Participant Guide: Part 1

ADLARITY® Training

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Welcome to ADLARITY Training!

We are looking forward to connecting, learning, and collaborating as a team.

Our hope is that this Participant Guide will help keep you on track as you navigate the eLearning modules and attend the workshop sessions.

Included in this Participant Guide, you will find:

eLearning Modules Study Guides

Each eLearning module has an accompanying Study Guide that is included in this Participant Guide. These Study Guides provide an opportunity to record key details from the eLearning modules that will help support your field efforts and future assessments. Answer Keys to each of the Study Guides can be found in the Appendix.

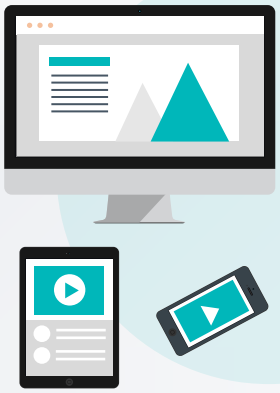
Resources

This Participant Guide includes the following resources:

- ✓ Market Access Brief
- ✓ Competitive Landscape Table
- ✓ C.A.R.E. Customer Engagement Framework

Tech Readiness Tips

To ensure your technology is ready for a virtual meeting, read through the tips below and address any tech issues before the start of the virtual sessions.



Check Your Technology

- ✓ Ensure your internet connection is fast and stable
- ✓ Test all devices and check batteries
- ✓ Review all meeting software functionality (eg, how to mute, show your webcam)
- ✓ Choose the right lighting, background, and camera angle

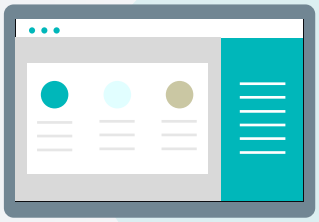
Is my internet fast enough?

Minimally, you need:

- ✓ At least 10 Mbps download speed per person
- ✓ At least 1 Mbps upload speed per person

Check your internet speed at: https://www.speedtest.net/

If you do run into issues with video conferencing, your upload speed is most likely the culprit. Internet providers generally give customers much less upload speed than download speed, which can cause problems with large group meetings. If you've had trouble in the past, talk with your internet provider prior to the meeting.



Still having internet issues?

If your WiFi is still running slow, try turning it off and turning on the cellular connection on your iPad (so long as you have cellular service).

Training Expectations

- ✓ Be on time
- ✓ Be prepared to learn
- ✓ Be prepared to participate
- ✓ Be vulnerable
- ✓ Celebrate success
- ✓ Embrace technology
- ✓ Keep your camera on when appropriate
- ✓ HAVE FUN!

Study Guides

Anatomy and Physiology of the Human Brain, Neurotransmission, and Introduction to Memory eLearning Module

Study Guide

OVERVIEW OF THE BRAIN

Cerebrum

- The adult brain consists of _____ main parts, one of which is the cerebrum, which is the _____ part of the brain.
- It is known as the "seat of _____" and allows individuals the ability to:
    - Read, _____, and speak
    - Perform calculations and compose _____
    - Remember the past, plan for the future, and imagine things that have never _____ before

Cerebral Cortex

- The cerebral cortex is a region of _____ _____that forms the outer rim of the cerebrum.
- While it is only _____ millimeters thick, it contains billions of neurons arranged in distinct layers.

Hippocampus and Temporal Cortical Areas

- The hippocampus and surrounding temporal cortical areas play a major role in memory _____ by communicating with the thalamus and prefrontal cortex.
- Thalamus: serves as the major _____ station for most sensory impulses that reach the primary sensory areas of the cerebral cortex from the spinal cord and brainstem.
- _____ _____: an extensive area in the anterior portion of the frontal lobe; concerned with the makeup of a person's personality, intellect, complex learning abilities, recall of information, initiative judgment, foresight, reasoning conscience, intuition, mood, planning for the future, and development of abstract ideas
- Hippocampus: _____ _____ structure that plays a role in converting new information into long-term memories

INTRODUCTION TO AMYLOID PRECUROSR PROTEIN AND AMYLOID-β PEPTIED

Amyloid Precursor Protein

- The amyloid precursor protein (APP) is a protein in a family of _____ transmembrane proteins with large extracellular domains.
- APP is produced in _____ quantities in neurons and metabolized very _____.
- APP undergoes hydrolysis by various pathways
    - One pathway (amyloidogenic) produces amyloid beta (amyloid-β) peptide, a protein involved in the _____ of Alzheimer's disease
        - APP is first _____ by β-secretase and γ-secretase; this results in the production of CTF-β, soluble peptide APPβ (SAPPβ), and amyloid-β, including amyloid-β_{42} ($A\beta_{42}$), which is more prone to aggregation and plaque formation, and amyloid-β_{40} ($A\beta_{40}$), which is neurotoxic. This is known as the amyloidogenic pathway
    - The other pathway (non-amyloidogenic) does not produce this peptide
        - APP can be hydrolyzed by alpha-secretase (α-secretase) and gamma-secretase (γ-secretase), leading to the production of products that are neurotrophic and neuroprotective for nerve cells, such as the C-terminal fragment (CTF-α), the soluble ectodomain of APP-α (sAPPα), and other smaller fragments. This process does not produce amyloid-β and is known as the _____ pathway.
- In individuals with Alzheimer's disease, _____ levels of amyloid-β clump together to form amyloid plaques that collect between neurons and disrupt cell function.

INTRODUCTION TO TAU

Overview

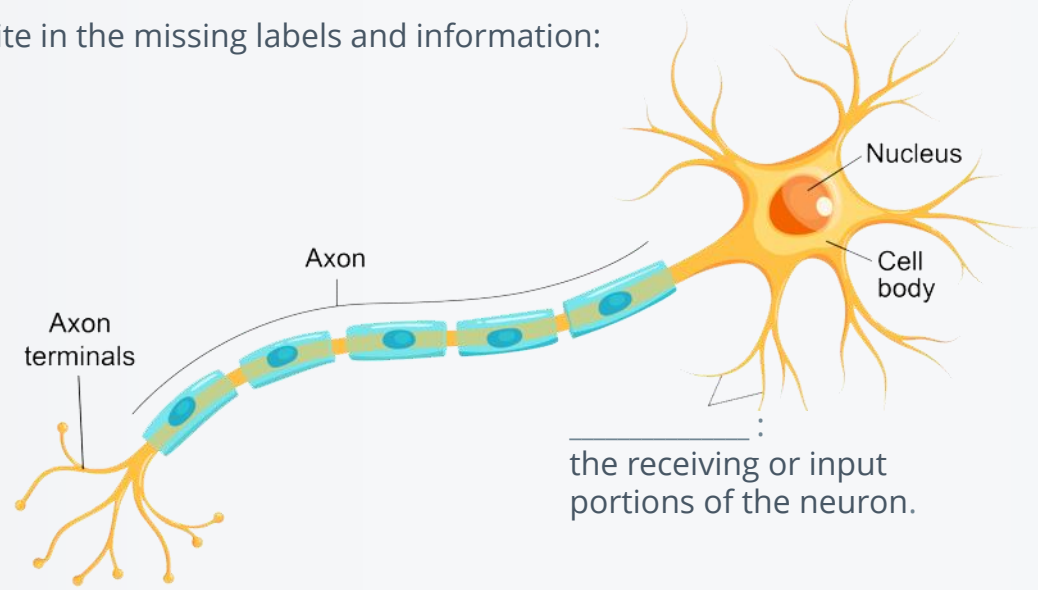
- Neurons are supported internally by _____.
- _____ is the major microtubule-associated phosphoprotein of a normal mature neuron.

- The function of tau is the promotion of the assembly of _____ into microtubules and stabilization of their structure.
- In a healthy brain, _____ residues on the tau protein are phosphorylated.
- In contrast, in an individual with Alzheimer's disease, approximately ____ residues per module of tau protein are phosphorylated (hyperphosphorylation).
- Ultimately, tau hyperphosphorylation leads to tau _____ from the microtubules, _____ to other tau molecules, and aggregating into neurofibrillary _____.

NEURONS

Introduction

- The role of neurons in the brain is to process and transmit information through electrical and chemical _____.
- Write in the missing labels and information:



_____ :
the receiving or input portions of the neuron.

- In people with Alzheimer's disease, healthy neurons _____ functioning, lose connections with other neurons, and eventually _____.

Microtubules

- Healthy neurons, in part, are supported _____ by microtubules, which help guide nutrients and molecules from the cell body to the axon and dendrites.
    - _____ binds to and stabilizes the microtubules.
- In a diseased brain, such as one in an individual with Alzheimer's disease, tau becomes abnormally hyperphosphorylated, which ultimately causes the microtubule to _____.
    - The free tau forms neurofibrillary _____.

COMMUNICATION BETWEEN NEURONS

Introduction

- Neurons _____ with each other.
- When stimulated, a neuron generates an action potential (nerve impulse), which is an _____ signal.
- The impulse travels along the _____ from the cell body toward the axon terminals.
- When the impulse reaches the axon terminal, it causes _____ to be released into the narrow gap between the axon terminal of a neuron and the receptive surface of the next cell.
- This gap is known as the _____.
- Neurotransmitters _____ across the synaptic cleft and _____ to specific receptors on the postsynaptic membrane.
- This process triggers a signal that either _____ or _____ activity in the neuron receiving the signal.

Neurotransmitters Important in Alzheimer's Disease

1. Acetylcholine:
    - An important neurotransmitter used by _____ neurons
    - Involved in processes including but not limited to learning and _____
    - Damage to cholinergic neurons is a change that _____ with cognitive impairment and occurs in people with Alzheimer's disease

2. _____:

   - A chemical messenger that helps the brain process information
   - Excessive glutamate buildup at the N-methyl-D-aspartate (NMDA) receptor due to inefficient removal mechanisms at the synaptic cleft results in the overactivation of the NMDA receptor, leading to chronic excitotoxicity
   - This may contribute to neuronal loss and subsequent cognitive impairment

OVERVIEW OF THE CHOLINERGIC SYSTEM

Introduction

- The cholinergic system is involved in many important processes, including but not limited to _____, learning, memory, stress response, wakefulness, and _____.
- The cholinergic neurons are widely distributed in the central nervous system, and _____ is the neurotransmitter used by all of these neurons.
- _____ in cholinergic transmission can potentially influence all aspects of cognition and behavior.
    - The _____ of cholinergic neurons and cholinergic innervation _____ takes place in individuals with Alzheimer's disease and contributes to memory loss

INTRODUCTION TO MEMORY

Overview

- Memory is the process through which information obtained from _____ is stored and retrieved. There are various types of memory, including:
- **Declarative Memory** (remembering names, faces, words, and dates)
    1. Short-term memory:
        - Also known as _____ memory
        - The first step in memory
        - Is limited to _____chunks of information
        - A _____ container for information that individuals may or may not want to retain

2. Long-term memory:
    - Has a _____ capacity
    - Long-tern memories can be _____, and our memory bank continually changes over time

- **Procedural memory** (remembering _____ such as playing the piano)
- _____ **memory** (remembering how to ride a bike, for example)
- **Emotional memory** (a pounding heart when a snake is nearby, for example)
- The ability to store and retrieve information from long-term memory _____ with age.

Information Transfer

- _____ may be transferred from short-term memory to long-term memories.
- Many factors can affect this transfer:
    - _____ State: individuals learn best when they are alert, motivated, surprised, or aroused
    - Rehearsal: repeating or rehearsing the information _____ the chance of transfer to long-term memory.
    - Association: _____ "new" information to "old" information already stored in long-term memory can aid in remembering information.
    - Automatic: some information that moves into long-term memory may not be _____ formed
- The symptoms of Alzheimer's disease occur because _____ in parts of the brain involved in thinking, learning, and memory have been damaged or destroyed.
- The first lesions characteristic of Alzheimer's disease appear in neurons in system areas related to memory and learning, such as the _____ and association cortex.

Alzheimer's Disease State Overview eLearning Module

Study Guide

INTRODUCTION TO ALZHEIMER'S DISEASE

COGNITIVE IMPAIRMENT

Dementia

- *Dementia* is a _____ term used to designate a wide range of diseases, including but not limited to Alzheimer's disease, vascular dementia, and frontotemporal dementia.
- Dementia is the result of changes in the _____ that causes neurons to stop working and eventually die.
- _____ is the biggest risk factor for the development of dementia.

Age-Related Cognitive Decline

- Age-related cognitive decline is when certain areas of memory, thinking, and information processing slow with age but _____ remains unchanged.
- Unlike dementia, the condition is not _____.

Mild Cognitive Impairment

- The stage _____ normal age-related cognitive changes and more serious symptoms that indicate dementia is known as *mild cognitive impairment*.
- An individual with mild cognitive impairment may have a _____ risk of eventually developing Alzheimer's disease or another type of dementia.
- However, this condition does not always progress to _____.
- Symptoms of mild cognitive impairment include problems with thinking, judgment, memory, and language; however, these issues do not significantly interfere with the ability to handle _____ activities.

TYPES OF DEMENTIA

5 most common forms of dementia:

1. Alzheimer's disease
    - The most common type of dementia and accounts for up to _____ of all dementia diagnoses
2. Vascular dementia
    - Caused by conditions that block or reduce _____to parts of the brain
    - The _____ most common type of dementia
    - It is more common as part of mixed dementia
3. Lewy body dementia
    - Characterized by an _____ accumulation of alpha-synuclein proteins in the brain
    - These clumps are known as *Lewy bodies*
    - These proteins build up within _____ in areas of the brain relating to thinking, memory, and motor control
    - The buildup of these proteins causes neurons to not function properly and the neurons to eventually die
4. _____ dementia
    - Caused by a group of disorders that gradually damage the brain's frontal and temporal lobes
    - This damage results in changes in thinking and behaviors
    - This is a _____ type of dementia and typically occurs at a younger age than other dementias
    - This form of dementia is _____, with symptoms starting slowly and worsening over time
    - The cause is not completely understood
    - Individuals with frontotemporal dementia have abnormal amounts or forms of the protein tau and transactive response DNA-binding protein 43 (TDP-43) inside of neurons in the brain
    - The _____ of these proteins causes damage to the neurons and neuronal death
5. Mixed dementia
    - Many people have brain changes associated with _____ type of dementia
    - This is known as *mixed dementia*
    - The likelihood of having mixed dementia _____ with age and is highest in people ages 85 and older

STAGES OF ALZHEIMER'S DISEASE

Overview

- The Alzheimer's disease continuum illustrates the _____ from brain changes that are unnoticeable to a person affected with brain changes that impact memory and eventually physical disability.
- There are 3 broad phases:
    1. _____ Alzheimer's disease:
        - Changes occur in the brain for years before any signs of Alzheimer's disease are apparent
        - Typically identified only in research settings
        - Can last for years and sometimes even decades
    2. Mild cognitive impairment due to Alzheimer's disease
        - The affected individual has _____ problems with memory and thinking
        - There is also _____ evidence of Alzheimer's disease brain changes
    3. Dementia due to Alzheimer's disease
        - Characterized by _____ thinking, memory, or behavioral symptoms that hinder an individual's ability to function in dial life
        - There is also biomarker evidence of Alzheimer's disease-related brain changes
        - There are 3 stages:
            a) Mild (early Alzheimer's disease)
                - Also known as *early-stage Alzheimer's disease*
                - An individual may function independently but need assistance with some activities in order to remain safe and maximize independence
                - While symptoms may not be apparent at this stage to may people, family and close friends may notice changes
                - At this stage a doctor would be able to identify symptoms using diagnostic tools
                - People are often diagnosed at this stage

b) Moderate (middle-stage Alzheimer's disease)

- Typically the _____ stage of the disease
- The individual may have difficulties communicating and performing activities of daily living
- The individual will probably require assistance to participate in daily activities
- The individual may also sometimes become _____
- The individual's personality and behaviors may change
- As the condition progresses, the person with Alzheimer's will need a greater level of care
- Symptoms are more _____ during this stage

c) _____ (late-stage Alzheimer's disease)

- Affected individuals lose the ability to respond to their environment, hold a conversation, and eventually control movement
- _____ may benefit patients and their family at this stage

EPIDEMIOLOGY OF ALZHEIMER'S DISEASE

- Alzheimer's disease is the _____ leading cause of death in the United States and the only disease in the list of the top 10 causes of death that is still significantly _____

U.S. Prevalence

- An estimated 6.2 million Americans ages _____ had Alzheimer's dementia in 2021; _____ were age 75 or older

Incidence

- Approximately _____ people age 65 or older developed Alzheimer's dementia in the US in 2011

Prevalence

- More than _____ people ages 65 and older had Alzheimer's dementia in 2021, and the percent increases with _____

Gender

- Almost two-thirds of people with Alzheimer's disease in the US are _____

Racial and Ethnic Differences

- Black (18.6%) and Hispanic Americans (14%) ages 65 and older are disproportionately _____ likely than White Americans (10%) ages 65 and older to have Alzheimer's dementia or other dementias.

