerebellum: Located above the brainstem and beneath the occipital lobes at the base of the skull. The cerebellum or "little brain", is similar to the cerebrum in that it has two hemispheres and has a highly folded surface or cortex. This structure is associated with coordination of voluntary movements, while walking, swimming, riding, etc., stores memory for reflex motor acts, coordinates simultaneous subconscious actions like eating while talking or listening etc.
**Pons medulla**: The top portion of the brain stem is the pons, the respiratory Center. It has control over skin of face, tongue, teeth, muscle of mastigation, muscle of eye which rotates eye outward, facial muscles of expression, internal auditory passage. It plays an important role in the level of arousal or consciousness and sleep and is involved in controlling autonomic body functions. At the bottom of the brain stem and the top end of the spinal cord is the medulla, also known as the medulla oblongata. In the time it takes you to say these two words, the medulla oblongata will have regulated your breathing, blood pressure, heart rate and wakefulness.

**Spinal Cord**: The Spinal Cord is a major part of the central nervous system which conducts sensory and motor nerve impulses to and from the brain; a long tube-like structure extending from the base of the brain through the vertebral canal to the upper lumbar region. Enclosed in the protective backbone, the spinal cord is essentially the 'motorway' to the Central Nervous System and is involved in the co-ordination of movement. There are four main groups of spinal nerves which exit at different levels of the spinal cord. These are in descending order down the vertebral column:

- **Cervical Nerves "C"**: (nerves in the neck) supply movement and feeling to the arms, neck and upper trunk.
- **Thoracic Nerves "T"**: (nerves in the upper back) supply the trunk and abdomen.
- **Lumbar Nerves "L" and Sacral Nerves "S"**: (nerves in the lower back) supply the legs, the bladder, bowel and sexual organs.

**NEUROLOGICAL DISORDERS AND DISEASES**

A neurological disorder is a disorder that involves the nervous system and can be caused by either a disease, such as multiple sclerosis or a trauma or injury to the nervous system. Neurological disorders can be remarkably difficult to treat and are often debilitating. Symptoms of neurological disorders can include slow loss of coordination, balance, or ability to speak clearly. Often symptoms start with a mild and intermittent twitching or numbness in one extremity, tremors, rigid muscles, slowed motion, difficulty in swallowing, loss of automatic movements such as blinking, swinging the arms, and unconscious acts, and eventually dementia. Public health challenges described and discussed the increasing global public health importance of common neurological disorders such as dementia, epilepsy, headache disorders, multiple sclerosis and neuroinfections, neurological disorders associated
with malnutrition, pain associated with neurological disorders, Parkinson's disease, stroke and traumatic brain injuries. Disorders of the Central Nervous System (CNS) are some of the most prevalent, devastating and yet poorly treated illnesses. There are many parallels between different neurodegenerative disorders including typical protein assemblies as well as induced cell death (Bredesen et al., 2006, Rubinsztaja, 2006).

Multiple Sclerosis: The French neurologist Jean-Martin Charcot (1825–1893) was the first person to recognize multiple sclerosis as a distinct disease in 1868 (Compston, 1988). Multiple sclerosis (MS) is a demyelinating disease, a non-contagious chronic autoimmune disorder of the central nervous system which can present with a variety of neurological symptoms occurring in attacks or slowly progressing over time. It has no cure yet and the exact cause remains unknown. Due to its effects on the nervous system, it can lead to long-term impaired mobility and disability in severe cases. Multiple sclerosis is a slowly progressive autoimmune disease in which the body's immune system attacks the protective myelin sheaths that surround the nerve cells of the brain and spinal cord (a process called demyelination), resulting in damaged areas that are unable to transmit nerve impulses.

Cerebral palsy: Cerebral palsy, formerly known as "Cerebral Paralysis," was first identified by English surgeon William Little (1860). Cerebral palsy is a group of disorders associated with developmental brain injuries that occur during fetal development, birth or shortly after birth. It is characterized by a disruption of motor skills, with symptoms such as spasticity, paralysis or seizures. Cerebral palsy is also known as static encephalopathy and Little's disease (which is strictly speaking only the "spastic diplegia" form of CP). It is no longer considered a disease, but rather it is a chronic nonprogressive neurological disorder. The incidence is about 1.5 to 4 per 1000 live births. There is no cure, but therapy may be helpful. It has one of the highest lifetime costs of any birth defect.

Parkinson's disease: In 1817 an English doctor, James Parkinson, published his essay reporting six cases of paralysis agitans (Lees, 2007). Parkinson's disease is a neurodegenerative disease of the substantia nigra. Parkinson's disease involves a breakdown of the nerve cells in the motor area of the brain. As the cells break down, there is a shortage of dopamine. Dopamine is a neurotransmitter that carries messages
to the body. When there is a shortage of dopamine, the messages that regulate movement aren't sent properly.

Headaches: In the 20th century, Harold Wolff (1950) developed an experimental approach to the study of headache. A headache is a condition of mild to severe pain in the head; sometimes upper back or neck pain may also be interpreted as headache. Most headaches are due to tension, migraine, or a combination of the two. Serious underlying causes of headaches, like a tumor or a stroke, are extremely rare, despite the fact that many people worry about these possibilities. Migraine headache is a primary headache disorder with almost certainly, a genetic basis. Activation of a mechanism deep in the brain causes release of pain-producing inflammatory substances around the nerves and blood vessels of the head leading to headache.

Epilepsy: It is a common chronic neurological disorder characterized by seizures (Blume et al., 2001) or episodes of disturbed brain function that cause changes in attention or behavior. These seizures are transient signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain (Fisher et al., 2005).

Neuropathy: Neuropathy, a disease of the nervous system is a disturbance in the function of a nerve or particular group of nerves. Many people who have had diabetes for a while have nerve damage. The three major forms of nerve damage are: peripheral neuropathy, autonomic neuropathy, and mononeuropathy. The most common form is peripheral neuropathy, which mainly affects the feet and legs. Neuropathy can lead to disability, amputation, decreased ambulation as well as foot and leg ulceration because of loss or damage to nerves which feel sensation in the lower limbs.

Schizophrenia: The term schizophrenia was coined by Eugen Bleuler (1908). It is a mental disorder characterized by disintegration of thought processes and of emotional responsiveness (Medical Dictionary. Oxford University Press, 2010). It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and is accompanied by significant social or occupational dysfunction.
Huntington's disorder: The first thorough description of the disease was made by Huntington (1872). It is a neurodegenerative genetic disorder affecting muscle coordination and leads to cognitive decline and dementia. It typically becomes noticeable in middle age. HD is the most common genetic cause of abnormal involuntary writhing movements called chorea and is much more common in people of Western Europeans than Asia and Africa.

ALZHEIMER'S DISEASE (AD)

Alzheimer's disease is an irreversible, progressive brain disorder related to changes in nerve cells that result in the death of brain cells eventually leading to gradual loss of memory, judgment and ability to function. This disorder usually appears in people older than age 65, but less common forms of the disease appear earlier in adulthood (Brookmeyer et al., 1998; Giacobini, 2002; Sano, 2002).

HISTORY

German neuropathologist Dr. Alois Alzheimer (1864-1915) interviewed a patient named Auguste D, who was first admitted to Frankfurt's Hospital for the Mentally Ill and Epileptics in 1901. On November 3, 1906, he presented Auguste D's case to the 37th Assembly of Southwest. Even though she was only 51, Auguste D. was severely divorced from reality, suffering from disorientation, hallucinations and paranoia (Esenstein, 1998). Her speech also was extremely limited. Alzheimer followed her until she died in 1906, when he first reported the case publicly (Alzheimer Alois, 1907).