ECONOMIC IMPACT OF ALZHEIMER'S DISEASE

Cost of Care

- Total cost of care for Americans age 65 and older with Alzheimer's disease or other dementias in 2021 was $ _____ billion
- The costs of healthcare and long-term care for individuals with Alzheimer's disease are substantial, making it one of the _____ conditions to society.
- Alzheimer's disease care total costs are estimated to climb to more than $1 _____ by 2050.

Direct and Indirect Costs

Direct Costs:

- Direct medical costs associated with the treatment of Alzheimer's disease include _____ visits, emergency visits, hospitalizations, long-term care or skilled nursing facility care, and _____.
- Direct _____ costs include transportation to medical care, home healthcare, and modifications to adapt to alterations in physical function.

Indirect Costs:

- Indirect costs of care associated with Alzheimer's disease include caregiver _____ and associated healthcare utilization and costs.

RISK FACTORS FOR ALZHEIMER'S DISEASE

Overview

The 3 greatest risk factors for Alzheimer's disease are:

- Age: the greatest risk factor for Alzheimer's disease is _____ age
- Genetics
    - There are several _____ that increase the risk of developing Alzheimer's disease.
    - The gene with the _____ impact on the increased risk of developing late-onset Alzheimer's disease is the apolipoprotein E gene (APOE)-e4 gene.
- Family history of Alzheimer's: It is estimated that people with at least 1 first-degree relative with Alzheimer's were _____times more likely to develop the disease than those without a first-degree relative with Alzheimer's disease.

CAUSES OF ALZHEIMER'S DISEASE

- It is not fully understood what _____ Alzheimer's disease

Introduction

- In people who have _____ Alzheimer's disease, a genetic mutation may have been the cause.
- Late-onset Alzheimer's disease arises from complex changes occurring in the brain over several decades. The causes likely include:
  - Genetics
    - Familial autosomal dominant Alzheimer's disease is _____ (<1%), most often manifests in early-onset Alzheimer's disease, and is caused by _____ in presenilin 1, amyloid precursor protein, or presenilin 2.
    - The risk of developing Alzheimer's disease is estimated to be _____ attributable to genetic factors, which differ between early-onset and late-onset Alzheimer's disease
    - The major risk or susceptibility gene in sporadic late-onset Alzheimer's disease involves _____
  - Environmental factors
  - Lifestyle factors

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

OVERVIEW OF PATHYPHYSIOLOGY

- Signs of Alzheimer's disease may be found in the patient's brain _____ years before the first symptoms appear.

Overview

The 4 main characteristic hallmarks of Alzheimer's disease include:

1. Amyloid-β peptide plaques (also known as β-amyloid plaques)
   - Amyloid-β is a protein produced by the _____ of the amyloid-β precursor protein (APP).
   - Amyloid-β becomes deposited in the hippocampus and basal segment—in the form of neurotoxic amyloid _____—and recruits more amyloid-β.
   - This leads to the formation of insoluble _____ and induces mitochondrial damage, unstable homeostasis, and synaptic dysfunction.

2. Neurofibrillary tangles

    - Tau is the major microtubule-associated _____ of a normal mature neuron.

    - In people with Alzheimer's disease, tau protein is abnormally hyperphosphorylated and aggregated into neurofibrillary _____ comprised of paired helical filaments comprised of tau.

    - In the Alzheimer's brain, the tau is seen as tangles _____ neurons.

3. Synaptic dysfunction

    - Synaptic connectivity between _____ is essential for learning and memory.

    - Alteration of synaptic protein expression and synaptic plasticity are _____ events in Alzheimer's disease progression in humans.

    - Synapse _____ is strongly correlated with cognitive impairment in Alzheimer's disease.

4. Neuroinflammation

    - The brain _____ in people with Alzheimer's disease exhibits inflammation.

Consequences of Changes in the Brain

- In people with Alzheimer's disease, formerly healthy neurons cease _____, lose connections with other neurons, and eventually die.

SIGNS AND SYMPTOMS OF ALZHEIMER'S DISEASE

DESCRIPTION OF SIGNS AND SYMPTOMS

Overview

- Individuals who experience _____ changes should consult with a healthcare professional to determine if the changes are normal for their age, reversible, or a symptom of Alzheimer's disease or another type of dementia.

- Examples of incidences in which memory loss is _____ include but are not limited to chronic alcoholism, an effect of a medication or combination of medications, and vitamin B-12 deficiency.

The main warning signs and symptoms of Alzheimer's disease:

- Memory loss that _____ daily life
- Challenges in planning or solving problems
- Difficulty completing _____ tasks at home, at work, or at leisure
- Confusion with time or place
- Trouble understanding visual images and spatial relationships
- New problems with _____ in speaking or writing
- Misplacing things and losing the ability to retrace steps
- Decreased or poor _____
- Withdrawal from work or social activities
- Changes in _____ or personality

Symptoms Unrelated to Memory

- Individuals with Alzheimer's disease also have non-mnemonic symptoms—those that are _____ to cognition.
- Examples include _____, depression-like behavior, _____ disturbances, aggression, and _____.
- Individuals with Alzheimer's disease may experience _____ involving hearing, seeing, smelling, or feeling things that are not really there.
- _____ are false beliefs that the person thinks are real.
- Individuals with Alzheimer's disease may also become _____ and fearful, suspicious, or _____ of people.

DIAGNOSIS AND ASSESSMENT OF ALZHEIMER'S DISEASE

OVERVIEW – DIAGNOSIS AND ASSESSMENT

- There is no _____ for dementia due to Alzheimer's disease.

Diagnostic Criteria

- Alzheimer's disease diagnostic criteria were originally developed in _____.
- In 2011, the National Institute on Aging-Alzheimer's Association (NIA-AA) _____ the clinical criteria for the diagnosis of mild cognitive impairment and the various stages of dementia due to Alzheimer's disease.
- Alzheimer's disease is diagnosed with complete certainty only after _____, when microscopic examination of the brain reveals characteristic plaque and tangles.

DIAGNOSTIC PROCESS

Introduction

- Several methods and tools are used to determine whether an individual's _____ issues are due to Alzheimer's disease.
- Various potential components of the process:
  - _____ : the patient, as well as a family member or friend of the patient is interviewed to learn about
    - Overall health
    - Use of prescription and over-the-counter medications
    - Past medical history and/or diet
    - Symptoms and their impact on daily activities
    - Identifying any changes in thinking skills, behavior and personality
  - History of present illness: information should be gathered about the patient's _____ symptoms, complaints, and problems and how things have _____ or progressed.
  - Standard _____ testing: a physician may order blood, urine, and other standard medical tests to help identify other causes of cognitive impairment
  - _____ examination: The purpose of a psychiatric examination is to determine whether depression or another mental health condition is causing or contributing to a person's symptoms
  - Mental cognitive status tests: Many _____ brief cognitive status tests are used to evaluate memory, thinking, and problem-solving abilities.
  - Neuropsychological evaluation: Neuropsychological tests use validated _____ material, oral questions, and written tests for an objective assessment of several cognitive and emotional functions.
    - The accuracy is _____ when combined with imaging results and evaluations with subspecialists

- _____ : A standard workup for Alzheimer's disease includes images of the brain taken by magnetic resonance imaging (MRI) or computed tomography (CT).
- Biomarker _____ : Biomarkers or biologic markers are any types of substances, structures, or processes that can be measured inside or outside the body and that may influence any changes in the body and probable prevalence of any disease in the body.
    - 3 biomarkers collected in the CSF used as part of the Alzheimer's disease diagnostic process include: amyloid-β, tau protein, and phosphorylated tau

MANAGEMENT AND TREATMENT OF ALZHEIMER'S DISEASE

TREATMENT OVERVIEW

- There is no _____ for Alzheimer's disease.

Introduction

- Treatment of Alzheimer's disease can have _____ components, including:
    - Medications that may change disease _____
    - Medications that may improve Alzheimer's disease _____
    - _____ aspects of treatment, such as monitoring patients' cognition and supporting them and their families

PHARMACOLOGIC TREATMENT

Introduction

There are 2 categories of medications used for treating Alzheimer's disease:

1. Drugs that may change the _____ of Alzheimer's disease
    - Aduhelm® (aducanumab-avwa) is the only _____ medication that may change the disease progression of Alzheimer's disease.
        - Aduhelm® is indicated for patients who have _____ cognitive impairment or are at the mild dementia stage of the disease.
2. Drugs that may mitigate some _____ of Alzheimer's disease
    - Chlolinesterase inhibitors:
        - Aricept® (donepezil), which is approved to treat all stages of dementia of the Alzheimer's type.
        - Exelon® (rivastigmine), which is approved to treat mild to moderate dementia of the Alzheimer's type.
        - Razadyne® (galantamine), which is approved to treat mild to moderate dementia of the Alzheimer's type.

- Glutamate regulators
  - Namenda® (memantine) is the glutamate regulator approved to treat the symptoms in individuals with _____ dementia of the Alzheimer's type.
- Cholinesterase inhibitor plus glutamate regulator
  - Namzaric® (donepezil and memantine) is a _____ of a cholinesterase inhibitor and a glutamate regulator approved to treat the symptoms in individuals with moderate to severe dementia of the Alzheimer's type.

NONPHARMACOLOGIC TREATMENT

Introduction

- Healthcare providers treating Alzheimer's disease patients must also focus on aspects other than _____ that relate to well-being.
  - Monitoring: After an individual is diagnosed with Alzheimer's disease and a treatment plan is established, the individual should be _____ on a regular basis.
    - Due to the nature of the disease, a family member, friend, or caregiver should also _____ follow-up visits.
    - Examples of what should be monitored included but are not limited to changes in daily functioning, _____ status, comorbidities, behavioral symptoms, medication requirements, and _____ needs.
  - _____ : It is important to keep an individual with Alzheimer's disease safe in order to prevent _____, maximize function, minimize stress and agitation, and reduce caregiver burden.
  - Support: Individuals with Alzheimer's disease may find value in joining a _____.
  - Legal considerations: Individuals with Alzheimer's disease and their caregivers should plan for when the individuals will have _____by seeking legal assistance to put in place _____ such as the necessary power of attorney and end-of-life preferences, including a will and living will.

THE ROLE OF THE CAREGIVER

Overview

- *Caregiving* is a term that means attending to another person's _____ and _____.
- Some examples of assistance caregivers may provide to someone with Alzheimer's disease:
  - Helping with proper medication administration
  - Helping the person adhere to treatment recommendations for Alzheimer's disease and/or other medical conditions
  - Helping with _____
  - Assisting with instrumental ADLs (IADLs)
  - Managing the behavioral symptoms of the disease
  - Finding and using support services
  - Finding and arranging for care
  - Providing _____ support and a sense of security

Caring for the Caregiver

- The caregiver (also known as a *care partner*) may experience many emotions, including _____, fear, stress, anxiety, _____, frustration, grief, and depression, among others.
- It is very important for caregivers to also take care of _____.
- Strategies include being physically active, building a support _____, and asking others to help with the care in order to spend some time _____.

Diagnosis and Assessment of Alzheimer's eLearning Module

Study Guide

INTRODUCTION TO THE DIAGNOSTIC PROCESS

OVERVIEW OF THE DIAGNOSTIC PROCESS

- There is no _____ diagnostic test that can determine if a person has Alzheimer's disease.

Historical Perspective of Diagnostic Criteria

- 1984: Release of criteria for Alzheimer's disease dementia
- 2011: Updated recommendations released on diagnostic guidelines for Alzheimer's disease

HISTORY, PHYSICAL EXAMINIATION, AND LABORATORY TESTING

OVERVIEW OF HISTORY, PHYSICAL EXAMINATION, AND LABORATORY TESTING

- To diagnose dementia, health care providers first assess whether an individual has an _____ treatable condition.

Medical and Family History

- Obtaining the patient's history may involve _____ the patient as well as a family member or close friend.
- The healthcare provider should also ask about prescription and over-the-counter _____ the individual is currently taking, as some medications can have potential cognitive _____.

History of Present Illness

- The health care provider will ask questions about the _____ that prompted the visit and the concern.

Physical Examination and Laboratory Testing

- As part of the evaluation, the health care provider may:
    - Assess blood pressure, temperature, and pulse
    - Listen to the heart and lungs
    - Inquire about nutrition and use of alcohol

Laboratory Testing

- There are some other disorders that can cause symptoms _____ to Alzheimer's disease such as thyroid disorder or a vitamin B-12 deficiency.
- Testing a person's blood and serum, as well as checking various chemicals, hormones, and vitamin levels, can _____ or _____ other conditions that may be causing memory loss.

NEUROLOGICAL EVALUATION

OVERVIEW OF NEUROLOGICAL AND PSYCHIATRIC EVALUATIONS

Introduction

- Neurological Evaluation:
  - A neurological examination can discover problems that may signal _____other than Alzheimer's disease.
  - The neurological evaluation will test _____, coordination, muscle tone, muscle strength, eye movement, _____, and sensory response.
- Electroencephalogram
  - An electroencephalogram may be done to check for abnormal _____ brain activity.
  - An electroencephalogram is the _____ of the analysis of the electrical activity of the brain.
- Psychiatric Evaluation
  - A psychiatric evaluation is important to determine if _____ or another _____ health condition is causing or contributing to the patient's dementia symptoms.
  - Depression or other mood disorders can cause memory problems, loss of interest in life, and other symptoms that can overlap with dementia.

COGNITIVE TESTING

Introduction

- Mental cognitive testing evaluates _____, thinking, and simple _____ abilities.

Patient Assessment Tools

- Mini-Mental State Exam (MMSE)
  - Best known and most widely used measure of _____ in clinical practice
  - The scale can easily be administered with _____ training and it only takes approximately _____ minutes to assess cognitive function with this tool.
- General practitioner assessment of cognition (GPCOG)
  - This is a screening tool for cognitive _____.
  - Components and scoring of the text:
    - Name and address for subsequent recall test: this part of the assessment is not scored
    - Time _____ : They receive 1 point if the date is exactly correct
    - _____ drawing: This question portion of the assessment has a potential score of 0,1, or 2
    - Information: Only a _____ answer is scored as correct and 1 point is given
    - Recall: Each component of the name and address are scored as correct or incorrect; there are a total of 5 possible points, 1 for each component of the address
    - Scoring
      - Each correct answer scores one point.
      - The total is calculated by adding the points for the correctly answered items.
      - The total score ranges between 0 and 9.
      - A score of 9 indicates no _____ cognitive impairment and further testing is _____ required.
      - If the patient scores between 5 and 8, _____ information is needed, and the _____ GPCOG interview should be conducted.
      - A score of 0 to 4 out of 9 indicates cognitive impairment—_____ evaluation is the next step.

- Mini-Cog®
  - a ____ minute screening tool for dementia
  - Steps of the assessment:
    - The first step is _____ registration
    - The next step is drawing a _____
    - The last step is 3-word _____.
- **Informant Assessment Tools**
- One aspect of dementia that is different than other neurological disorders is the _____ reliance on others to assess the patient's condition.
- Dementia can impact judgment, speech, and memory, thereby making the patient's input less _____.
- Therefore, information may be partially or completely derived from family or other _____.
- Informant assessment tools:
  - _____: 8-question interview used to distinguish between normal signs of aging and mild dementia
  - GPCOG informant interview: The informant is asked 6 questions on how the patient _____ to when they were well (approximately 5-10 years ago).
  - Short informant questionnaire on cognitive decline in the elderly (IQCODE): This tool asks the informant 16 questions comparing how the patient is now compared with _____ years ago.

NEUROPSYCHOLOGICAL EVALUATION

Introduction

- Based on the results of a cognitive screening, an individual may be referred to a _____ for neuropsychological testing.
- The aim of the consultation is to help characterize cognitive _____ and clarify the diagnosis.

Testing

- Neuropsychologists use _____ puzzle-based materials, oral questions, and written tests to _____ assess multiple cognitive and emotional functions.
- The results of the tests are integrated with other sources of information to provide a _____ assessment of an individual's cognitive functioning.
- Neuropsychological testing can differentiate Alzheimer's dementia from nondementia with nearly _____% accuracy.
- Neuropsychological assessments are helpful in tracking _____ that may affect daily functioning as cognitive impairment and dementia _____.

IMAGING AND CEREBROSPINAL FLUID ANALYSIS

IMAGING FOR DIAGNOSING ALZHEIMER'S DISEASE

- Imaging of the brain can:
    1. Rule out other _____, such as a brain tumor or a stroke
    2. Distinguish between different _____ of degenerative brain diseases
    3. Establish a _____ about the degree of degeneration
- A _____ medical workup for Alzheimer's disease often includes imaging.
- The two _____ imaging tools used in Alzheimer's disease are magnetic resonance imaging (MRI) and positron emission tomography (PET).

Magnetic Resonance Imaging (MRI)

- MRI is an imaging technique that uses a _____ field and computer-generated radio waves to create detailed images of organs (such as the brain) and tissues in the body.
- There are 2 types of MRI:
    - Structural MRI
        - The type _____ used in the Alzheimer's diagnostic process
        - MRI does not have the ability to measure amyloid _____ or neurofibrillary _____.
    - _____ MRI
        - Functional MRI is being increasingly used to evaluate the functional integrity of brain networks supporting memory and other cognitive domains in early Alzheimer's disease

Position Emission Tomography (PET)

- Positron emission tomography (PET) is an imaging technique that uses _____ substances injected into patients to provide images of the body using specialized scanners.
- These PET images provide information about the _____ and _____ of the body's organs, in contrast to CT and MRI, which show the body's anatomy and structure.
- Different types used in the Alzheimer's disease diagnostic process:
  - _____ PET
    - After injection of a radiolabeled tracer agent, patients undergo a specialized PET scan that detects the deposition of amyloid-β (Aβ) peptides in plaques in the living brain
    - Amyloid _____ include:
      - Florbetaben
      - Flutemetamol
      - Florbetapir
    - Amyloid PET can _____ diagnose the disease (later autopsy proven) using this method with up to 96% sensitivity and 100% specificity.
    - The use of amyloid PET imaging in practice is still limited owing to its cost for most patients, as it is not covered by most insurance carriers.
    - Currently, the majority of patients who undergo amyloid PET imaging do so as part of participation in _____.
  - Fluoro-deoxy-D-glucose (FDG) PET
    - The brain relies primarily on _____ as its source of energy.
    - The glucose analog fluoro-deoxy-D-glucose (FDG) is a suitable indicator of brain _____.
    - FDG PET is widely accepted to be a valid _____ of overall brain metabolism and of synaptic activity.
    - FDG PET abnormalities are believed to be the net result of some combination of processes impacting the pathogenesis of Alzheimer's disease.

CEREBROSPINAL FLUID ANALYSIS (CSF)

Introduction

- CSF is a clear, colorless liquid that is in the _____ and the spinal cord.
- CSF analysis is a group of tests that look at this fluid to help _____ diseases.
- The CSF is collected through a _____ puncture (spinal tap) in which, after the injection of anesthesia into the back, a thin, hollow needle is inserted between two vertebrae in the lower spine and a small amount of fluid is removed for _____.
- In the diagnostic process for Alzheimer's disease, the CSF is evaluated for _____, hyperphosphorylated tau peptide, and _____ tau protein content.
- CSF analysis is _____ invasive than an amyloid PET scan and also has slightly _____ diagnostic accuracy (85%-90%) than an amyloid PET scan.

GENETIC TESTING

OVERVIEW

Overview of Genetic Testing

- Researchers have identified certain genes that _____ the risk of developing Alzheimer's disease, and some rare genes that _____ cause Alzheimer's disease.
- Although genetic tests are available for some of these genes, health care providers do _____ currently recommend routine genetic testing for Alzheimer's disease.

DIAGNOSTIC CRITERIA

Terminology

- The Alzheimer's disease pathophysiological process is used to encompass the antemortem biological changes that precede the _____ neuropathological diagnosis of Alzheimer’s disease as well as the neuropathological substrate

CORE CLINICAL CRITERIA FOR ALL-CAUSE DEMENTIA

- Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:
    - Interfere with the ability to _____ at work or at usual activities; and
    - Represent a _____ from previous levels of functioning and performing; and
    - Are not _____ by delirium or major psychiatric disorder;

- Cognitive impairment is _____ through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment
    - The cognitive assessment can be a "bedside" mental status examination or neuropsychological testing
    - The neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis
- The cognitive or behavioral impairment involves a minimum of ____ of the following domains:
    - Impaired ability to acquire and remember _____ information
    - _____ reasoning and handling of complex tasks, poor judgment
    - Impaired _____ abilities
    - Impaired _____ functions (speaking, reading, writing)
    - Changes in _____, behavior, or comportment

CRITERIA FOR ALZHEIMER'S DISEASE DEMENTIA

- There are 3 terms used to classify individuals with dementia caused by Alzheimer's disease:

1. Probable Alzheimer's disease dementia
    - Diagnosed when the patient meets the core clinical criteria for "all-cause dementia" and has the _____ following characteristics:
        - Insidious onset. The symptoms have a _____ onset over months to years, not sudden over hours or days;
        - Clear-cut history of _____ of cognition by report or observation; and
        - The initial and most prominent cognitive deficits are evident on history and examination in _____ of the following categories:
            - Amnestic presentation: the most common syndromic presentation of Alzheimer's disease dementia; deficits should include impairment in learning and recall of recently learned information
            - Nonamnestic presentation: language presentation, visuospatial presentation, executive dysfunction

2. Possible Alzheimer's disease dementia

    - There are 2 circumstances in which a diagnosis of possible Alzheimer's disease dementia is made:

        - Atypical course: meets the core clinical criteria in terms of the nature of the cognitive deficits for Alzheimer's disease dementia, but either has a _____ onset of cognitive impairment or demonstrates _____ historical detail or objective cognitive documentation of progressive decline

        - Etiologically _____ presentation: meets all core clinical criteria for AD dementia but has evidence of:

            - Concomitant cerebrovascular disease, defined by a history of _____ temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or

            - Features of dementia with _____ bodies other than dementia itself; or

            - Evidence for another _____ disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition

3. Probable or possible Alzheimer's disease dementia with evidence of Alzheimer's disease pathophysiological process

    - In people who meet the core clinical _____ for probable Alzheimer's disease dementia, biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the Alzheimer's disease pathophysiological process.

        - However, the use of Alzheimer's disease biomarker tests for routine diagnostic purposes is not recommended at the present time.

        - The use of biomarkers to enhance certainty of Alzheimer's disease pathophysiological process may be useful in three circumstances: _____ studies, clinical _____, and as optional clinical tools for use where available and when deemed appropriate by the clinician.

    - Possible Alzheimer's disease dementia with evidence of the Alzheimer's disease pathophysiological process is for persons who meet clinical criteria for a non-Alzheimer's disease dementia but who have either biomarker evidence of Alzheimer's disease pathophysiological process, or meet the _____ criteria for AD.

Management and Treatment of Alzheimer's Disease eLearning Module

Study Guide

INTRODUCTION TO MANAGEMENT AND TREATMENT

INTRODUCTION

Treatment Goals

- There are 4 main goals of Alzheimer's disease treatment:
    1. Regular _____ of the patient's health and cognition
    2. _____ and support to patients and their families
    3. Initiation of pharmacologic and non-pharmacologic _____ as appropriate
    4. Evaluation of patient/family motivation to volunteer for a _____

Introduction to Pharmacologic Treatment

- Medications cannot _____ Alzheimer's disease.
- There are 2 main categories of Alzheimer's disease treatment medications:
    - FDA-approved drug that may change disease _____
    - FDA approved drugs that may _____ mitigate the symptoms
- The FDA also has approved drugs to address _____ in people living with dementia.

PHARMACOLOGIC TREATMENT OF ALHEIMER'S DISEASE

FDA-APPROVED DRUG THAT MAY CHANGE ALZHEIMER'S DISEASE PROGRESSION

Introduction to Aducanumab (Aduhelm®)

- Indication: Aducanumab is indicated for the treatment of Alzheimer's disease.
    - Treatment with aducanumab should be initiated in patients with _____ cognitive impairment or mild _____ stage of disease, the population in which treatment was initiated in clinical trials.

- Mechanism of Action: Aducanumab targets aggregated soluble and insoluble forms of _____.
    - Based on clinical studies, aducanumab _____ amyloid-β plaques.
- Administration: Aducanumab is administered as an _____.
- Common Adverse Reactions: The most common adverse reactions (at least 10% and higher incidence compared to placebo) include:
    - ARIA-E
    - Headache
    - _____
    - ARIA-H superficial siderosis
    - _____
- MRI: The patient must obtain a recent (within one year) _____ MRI prior to initiating treatment.
- Efficacy: The efficacy of aducanumab was evaluated in _____ separate studies representing a total of 3,482 patients.

FDA-APPROVED DRUG THAT TREAT ALZHEIMER'S DISEASE DEMENTIA SYMPTOMS

Cholinesterase Inhibitors

- There are 3 _____ prescribed in patients with dementia of the Alzheimer's type:
    1. Donepezil (Aricept®)
    2. Rivastigmine (Exelon®)
    3. Galantamine (Razadyne®)
- Cholinesterase inhibitors _____ cholinergic function.
- Based on randomized controlled trials, all three cholinesterase inhibitors have demonstrated treatment _____ of improving, stabilizing, or delaying decline in cognition, activities of daily living, global status, behavioral and psychological symptoms of dementia

Donepezil (Aricept®)

- Indication: Donepezil is indicated for the treatment of dementia of the Alzheimer's type.
    - Efficacy has been demonstrated in patients with _____, _____, and _____ dementia of the Alzheimer's type.
- Dosing in Mild to Moderate with dementia of the Alzheimer's type. The recommended starting dosage of donepezil is 5 mg _____ administered once per day in the evening, just prior to retiring.
    - The maximum recommended dosage of donepezil in patients with mild to moderate dementia of the Alzheimer's type is _____per day.
- Dosing in Moderate to Severe with dementia of the Alzheimer's type: The recommended starting dosage of donepezil is _____oral tablet administered once per day in the evening, just prior to retiring.
    - The maximum recommended dosage of donepezil in patients with moderate to severe with dementia of the Alzheimer's type is _____ per day.
- Adverse Reactions: The most common adverse reactions, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day donepezil and twice the placebo rate, include _____, diarrhea, insomnia, _____, muscle cramps, fatigue, and anorexia.

Rivastigmine (Exelon®)

Rivastigmine Capsules/Oral Solution:

- The indication for this formulation is for the treatment of _____ dementia of the Alzheimer's type.
- Rivastigmine should be taken with meals in _____ doses in the morning and evening.
- Rivastigmine is also available as an _____containing rivastigmine tartrate equivalent to 2 mg/mL of rivastigmine base.
- The most common adverse reactions associated with rivastigmine use include nausea, vomiting, _____, dyspepsia, and _____.

Rivastigmine Patch:

- The rivastigmine patch is indicated for the treatment of _____ of the Alzheimer's type.
- Efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer's disease.
- Treatment should be initiated with one 4.6 mg/24 rivastigmine patch applied to the skin _____ daily.

- Doses higher than _____confer to appreciable additional benefit and are associated with an increase in the incidence of adverse reactions.
- The most common adverse reactions with the use of the rivastigmine patch (defined as those occurring at a frequency of at least 5% and at a frequency at higher than in the placebo group) include nausea, vomiting, and diarrhea.

Switching to the Rivastigmine Patch from Capsules or Oral Solution:

- Write in the missing information:

Galantamine (Razadyne®)

- Indications: Galantamine and galantamine ER are indicated for the treatment of _____ to _____ dementia of the Alzheimer's type.
- Dosage forms and strengths:
  - Galantamine ER extended-release _____ are available in 8 mg, 16 mg, and 24 mg strengths
  - Galantamine _____ are available in 4 mg, 8 mg, and 12 mg strengths
- Dosing:
  - Galantamine ER should be administered once daily in the _____, preferably with food.
    - The recommended starting dosage is _____.
    - Dosage _____ should be based upon assessment of clinical benefit and tolerability of the previous dose.
  - The recommended starting dosage of galantamine _____ is 4 mg twice a day (8 mg/day).
    - Dosage increases should be based upon assessment of _____ benefit and _____ of the previous dose.
  - Patients currently being treated with galantamine tablets can _____ to galantamine ER by taking their last dose of galantamine tablets in the evening and starting galantamine ER once-daily treatment the next morning.
  - Converting from galantamine to galantamine ER should occur at the _____ total daily dosage.

- Adverse reactions: The most common adverse reactions in galantamine-treated patients (≥5%) were nausea, vomiting, _____, dizziness, headache, _____, and a decrease in weight.

Glutamate Regulator

- Memantine (_____ ®) is a glutamate regulator indicated for the treatment of moderate to severe dementia of the Alzheimer's type and is distributed by Allergan.
- The mechanism of action of memantine is as a low to moderate affinity uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, which binds preferentially to the NMDA receptor-operation cation channels.

Combination of Cholinesterase Inhibitor Plus Glutamate Regulator

- There is one medication that is a combination of memantine hydrochloride and donepezil hydrochloride (_____ ®) manufactured by Allergan.
- It is indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg of _____ once daily.
- The most common adverse reactions (define as those occurring at a frequency of ≥ 5% and at a higher frequency than placebo) associated with use include headache, _____, and dizziness.

FDA-APPROVED DRUG TO ADDRESS INSOMNIA IN PEOPLE LIVING WITH DEMENTIA

Introduction

- Suvorexant (_____ ®) is an orexin receptor antagonist indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance manufactured by Merck & co., Inc.
- While the _____ for suvorexant does not specify Alzheimer's disease, one of the studies in the suvorexant prescribing information was in patients with mild-to-moderate Alzheimer's disease.
- Individuals should use the _____ effective dose and take no more than once per night, within _____ minutes of going to bed (with at least 7 hours remaining prior to planned awakening).
- The recommended dose is ____mg, but if the 10 mg dose is well tolerated but not effective, the dose can be increased.
- The _____ recommended dose of suvorexant is 20 mg taken no more than once per night.

DRUG DELIVERY SSTEMS

Overview

- Most medications indicated for treating Alzheimer's disease are administered _____.
- Aducanumab is administered as an _____ and rivastigmine has a transdermal _____ formulation (in addition to an oral form).
- There are some _____ of oral administration with the approved medications in general and specifically in people with Alzheimer's disease.
    - The current dosage forms of approved medications at higher doses cause adverse reactions such as _____ pain, nausea, _____, and anorexia.
    - Another disadvantage of these medications is the variation in _____ levels.
    - Individuals with Alzheimer's disease may have low _____ due to memory loss.

Transdermal administration:

- There are some _____ to transdermal administration, particularly in Alzheimer's disease patients:
    - When a medication is administered transdermally, it _____ first-pass metabolism.
    - Therefore, because drugs are absorbed directly into the blood through the skin, _____ doses can be used.
    - Additionally, transdermal drug delivery can offer therapeutic levels of the drug in systemic circulation through a _____ drug delivery, while decreasing side effects by avoiding large fluctuations of plasma concentration of the drug.
    - In patients with Alzheimer's disease, transdermal patches may improve patient _____ as well as the benefit provided by the prolonged use of drugs.
    - Transdermal patches may also be preferred by _____ during long-term treatment of disease.
    - Transdermal patches are also useful in patients with difficulty in _____.

NON-PHARMAOLOGIC TREATMENT

OVERVIEW

Creating A Safe and Supportive Environment

- One important component of treating an individual with Alzheimer's disease is to _____ tasks that demand memory.
- It is important to establish and strengthen _____.

Healthy Lifestyle Choices

- Physical Activity: There may be benefits of physical exercise on the _____ of Alzheimer's disease.
- Nutrition: There are studies that suggest what we eat affects the _____ brain's ability to think and to remember.

Social Engagement and Activities

- Remaining socially _____ and involved in activities can help support the skills and abilities that are preserved in an individual with Alzheimer's disease.
- Additionally, doing things that are meaningful and enjoyable is important for the overall _____ of a person with Alzheimer's disease.

Coping and Support

- There are some things _____ can do to provide support such as:
  - _____ to the person express their emotions
  - Reassuring the person that life can still be enjoyed
  - Providing support
  - Helping the person retain _____ and self-respect

Patient Monitoring

- Clinicians need to regularly assess patients for _____ in daily functioning, cognitive status, comorbidities, behavioral symptoms, medication requirements, and care needs.

HOSPICE

- Hospice care focuses on comfort and dignity at the _____ of life.
- It provides _____ to a terminally ill patient and _____ to the patient's family in the final stages of Alzheimer's disease.
- The primary focus of hospice care is to manage _____ and other symptoms during the last 6 months of life.
- The focus of care shifts from _____ the underlying disease to providing _____ measures.
- Hospice care can be provided in a _____ (such as a nursing home), in a hospice facility, in a hospice unit at a hospital, or in a patient's _____.