Alois Alzheimer  Auguste D

In Auguste D.'s brain samples, Alzheimer noticed something in the slides that was extremely rare—gum-like clumps outside some cells and abnormal collections of proteins inside others, that is plaques and tangles respectively. A fresh look at the recently rediscovered Auguste D. slides confirms Alzheimer's claims. Her cortex
displayed what are now accepted as the classic pathological signs of the disease named after him: amyloid plaques and neurofibrillary tangles. Indeed, neurofibrillary tangles were described for the first time ever in this brain (Graeber et al., 1998). During the next five years, eleven similar cases were reported in the medical literature, some of them already using the term Alzheimer's disease (Berchtold and Cotman, 1998). The disease was first described as a distinctive disease by Emil Kraepelin after suppressing some of the clinical (delusions and hallucinations) and pathological features (arteriosclerotic changes) contained in the original report of Auguste D (Berrios, 1990). He included Alzheimer's disease, also named presenile dementia as a subtype of senile dementia in the eighth edition of his Textbook of Psychiatry, published in 1910 (Kraepelin Emil and Diefendorf Ross, 2007).

For most of the twentieth century, the diagnosis of Alzheimer's disease was reserved for individuals between the ages of 45 and 65 who developed symptoms of pre-senile dementia. Until the late 1970s, senile dementia was considered to be a normal part of the aging process. In the late 1970s and early 1980s, the name "Alzheimer's disease" began to be used both within and outside the medical profession for individuals aged 65 and older (Boller and Forbes, 1998) with senile dementia, because the symptoms and brain pathology were identical. Eventually, the term was adopted formally for all individuals with the common symptom pattern and disease course in the psychiatric and neurological nomenclature (Boller and Forbes, 1998) to describe individuals of all ages with the characteristic common symptom pattern, disease course, and neuropathology (Amaducci et al., 1986).

EPIDEMIOLOGY

Epidemiological studies are used in two main measures, they are: incidence and prevalence. Incidence is the number of new cases per unit of person-time at risk (usually number of new cases per thousand person-years); while prevalence is the total number of cases of the disease in the population at any given time. Regarding incidence, cohort longitudinal studies (studies where a disease-free population is followed over the years) provide rates between 10 and 15 per thousand person-years for all dementias and 5–8 for AD, which means that half of new dementia cases each year are AD. Advance age is a most important risk factor for the disease and incidence rates are not equal for all ages: every five years after the age of 65, the risk of acquiring the disease approximately doubles, rising from 3 to as much as 69 per
thousand person years (Di Carlo et al., 2002; Bermejo-Pareja et al., 2008). The World Health Organization estimated that in 2005, 0.379% of people worldwide had dementia, and that the prevalence would increase to 0.441% in 2015 and to 0.556% in 2030 (Ferri et al., 2005; World Health Organization, 2006). It was also reported that 0.40% of the world population (range 0.17–0.89%; absolute number 26.6 million, range 11.4–59.4 million) were afflicted by AD, and that the prevalence rate would triple and the absolute number would quadruple by 2050 (Brookmeyer et al., 2007). There are also sex differences in the incidence rates, women having a higher risk of developing AD particularly in the population older than 85 (Andersen et al., 1999; Di Carlo et al., 2002).

<table>
<thead>
<tr>
<th>Incidence rates after age 65</th>
<th>Newly affected persons per thousand per year</th>
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<td>Age</td>
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<td>65-69</td>
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Prevalence of AD in populations is dependent upon different factors including incidence and survival. Since the incidence of AD increases with age, it is particularly important to include the mean age of the population of interest. In the United States, Alzheimer prevalence was estimated to be 1.6% in 2000 both overall and in the 65–74 age groups, with the rate increasing to 19% in the 75–84 groups and to 42% in the greater than 84 group (Hebert et al., 2003). Prevalence rates in less developed regions are lower (Ferri et al., 2005).
TYPES OF ALZHEIMER'S DISEASE

Three types of Alzheimer's disease viz. Early onset Alzheimer's, late onset Alzheimer's and Familial Alzheimer's disease (FAD) are categorized and diagnosed based on the information given below (Jerry, 2009).

Early onset Alzheimer's: Early onset Alzheimer's affects less than 10% of those diagnosed with Alzheimer's disease. This form of Alzheimer's affects those under age 65. People with Down syndrome are particularly at high risk for early onset Alzheimer's disease and can often contrast the disease in their mid 40's or 50's. It appears to be linked with a genetic defect on chromosome 14. (Christopher et al., 1986)

Late onset Alzheimer's: Accounting for about 90% of Alzheimer's cases, late onset Alzheimer's is the most common form of Alzheimer's disease. This type of Alzheimer's disease usually occurs after age 65. More than 50% of those diagnosed with late onset Alzheimer's are over the age 85. It is unknown whether late onset Alzheimer's disease is hereditary or not. Late-onset dementia is also called "sporadic Alzheimer's disease". It appears to be linked with a genetic defect on chromosome 12 (Kennedy et al., 2003; Pastor and Goate, 2004)

Familial Alzheimer's disease: Often affects people in their 40's and 50's. This type of Alzheimer's is extremely rare accounting for less than 1% of all Alzheimer's cases. Familial Alzheimer's disease is very unique since it is easily traced through multiple generations of family members. The genetic causes of AD are summarized in "Decoding Darkness: The Search for the Genetics Causes of Alzheimer's Disease" (Tanzi and Parson, 2000). These families usually inherit a genetic fault on specific chromosomes viz. 21, 14 or 1. Familial Alzheimer disease is caused by mutations in at least 3 genes: presenilin-1, amyloid precursor protein and presenilin-2 (Ertekin-taner, 2007; Bertram and Tanzi, 2008; Williamson et al., 2009).
STAGES AND SYMPTOMS OF ALZHEIMER'S DISEASE

Preclinical AD: AD begins in the entorhinal cortex, which is near the hippocampus and has direct connections to it. It then proceeds to the hippocampus, the structure that is essential to the formation of short-term and long-term memories. Affected regions begin to atrophy (shrink). These brain changes probably start 10 to 20 years before any visible signs and symptoms appear. Memory loss, the first visible sign, is the main feature of mild cognitive impairment (MCI). Many scientists think MCI is often an initial transitional phase between normal brain aging and AD.

Mild AD: As the disease begins to affect the cerebral cortex, memory loss continues and changes in other cognitive abilities emerge. The clinical diagnosis of AD is usually made during this stage. Signs of mild AD can include:

- Memory loss
- Confusion about the location of familiar places (getting lost begins to occur)
- Taking longer time to accomplish normal daily tasks
- Trouble in handling money and paying bills
- Poor judgment leading to bad decisions
- Loss of spontaneity and sense of initiative
- Mood and personality changes and increased anxiety

The growing number of plaques and tangles first damage areas of brain that control memory, language, and reasoning. It is not until later in the disease that physical abilities decline. This leads to a situation in mild AD in which a person seems to be healthy, but is actually having more and more trouble making sense of the world around him or her. The realization that something is wrong often comes gradually because the early signs can be confused with changes that can happen
normally with aging. Accepting these signs and deciding to go for diagnostic tests can be a big hurdle for patients and families to cross.