LEGAL ASPECTS RELATING TO ALZHEIMER'S DISEASE

LEGAL ISSUES

Advance Directives

- Ideally, a person with Alzheimer's disease has put in place advance directives that _____ his or her _____.
- Without such documents in place, families must make choices based on what _____ think the individual with Alzheimer's disease would want.
- Advance directives are _____ papers specifying the type of _____ care a person wants to receive once they no longer have the capacity to make such decisions, and who should be in charge of making them.
- Advance directives should be made when the person with dementia has the level of judgment and decision-making ability needed to _____ official documents or to make medical and financial _____.
- It is best to put advance directives in place soon after _____.

Living Will

- A living will is a set of _____ instructions that provides specific preferences about the kind of medical treatment a patient would or would not want to have.

Durable Power of Attorney for Health Care

- A durable power of attorney for health care allows an individual to _____ someone (spouse, family member, or trusted friend) to make _____ about health care and treatment when they are no longer able to do so.

THE ROLE OF THE CAREGIVER

OVERVIEW OF THE ROLE OF THE CAREGIVER

Overview

- Caregiving is a term that means _____ to another person's health and well-being.

- Write in the missing information:

Reasons Caregivers Provide Assistance to an Individual With Alzheimer's Disease

- There are many reasons why an individual chooses to provide care, including but not limited to:
  - The desire to keep the individual with Alzheimer's disease at _____
  - The _____ to the person with Alzheimer's disease
  - The caregiver's perceived _____ to the person with Alzheimer's disease

Early Stage of Caregiving

- In the early stage of caregiving, the individual with Alzheimer's disease probably functions _____.
- Some of the primary caregiver tasks are providing _____ and companionship.
- It is also important to help the individual plan for the future in terms of _____ documents, _____, and long-term _____ planning.

Caring for the Caregiver

- It is also very important for the caregiver of someone with Alzheimer's disease to take care of their _____ and _____ health as well.

Overview of ADLARITY eLearning Module

Study Guide

INTRODUCTION TO ADLARITY

ADLARITY FORMULATION

Introduction to ADLARITY

- ADLARITY (donepezil transdermal system) is a _____ transdermal formulation of _____ that continuously delivers consistent medication doses through the skin over a 7-day period.
- The most _____ prescribed medications for Alzheimer's disease (AD) dementia are acetylcholinesterase inhibitors (AChEI).
- Of the available AChEIs, oral _____ is the most widely prescribed.

ADLARITY Indication and Dosage Strengths

- ADLARITY is indicated for the treatment of _____, _____, or _____ dementia of the Alzheimer's type and is available in 2 dosage strengths: ____mg/day and _____ mg/day.

Composition of ADLARITY Transdermal System

- ADLARITY is a rectangular patch with a _____ laminate composition.

- The first layer of the Adlarity patch contains 2 parts: an overlay backing on _____ and an _____ layer just below the overlay backing.
- Layer 2 is a _____ layer between the overlay backing/adhesive layer above it and the drug matrix layer below it.
- Layer 3 is the drug matrix layer that contains _____.
- Layer 4 is a _____ membrane that separates the drug matrix layer above it from the contact adhesive layer below it. This microporous membrane controls the _____ of donepezil delivery to the skin.
- Layer 5 is the contact _____ layer that adheres the patch to the patient's skin.
- Layer 6: The release liner is _____ before the patch is applied to the skin.

Rationale for Transdermal Delivery of Donepezil

- AChEIs, including donepezil, rivastigmine, and galantamine, _____ to acetylcholinesterase (AChE) in neuronal synapses to exert a pharmacologic effect in patients with dementia of the Alzheimer's type.
- AChEIs prevent the breakdown of _____, a chemical messenger important for memory and learning.
- Preventing the breakdown of acetylcholine increases the concentration of acetylcholine in neuronal synapses, thereby _____ cholinergic function.

Oral Administration of AChEIs

- Most AD medications are administered _____.
- GI Adverse Reactions: High doses of AChEI formulations may cause _____ adverse reactions, such as abdominal pain, nausea, vomiting, diarrhea, and anorexia.
- Medication Adherence: Orally administered AD medications also may be associated with low rates of medication _____ because of memory loss.
    - A high incidence of _____ (difficulty swallowing) in patients with AD dementia can also reduce medication adherence.

Transdermal Administration of AChEIs

- For patients with AD, there are several potential _____ with transdermal administration of AChEIs.

Greater Patient Compliance:

- Patients with dysphagia can _____ the need to swallow or chew a pill by receiving medication through a patch.
- In addition, caregivers who need to keep _____ of medication administration may find it easier to apply a patch to a patient once weekly than to administer oral medications daily.

Avoidance of First-Pass Metabolism:

- In transdermal AChEI administration the medication is absorbed directly into the _____ through the skin and therefore bypasses first-pass metabolism in the GI tract and liver.
- By avoiding first-pass metabolism, there is a potential for _____ medication doses to be administered to achieve a therapeutic effect, and lower doses may be associated with fewer _____.

- The ADLARITY transdermal system provides a slow, steady, continuous release of _____ through the skin.
- The transdermal formulation is designed to _____ medication absorption in the GI tract and associated GI AEs.
- Oral donepezil administration is associated with fluctuating plasma levels, whereas the slow, steady release of donepezil from the ADLARITY patch is associated with _____ plasma medication levels that maintain the level of medicine needed for effective treatment.

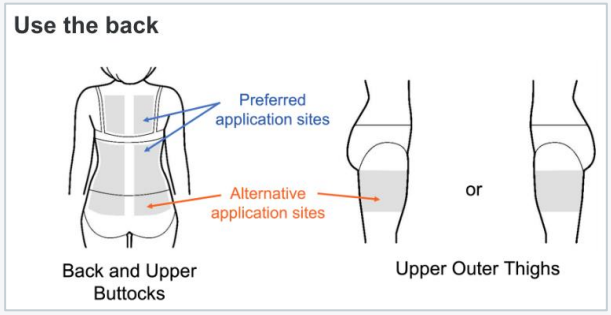
USE OF ADLARITY

Adlarity Dosage

- Recommended Dosage:
  - The recommended starting dosage of ADLARITY is _____ 5 mg/day transdermal system applied to the skin once _____.
  - After 4 to 6 weeks, the dosage may be increased to the maximum recommended dosage of ADLARITY ____ mg/day once _____.
  - Doses of ADLARITY _____ than 10 mg/day have not been evaluated.
- Switching to ADLARITY From Donepezil Tablets or Donepezil ODT
  - Patients treated with donepezil 5 mg or 10 mg _____ may be switched to ADLARITY.
  - A patient who is being treated with a total daily dose of _____ mg of oral donepezil can be switched to the once-weekly 5 mg/day ADLARITY _____.
    - Patients may be switched _____ to the once-weekly 10 mg/day patch if the patient has been on 5 mg oral donepezil for at least 4 to 6 weeks.
  - A patient who is being treated with a total daily dose of 10 mg of _____ donepezil can be switched to the once-weekly _____ mg/day ADLARITY patch.

ADLARITY Administration

- Timing: each ADLARITY transdermal system (ie, patch) is designed to continuously deliver donepezil for ___ days (1 week).
    - At the end of 7 days, the used transdermal system is _____, and a new transdermal system is applied.
    - Only __ transdermal system should be applied at a time.
- Missed Dose: If an ADLARITY patch falls off or a dose is missed, a new patch should be applied _____, and then this patch should be replaced 7 days later to start a new 1-week cycle.
- Application: ADLARITY is intended for _____ use on _____ skin.
    - The _____ application site is the back (avoiding the spine).
    - If needed, the upper buttocks or upper outer thigh may be used.



- Change _____ of patch application weekly
    - Do not use the same application site for at least _____ after removal of a patch from that location.
- ADLARITY adhesion is maintained in _____ conditions; therefore, ADLARITY use does not need to be interrupted due to bathing or hot weather.
- ADLARITY Storage:
    - _____ of patches is required (36°F to 46°F)
    - Patches should not be _____
    - The pouch containing the ADLARITY patch should be removed from the refrigerator and allowed to reach _____ temperature before removing the new transdermal system for application

UNMET NEEDS IN THE TREATMENT OF AD Dementia

Treatment Challenges in Patients with AD Dementia

Introduction:

- There are several treatment _____ for patients with AD dementia and their caregivers.
- Oral AChEIs are associated with _____ that may limit the dose of medication that a patient can tolerate or result in discontinuation of a medication.
- In addition, taking an orally administered medication may be _____ for some patients with AD dementia.
- Oral administration of AChEIs results in fluctuating plasma medication levels that may be associated with an _____ likelihood of adverse reactions when plasma levels are high or reduced _____ when plasma levels are low.

Adverse Reactions Associated With Oral Donepezil:

- Although oral donepezil treatment improves _____ in patients with AD dementia, it is associated with GI, CNS, and other adverse reactions.
    - The most common adverse reactions (defined as those occurring at a frequency of ≥ 5% and twice the placebo rate) are _____ by the cholinergic effects of donepezil.
    - These include _____, diarrhea, insomnia, _____, muscle cramps, fatigue, and anorexia.
- In general, adverse reactions with oral donepezil occurred _____ frequently in female and older patients.
- Adverse reactions associated with donepezil are often _____ and resolve during continued treatment without the need for dose _____.
- However, the _____ adverse reactions of donepezil can be particularly bothersome for some patients, which may potentially prevent the AChEI dose from being increased to achieve optimal medication effectiveness and/or result in medication discontinuation.

Challenges With Oral Administration of AD Dementia Medications:

- Administration of oral medications to patients with AD dementia are associated with 2 key challenges: _____ (difficulty swallowing) and treatment _____.
- _____ challenges associated with AChEIs along with dysphagia and impaired memory can all impact the ability of patients with AD dementia to experience optimal effectiveness of orally administered AChEIs.

ADLARITY Path to Approval

CLINICAL DEVELOPMENT OF ADLARITY

The Challenges in Developing a Transdermal Delivery System

- Medication formulated in a transdermal delivery system has to _____ the various layers of skin to reach the systemic circulation.
- Permeation involves _____ of drug molecules from one layer of skin (ie, epidermis) into subsequent layers (ie, dermis).
- After medication molecules reach the blood vessels in the dermis, they are _____ into the systemic circulation.
- Low Rate of Permeability: One challenge of donepezil transdermal delivery is that the medication molecule has a _____ rate of permeability through the skin.
    - The addition of permeation enhancers to transdermal donepezil delivery systems was associated with skin _____ problems.
- Solid Medication Crystals: Another issue with transdermal donepezil delivery is that solid medication crystals can form over time in _____ patches.
    - These solid crystals led to _____ patch adhesion to skin and an uneven skin permeation rate for donepezil in previous transdermal delivery systems.
- The need for transdermal medication delivery of donepezil led to the development of ADLARITY using _____ technology.

Corplex Technology

- ADLARITY utilizes Corium's _____ Corplex technology.
- Corium's Corplex system is a novel commercial-stage platform technology designed to broadly enable the _____ delivery of small molecules, such as donepezil, that have not previously been amenable to transdermal delivery.
- This technology is a _____ patch designed to consistently deliver donepezil over a 7-day period.
- In a matrix-type transdermal delivery system, the medication is _____ in a liquid or gel-based reservoir.
- Corplex technology allows the donepezil medication molecule to be delivered through the skin with a _____ rate of skin irritation.
- The ADLARITY patch is designed to _____ deliver donepezil, leading to plasma levels that remain within the therapeutic window for the medication.

Path to FDA Approval

- FDA approval of ADLARITY was based on a New Drug Application (NDA) that followed the _____ regulatory pathway.
- Because donepezil was previously approved as Aricept, the FDA agreed that a 505(b)(2) NDA was _____.
- Demonstration of _____ between the ADLARITY 10 mg/day patch and oral donepezil 10 mg once daily was the basis of the FDA's approval.
- Using the 505(b)(2) pathway, Corium was able to rely on previously completed Aricept clinical studies that demonstrated donepezil _____.
- These clinical studies in patients with mild to moderate dementia of the Alzheimer's type and moderate to severe dementia of the Alzheimer's type are reviewed in the _____.
- The ADLARITY PI includes adverse reaction data from an ADLARITY _____study and also adverse reaction data from clinical studies of _____ donepezil.
- The ADLARITY clinical development program was performed in _____ volunteers and not in patients with AD.

ADLARITY PHARMACOKINETIC STUDIES

Overview

- An ADLARITY 10 mg/day patch is considered _____ to oral donepezil 10 mg taken once daily.
    - *Bioequivalence* means that 2 medications have the _____ biologic effects.
- PK studies are used to evaluate the _____ concentrations of a medication (such as donepezil) over time following medication administration.
- PK studies determine what the _____ does to the drug, including:
    - _____ of the drug into the body
    - Distribution of the drug _____ the body
    - _____ of the drug by the body
    - Excretion of the drug _____ the body

Pivotal Bioequivalence Study

- Objective: The objective of the pivotal bioequivalence study was to _____ the bioequivalence of ADLARITY 10 mg/day and oral Aricept 10 mg once daily in healthy adults.
- Study Design: The pivotal bioequivalence study was a phase 1, _____, randomized, 3-period, 3-treatment, crossover PK study in _____ volunteers
  - During the first treatment period, each volunteer received _____ 5 mg/day for 5 weeks (meaning that 1 patch was applied each week for 5 weeks).
  - Volunteers were then _____ to receive each of the other 2 treatments in random order, either ADLARITY 10 mg/day for 5 weeks followed by Aricept 10 mg tablet orally once daily for 5 weeks or Aricept 10 mg tablet orally once daily followed by ADLARITY 10 mg/day for 5 weeks.
- Assessment of Bioequivalence: Bioequivalence was evaluated by comparing plasma concentration–time _____ of donepezil after administration of the commercial formulation of ADLARITY 5 mg/day and 10 mg/day with oral administration of Aricept tablets 10 mg once daily.
  - These PK data were used to demonstrate the _____ of ADLARITY 10 mg/day to Aricept 10 mg once daily based on FDA criteria for bioequivalence of 2 medications.
- Results: Results of the pivotal bioequivalence study _____ bioequivalence of ADLARITY 10 mg/day to Aricept 10 mg once daily.
  - Bioequivalence of the ADLARITY _____ dosage strength was also demonstrated.

Bioequivalence of ADLARITY Application at Alternative Body Sites

- Objective: The objective of this PK study was to compare the bioequivalence of ADLARITY 10 mg/day applied to the _____ versus the back and the buttock versus the _____.
- Study Design: This was a randomized, _____, 3-way crossover PK study of 66 healthy adult volunteers.
  - Each volunteer received ADLARITY 10 mg/day applied to the back, upper buttocks, or upper outer thigh in _____ order.
  - Each 7-day treatment period was separated by a 35-day _____ period (ie, no ADLARITY patch was applied during the washout period).
  - In this study, thigh and buttock application are considered the _____ condition and back application is considered the _____ condition.

- Results:
  - ADLARITY application to the upper buttock and the back were _____ bioequivalent.
  - ADLARITY application to the upper outer thigh and the back were _____ bioequivalent.

Bioequivalence of ADLARITY Application in the Prescence or Absence of Heat

- Objective: The objective of this PK study was to compare the bioequivalence of ADLARITY 5 mg/day applied to the back in the presence and absence of a _____.
- Study Design: This study was a _____, open-label, 2-way _____ study of 24 healthy adults.
  - Each volunteer was randomized to wear an ADLARITY 5 mg/day patch for 1 week in the _____ or _____ of a heating pad and then _____ to the other treatment condition for 1 week.
  - There was a 35-day washout period between the 2 treatment conditions.
- Results: The mean plasma donepezil concentration-versus-time profiles were _____ with or without applied heat.
  - Small, transient increases in plasma donepezil concentrations were observed during the heat sessions, but the overall results indicated plasma exposure to donepezil was not _____ significantly different in the presence and absence of heat.
  - ADLARITY 5 mg/day applied in the presence of heat was _____ to ADLARITY 5 mg/day applied in the absence of heat.

ADLARITY Adhesion

- The ADLARITY clinical development program also included evaluations of _____ adhesion during the studies.

DONEPEZIL CLINICAL STUDIES IN MILD, MODERATE, AND SEVERE DEMENTIA OF THE ALZHEIMER'S TYPE

- The _____ of donepezil as a treatment for mild, moderate, and severe dementia of the Alzheimer's type was demonstrated in 2 randomized, double-blind, placebo-controlled clinical investigations of donepezil tablets in patients with AD, including a 30-week study and a 15-week study.
- Outcome Measures: In each study, the effectiveness of donepezil treatment was evaluated using a _____ assessment that included assessment of both the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview-Based Impression of Change with the use of caregiver information (CIBIC-plus).

- ADAS-COG: The cognitive subscale of the ADAS-cog was used to assess the ability of donepezil to _____ cognitive performance in patients with dementia of the Alzheimer's type.

- CIBIC-PLUS: The CIBIC-plus was used to assess the overall _____ effect of donepezil.

30-week Study

- Objective: The objective of the 30-week study was to compare the _____ of donepezil tablets 5 mg once daily or 10 mg once daily with placebo in patients with mild, moderate, or severe dementia of the Alzheimer's type.

- Study Design: A total of 473 patients were _____ to receive once-daily doses of donepezil 5 mg, donepezil 10 mg, or placebo tablets.

  - Patients randomized to receive donepezil 10 mg once daily received 5 mg once daily for the first week before increasing to 10 mg once daily to _____ acute cholinergic effects

  - The 30-week study was divided into a _____-week double-blind active treatment phase (ie, patients received donepezil 5 mg once daily, donepezil 10 mg once daily, or placebo) followed by a ____-week single-blind placebo washout period (ie, all patients received placebo)

- Results:

  - ADAS-cog scores: After ____ weeks of treatment, the mean differences in the ADAS-cog change scores for donepezil compared with placebo patients were 2.8 points for donepezil 5 mg once daily and 3.1 points for donepezil 10 mg once daily.

    - Both differences between donepezil and placebo were statistically _____.

    - Although the treatment effect size may appear to be slightly greater for donepezil 10 mg once daily than for donepezil 5 mg once daily, there was ___ statistically significant difference between the 2 donepezil dosage regimens.

    - Following 6 weeks of placebo washout, the ADAS-cog scores for patients who had received either donepezil 5 mg once daily or 10 mg once daily were _____ from the ADAS-cog scores for patients who had received only placebo for 30 weeks.

      - This suggests that the beneficial effects of donepezil _____ during the 6 weeks following treatment discontinuation, indicating that improvements in the ADAS-cog that were measured during the first 24 weeks of the study represent _____ improvement rather than a change in the underlying disease.

- CIBIC-plus: The differences between donepezil and placebo were both statistically _____.
    - However, there was no statistically significant difference between the 2 donepezil dosage _____.

15-week Study

- Objective: The objective of the 15-week study was to compare the _____ of donepezil tablets 5 mg once daily or 10 mg once daily with placebo in patients with mild, moderate, and severe dementia of the Alzheimer's type.
- Study Design:
    - Patients were _____ to receive once-daily doses of donepezil 5 mg, donepezil 10 mg, or placebo tablets
    - Patients randomized to receive donepezil 10 mg once daily received 5 mg once daily for the first week before increasing to 10 mg once daily to _____ acute cholinergic effects
    - The 15-week study was divided into a _____-week double-blind active treatment phase (ie, patients received donepezil 5 mg once daily, donepezil 10 mg once daily, or placebo) followed by a 3-week single-blind placebo _____ period (ie, all patients received placebo)
- Results:
    - ADAS-cog scores: After ____ weeks of treatment, the mean differences in ADAS-cog change scores for donepezil compared with placebo patients were 2.7 points for donepezil 5 mg once daily and 3.0 points for donepezil 10 mg once daily.
        - Both differences between donepezil and placebo were statistically _____.
        - Although the treatment effect size may appear to be slightly greater for donepezil 10 mg once daily than for 5 mg once daily, there was no statistically significant _____ between the 2 donepezil dosage regimens.
        - Following 3 weeks of placebo washout, ADAS-cog scores for patients who had received donepezil 5 mg once daily or 10 mg once daily _____, indicating that donepezil discontinuation resulted in a _____ of its treatment effect.
    - CIBIC-plus: The differences between donepezil and placebo were both statistically _____.

Conclusions

- The 2 randomized controlled studies in patients with mild, moderate, and severe dementia of the Alzheimer's type demonstrated that the higher dose of donepezil 10 mg once daily did _____ provide a statistically significantly greater clinical benefit than donepezil 5 mg once daily.
- However, additional data analyses suggested that donepezil 10 mg once daily might provide additional _____ for some patients.

DONEPEZIL CLINICAL STUDIES IN MODERATE TO SEVERE DEMENTIA OF THE ALZHEIMER'S TYPE

- The _____ of donepezil as a treatment for patients with moderate to severe AD was demonstrated in 2 randomized, double-blind, placebo-controlled clinical investigations of Aricept (donepezil tablets) in patients with AD.

Swedish 6-month Study

- Objective: The objective of the 6-month study was to compare the effectiveness of donepezil 10 mg once daily with _____ in patients with moderate to severe AD dementia.
- Study Design:
  - A total of 248 patients were randomized to receive once-daily doses of donepezil 10 mg or placebo tablets for ____ months
  - Patients randomized to receive donepezil 10 mg once daily received 5 mg once daily for the first ___ days before increasing to 10 mg once daily to _____ acute cholinergic effects
  - By the end of the 6-month study, _____ of donepezil patients were receiving the 10 mg once-daily dose
- Results:
  - SIB: At 6 months of treatment, the mean difference in SIB change scores for donepezil compared with placebo patients was _____ points.
    - Donepezil treatment resulted in statistically significantly greater clinical _____ than placebo.
  - ADCS-ADL-severe: At 6 months of treatment, the mean difference in the ADCS-ADL-severe change scores for donepezil compared with placebo patients was _____ points.
    - Donepezil treatment was statistically significantly greater improvement in daily _____ than placebo.

Japanese 24-week Study

- Objective: The objective of the 24-week study was to compare the effectiveness of donepezil tablets 5 or 10 mg once daily with placebo in Japanese patients with _____ AD dementia.
- Study Design:
  - Patients were randomized to receive once-daily doses of donepezil 5 mg, donepezil 10 mg, or placebo tablets for _____ weeks
  - Patients randomized to receive donepezil were to receive their assigned doses by _____ during a 6-week period, beginning with 3 mg once daily to avoid acute cholinergic effects
- Results: After 24 weeks of treatment, statistically _____ differences were observed between the donepezil 10 mg once-daily dose and placebo on both the SIB and CIBIC-plus.
  - A statistically significant difference between the donepezil 5 mg once-daily dose and placebo was observed on the _____ but not on the _____.

SAFETY DATA FOR ADLARITY

Overview

- Adverse reactions and application-site reactions associated with ADLARITY were assessed in _____, human volunteers who enrolled in the pivotal bioequivalence study of ADLARITY, not in patients with AD dementia.
- The most common adverse reactions in the ADLARITY PI are from clinical studies of _____ (oral donepezil) in patients with AD dementia.

ADLARITY Adverse Reactions in Pivotal Bioequivalence PK Study

- The pivotal PK study that was used to establish the _____ of ADLARITY 10 mg/day to orally administered Aricept 10 mg once daily also evaluated adverse reactions.
- The most common adverse reactions listed in the Highlights section of the ADLARITY PI (>5% with donepezil tablets and twice the placebo rate) are _____, diarrhea, insomnia, vomiting, muscle cramps, _____, and anorexia.
- GI Adverse Events: Overall, the types of adverse reactions reported by healthy volunteers receiving the ADLARITY patch in the pivotal bioequivalence PK study were _____ with those reported by patients with AD dementia receiving oral donepezil therapy in clinical trials.

- However, ADLARITY 10 mg/day was associated with a _____ incidence of all GI AEs compared with oral donepezil 10 mg once daily in healthy volunteers.
- In the pivotal bioequivalence study in healthy adults, the incidence of all GI AEs was ~ _____ times lower with ADLARITY 10 mg/day than with oral donepezil 10 mg once daily.
- The incidence of nausea was ~ _____ times lower, and the incidences of vomiting, diarrhea, and constipation were also lower.

- CNS Adverse Events: ADLARITY 10 mg/day was also associated with a _____ incidence of CNS AEs compared with oral donepezil 10 mg once daily, including dizziness and somnolence.

Application-site Reactions With Adlarity

- In the pivotal bioequivalence PK study, an investigator-rated skin _____ scale was used to capture cases of skin irritation after ADLARITY removal.
- Skin irritation was observed, including erythema (64.6%), papules (16.0%), and edema (0.4%), following the removal of 268 ADLARITY 10 mg/day transdermal systems; none of the ADLARITY transdermal systems were _____ because of skin irritation.
- All application-site AEs were reported as _____.
- In a clinical study investigating the skin-sensitizing potential of ADLARITY in 229 healthy adults, _____ cases of potential sensitization were observed (4/229 = 1.7%).

Adverse Reactions Leading to Discontinuation in Donepezil Clinical Trials

- Clinical Trials of Patients With Mild to Moderate AD dementia: Patient discontinuation rates from controlled clinical trials of donepezil tablets due to adverse reactions for donepezil 5 mg once daily were _____ to discontinuation rates for placebo (~ 5% of patients in both groups).
    - However, the discontinuation rate for patients who received 7-day escalations of donepezil tablets from 5 mg once daily to 10 mg once daily was _____ (13%).

Clinical Trials of Patients With Severe AD dementia

- In patients with severe AD dementia, patient _____ rates from controlled donepezil clinical trials due to adverse reactions were ~ 12% donepezil compared with 7% for placebo patients.

Annotated PI

Notes

Competitive Landscape Table

ALZHEIMER'S DISEASE MEDICATION COMPETITIVE LANDSCAPE:
Acetylcholinesterase Inhibitors

INFORMATION PER PI	ADLARITY®	Aricept®	Aricept® ODT	Rivastigmine Capsules	Exelon® Patch	Razadyne® Tablets and ER Capsules
Generic Name	Donepezil transdermal system	Donepezil tablets	Donepezil ODT	Rivastigmine	Rivastigmine transdermal system	Galantamine
Mechanism of Action	Acetylcholinesterase inhibitor	Acetylcholinesterase inhibitor	Acetylcholinesterase inhibitor	Acetylcholinesterase inhibitor	Acetylcholinesterase inhibitor	Acetylcholinesterase inhibitor
Indication(s)	• Dementia of the Alzheimer's type	• Mild, moderate, and severe dementia of the Alzheimer's type	• Mild, moderate, and severe dementia of the Alzheimer's type	• Mild to moderate dementia of the Alzheimer's type	• Mild, moderate, and severe dementia of the Alzheimer's type	• Mild to moderate dementia of the Alzheimer's type
Formulation	Transdermal patch that continuously delivers donepezil over 7 days	Film-coated tablets	ODT	Capsules	Transdermal patch that delivers rivastigmine over 24 hours	IR tablets ER capsules
Dosing Frequency	Once-weekly dosing Initial = 5 mg/day patch weekly Maintenance = 10 mg/day patch weekly	Once-daily oral dosing Initial = 5 mg Mild to moderate AD • Maintenance = 10 mg Moderate to severe AD • Maintenance = 10–23 mg	Once-daily oral dose Initial = 5 mg Mild to moderate AD • Maintenance = 10 mg Moderate to severe AD • Maintenance = 10–23 mg	Twice-daily oral dose Initial (AD, PDD) = 3 mg total daily dose Maintenance (AD, PDD) = 6–12 mg total daily dose	Once-daily dosing Initial (AD and PDD) • 4.6 mg/24 hrs patch daily Maintenance, mild to moderate AD and PDD • 9.5 mg/24 hrs or 13.3 mg/24 hrs patch daily Maintenance, severe AD • 13.3 mg/24 hrs patch daily	IR tablets: twice-daily dose ER capsules: once-daily dose Initial = 8 mg total daily dose Maintenance = 16–24 mg total daily dose
Dosage Strengths	• 5 mg/day • 10 mg/day	• 5 mg • 10 mg • 23 mg	• 5 mg • 10 mg	• 1.5 mg • 3 mg • 4.5 mg • 6 mg	• 4.6 mg/24 hrs • 9.5 mg/24 hrs • 13.3 mg/24 hrs	IR tablets • 4 mg, 8 mg, 12 mg ER capsules • 8 mg, 16 mg, 24 mg
Most Common Adverse Reactions	Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia	Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia	Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia	Nausea, vomiting, anorexia, dyspepsia, asthenia	Nausea, vomiting, diarrhea	Nausea, vomiting, diarrhea, dizziness, headache, decreased appetite

Adlarity® (donepezil transdermal system)

AD, Alzheimer's disease; ER, extended release; hrs, hours; IR, immediate release; ODT, orally disintegrating tablets; PDD, Parkinson's disease dementia; PI, prescribing information.

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Competitive Landscape Table

ALZHEIMER'S DISEASE MEDICATION COMPETITIVE LANDSCAPE:
Other Mechanisms

INFORMATION PER PI	Aduhelm®	Namenda® Tablets	Namzaric® ER Capsules
Generic Name	Aducanumab-avwa	Memantine	Memantine and donepezil
Mechanism of Action	Amyloid beta-directed monoclonal antibody	NMDA receptor antagonist	NMDA-receptor antagonist and acetylcholinesterase inhibitor
Indications	AD • Treatment initiated in patients with MCI or mild dementia	Moderate to severe dementia of the Alzheimer's type	Moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg donepezil once daily
Formulation	IV solution	Film-coated tablets	ER capsules
Dosing Frequency	1-hour infusion every 4 weeks, with each infusion ≥ 3 weeks apart • Infusions 1 + 2 = 1 mg/kg • Infusions 3 + 4 = 3 mg/kg • Infusions 5 + 6 = 6 mg/kg • Infusion 7/Maintenance = 10 mg/kg	Twice-daily dosing • Initial = 5 mg once daily • Maintenance = 10 mg twice daily The recommended interval between dose increases is ≥ 1 week	Once-daily dosing (memantine/donepezil) • Initial (not on memantine, stable on donepezil 10 mg) = 7 mg/10 mg in evening • Initial (stable on memantine 10 mg IR twice daily or 28 mg ER once daily and donepezil 10 mg) = 28 mg/10 mg in evening • Maintenance = 28 mg/10 mg
Dosage Strengths	• 170 mg/1.7 mL (100 mg/mL) single-dose vial • 300 mg/3 mL (100 mg/mL) single-dose vial	• 5 mg • 10 mg	• 7 mg memantine/10 mg donepezil • 14 mg memantine/10 mg donepezil • 21 mg memantine/10 mg donepezil • 28 mg memantine/10 mg donepezil
Most Common Adverse Reactions	ARIA-E, headache, ARIA-H microhemorrhage, ARIA-H superficial siderosis, fall	Dizziness, headache, confusion, constipation	Memantine: headache, diarrhea, dizziness Donepezil: diarrhea, anorexia, vomiting, nausea, and ecchymosis

Adlarity® (donepezil transdermal system)

AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema; ARIA-H, ARIA-hemosiderin deposition; ER, extended release; IR, immediate release; IV, intravenous solution; MCI, mild cognitive impairment; NMDA, N-methyl-D-aspartate; PI, prescribing information.

Pharmacy Shelf

Notes

C.A.R.E. CUSTOMER ENGAGEMENT FRAMEWORK

The Corium C.A.R.E Customer Engagement Framework is one that:

- Provides a structure for call preparation, self-management, coaching, and training
- Builds a common language for customer engagement
- Creates the environment for *authentic,* two-way conversation
- Fosters a genuine interest with our conversation partners
- Enables us to discover the needs of our customers and offer solutions to benefit our patients
- Allows for flexibility as representatives engage in face-to-face or virtual interactions

PRE-CALL
Utilize business planning fundamentals for developing personality styles, use of proper resources, and a call objective, which includes prescribing continuum, fundamental elements, and selling messages.

CAPTIVATE
Captivate your audience with an intriguing statement to open the conversation about the product or disease state or solicit insight from the customer in a non-threatening way.

ASK
Ask open-ended questions that promote thinking and discovery and deepen understanding of physician's need by clarifying and paraphrasing.

RESPOND
Respond confidently and persuasively to position product features and benefits to meet the needs of the customer while using CMLR-approved marketing materials. Clarify/Acknowledge the concern, successfully respond, and gain agreement before moving forward.

EARN
Earn a close by listening to your customer, addressing their concerns, and responding appropriately to summarize the call before using a direct, assertive close that motivates the HCP to an action.

POST-CALL
Reflect on execution of the call and the physician's response to the information to formulate an action plan that advances the prescriber along the continuum for future calls.

Appendix

Study Guide Answer Keys:

Anatomy and Physiology of the Human Brain, Neurotransmission, and Introduction to Memory eLearning Module

Study Guide

OVERVIEW OF THE BRAIN

Cerebrum

- The adult brain consists of **4** main parts, one of which is the cerebrum, which is the **largest** part of the brain.
- It is known as the "seat of **intelligence**" and allows individuals the ability to:
    - Read, **write**, and speak
    - Perform calculations and compose **music**
    - Remember the past, plan for the future, and imagine things that have never **existed** before

Cerebral Cortex

- The cerebral cortex is a region of **gray matter** that forms the outer rim of the cerebrum.
- While it is only **2-4** millimeters thick, it contains billions of neurons arranged in distinct layers.