Moderate AD: By this stage, AD damage has spread further to the areas of the cerebral cortex that control language, reasoning, sensory processing and conscious thought. Affected regions continue to atrophy and signs and symptoms of the disease become more pronounced and widespread. Behaviour problems, such as wandering and agitation can occur. More intensive supervision and care become necessary, and this can be difficult for many spouses and families. The symptoms of this stage can include:

- Increase in memory loss and confusion
- Shortened attention span
- Problems in recognizing friends and family members
- Difficulty with language; problems with reading, writing, working with numbers
- Difficulty in organizing thoughts and thinking logically
- Inability to learn new things or to cope with new or unexpected situations
- Restlessness, agitation, anxiety, tearfulness, wandering - especially in the late afternoon or at night
- Repetitive statements or movement, occasional muscle twitches
- Hallucinations, delusions, suspiciousness or paranoia, irritability
- Loss of impulse control (shown though sloppy table manners, undressing at inappropriate times or places, or vulgar language)
- Perceptual-motor problems such as trouble in getting out of a chair

Behaviour is the result of complex brain processes, all of which take place in a fraction of a second in the healthy brain. In AD, many of these processes are disturbed, and this is the basis for many distressing or inappropriate behaviours. For example, people may angrily refuse to take a bath or get dressed because they do not understand what the caregiver has asked them to do. If they do understand, they may not remember how to do it. The anger is a mask for their confusion and anxiety. Or, a person with AD may constantly follow her husband or caregiver and fret when the person is out of sight. To a person who cannot remember the past or anticipate the future, the world around her can be strange and frightening. Sticking close to a trusted and familiar caregiver may be the only thing that makes sense and provides security.
Tahng off clothes may seem reasonable to a person with AD who feels hot and doesn’t understand or remember that undressing in public is not acceptable.

Severe AD: In this last stage of AD, plaques and tangles are widespread throughout the brain, and many areas of the brain have atrophied further. Patients cannot recognize family and loved ones or communicate in any way. They are completely dependent on others for care. All sense of self seems to vanish. Other symptoms can include:

- Weight loss
- Seizures, skin infections, difficulty in swallowing
- Groaning, moaning or grunting
- Increased sleeping
- Lack of bladder and bowel control

At the end, patients may be in bed all of the time. Most people with AD die from other illnesses, frequently aspiration pneumonia. This type of pneumonia happens when a person is not able to swallow properly and breathes food or liquids into the lungs.

*Pictures showing the major changes in human brain at various stages of AD*

**THERAPIES**

*Three major competing hypotheses exist to explain the cause of the disease.*

The oldest, on which most currently available drug therapies are based, is the cholinergic hypothesis, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective. Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid (Shen, 2004), leading to generalised neuroinflammation (Wenk, 2003).
In 1991, the amyloid hypothesis postulated that amyloid beta (Aβ) deposits are the fundamental cause of the disease (Hardy and Allsop, 1991; Mudher and Lovestone, 2002). It is a compelling theory because the gene for the amyloid beta precursor (APP) is located on chromosome 21, and people with trisomy 21 (Down Syndrome) who thus have an extra gene copy almost universally exhibit AD by 40 years of age (Lott and Head, 2005; Nistor et al., 2007). Also APOE4, the major genetic risk factor for AD, leads to excess amyloid buildup in the brain before AD symptoms arise. Thus, Aβ deposition precedes clinical AD (Polvikoski et al., 1995). Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology (Games et al., 1995; Hsiao et al., 1996; Masliah et al., 1996). An experimental vaccine was found to clear the amyloid plaques in early human trials, but it did not have any significant effect on dementia (Holmes et al., 2008).

Deposition of amyloid plaques does not correlate well with neuron loss (Schmitz et al., 2004). This observation supports the tau hypothesis, the idea that tau protein abnormalities initiate the disease cascade (Mudher and Lovestone, 2002). In this model, hyperphosphorylated tau begins to pair with other threads of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies (Goedert et al., 1991). When this occurs, the microtubules disintegrate, collapsing the neuron's transport system. This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells (Chun and Johnson, 2007).

**PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE**

Neuromaging of patients with AD revealed atrophy of the brain, such as enlarged ventricles and sulci and narrowed gyri, although these features are not always present. Microscopically, AD is characterized by the presence of senile plaques and neurofibrillary tangles (NFTs). Plaques are extra cellular deposits of filamentous β-amyloid, a protease cleavage product of amyloid precursor protein. NFTs are formed intracellular by an abnormal rearrangement of microtubule-associated proteins, such as tau. However, the plaques seen in normal brains or early-stage of AD are diffused and relatively benign deposits of β-amyloid, whereas at later stages, the plaques assume a compact β-pleated conformation and subsequently become associated with dystrophic neuritis. These later-stage plaques are thought to represent a more neurotoxic form of AD (Geldmacher and Whitehouse, 1997).
PROGNOSIS

The early stages of Alzheimer's disease are difficult to diagnose. A definitive diagnosis is usually made once cognitive impairment compromises daily living activities, although the person may still be living independently. He will progress from mild cognitive problems, such as memory loss through increasing stages of cognitive and non-cognitive disturbances, eliminating any possibility of independent living (Forstl and Kurz, 1999). Further, it is also reported that life expectancy of the population with the disease is reduced (Molsa et al., 1986; Bowen et al., 1996; Dodge et al., 2003). The mean life expectancy following diagnosis is approximately seven years. Fewer than 3% of patients live more than fourteen years (Molsa et al., 1995). Disease features significantly associated with reduced survival are an increased severity of cognitive impairment, decreased functional level, history of falls, and disturbances in the neurological examination. Other coincident diseases such as heart problems, diabetes or history of alcohol abuse are also related with shortened survival (Jaggar et al., 1995; Bowen et al., 1996; Larson et al., 2004). While earlier the age at onset, higher the total survival years. Life expectancy is particularly reduced when compared to the healthy population among those who are younger (Dodge et al., 2003). Men have a less favourable survival prognosis than women (Molsa et al., 1995; Ganguli et al., 2005). The disease is the underlying cause of death in 70% of all cases. Pneumonia and dehydration are the most frequent immediate causes of death, while cancer is a less frequent cause of death than in the general population (Molsa et al., 1986; Ganguli et al., 2005).
DIAGNOSIS

Alzheimer's disease is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alternative conditions (Klafki et al., 2006; Mendez, 2006). Advanced medical imaging with Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), and with single photon Emission Computed Tomography (SPECT) or positron Emission Tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia (Bouye et al., 2006; Dementia quick reference guide, 2006). Assessment of intellectual functioning including memory testing can further characterize the state of the disease (Waldmer et al., 2007).

DIAGNOSTIC CRITERIA

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association) established the most commonly used diagnostic criteria for Alzheimer's disease (Dubois et al., 2007). These criteria require the presence of cognitive impairment, and a suspected dementia syndrome, be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD. A histopathologic confirmation including a microscopic examination of brain tissue is required for a definitive diagnosis. Good statistical reliability and validity have been shown between the diagnostic criteria and definitive histopathological confirmation (Blacker et al., 1994). Eight cognitive domains are most commonly impaired in AD—memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities. These domains are equivalent to the NINCDS-ADRDA Alzheimer's Criteria as listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) published by the American Psychiatric Association (Ito, 1996; American Psychiatric Association, 2000).