Hippocampus and Temporal Cortical Areas

- The hippocampus and surrounding temporal cortical areas play a major role in memory **consolidation** by communicating with the thalamus and prefrontal cortex.
- Thalamus: serves as the major **relay** station for most sensory impulses that reach the primary sensory areas of the cerebral cortex from the spinal cord and brainstem.
- **Prefrontal cortex**: an extensive area in the anterior portion of the frontal lobe; concerned with the makeup of a person's personality, intellect, complex learning abilities, recall of information, initiative judgment, foresight, reasoning conscience, intuition, mood, planning for the future, and development of abstract ideas
- Hippocampus: **limbic system** structure that plays a role in converting new information into long-term memories

INTRODUCTION TO AMYLOID PRECUROSR PROTEIN AND AMYLOID-β PEPTIED

Amyloid Precursor Protein

- The amyloid precursor protein (APP) is a protein in a family of **single-pass** transmembrane proteins with large extracellular domains.
- APP is produced in **large** quantities in neurons and metabolized very **quickly**.
- APP undergoes hydrolysis by various pathways
    - One pathway (amyloidogenic) produces amyloid beta (amyloid-β) peptide, a protein involved in the **pathophysiology** of Alzheimer's disease
        - APP is first **cleaved** by β-secretase and γ-secretase; this results in the production of CTF-β, soluble peptide APPβ (SAPPβ), and amyloid-β, including amyloid-β_{42} ($A\beta_{42}$), which is more prone to aggregation and plaque formation, and amyloid-β_{40} ($A\beta_{40}$), which is neurotoxic. This is known as the amyloidogenic pathway
    - The other pathway (non-amyloidogenic) does not produce this peptide
        - APP can be hydrolyzed by alpha-secretase (α-secretase) and gamma-secretase (γ-secretase), leading to the production of products that are neurotrophic and neuroprotective for nerve cells, such as the C-terminal fragment (CTF-α), the soluble ectodomain of APP-α (sAPPα), and other smaller fragments. This process does not produce amyloid-β and is known as the **non-amyloidogenic** pathway.
- In individuals with Alzheimer's disease, **abnormal** levels of amyloid-β clump together to form amyloid plaques that collect between neurons and disrupt cell function.

INTRODUCTION TO TAU

Overview

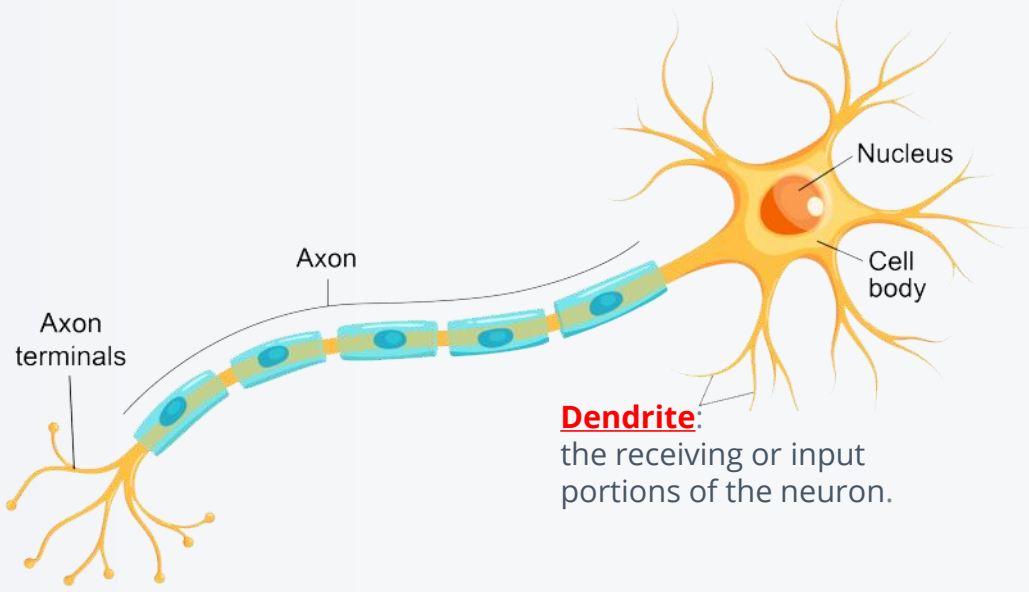
- Neurons are supported internally by **microtubules**.
- **Tau** is the major microtubule-associated phosphoprotein of a normal mature neuron.

- The function of tau is the promotion of the assembly of **tubulin** into microtubules and stabilization of their structure.
- In a healthy brain, **2 or 3** residues on the tau protein are phosphorylated.
- In contrast, in an individual with Alzheimer's disease, approximately **9** residues per module of tau protein are phosphorylated (hyperphosphorylation).
- Ultimately, tau hyperphosphorylation leads to tau **detaching** from the microtubules, **sticking** to other tau molecules, and aggregating into neurofibrillary **tangles**.

NEURONS

Introduction

- The role of neurons in the brain is to process and transmit information through electrical and chemical **signals**.
- Write in the missing labels and information:



- In people with Alzheimer's disease, healthy neurons **stop** functioning, lose connections with other neurons, and eventually **die**.

Microtubules

- Healthy neurons, in part, are supported **internally** by microtubules, which help guide nutrients and molecules from the cell body to the axon and dendrites.
    - **Tau** binds to and stabilizes the microtubules.
- In a diseased brain, such as one in an individual with Alzheimer's disease, tau becomes abnormally hyperphosphorylated, which ultimately causes the microtubule to **disassemble**.
    - The free tau forms neurofibrillary **tangles**.

COMMUNICATION BETWEEN NEURONS

Introduction

- Neurons **communicate** with each other.
- When stimulated, a neuron generates an action potential (nerve impulse), which is an **electrical** signal.
- The impulse travels along the **axon** from the cell body toward the axon terminals.
- When the impulse reaches the axon terminal, it causes **neurotransmitters** to be released into the narrow gap between the axon terminal of a neuron and the receptive surface of the next cell.
- This gap is known as the **synapse**.
- Neurotransmitters **diffuse** across the synaptic cleft and **bind** to specific receptors on the postsynaptic membrane.
- This process triggers a signal that either **stimulates** or **inhibits** activity in the neuron receiving the signal.

Neurotransmitters Important in Alzheimer's Disease

1. Acetylcholine:
    - An important neurotransmitter used by **cholinergic** neurons
    - Involved in processes including but not limited to learning and **memory**
    - Damage to cholinergic neurons is a change that **correlates** with cognitive impairment and occurs in people with Alzheimer's disease

2. **Glutamate**:
    - A chemical messenger that helps the brain process information
    - Excessive glutamate buildup at the N-methyl-D-aspartate (NMDA) receptor due to inefficient removal mechanisms at the synaptic cleft results in the overactivation of the NMDA receptor, leading to chronic excitotoxicity
    - This may contribute to neuronal loss and subsequent cognitive impairment

OVERVIEW OF THE CHOLINERGIC SYSTEM

Introduction

- The cholinergic system is involved in many important processes, including but not limited to **attention**, learning, memory, stress response, wakefulness, and **sleep**.
- The cholinergic neurons are widely distributed in the central nervous system, and **acetylcholine** is the neurotransmitter used by all of these neurons.
- **Defects** in cholinergic transmission can potentially influence all aspects of cognition and behavior.
    - The **degeneration** of cholinergic neurons and cholinergic innervation **loss** takes place in individuals with Alzheimer's disease and contributes to memory loss

INTRODUCTION TO MEMORY

Overview

- Memory is the process through which information obtained from **learning** is stored and retrieved. There are various types of memory, including:
- **Declarative Memory** (remembering names, faces, words, and dates)
    1. Short-term memory:
        - Also known as **working** memory
        - The first step in memory
        - Is limited to **7 to 8** chunks of information
        - A **temporary** container for information that individuals may or may not want to retain

2. Long-term memory:
    - Has a **limitless** capacity
    - Long-tern memories can be **forgotten**, and our memory bank continually changes over time

- **Procedural memory** (remembering **skills** such as playing the piano)
- **Motor memory** (remembering how to ride a bike, for example)
- **Emotional memory** (a pounding heart when a snake is nearby, for example)
- The ability to store and retrieve information from long-term memory **declines** with age.

Information Transfer

- **Information** may be transferred from short-term memory to long-term memories.
- Many factors can affect this transfer:
    - **Emotional** State: individuals learn best when they are alert, motivated, surprised, or aroused
    - Rehearsal: repeating or rehearsing the information **increases** the chance of transfer to long-term memory.
    - Association: **linking** "new" information to "old" information already stored in long-term memory can aid in remembering information.
    - Automatic: some information that moves into long-term memory may not be **consciously** formed
- The symptoms of Alzheimer's disease occur because **neurons** in parts of the brain involved in thinking, learning, and memory have been damaged or destroyed.
- The first lesions characteristic of Alzheimer's disease appear in neurons in system areas related to memory and learning, such as the **hippocampus** and association cortex.

Alzheimer's Disease State Overview eLearning Module

Study Guide

INTRODUCTION TO ALZHEIMER'S DISEASE

COGNITIVE IMPAIRMENT

Dementia

- *Dementia* is a **general** term used to designate a wide range of diseases, including but not limited to Alzheimer's disease, vascular dementia, and frontotemporal dementia.
- Dementia is the result of changes in the **brain** that causes neurons to stop working and eventually die.
- **Age** is the biggest risk factor for the development of dementia.

Age-Related Cognitive Decline

- Age-related cognitive decline is when certain areas of memory, thinking, and information processing slow with age but **intelligence** remains unchanged.
- Unlike dementia, the condition is not **disabling**.

Mild Cognitive Impairment

- The stage **between** normal age-related cognitive changes and more serious symptoms that indicate dementia is known as *mild cognitive impairment*.
- An individual with mild cognitive impairment may have a **greater** risk of eventually developing Alzheimer's disease or another type of dementia.
- However, this condition does not always progress to **dementia**.
- Symptoms of mild cognitive impairment include problems with thinking, judgment, memory, and language; however, these issues do not significantly interfere with the ability to handle **everyday** activities.

TYPES OF DEMENTIA

5 most common forms of dementia:

1. Alzheimer's disease
    - The most common type of dementia and accounts for up to **80%** of all dementia diagnoses
2. Vascular dementia
    - Caused by conditions that block or reduce **blood flow** to parts of the brain
    - The **second** most common type of dementia
    - It is more common as part of mixed dementia
3. Lewy body dementia
    - Characterized by an **abnormal** accumulation of alpha-synuclein proteins in the brain
    - These clumps are known as *Lewy bodies*
    - These proteins build up within **neurons** in areas of the brain relating to thinking, memory, and motor control
    - The buildup of these proteins causes neurons to not function properly and the neurons to eventually die
4. **Frontotemporal** dementia
    - Caused by a group of disorders that gradually damage the brain's frontal and temporal lobes
    - This damage results in changes in thinking and behaviors
    - This is a **rare** type of dementia and typically occurs at a younger age than other dementias
    - This form of dementia is **progressive**, with symptoms starting slowly and worsening over time
    - The cause is not completely understood
    - Individuals with frontotemporal dementia have abnormal amounts or forms of the protein tau and transactive response DNA-binding protein 43 (TDP-43) inside of neurons in the brain
    - The **buildup** of these proteins causes damage to the neurons and neuronal death
5. Mixed dementia
    - Many people have brain changes associated with **more than 1** type of dementia
    - This is known as *mixed dementia*
    - The likelihood of having mixed dementia **increases** with age and is highest in people ages 85 and older

STAGES OF ALZHEIMER'S DISEASE

Overview

- The Alzheimer's disease continuum illustrates the **progression** from brain changes that are unnoticeable to a person affected with brain changes that impact memory and eventually physical disability.
- There are 3 broad phases:
    1. **Preclinical** Alzheimer's disease:
        - Changes occur in the brain for years before any signs of Alzheimer's disease are apparent
        - Typically identified only in research settings
        - Can last for years and sometimes even decades
    2. Mild cognitive impairment due to Alzheimer's disease
        - The affected individual has **subtle** problems with memory and thinking
        - There is also **biomarker** evidence of Alzheimer's disease brain changes
    3. Dementia due to Alzheimer's disease
        - Characterized by **noticeable** thinking, memory, or behavioral symptoms that hinder an individual's ability to function in dial life
        - There is also biomarker evidence of Alzheimer's disease-related brain changes
        - There are 3 stages:
            a) Mild (early Alzheimer's disease)
                - Also known as *early-stage Alzheimer's disease*
                - An individual may function independently but need assistance with some activities in order to remain safe and maximize independence
                - While symptoms may not be apparent at this stage to may people, family and close friends may notice changes
                - At this stage a doctor would be able to identify symptoms using diagnostic tools
                - People are often diagnosed at this stage

b) Moderate (middle-stage Alzheimer's disease)

- Typically the **longest** stage of the disease
- The individual may have difficulties communicating and performing activities of daily living
- The individual will probably require assistance to participate in daily activities
- The individual may also sometimes become **incontinent**
- The individual's personality and behaviors may change
- As the condition progresses, the person with Alzheimer's will need a greater level of care
- Symptoms are more **obvious** during this stage

c) **Severe** (late-stage Alzheimer's disease)

- Affected individuals lose the ability to respond to their environment, hold a conversation, and eventually control movement
- **Hospice** may benefit patients and their family at this stage

EPIDEMIOLOGY OF ALZHEIMER'S DISEASE

- Alzheimer's disease is the **sixth** leading cause of death in the United States and the only disease in the list of the top 10 causes of death that is still significantly **increasing**

U.S. Prevalence

- An estimated 6.2 million Americans ages **65 and older** had Alzheimer's dementia in 2021; **72%** were age 75 or older

Incidence

- Approximately **910,000** people age 65 or older developed Alzheimer's dementia in the US in 2011

Prevalence

- More than **1 in 9 (11.3%)** people ages 65 and older had Alzheimer's dementia in 2021, and the percent increases with **age**

Gender

- Almost two-thirds of people with Alzheimer's disease in the US are **women**

Racial and Ethnic Differences

- Black (18.6%) and Hispanic Americans (14%) ages 65 and older are disproportionately **more** likely than White Americans (10%) ages 65 and older to have Alzheimer's dementia or other dementias.

ECONOMIC IMPACT OF ALZHEIMER'S DISEASE

Cost of Care

- Total cost of care for Americans age 65 and older with Alzheimer's disease or other dementias in 2021 was $**355** billion
- The costs of healthcare and long-term care for individuals with Alzheimer's disease are substantial, making it one of the **costliest** conditions to society.
- Alzheimer's disease care total costs are estimated to climb to more than $1 **trillion** by 2050.

Direct and Indirect Costs

Direct Costs:

- Direct medical costs associated with the treatment of Alzheimer's disease include **physician** visits, emergency visits, hospitalizations, long-term care or skilled nursing facility care, and **medications**
- Direct **nonmedical** costs include transportation to medical care, home healthcare, and modifications to adapt to alterations in physical function

Indirect Costs:

- Indirect costs of care associated with Alzheimer's disease include caregiver **burden** and associated healthcare utilization and costs.

RISK FACTORS FOR ALZHEIMER'S DISEASE

Overview

The 3 greatest risk factors for Alzheimer's disease are:

- Age: the greatest risk factor for Alzheimer's disease is **increasing** age
- Genetics
    - There are several **genes** that increase the risk of developing Alzheimer's disease.
    - The gene with the **strongest** impact on the increased risk of developing late-onset Alzheimer's disease is the apolipoprotein E gene (APOE)-e4 gene.
- Family history of Alzheimer's: It is estimated that people with at least 1 first-degree relative with Alzheimer's were **1.73** times more likely to develop the disease than those without a first-degree relative with Alzheimer's disease

CAUSES OF ALZHEIMER'S DISEASE

- It is not fully understood what **causes** Alzheimer's disease

Introduction

- In people who have **early-onset** Alzheimer's disease, a genetic mutation may have been the cause.
- Late-onset Alzheimer's disease arises from complex changes occurring in the brain over several decades. The causes likely include:
  - Genetics
    - Familial autosomal dominant Alzheimer's disease is **rare** (<1%), most often manifests in early-onset Alzheimer's disease, and is caused by **mutations** in presenilin 1, amyloid precursor protein, or presenilin 2.
    - The risk of developing Alzheimer's disease is estimated to be **70%** attributable to genetic factors, which differ between early-onset and late-onset Alzheimer's disease
    - The major risk or susceptibility gene in sporadic late-onset Alzheimer's disease involves **apolipoprotein E gene (APOE)-e4 gene**
  - Environmental factors
  - Lifestyle factors

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

OVERVIEW OF PATHYPHYSIOLOGY

- Signs of Alzheimer's disease may be found in the patient's brain **20** years before the first symptoms appear.

Overview

The 4 main characteristic hallmarks of Alzheimer's disease include:

1. Amyloid-β peptide plaques (also known as β-amyloid plaques)
   - Amyloid-β is a protein produced by the **hydrolysis** of the amyloid-β precursor protein (APP).
   - Amyloid-β becomes deposited in the hippocampus and basal segment—in the form of neurotoxic amyloid **plaques**—and recruits more amyloid-β.
   - This leads to the formation of insoluble **aggregates** and induces mitochondrial damage, unstable homeostasis, and synaptic dysfunction.

2. Neurofibrillary tangles

    - Tau is the major microtubule-associated **protein** of a normal mature neuron.
    - In people with Alzheimer's disease, tau protein is abnormally hyperphosphorylated and aggregated into neurofibrillary **tangles** comprised of paired helical filaments comprised of tau.
    - In the Alzheimer's brain, the tau is seen as tangles **within** neurons.

3. Synaptic dysfunction

    - Synaptic connectivity between **neurons** is essential for learning and memory.
    - Alteration of synaptic protein expression and synaptic plasticity are **early** events in Alzheimer's disease progression in humans.
    - Synapse **loss** is strongly correlated with cognitive impairment in Alzheimer's disease.

4. Neuroinflammation

    - The brain **tissue** in people with Alzheimer's disease exhibits inflammation.

Consequences of Changes in the Brain

- In people with Alzheimer's disease, formerly healthy neurons cease **functioning**, lose connections with other neurons, and eventually die.

SIGNS AND SYMPTOMS OF ALZHEIMER'S DISEASE

DESCRIPTION OF SIGNS AND SYMPTOMS

Overview

- Individuals who experience **cognitive** changes should consult with a healthcare professional to determine if the changes are normal for their age, reversible, or a symptom of Alzheimer's disease or another type of dementia.
- Examples of incidences in which memory loss is **reversible** include but are not limited to chronic alcoholism, an effect of a medication or combination of medications, and vitamin B-12 deficiency.

The main warning signs and symptoms of Alzheimer's disease:

- Memory loss that **disrupts** daily life
- Challenges in planning or solving problems
- Difficulty completing **familiar** tasks at home, at work, or at leisure
- Confusion with time or place
- Trouble understanding visual images and spatial relationships
- New problems with **words** in speaking or writing
- Misplacing things and losing the ability to retrace steps
- Decreased or poor **judgment**
- Withdrawal from work or social activities
- Changes in **mood** or personality

Symptoms Unrelated to Memory

- Individuals with Alzheimer's disease also have non-mnemonic symptoms—those that are **unrelated** to cognition.
- Examples include **apathy**, depression-like behavior, **sleep** disturbances, aggression, and **anxiety**.
- Individuals with Alzheimer's disease may experience **hallucinations** involving hearing, seeing, smelling, or feeling things that are not really there.
- **Delusions** are false beliefs that the person thinks are real.
- Individuals with Alzheimer's disease may also become **paranoid** and fearful, suspicious, or **jealous** of people.

DIAGNOSIS AND ASSESSMENT OF ALZHEIMER'S DISEASE

OVERVIEW – DIAGNOSIS AND ASSESSMENT

- There is no **single test** for dementia due to Alzheimer's disease.

Diagnostic Criteria

- Alzheimer's disease diagnostic criteria were originally developed in **1984**.
- In 2011, the National Institute on Aging-Alzheimer's Association (NIA-AA) **revised** the clinical criteria for the diagnosis of mild cognitive impairment and the various stages of dementia due to Alzheimer's disease.
- Alzheimer's disease is diagnosed with complete certainty only after **death**, when microscopic examination of the brain reveals characteristic plaque and tangles.

DIAGNOSTIC PROCESS

Introduction

- Several methods and tools are used to determine whether an individual's **memory** issues are due to Alzheimer's disease.
- Various potential components of the process:
  - **Interviews**: the patient, as well as a family member or friend of the patient is interviewed to learn about
    - Overall health
    - Use of prescription and over-the-counter medications
    - Past medical history and/or diet
    - Symptoms and their impact on daily activities
    - Identifying any changes in thinking skills, behavior and personality
  - History of present illness: information should be gathered about the patient's **current** symptoms, complaints, and problems and how things have **changed** or progressed.
  - Standard **medical** testing: a physician may order blood, urine, and other standard medical tests to help identify other causes of cognitive impairment
  - **Psychiatric** examination: The purpose of a psychiatric examination is to determine whether depression or another mental health condition is causing or contributing to a person's symptoms
  - Mental cognitive status tests: Many **office-based** brief cognitive status tests are used to evaluate memory, thinking, and problem-solving abilities.
  - Neuropsychological evaluation: Neuropsychological tests use validated **puzzle-based** material, oral questions, and written tests for an objective assessment of several cognitive and emotional functions.
    - The accuracy is **increased** when combined with imaging results and evaluations with subspecialists

- **Imaging**: A standard workup for Alzheimer's disease includes images of the brain taken by magnetic resonance imaging (MRI) or computed tomography (CT).
- Biomarker **Evidence**: Biomarkers or biologic markers are any types of substances, structures, or processes that can be measured inside or outside the body and that may influence any changes in the body and probable prevalence of any disease in the body.
    - 3 biomarkers collected in the CSF used as part of the Alzheimer's disease diagnostic process include: amyloid-β, tau protein, and phosphorylated tau

MANAGEMENT AND TREATMENT OF ALZHEIMER'S DISEASE

TREATMENT OVERVIEW

- There is no **cure** for Alzheimer's disease.

Introduction

- Treatment of Alzheimer's disease can have **multiple** components, including:
    - Medications that may change disease **progression**
    - Medications that may improve Alzheimer's disease **symptoms**
    - **Nonpharmacologic** aspects of treatment, such as monitoring patients' cognition and supporting them and their families

PHARMACOLOGIC TREATMENT

Introduction

There are 2 categories of medications used for treating Alzheimer's disease:

1. Drugs that may change the **progression** of Alzheimer's disease
    - Aduhelm® (aducanumab-avwa) is the only **approved** medication that may change the disease progression of Alzheimer's disease.
        - Aduhelm® is indicated for patients who have **mild** cognitive impairment or are at the mild dementia stage of the disease.
2. Drugs that may mitigate some **symptoms** of Alzheimer's disease
    - Chlolinesterase inhibitors:
        - Aricept® (donepezil), which is approved to treat all stages of with dementia of the Alzheimer's type
        - Exelon® (rivastigmine), which is approved to treat mild to moderate with dementia of the Alzheimer's type
        - Razadyne® (galantamine), which is approved to treat mild to moderate with dementia of the Alzheimer's type

- Glutamate regulators
  - Namenda® (memantine) is the glutamate regulator approved to treat the symptoms in individuals with **moderate to severe** dementia of the Alzheimer's type.
- Cholinesterase inhibitor plus glutamate regulator
  - Namzaric® (donepezil and memantine) is a **combination** of a cholinesterase inhibitor and a glutamate regulator approved to treat the symptoms in individuals with moderate to severe dementia of the Alzheimer's type.

NONPHARMACOLOGIC TREATMENT

Introduction

- Healthcare providers treating Alzheimer's disease patients must also focus on aspects other than **medications** that relate to well-being.
  - Monitoring: After an individual is diagnosed with Alzheimer's disease and a treatment plan is established, the individual should be **evaluated** on a regular basis
    - Due to the nature of the disease, a family member, friend, or caregiver should also **attend** follow-up visits.
    - Examples of what should be monitored included but are not limited to changes in daily functioning, **cognitive** status, comorbidities, behavioral symptoms, medication requirements, and **care** needs.
  - **Safety**: It is important to keep an individual with Alzheimer's disease safe in order to prevent **injuries**, maximize function, minimize stress and agitation, and reduce caregiver burden.
  - Support: Individuals with Alzheimer's disease may find value in joining a **support group**.
  - Legal considerations: Individuals with Alzheimer's disease and their caregivers should plan for when the individuals will have **diminished capacity** by seeking legal assistance to put in place **advanced directives** such as the necessary power of attorney and end-of-life preferences, including a will and living will

THE ROLE OF THE CAREGIVER

Overview

- *Caregiving* is a term that means attending to another person's **health** and **well-being**.
- Some examples of assistance caregivers may provide to someone with Alzheimer's disease:
    - Helping with proper medication administration
    - Helping the person adhere to treatment recommendations for Alzheimer's disease and/or other medical conditions
    - Helping with **ADLs**
    - Assisting with instrumental ADLs (IADLs)
    - Managing the behavioral symptoms of the disease
    - Finding and using support services
    - Finding and arranging for care
    - Providing **emotional** support and a sense of security

Caring for the Caregiver

- The caregiver (also known as a *care partner*) may experience many emotions, including **denial**, fear, stress, anxiety, **anger**, frustration, grief, and depression, among others.
- It is very important for caregivers to also take care of **themselves**.
- Strategies include being physically active, building a support **network**, and asking others to help with the care in order to spend some time **away**.

Diagnosis and Assessment of Alzheimer's eLearning Module

Study Guide

INTRODUCTION TO THE DIAGNOSTIC PROCESS

OVERVIEW OF THE DIAGNOSTIC PROCESS

- There is no **single** diagnostic test that can determine if a person has Alzheimer's disease.

Historical Perspective of Diagnostic Criteria

- 1984: Release of criteria for Alzheimer's disease dementia
- 2011: Updated recommendations released on diagnostic guidelines for Alzheimer's disease

HISTORY, PHYSICAL EXAMINIATION, AND LABORATORY TESTING

OVERVIEW OF HISTORY, PHYSICAL EXAMINATION, AND LABORATORY TESTING

- To diagnose dementia, health care providers first assess whether an individual has an **underlying** treatable condition.

Medical and Family History

- Obtaining the patient's history may involve **interviewing** the patient as well as a family member or close friend.
- The healthcare provider should also ask about prescription and over-the-counter **medications** the individual is currently taking, as some medications can have potential cognitive **side effects**.

History of Present Illness

- The health care provider will ask questions about the **symptoms** that prompted the visit and the concern.

Physical Examination and Laboratory Testing

- As part of the evaluation, the health care provider may:
  - Assess blood pressure, temperature, and pulse
  - Listen to the heart and lungs
  - Inquire about nutrition and use of alcohol

Laboratory Testing

- There are some other disorders that can cause symptoms **similar** to Alzheimer's disease such as thyroid disorder or a vitamin B-12 deficiency.
- Testing a person's blood and serum, as well as checking various chemicals, hormones, and vitamin levels, can **identify** or **rule out** other conditions that may be causing memory loss.

NEUROLOGICAL EVALUATION

OVERVIEW OF NEUROLOGICAL AND PSYCHIATRIC EVALUATIONS

Introduction

- Neurological Evaluation:
  - A neurological examination can discover problems that may signal **brain disorders** other than Alzheimer's disease.
  - The neurological evaluation will test **reflexes**, coordination, muscle tone, muscle strength, eye movement, **speech**, and sensory response.
- Electroencephalogram
  - An electroencephalogram may be done to check for abnormal **electrical** brain activity.
  - An electroencephalogram is the **recording** of the analysis of the electrical activity of the brain.
- Psychiatric Evaluation
  - A psychiatric evaluation is important to determine if **depression** or another **mental** health condition is causing or contributing to the patient's dementia symptoms.
  - Depression or other mood disorders can cause memory problems, loss of interest in life, and other symptoms that can overlap with dementia.

COGNITIVE TESTING

Introduction

- Mental cognitive testing evaluates **memory**, thinking, and simple **problem-solving** abilities.

Patient Assessment Tools

- Mini-Mental State Exam (MMSE)
  - Best known and most widely used measure of **cognition** in clinical practice
  - The scale can easily be administered with **minimal** training and it only takes approximately **10** minutes to assess cognitive function with this tool.
- General practitioner assessment of cognition (GPCOG)
  - This is a screening tool for cognitive **impairment**.
  - Components and scoring of the text:
    - Name and address for subsequent recall test: this part of the assessment is not scored
    - Time **orientation**: They receive 1 point if the date is exactly correct
    - **Clock** drawing: This question portion of the assessment has a potential score of 0,1, or 2
    - Information: Only a **specific** answer is scored as correct and 1 point is given
    - Recall: Each component of the name and address are scored as correct or incorrect; there are a total of 5 possible points, 1 for each component of the address
    - Scoring
      - Each correct answer scores one point.
      - The total is calculated by adding the points for the correctly answered items.
      - The total score ranges between 0 and 9.
      - A score of 9 indicates no **significant** cognitive impairment and further testing is **not** required.
      - If the patient scores between 5 and 8, **more** information is needed, and the **informant** GPCOG interview should be conducted.
      - A score of 0 to 4 out of 9 indicates cognitive impairment—**additional** evaluation is the next step.

- Mini-Cog®
  - a **3**-minute screening tool for dementia
  - Steps of the assessment:
    - The first step is **3-word** registration
    - The next step is drawing a **clock**
    - The last step is 3-word **recall**.
- **Informant Assessment Tools**
- One aspect of dementia that is different than other neurological disorders is the **increased** reliance on others to assess the patient's condition.
- Dementia can impact judgment, speech, and memory, thereby making the patient's input less **reliable**.
- Therefore, information may be partially or completely derived from family or other **informants**.
- Informant assessment tools:
  - **AD8**: 8-question interview used to distinguish between normal signs of aging and mild dementia
  - GPCOG informant interview: The informant is asked 6 questions on how the patient **compares** to when they were well (approximately 5-10 years ago).
  - Short informant questionnaire on cognitive decline in the elderly (IQCODE): This tool asks the informant 16 questions comparing how the patient is now compared with **10** years ago.

NEUROPSYCHOLOGICAL EVALUATION

Introduction

- Based on the results of a cognitive screening, an individual may be referred to a **neuropsychologist** for neuropsychological testing.
- The aim of the consultation is to help characterize cognitive **deficits** and clarify the diagnosis.

Testing

- Neuropsychologists use **validated** puzzle-based materials, oral questions, and written tests to **objectively** assess multiple cognitive and emotional functions.
- The results of the tests are integrated with other sources of information to provide a **comprehensive** assessment of an individual's cognitive functioning.
- Neuropsychological testing can differentiate Alzheimer's dementia from nondementia with nearly **90**% accuracy.
- Neuropsychological assessments are helpful in tracking **changes** that may affect daily functioning as cognitive impairment and dementia **progress**.

IMAGING AND CEREBROSPINAL FLUID ANALYSIS

IMAGING FOR DIAGNOSING ALZHEIMER'S DISEASE

- Imaging of the brain can:
    1. Rule out other **causes**, such as a brain tumor or a stroke
    2. Distinguish between different **types** of degenerative brain diseases
    3. Establish a **baseline** about the degree of degeneration
- A **standard** medical workup for Alzheimer's disease often includes imaging.
- The two **primary** imaging tools used in Alzheimer's disease are magnetic resonance imaging (MRI) and positron emission tomography (PET).

Magnetic Resonance Imaging (MRI)

- MRI is an imaging technique that uses a **magnetic** field and computer-generated radio waves to create detailed images of organs (such as the brain) and tissues in the body.
- There are 2 types of MRI:
    - Structural MRI
        - The type **primarily** used in the Alzheimer's diagnostic process
        - MRI does not have the ability to measure amyloid **plaques** or neurofibrillary **tangles**.
    - **Functional** MRI
        - Functional MRI is being increasingly used to evaluate the functional integrity of brain networks supporting memory and other cognitive domains in early Alzheimer's disease

Position Emission Tomography (PET)

- Positron emission tomography (PET) is an imaging technique that uses **radioactive** substances injected into patients to provide images of the body using specialized scanners.
- These PET images provide information about the **function** and **metabolism** of the body's organs, in contrast to CT and MRI, which show the body's anatomy and structure.
- Different types used in the Alzheimer's disease diagnostic process:
  - **Amyloid** PET
    - After injection of a radiolabeled tracer agent, patients undergo a specialized PET scan that detects the deposition of amyloid-β (Aβ) peptides in plaques in the living brain
    - Amyloid **tracers** include:
      - Florbetaben
      - Flutemetamol
      - Florbetapir
    - Amyloid PET can **accurately** diagnose the disease (later autopsy proven) using this method with up to 96% sensitivity and 100% specificity.
    - The use of amyloid PET imaging in practice is still limited owing to its cost for most patients, as it is not covered by most insurance carriers.
    - Currently, the majority of patients who undergo amyloid PET imaging do so as part of participation in **clinical trials**.
  - Fluoro-deoxy-D-glucose (FDG) PET
    - The brain relies primarily on **glucose** as its source of energy.
    - The glucose analog fluoro-deoxy-D-glucose (FDG) is a suitable indicator of brain **metabolism**.
    - FDG PET is widely accepted to be a valid **biomarker** of overall brain metabolism and of synaptic activity.
    - FDG PET abnormalities are believed to be the net result of some combination of processes impacting the pathogenesis of Alzheimer's disease.