DIAGNOSTIC TOOLS

Neuropsychological screening tests can help in the diagnosis of AD. Neuropsychological tests such as the Mini-Mental State Examination (MMSE) are widely used to evaluate the cognitive impairments needed for diagnosis. More comprehensive test arrays are necessary for high reliability of results, particularly in the earliest stages of the disease (Tom Baugh and Mc Intyre, 1992; Pasqueir,
1999). Neurological examination in early AD will usually provide normal results, except for obvious cognitive impairment, which may not differ from standard dementia. Further neurological examinations are crucial in the differential diagnosis of AD and other diseases (Waldmar et al., 2007). Interviews with family members are also utilized in the assessment of the disease. Caregivers can supply important information on the daily living abilities, as well as on the decrease, over time, of the person's mental function (Harvey et al., 2005). A caregiver's viewpoint is particularly important, since a person with AD is commonly unaware of his own deficits (Antolne et al., 2004). Many times, families also have difficulties in the detection of initial dementia symptoms and may not communicate accurate information to a physician (Cruz et al., 2004). Supplemental testing provides extra information on some features of the disease or is used to rule out other diagnoses. Blood tests can identify other causes for dementia than AD (Waldmar et al., 2007)—causes which may, in rare cases, be reversible (Clarfield, 2003). Psychological tests for depression are employed, since depression can either be concurrent with AD or be the cause of cognitive impairment (Geldmacher and Whitehouse, 1997; Potter and Steffens, 2007).

When available as a diagnostic tool, SPECT and PET neuroimaging are used to confirm a diagnosis of Alzheimer's in conjunction with evaluations involving mental status examination (Bonte et al., 2006). The ability of SPECT to differentiate Alzheimer's disease from other possible causes in somebody already known to be suffering from dementia appears to be superior to attempts to diagnose by mental testing and history (Dougall et al., 2004). A new technique known as PiB PET has been developed for directly and clearly imaging beta-amyloid deposits in vivo was using a tracer that binds selectively to the Amyloid beta deposits (Ikonomovic et al., 2008; Jack et al., 2008; Kemppainen et al., 2008). Another recent objective marker of the disease is the analysis of cerebrospinal fluid for amyloid beta or tau proteins (Marksteiner et al., 2007). Both advances have led to the proposal of new diagnostic criteria (Dubois et al., 2007; Waldemar et al., 2007).

DISEASE MECHANISM

Exactly how disturbances of production and aggregation of the beta amyloid peptide gives rise to the pathology of AD is not known (Van Broeck et al., 2007). The amyloid hypothesis traditionally points to the accumulation of beta amyloid
peptides as the central event triggering neuron degeneration. Accumulation of
aggregated amyloid fibrils, which are believed to be the toxic form of the protein
responsible for disrupting the cell's calcium ion homeostasis, induces programmed
cell death (apoptosis) (Yankner et al., 1990). It is also known that Aβ selectively
builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also
inhibits certain enzyme functions and the utilisation of glucose by neurons (Chen
and Yan, 2006). Inflammation is a general marker of tissue damage in any disease,
and may be either secondary to tissue damage in AD or a marker of an immunological
response (Greig et al., 2004).

GENETICS

While the rare, early-onset form of Alzheimer's disease is mainly explained by
mutations in three genes, the most common form has yet to be explained by a purely
genetic model. The APOE gene is the strongest genetic risk factor for Alzheimer's
discovered so far, but its presence is far from explaining all occurrences of the disease
(Waring and Rosenberg, 2008). Less than 10% of AD cases occurring before 60
years of age are due to autosomal dominant (familial) mutations, which therefore
represent less than 0.01% of all cases (Campion et al., 1999; Hoenicka, 2006;
Waring and Rosenberg, 2008). These mutations have been discovered in three
different genes: Amyloid Precursor Protein (APP) and presenilins 1 and 2 (Waring
and Rosenberg, 2008). Most mutations in the APP and presenilin genes increase the
production of a small protein called Abeta42, which is the main component of senile
plaques (Selkoe, 1999). Most cases of Alzheimer's disease do not exhibit familial inheritance, but genes may act as risk factors. The best known genetic risk factor is the inheritance of the e4 allele of the apolipoprotein E (APOE). This gene is implicated in up to 50% of late-onset sporadic Alzheimer's cases (Strittmatter et al., 1993). Geneticists agree that numerous other genes also act as risk factors or have protective effects that influence the development of late onset Alzheimer's disease. Over 400 genes have been tested for association with late-onset sporadic AD (Warling and Rosenberg, 2008). One example is a variant of the reelin gene that may contribute to Alzheimer's risk in women (Seripa et al., 2008).

**BIOCHEMISTRY**

Alzheimer's disease has been identified as a protein misfolding disease (proteopathy), caused by accumulation of abnormally folded A-beta and tau proteins in the brain (Hashimoto et al., 2003). Plaques are made up of small peptides, 39–43 amino acids in length, called beta-amyloid (also written as A-beta or Aß). Beta-amyloid is a fragment from a larger protein called Amyloid Precursor Protein (APP), a transmembrane protein that penetrates through the neuron's membrane. APP is critical to neuron growth, survival and post-injury repair (Prillier et al., 2006; Turner et al., 2003). In Alzheimer's disease, an unknown process causes APP to be divided into smaller fragments by enzymes through proteolysis (Hooper, 2005). One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques (Ohnishi and Takano, 2004; Tirabosi et al., 2004).

AD is also considered a tauopathy due to abnormal aggregation of the tau protein. Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubules. These microtubules act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back. A protein called tau stabilises the microtubules when phosphorylated, and is therefore called a microtubule-associated protein. In AD, tau undergoes chemical changes, becoming hyperphosphorylated; it then begins to pair with other threads, creating neurofibrillary tangles and disintegrating the neuron's transport system (Hernandez and Avila, 2007).
SOCIAL COSTS

Dementia, and specifically Alzheimer's disease, may be among the most costliest diseases for society in the developed countries (Bonin-Guillaume et al., 2005), while their cost in developing countries such as Argentina (Allegri et al., 2007), or developed South Korea (Suh et al., 2006), is also high and rising. These costs will probably increase with the ageing of society, becoming an important social problem. AD associated costs include direct medical costs such as nursing home care, direct nonmedical costs such as in-home day care, and indirect costs such as lost productivity of both patient and caregiver (Meek et al., 1991). Numbers vary between studies but dementia costs worldwide have been calculated around $160 billion (Wimo et al., 2006), while costs of Alzheimer in the United States may be $100 billion each year (Meek et al., 1998). Costs increase with dementia severity and the presence of behavioural disturbances (Jonsson et al., 2006), and are related to the increased caregiving time required for the provision of physical care (Moore et al., 2001). Therefore any treatment that slows cognitive decline, delays institutionalisation or reduces caregivers' hours will have economic benefits. Economic evaluations of current treatments have shown positive results (Meek et al., 1998).
TREATMENT

There is presently no cure for Alzheimer's disease. None of the currently approved drugs is known to stop the underlying degeneration of brain cells, but some drugs may temporarily delay memory decline for some people with the disease. The emotional and behavioral symptoms of the disease can also be treated with some drugs approved to treat other illnesses. Four medications are currently approved by regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) to treat the cognitive manifestations of AD: three are acetylcholinesterase inhibitors and the other is memantine, an NMDA receptor antagonist. No drug has an indication for delaying or halting the progression of the disease.

Reduction in the activity of the cholinergic neurons is a well-known feature of Alzheimer's disease (Geula and Mesulam, 1995). Acetylcholinesterase inhibitors are employed to reduce the rate at which acetylcholine (ACh) is broken down, thereby increasing the concentration of ACh in the brain and combating the loss of ACh caused by the death of cholinergic neurons (Stahl, 2000). As of 2008, the cholinesterase inhibitors approved for the management of AD symptoms are donepezil (brand name Aricept), galantamine (Razadyne), and rivastigmine (branded as Exelon and Exelon Patch (U.S. National Library of Medicine, 2007). There is evidence for the efficacy of these medications in mild to moderate Alzheimer's disease, and some evidence for their use in the advanced stage. Only donepezil is approved for treatment of advanced AD dementia (Birks and Harvey, 2006). The use of these drugs in mild cognitive impairment has not shown any effect in delaying of the onset of AD (Raschetti et al., 2007). The most common side effects, such as nausea and vomiting, both of which are linked to cholinergic excess arise in approximately ten to twenty percent of users and are mild to moderate in severity. Less common secondary effects include muscle cramps, bradycardia, decreased appetite and weight, and increased gastric acid production (Exelon, 2007). Glutamate, a useful excitatory neurotransmitter of the nervous system, if produced in excess amounts in the brain can lead to cell death excitotoxicity which occurs not only in Alzheimer's disease, but also in other neurological diseases such as Parkinson's disease and multiple sclerosis (Lipton, 2006). Memantine (brand names Akatinol, Axura, Ebixa/Abixa, Memox and Namenda) is a noncompetitive NMDA receptor
antagonist first used as an anti-influenza agent. It acts on the glutamatergic system by blocking NMDA receptors and inhibiting their over stimulation by glutamate (Lipton, 2006). Memantine has been shown to be moderately efficacious in the treatment of moderate to severe Alzheimer's disease. Its effects in the initial stages of AD are unknown (Areosa Sastre et al., 2004). Reported adverse events with memantine are infrequent and mild, including hallucinations, confusion, dizziness, headache and fatigue. The combination of memantine and donepezil has been shown to be "of statistically significant but clinically marginal effectiveness" (Raina et al., 2008).

Antipsychotic drugs are modestly useful in reducing aggression and psychosis in Alzheimer's patients with behavioural problems, but are associated with serious adverse effects, such as cerebrovascular events, movement difficulties or cognitive decline, that do not permit their routine use (Ballard et al., 2008; Ballard et al., 2009).

**POTENTIAL TREATMENTS**

**Vaccine**: There are ongoing tests on Alzheimer's disease vaccine. The vaccine is based on the idea that if the immune system could be trained to recognize and attack beta-amyloid, the immune system might reverse deposition of amyloid and thus stop the disease. Initial results in animals were promising, but researchers had to stop a human trial in 2002 after 18 participants developed potentially fatal brain inflammation called meningoencephalitis. Follow-up with some participants in the halted trials showed that the vaccine had cleared plaques from the brains of people with the disease (Janus, 2003). In 2006, a new vaccine developed by Japanese researchers showed promising results. Amyloid deposits were reduced between 15.5 percent and 38.5 percent in mice, with no adverse side effects (Okura, 2006). In 2006, researchers began tests in monkeys, expecting to follow with human trials about three years later if successful.

**Ginkgo biloba**: The earlier studies have suggested that ginkgo biloba showed positive effect for alleviating Alzheimer's (Ahlemeyer, 2003; Schulz, 2003; Sterpina, 2003). However, further research is required, as consumption of ginkgo biloba can have undesirable side-effects, especially for those with blood circulation disorders and those taking certain medications (Witkam, 2004). Ginkgo should not be used by anyone taking anti-coagulants, pregnant women, or anyone using the antidepressant drugs known as monoamine oxidase inhibitors (MAOIs).
GALANTAMINE HYDROBROMIDE

Now-a-days, there are several drugs that have been approved for the treatment of Alzheimer's disease, but one drug in particular requires further exploration. Galantamine or Razadyne is one of the latest drugs available on the drug market. It is a reversible competitive inhibitor of acetylcholinesterase used as the hydrobromide salt in the treatment of mild to moderate Alzheimer's disease (Anon. Reminyl, 2001; Lyseng-Williamson and Plosker, 2002).

STRUCTURE, NOMENCLATURE, COMPOSITION AND FORMULATION OF GALANTAMINE

The chemical description and nature of galantamine: Galantamine is a tertiary alkaloid, belonging to the phenanthrene chemical class, which occurs naturally in the daffodil (Narcissus tazetta), snowdrop (Galanthus nivalis) and the snowflake (Leucojum aestivum) (Cronin, 2001; Food and Drug Administration, 2001; Jann et al., 2002). The drug also belongs to a class of drugs called cholinesterase inhibitors (drugs that block the activity of the enzyme, acetylcholinesterase) and include tacrine, donepezil and rivastigmine (Anonymous, 2005). The active ingredient is the salt galantamine hydrobromide, a white powder with the chemical name \((4aS,6R,8aS)-4a,5,9,10,11,12\text{-hexahydro-3-methoxy-11-methyl - 6 H - benzofuro [3a, 3, 2ef] [2] benzazepin - 6 - ol hydrobromide}\) (Heinrich, 2004; Drugdex, 2005).

![Snowdrop plant](image1)

![Structure of Galantamine hydrobromide](image2)

The early years of Galantamine's development

Most of the early investigation on Galantamine was conducted in Bulgaria and the USSR during the coldest period of the Cold War.
### Historical development of Galantamine as a clinically used drug

<table>
<thead>
<tr>
<th>Year</th>
<th>Development of Galantamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early 1950s</td>
<td>According to un confirmed reports, a Russian pharmacologist discovered that local villagers living at the foot of Ural mountain used wild Caucasian snowdrop to treat (what he considers to be) poliomyelitis in children.</td>
</tr>
<tr>
<td>1951</td>
<td>Maskovsky and Kruglikova-Lyova demonstrated galantamine's AChE inhibiting properties and its antagonizing effects on curare's action.</td>
</tr>
<tr>
<td>1952</td>
<td>Galantamine was first isolated from <em>Galanthus woronowii</em>.</td>
</tr>
<tr>
<td>1956/7</td>
<td>Suggestions for alternative sources of galantamine incl. the leaves of <em>Naracissus</em> spp. and <em>Galanthus nivalis</em> as well as <em>leucojum aestivum</em> (the main source of galantamine in the Eastern European countries until its introduction onto the Western pharmaceutical market).</td>
</tr>
<tr>
<td>Late 1950s</td>
<td>Various pre-clinical studies on the pharmacology of Galantamine on neuromuscular preparations of cat, rat and frog have demonstrated that Galantamine has antagonistic effects against non-depolarising neuromuscular blocking agents. Subsequently, Galantamine was registered under the trade name &quot;NIVALIN&quot; and is commercially available in Bulgaria.</td>
</tr>
<tr>
<td>Early 1960s</td>
<td>The first data on anti-cholinesterase activity of galantamine was reported from an in vivo study in an anaesthetized cat.</td>
</tr>
<tr>
<td>1980s</td>
<td>Pre-clinical development: Researchers searching for novel treatments of Alzheimer's disease started investigating the therapeutic effects of galantamine.</td>
</tr>
<tr>
<td>1990s</td>
<td>Clinical development of galantamine into a medication for Alzheimer's disease.</td>
</tr>
<tr>
<td>1996</td>
<td>Sanochemia pharmazeutika obtained the first patent on the synthetic process of galantamine.</td>
</tr>
<tr>
<td>1997</td>
<td>Sanochemia began collaboration with a Belgium-based company (Janssen Pharmaceuticals) and an emerging British Company (Shire Pharmaceuticals Group plc).</td>
</tr>
<tr>
<td>2000</td>
<td>Galantamine licensed in the first countries (Iceland, Ireland, Sweden, UK) for the treatment of Alzheimer's Disease.</td>
</tr>
<tr>
<td>Currently (2003-2004)</td>
<td>Galantamine has been approved for use in United States, many European countries and some Asian countries.</td>
</tr>
</tbody>
</table>
Many pre-clinical studies were carried out in animals for testing the pharmacological activity of Galantamine. Initially, Nivalin was used in anesthesiology to antagonize the effects on non-depolarising muscle relaxants, and since then it was rapidly introduced in other areas of medicine, i.e. neurology, ophthalmology, gastroenterology, intensive care and resuscitation, cardiology, physiotherapy (Nastev, 1960; Stoyanov, 1964; Mayrhofer, 1967). After a few years, penetration of Galantamine through the blood-brain barrier, and its effects on the central nervous system became established. Based on the knowledge of Galantamine in both peripheral and central nervous system, many countries in Eastern Europe had used it as a acknowledged treatment in myasthenia gravis and muscular dystrophy, residual poliomyelitis paralysis symptoms, trigeminal neuronal and other forms of neuritides. In 1960, Galantamine producing species which are easier to cultivate were identified, and the full chemical synthesis was published. This was a biomimetic laboratory process with a yield of below 1% and had been designed as proof of structure, not for industrial production (Rainer, 1997).

The formulations available and their composition: Galantamine is available as tablets of 4 mg, 8 mg and 12 mg. Each 4, 8 and 12 mg tablet contains 5.125, 10.253 and 15.379 mg of galantamine hydrobromide. The inactive ingredients (excipients) in this formulation are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactosemonohydrate, magnesium state, microcrystalline cellulose, propylene glycol, talc and titanium dioxide. The extended release capsules are available in 8 mg, 16 mg and 24 mg and each capsule contains the same amount of galantamine hydrobromide (8 mg, 16 mg and 24 mg of the active ingredient). The 16 mg capsule contains red ferric oxide; the 24 mg capsule contains both red and yellow ferric oxide, while the 8 mg capsule lacks ferric oxide in its formulation (Food and Drug Administration, 2001). Lastly, the oral solution contains 4 mg/mL of galantamine hydrobromide and the inactive ingredients are methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium saccharin, sodium hydroxide and purified water (Anonymous, 2005).

THE PHARMACOKINETICS OF GALANTAMINE

Absorption & bioavailability: According to Kewitz (1997), the pharmacokinetics of Galantamine in healthy patients appear to be first-order and linear at wide dose ranges (5-35 mg). Galantamine through oral administration is absorbed rapidly and
completely and the time it takes to reach peak concentration ($t_{\text{max}}$) is about an hour (Food and Drug Administration, 2001; Maltz and Kirschenbaum, 2002; Anonymous, 2005). The oral bioavailability is quite high, approximately 90%, suggesting that each dose is rapidly absorbed into the bloodstream. It was determined, that the bioavailability of the tablet is the same as that of the oral solution (Food and Drug Administration, 2001; Anonymous, 2005). Using tables, the mean lag time was 15.6 min, the maximal concentration in the blood was reached after 52 min and the half-life of the absorption process was 20.4 min. With a solution, the mean lag time was shorter (10.2 min), the maximal concentration in the blood was reached earlier (after 15 min) and the half-life of the absorption process was 21.6 min.

The rate of absorption ($t_{\text{max}}$) can be delayed by the introduction of food, thus reducing the peak concentration ($C_{\text{max}}$) by 25% and $t_{\text{max}}$ by 1.5 hours. It was found that food does not significantly affect the extent of absorption (AUC) (Food and Drug Administration, 2001; Jann, 2002; Anonymous, 2005). However, the extended release capsules have a $C_{\text{max}}$ value that is 24% lower than that of the tablet. The presence of food has no effect on the extent of absorption (AUC) or the peak concentration ($C_{\text{max}}$), but $t_{\text{max}}$ is increased by 12% (Anonymous, 2005).

Distribution: One of the pharmacokinetic parameters is the volume of distribution ($V$) which describes the delivery of the drug from the bloodstream to the tissues. The average volume of distribution for galantamine is 175 L (Food and Drug Administration, 2001; Anonymous, 2005). This value is large and suggests that the absorption of galantamine is non-specific (Scott and Goa, 2000). The drug has a low plasma binding ability, with only 18% of galantamine bound (Helarich, 2004 and Drugdex, 2005). However, this finding has been questioned in patients with AD, as studies have shown that patients receiving 30 or 40 mg of galantamine have plasma protein binding between 28 to 34%, after two to three hours following dose administration. In whole blood, galantamine is mostly distributed to the blood cells (52.7%) and plasma water (39%) (Food and Drug Administration, 2001 and Anonymous, 2005). Yet, the proportion bound to plasma proteins is 8.4%. This value is considerably low and suggests that more of the drug is available for distribution. The ratio of blood to plasma concentration is 1:2.
Distribution of Galantamine from the central compartment into tissues and organs followed the rules of non-ionic passive diffusion of a weak base with a pKa value of 8.32. Since Galantamine is apparently not bound to plasma proteins, an intracellular accumulation has been observed according to a slight but considerably lower pH value of 7.0 inside of cells and 7.2 inside of erythrocytes compared to 7.4 in the plasma and extracellular fluid. There were exceptionally high concentrations of Galantamine in liver and kidney, the two main organs of elimination. For example, in mice the respective concentrations in kidneys and liver were 10- and 5- fold higher than the concentration in blood plasma. Galantamine has a large volume of distribution following oral administration, confirming the high non-specific absorption of this drug. In humans, according to the area under the concentration time curve (AUG), bioavailability after oral administration in tablets and liquid were 85 and 100% respectively. From the bioavailability data is can also be concluded that a first-pass effect does not play a significant role (Mihailova et al., 1989; Kewitz, 1997).

Metabolism: The primary route of galantamine metabolism occurs via hepatic cytochrome P450 isoenzymes in the liver, where approximately 75% of the drug dose is metabolized (Scott and Gos, 2000). Several in vitro studies confirm that cytochrome CYP2D6 and CYP3A4 were the main cytochrome P450 isoenzymes responsible for galantamine metabolism (Jann et al., 2002). Galantamine can be metabolised into the following metabolites: norgalantamine, O-demethylgalantamine, O-demethylnor-galantamine, epigalantamine and galantaminone. The active metabolites of galantamine are norgalantamine, O-and O-desmethyl-norgalantamine (Bachus et al., 1999). CYP2D6 is involved in the formation of O-desmethyl-galantamine, while CYP3A4 is responsible for the formation of galantamine-N-oxide (Jann et al., 2002; Farlow, 2003).

Excretion (Elimination): The second pharmacokinetic parameter is plasma clearance (CL) which is the volume of plasma cleared of drug per unit time (mL/min). About 20% of the dose was excreted unchanged in the urine after oral or intravenous administration within 24 hours. The renal clearance stands at 65 mL/min, indicating 20-25% of total plasma clearance (300 mL/min). The last parameter is terminal half-life (T1/2), which is 7-8 hours (Scott and Gos, 2000; Farlow, 2003). Patients with AD had a typical oral clearance of 121/h. While renal clearance of GAL in healthy
volunteers after oral administration was 0.0841/h/kg (6.21/h based on a mean bodyweight of 73.8 kg). Also, the population pharmacokinetic analysis indicated that the clearance is 20% lower in females than in males, with no clinically relevant differences observed in populations of different age or race (Bickel et al., 1991 a,b).

Galantamine is primarily excreted in the urine, although it is partially excreted in the faeces and bile. Studies investigating both the radioactivity and recovery period of this drug provide evidence confirming this assumption. Scott and Goa (2000) reported that seven days after a single oral dose of 4 mg galantamine was administered, 90-97% of radioactivity was found in the urine compared with 2.2 to 6.3% in the faeces. Further, they also showed that twenty-four hours after a dose of galantamine was administered, about 60% of the drug was recovered from the urine, with complete recovery by 72 hours. At least 5% of the dose was excreted in the faeces, with a further 0.2% excreted through the bile.

MECHANISM OF ACTION

Molecular target of action: The mechanism of action illustrates the way the drug acts in the body. Galantamine is a selective, competitive and reversible inhibitor of acetylcholinesterase activity. Acetylcholinesterase is the enzyme involved in the breakdown of the acetylcholine neurotransmitter in the neuromuscular junction (Scott and Goa, 2000). It is able to augment cholinergic function through a dual mechanism of action, specifically the inhibition of the enzyme acetylcholinesterase and the allosteric modulation of nicotinic receptors (Parys, 1998; Farlow, 2001).

The dual mechanism of action for Galantamine: acetylcholinesterase inhibitor and nicotinic modulation
Although the precise mechanism of action of galantamine is not completely understood, there appears to be a reduction in the acetylcholine producing neurons in the brains of AD sufferers. This type of cholinergic loss is related to the level of cognitive impairment and the density of amyloid plagues, which are representative features of AD (Food and Drug Administration, 2001; Anonymous, 2005). Galantamine is believed to exert its biological effect through the enhancement of cholinergic function. This is achieved by an increase in acetylcholine concentration through the reversible inhibition of its hydrolysis by cholinesterase. This dual mechanism of action may confer clinically beneficial effects for patients suffering from AD.

Modes of action: The acetylcholine neurotransmitter is produced in the pre-synaptic neuron and is subsequently released into the synaptic cleft (Scott and Goa, 2000). Once there, it interacts with two types of acetylcholine receptors: muscarinic and nicotinic receptors. The binding of galantamine to acetylcholinesterase slows down the catabolism of acetylcholine, resulting in an increase of acetylcholine levels in the synaptic cleft (Farlow, 2003). Activation of pre-synaptic nAChR also increases the release of other neurotransmitters thought to play an important part in memory, such as glutamate (Lawrence and Sahakian, 1998; Levin and Simon, 1998). Therefore, by potentiating nicotinic neurotransmitter, modulation of nAChR may produce important clinical benefits in AD, which includes delaying deterioration in patient functioning. Other than potentiating nicotinic neurotransmitter, Galantamine also increases the availability of Ach in the cholinergic synapse by competitively inhibiting the enzyme responsible for its breakdown, AChE. The binding of Galantamine to AChE slows down the catabolism of Ach and, as a consequence, Ach levels in the synaptic cleft are increased (Bores et al., 1996). Galantamine has a more than 10-fold selectivity for AChE compared with BuChE, which is in contrast to non-selective agents such as tacrine and physostigmine (Thomsen and Kewitz, 1990; Thomsen et al., 1991b). Although the precise clinical relevance of this selectivity for AChE is not known, it may improve tolerability. From the in vivo and in vitro studies carried out by Thomsen and Kewitz (1990), it was found that the inhibition of AChE ceases within 24h of discontinuing Galantamine indicating that anaesthetic agents and muscle relaxants can be administered safely within a short period after discontinuing Galantamine.
Galantamine binds to the allosteric site on the α-subunit nicotinic receptor at a location that differs from acetylcholine inducing a conformational change in the receptors (Farlow, 2001). Not only does this cause an increased release of acetylcholine, but also improved neuronal activity. This route enhances the channel activity of the pre-synaptic nicotinic receptors in response to acetylcholine, combined with an enhanced post-synaptic response (Bentue-Ferrer D et al., 2003).

**Cellular responses to the drug**: The stimulation of nicotinic receptors can result in improved cognitive function and neuro-protection against amyloid induced neurotoxicity (Anonymous, 2005). The modulation of nicotinic receptors could contribute to improved neurotransmitter release and the release of acetylcholine. It has been suggested that nicotinic receptor stimulation may be related to a reduction of amyloid plaques, one of the features of this disease and thus improves memory in AD sufferers (Greenblatt et al., 1999). Pre-synaptic nicotinic receptors are responsible for the release of multiple neurotransmitters (acetylcholine, serotonin, glutamate, noradrenaline) which are involved in controlling memory and mood (Farlow, 2003). Conversely, glutamate decline in Alzheimer’s may impair learning and memory abilities, while a reduction in serotonin may be associated with the emotional disturbances that are often experienced by patients with this condition. By manipulating other neurotransmitter systems, the modulation of nicotinic receptors may offer positive effects that are applicable to different areas of the disease (Farlow, 2001). As this disease is related to cholinergic deficiency, this provides an explanation for the use of cholinesterase inhibitors for treating the early symptoms of Alzheimer’s (Greenblatt et al., 1999).

**THERAPEUTIC APPLICATIONS**

The main indication of galantamine is the treatment of mild to moderate dementia of AD (Drugdex, 2005). Research indicates that a dose of 16-24 mg a day is sufficient to treat the symptoms of this disease (Lyeng-Williamson and Plosker, 2003; Abascal and Yarknelling, 2004). The therapeutic use of galantamine had been shown by several randomised studies which confirm that 16 – 24 mg a day of galantamine can lead to an improvement in cognition and activities in daily living, as well as preventing the establishment of behavioural symptoms experienced by patients who succumb to this disease. For instance, clinical efficacy of galantamine was investigated in several large clinical trials (n= 285 to 978) of 3 to 6 months.
SPECIFIC OUTCOMES AND BENEFITS OF TREATMENT

Therapy with galantamine can result in improved cognitive function such as memory, attention, reason and language. There may also be a decline in behavioural symptoms such as anxiety and hallucinations (American Pharmaceutical Association, 2003). In the short term (up to 6 months), galantamine improves cognition, function and activities of daily living in patients diagnosed with mild to moderate AD (Giacobini, 2001). It can also delay the development of behavioural disturbances and psychiatric symptoms. However, in the long term (up to 1 year), galantamine can maintain cognition and activities of daily living. This outcome is confirmed by several long term studies (12 months duration) which demonstrated that galantamine at 24mg per day can lead to the maintenance of cognitive function as well as activities of daily living (Scott and Gos, 2000). This suggests that if galantamine is given for extended periods of time, these beneficial effects can be sustained for much longer rather than for shorter periods. There doesn’t appear to be any indication that therapeutic monitoring is required for galantamine.

ADVERSE EFFECTS AND CONTRAINDICATIONS

Positive and negative effects of galantamine: An essential stimulus for the development of Galantamine in the treatment of AD was the need for a medication with a low risk of adverse events. In the following the main adverse events recorded in all clinical trials are summarized (Raskind et al., 2000). Some of the main positive side-effects of galantamine are the reduced burden on caregivers, preservation of independence, an improved quality of life and daily living as well as delaying institutionalization (Lyseng-Williamson and Plosker, 2003; American Pharmaceutical Association, 2003). For sufferers of this disease, this offers some hope of leading a partially normal life. One of the most important studies responsible for galantamine attaining FDA approval for the treatment of mild to moderate AD found that the drug had beneficial effects compared to placebo. These positive effects were seen in relation to functional ability and involved a range of daily activities which can be divided into instrumental (leisure, housework, finance and correspondence) and basic (personal care, dressing and eating) activities (Detal AK et al., 2004).
As with any drug treatment, there are particular adverse effects that must be taken into consideration. Adverse effects are the negative side-effects of drug therapy and their presence can determine if a drug continues to be sold as a therapeutic agent. Although studies indicate that galantamine appears to be well tolerated in patients with AD, adverse effects are expected from cholinesterase inhibitors. Majority of adverse effects are classified as cholinergic in nature and include nausea, vomiting, diarrhea, weight loss and anorexia (Scott and Goa, 2000; Lyseng-Williamson and Plosker, 2002 & 2003). Of these, nausea, vomiting and anorexia appeared to be more frequent in women (Anonymous, 2005). There was only one report of muscular weakness—in a Galantamine treated patient—which was judged as probably unrelated to treatment (Tariot et al., 2000).

The majority events in this study, including gastrointestinal symptoms, were mild in severity. The proportion of serious events was comparable across treatment groups, as were deaths. There were few reports of muscular weakness in patients receiving Galantamine and the incidence was similar to the one in the placebo group (Erkinjunti et al., 2002).

**The most common adverse effects of galantamine according to body system**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain, diarrhea, dyspepsia, nausea and vomiting</td>
</tr>
<tr>
<td>Metabolic/nutritional disorders</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Confusion, dizziness, headache and insomnia</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Anorexia and somnolence</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Rhinitis</td>
</tr>
<tr>
<td>Urinary</td>
<td>Urinary tract infections</td>
</tr>
<tr>
<td>Entire body</td>
<td>Fatigue, fall and injury</td>
</tr>
</tbody>
</table>

**Drug interactions**: Potential drug interactions include use with other anticholinergics in which galantamine can interfere with their activity (Food and Drug Administration, 2001). Anticholinergic drugs can antagonise the effects of cholinesterase inhibitors and should be subsequently avoided. If anticholinergic drugs are administered with cholinesterase inhibitors, the patient may experience a decline in cognition or anticholinergic adverse effects (Defilippi and Grisman, 2003).
drugs include atropine, benztropine (Cogentin) and trihexyphenidyl (Artane) and should be avoided during treatment with galantamine (Anonymous, 2005).

Because of the drug’s mechanism of action, it should not be administered with other cholinomimetics (Anonymous, 2005). For example, a synergistic effect can occur when cholinesterase inhibitors are administered at the same time with succinylcholine, neuromuscular blocking agents or cholinergic agonists such as bethanechol. Another effect that can be encountered with cholinomimetics is a pharmacodynamic interaction between galantamine and drugs that significantly reduce the heart rate such as digoxin or beta blockers (Scott and Goa, 2000; Farlow, 2003; Anonymous, 2005).

Implications of patient conditions: There are several patient conditions that render the drug either unsafe or ineffective. These are classified as cardiovascular, gastrointestinal, neurological, pulmonary and genitourinary conditions. Cholinesterase inhibitors (galantamine) may have vagotonic effects on the heart rate in patients with cardiovascular conditions, thus resulting in bradycardia. Patients that have a high risk of developing gastrointestinal conditions such as peptic ulcers, those with a known history of ulcer disease or who are taking non-steroidal anti-inflammatory drugs (NSAIDS) should be observed for potential symptoms. However, it has been noted that patients with gastrointestinal obstruction or who are recovering from surgery should not be given galantamine. Neurological conditions are associated with the development of seizures, as cholinesterase inhibitors are thought to induce convulsions. But it has been noted that seizures may be a direct consequence of Alzheimer’s disease. Galantamine should be prescribed with caution in patients with pulmonary conditions such as a severe history of asthma or obstructive pulmonary disease. The use of galantamine is not advised in patients with genitourinary conditions such as urinary outflow obstruction or those who have recently undergone bladder surgery (Food and Drug Administration, 2001; Anonymous, 2005).

SCOPE OF THE PRESENT STUDY

Fizzy drinks, the scourge of healthy diet campaigners, can improve the memory, according to experts today (Khalisha, 1998). Neuroscientists from Glasgow Caledonian University found that, consuming two cans of these soft drinks with high amount of glucose and other sugar substances can boost memory retention by a fifth and combat dementia in older people. Interestingly, it was observed that the drug.
Galantamine hydrobromide selected in the present study has more amount of lactose. Brain Speed Shake, Brain Speed Smoothie, Mocha Focus Delight etc., which are also now-a-days used as memory enhancing drinks are prepared by the mixing some FDA approved memory enhancing drugs like Detox, Phosphatidylserine. Biochemical studies have revealed that the chemical substances in these soft drinks are having some structural similarities with some memory enhancing drugs such as donepezil, galantamine, rivastigmine used to treat Alzheimer’s disease (Daniel et al., 2003; Malik et al., 2007). Huperzine A may possess almost similar skeletal structure to galantamine hydrobromide except some side groups. The mode of action of galantamine and donepezil may also have close relation with huperzine A.

**Structural similarities between galantamine hydrobromide (meant for treatment of AD) and Huperzine A (a plant product in health drinks)**

![Galantamine hydrobromide](image1.png) ![Huperzine A](image2.png)

Nootropics, also referred to as smart drugs, memory enhancers, and cognitive enhancers, are drugs, supplements, nutraceuticals, and functional foods which improve mental functions such as cognition, memory, intelligence, motivation, attention and concentration (Donalds Medical Dictionary and Lannl et al., 2008). Nootropics are thought to work by altering the availability of the brain's supply of neurotransmitters, enzymes, and hormones, by improving the brain's oxygen supply or by stimulating nerve growth. So, these nootropics are now-a-days preferred to be consumed along with memory drinks and food items or sometimes directly. They are also misused by shift workers who are switching from a day shift to a night shift or vice versa to reset the body’s biological clock in order to lessen the risk of on-the-job injuries caused by impaired alertness. People without Alzheimer’s disease are also using these nootropics and anti-Alzheimer drugs to
improve their memory, activeness and intelligence either directly or indirectly with other foods or drinks.

In view of this, in the present investigation, it is proposed to assess the long-term effects of memory enhancing drug, galantamine hydrobromide on the Morphometric and behaviour aspects. Cholinergic and Glutamatergic neurotransmitter system of male albino mice in the absence of AD. Further, validation of the Lipinski's Rule Five and evaluation of their toxic properties on some selected drugs, which are currently recommended for treating Alzheimer's disease has been tested with the help of the appropriate Bioinformatics software's.