CEREBROSPINAL FLUID ANALYSIS (CSF)

Introduction

- CSF is a clear, colorless liquid that is in the **brain** and the spinal cord.
- CSF analysis is a group of tests that look at this fluid to help **diagnose** diseases.
- The CSF is collected through a **lumbar** puncture (spinal tap) in which, after the injection of anesthesia into the back, a thin, hollow needle is inserted between two vertebrae in the lower spine and a small amount of fluid is removed for **testing**.
- In the diagnostic process for Alzheimer's disease, the CSF is evaluated for **Aβ42**, hyperphosphorylated tau peptide, and **total** tau protein content.
- CSF analysis is **more** invasive than an amyloid PET scan and also has slightly **less** diagnostic accuracy (85%-90%) than an amyloid PET scan.

GENETIC TESTING

OVERVIEW

Overview of Genetic Testing

- Researchers have identified certain genes that **increase** the risk of developing Alzheimer's disease, and some rare genes that **directly** cause Alzheimer's disease.
- Although genetic tests are available for some of these genes, health care providers do **not** currently recommend routine genetic testing for Alzheimer's disease.

DIAGNOSTIC CRITERIA

Terminology

- The Alzheimer's disease pathophysiological process is used to encompass the antemortem biological changes that precede the **postmortem** neuropathological diagnosis of Alzheimer’s disease as well as the neuropathological substrate

CORE CLINICAL CRITERIA FOR ALL-CAUSE DEMENTIA

- Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:
  - Interfere with the ability to **function** at work or at usual activities; and
  - Represent a **decline** from previous levels of functioning and performing; and
  - Are not **explained** by delirium or major psychiatric disorder;

- Cognitive impairment is **diagnosed** through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment
    - The cognitive assessment can be a "bedside" mental status examination or neuropsychological testing
    - The neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis
- The cognitive or behavioral impairment involves a minimum of **2** of the following domains:
    - Impaired ability to acquire and remember **new** information
    - **Impaired** reasoning and handling of complex tasks, poor judgment
    - Impaired **visuospatial** abilities
    - Impaired **language** functions (speaking, reading, writing)
    - Changes in **personality**, behavior, or comportment

CRITERIA FOR ALZHEIMER'S DISEASE DEMENTIA

- There are 3 terms used to classify individuals with dementia caused by Alzheimer's disease:

1. Probable Alzheimer's disease dementia
    - Diagnosed when the patient meets the core clinical criteria for "all-cause dementia" and has the **additional** following characteristics:
        - Insidious onset. The symptoms have a **gradual** onset over months to years, not sudden over hours or days;
        - Clear-cut history of **worsening** of cognition by report or observation; and
        - The initial and most prominent cognitive deficits are evident on history and examination in **one** of the following categories:
            - Amnestic presentation: the most common syndromic presentation of Alzheimer's disease dementia; deficits should include impairment in learning and recall of recently learned information
            - Nonamnestic presentation: language presentation, visuospatial presentation, executive dysfunction

2. Possible Alzheimer's disease dementia

    - There are 2 circumstances in which a diagnosis of possible Alzheimer's disease dementia is made:

        - Atypical course: meets the core clinical criteria in terms of the nature of the cognitive deficits for Alzheimer's disease dementia, but either has a **sudden** onset of cognitive impairment or demonstrates **insufficient** historical detail or objective cognitive documentation of progressive decline

        - Etiologically **mixed** presentation: meets all core clinical criteria for AD dementia but has evidence of:

            - Concomitant cerebrovascular disease, defined by a history of **stroke** temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or

            - Features of dementia with **Lewy** bodies other than dementia itself; or

            - Evidence for another **neurological** disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition

3. Probable or possible Alzheimer's disease dementia with evidence of Alzheimer's disease pathophysiological process

    - In people who meet the core clinical **criteria** for probable Alzheimer's disease dementia, biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the Alzheimer's disease pathophysiological process.

        - However, the use of Alzheimer's disease biomarker tests for routine diagnostic purposes is not recommended at the present time.

        - The use of biomarkers to enhance certainty of Alzheimer's disease pathophysiological process may be useful in three circumstances: **investigational** studies, clinical **trials**, and as optional clinical tools for use where available and when deemed appropriate by the clinician.

    - Possible Alzheimer's disease dementia with evidence of the Alzheimer's disease pathophysiological process is for persons who meet clinical criteria for a non-Alzheimer's disease dementia but who have either biomarker evidence of Alzheimer's disease pathophysiological process, or meet the **neuropathological** criteria for AD.

Management and Treatment of Alzheimer's Disease eLearning Module

Study Guide

INTRODUCTION TO MANAGEMENT AND TREATMENT

INTRODUCTION

Treatment Goals

- There are 4 main goals of Alzheimer's disease treatment:
    1. Regular **monitoring** of the patient's health and cognition
    2. **Education** and support to patients and their families
    3. Initiation of pharmacologic and non-pharmacologic **treatments** as appropriate
    4. Evaluation of patient/family motivation to volunteer for a **clinical trial**

Introduction to Pharmacologic Treatment

- Medications cannot **cure** Alzheimer's disease.
- There are 2 main categories of Alzheimer's disease treatment medications:
    - FDA-approved drug that may change disease **progression**
    - FDA approved drugs that may **temporarily** mitigate the symptoms
- The FDA also has approved drugs to address **insomnia** in people living with dementia.

PHARMACOLOGIC TREATMENT OF ALHEIMER'S DISEASE

FDA-APPROVED DRUG THAT MAY CHANGE ALZHEIMER'S DISEASE PROGRESSION

Introduction to Aducanumab (Aduhelm®)

- Indication: Aducanumab is indicated for the treatment of Alzheimer's disease.
    - Treatment with aducanumab should be initiated in patients with **mild** cognitive impairment or mild **dementia** stage of disease, the population in which treatment was initiated in clinical trials.

- Mechanism of Action: Aducanumab targets aggregated soluble and insoluble forms of **amyloid-beta (amyloid-β)**.
    - Based on clinical studies, aducanumab **reduces** amyloid-β plaques.
- Administration: Aducanumab is administered as an **intravenous (IV) infusion**.
- Common Adverse Reactions: The most common adverse reactions (at least 10% and higher incidence compared to placebo) include:
    - ARIA-E
    - Headache
    - **Microhemorrhage**
    - ARIA-H superficial siderosis
    - **Fall**
- MRI: The patient must obtain a recent (within one year) **brain** MRI prior to initiating treatment.
- Efficacy: The efficacy of aducanumab was evaluated in **three** separate studies representing a total of 3,482 patients.

FDA-APPROVED DRUG THAT TREAT ALZHEIMER'S DISEASE DEMENTIA SYMPTOMS

Cholinesterase Inhibitors

- There are 3 **cholinesterase inhibitors** prescribed in patients with dementia of the Alzheimer's type.:
    1. Donepezil (Aricept®)
    2. Rivastigmine (Exelon®)
    3. Galantamine (Razadyne®)
- Cholinesterase inhibitors **enhance** cholinergic function.
- Based on randomized controlled trials, all three cholinesterase inhibitors have demonstrated treatment **benefits** of improving, stabilizing, or delaying decline in cognition, activities of daily living, global status, behavioral and psychological symptoms of dementia

Donepezil (Aricept®)

- Indication: Donepezil is indicated for the treatment of dementia of the Alzheimer's type.
    - Efficacy has been demonstrated in patients with **mild**, **moderate**, and **severe** dementia of the Alzheimer's type.
- Dosing in Mild to Moderate with dementia of the Alzheimer's type. The recommended starting dosage of donepezil is 5 mg **oral tablet** administered once per day in the evening, just prior to retiring.
    - The maximum recommended dosage of donepezil in patients with mild to moderate with dementia of the Alzheimer's type **10 mg** per day.
- Dosing in Moderate to Severe with dementia of the Alzheimer's type: The recommended starting dosage of donepezil is **5 mg** oral tablet administered once per day in the evening, just prior to retiring.
    - The maximum recommended dosage of donepezil in patients with moderate to severe Alzheimer's disease is **23 mg** per day.
- Adverse Reactions: The most common adverse reactions, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day donepezil and twice the placebo rate, include **nausea**, diarrhea, insomnia, **vomiting**, muscle cramps, fatigue, and anorexia.

Rivastigmine (Exelon®)

Rivastigmine Capsules/Oral Solution:

- The indication for this formulation is for the treatment of **mild-to-moderate** dementia of the Alzheimer's type.
- Rivastigmine should be taken with meals in **divided** doses in the morning and evening.
- Rivastigmine is also available as an **oral solution** containing rivastigmine tartrate equivalent to 2 mg/mL of rivastigmine base.
- The most common adverse reactions associated with rivastigmine use include nausea, vomiting, **anorexia**, dyspepsia, and **asthenia**.

Rivastigmine Patch:

- The rivastigmine patch is indicated for the treatment of **dementia** of the Alzheimer's type.
- Efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer's disease.
- Treatment should be initiated with one 4.6 mg/24 rivastigmine patch applied to the skin **once** daily.

- Doses higher than **13.3 mg/24 hours** confer to appreciable additional benefit and are associated with an increase in the incidence of adverse reactions.
- The most common adverse reactions with the use of the rivastigmine patch (defined as those occurring at a frequency of at least 5% and at a frequency at higher than in the placebo group) include nausea, vomiting, and diarrhea.

Switching to the Rivastigmine Patch from Capsules or Oral Solution:

- Write in the missing information:

Galantamine (Razadyne®)

- Indications: Galantamine and galantamine ER are indicated for the treatment of **mild** to **moderate** dementia of the Alzheimer's type.
- Dosage forms and strengths:
  - Galantamine ER extended-release **capsules** are available in 8 mg, 16 mg, and 24 mg strengths
  - Galantamine **tablets** are available in 4 mg, 8 mg, and 12 mg strengths
- Dosing:
  - Galantamine ER should be administered once daily in the **morning**, preferably with food.
    - The recommended starting dosage is **8 mg/day**.
    - Dosage **increases** should be based upon assessment of clinical benefit and tolerability of the previous dose.
  - The recommended starting dosage of galantamine **tablets** is 4 mg twice a day (8 mg/day).
    - Dosage increases should be based upon assessment of **clinical** benefit and **tolerability** of the previous dose.
  - Patients currently being treated with galantamine tablets can **convert** to galantamine ER by taking their last dose of galantamine tablets in the evening and starting galantamine ER once-daily treatment the next morning.
  - Converting from galantamine to galantamine ER should occur at the **same** total daily dosage.

- Adverse reactions: The most common adverse reactions in galantamine-treated patients (≥5%) were nausea, vomiting, **diarrhea**, dizziness, headache, **decreased appetite**, and a decrease in weight.

Glutamate Regulator

- Memantine (**Namenda**®) is a glutamate regulator indicated for the treatment of moderate to severe dementia of the Alzheimer's type and is distributed by Allergan.
- The mechanism of action of memantine is as a low to moderate affinity uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, which binds preferentially to the NMDA receptor-operation cation channels.

Combination of Cholinesterase Inhibitor Plus Glutamate Regulator

- There is one medication that is a combination of memantine hydrochloride and donepezil hydrochloride (**Namzaric**®) manufactured by Allergan.
- It is indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg of **donepezil hydrochloride** once daily.
- The most common adverse reactions (define as those occurring at a frequency of ≥ 5% and at a higher frequency than placebo) associated with use include headache, **diarrhea**, and dizziness.

FDA-APPROVED DRUG TO ADDRESS INSOMNIA IN PEOPLE LIVING WITH DEMENTIA

Introduction

- Suvorexant (**Belsomra**®) is an orexin receptor antagonist indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance manufactured by Merck & co., Inc.
- While the **indication** for suvorexant does not specify Alzheimer's disease, one of the studies in the suvorexant prescribing information was in patients with mild-to-moderate Alzheimer's disease.
- Individuals should use the **lowest** effective dose and take no more than once per night, within **30** minutes of going to bed (with at least 7 hours remaining prior to planned awakening).
- The recommended dose is **10** mg, but if the 10 mg dose is well tolerated but not effective, the dose can be increased.
- The **maximum** recommended dose of suvorexant is 20 mg taken no more than once per night.

DRUG DELIVERY SYSTEMS

Overview

- Most medications indicated for treating Alzheimer's disease are administered **orally**.
- Aducanumab is administered as an **intravenous infusion** and rivastigmine has a transdermal **patch** formulation (in addition to an oral form).
- There are some **disadvantages** of oral administration with the approved medications in general and specifically in people with Alzheimer's disease.
    - The current dosage forms of approved medications at higher doses cause adverse reactions such as **abdominal** pain, nausea, **vomiting**, and anorexia.
    - Another disadvantage of these medications is the variation in **blood** levels.
    - Individuals with Alzheimer's disease may have low **compliance** due to memory loss.

Transdermal administration:

- There are some **advantages** to transdermal administration, particularly in Alzheimer's disease patients:
    - When a medication is administered transdermally, it **bypasses** first-pass metabolism.
    - Therefore, because drugs are absorbed directly into the blood through the skin, **low** doses can be used.
    - Additionally, transdermal drug delivery can offer therapeutic levels of the drug in systemic circulation through a **controlled** drug delivery, while decreasing side effects by avoiding large fluctuations of plasma concentration of the drug.
    - In patients with Alzheimer's disease, transdermal patches may improve patient **compliance** as well as the benefit provided by the prolonged use of drugs.
    - Transdermal patches may also be preferred by **caregivers** during long-term treatment of disease.
    - Transdermal patches are also useful in patients with difficulty in **swallowing**.

NON-PHARMAOLOGIC TREATMENT

OVERVIEW

Creating A Safe and Supportive Environment

- One important component of treating an individual with Alzheimer's disease is to **minimize** tasks that demand memory.
- It is important to establish and strengthen **routine habits**.

Healthy Lifestyle Choices

- Physical Activity: There may be benefits of physical exercise on the **progression** of Alzheimer's disease.
- Nutrition: There are studies that suggest what we eat affects the **aging** brain's ability to think and to remember.

Social Engagement and Activities

- Remaining socially **active** and involved in activities can help support the skills and abilities that are preserved in an individual with Alzheimer's disease.
- Additionally, doing things that are meaningful and enjoyable is important for the overall **well-being** of a person with Alzheimer's disease.

Coping and Support

- There are some things **caregivers** can do to provide support such as:
  - **Listening** to the person express their emotions
  - Reassuring the person that life can still be enjoyed
  - Providing support
  - Helping the person retain **dignity** and self-respect

Patient Monitoring

- Clinicians need to regularly assess patients for **changes** in daily functioning, cognitive status, comorbidities, behavioral symptoms, medication requirements, and care needs.

HOSPICE

- Hospice care focuses on comfort and dignity at the **end** of life.
- It provides **care** to a terminally ill patient and **support** to the patient's family in the final stages of Alzheimer's disease.
- The primary focus of hospice care is to manage **pain** and other symptoms during the last 6 months of life.
- The focus of care shifts from **curing** the underlying disease to providing **comfort** measures.
- Hospice care can be provided in a **facility** (such as a nursing home), in a hospice facility, in a hospice unit at a hospital, or in a patient's **home**.

LEGAL ASPECTS RELATING TO ALZHEIMER'S DISEASE

LEGAL ISSUES

Advance Directives

- Ideally, a person with Alzheimer's disease has put in place advance directives that **specify** his or her **wishes**.
- Without such documents in place, families must make choices based on what **they** think the individual with Alzheimer's disease would want.
- Advance directives are **legal** papers specifying the type of **medical** care a person wants to receive once they no longer have the capacity to make such decisions, and who should be in charge of making them.
- Advance directives should be made when the person with dementia has the level of judgment and decision-making ability needed to **sign** official documents or to make medical and financial **decisions**.
- It is best to put advance directives in place soon after **diagnosis**.

Living Will

- A living will is a set of **written** instructions that provides specific preferences about the kind of medical treatment a patient would or would not want to have.

Durable Power of Attorney for Health Care

- A durable power of attorney for health care allows an individual to **choose** someone (spouse, family member, or trusted friend) to make **decisions** about health care and treatment when they are no longer able to do so.

THE ROLE OF THE CAREGIVER

OVERVIEW OF THE ROLE OF THE CAREGIVER

Overview

- Caregiving is a term that means **attending** to another person's health and well-being.

- Write in the missing information:

Reasons Caregivers Provide Assistance to an Individual With Alzheimer's Disease

- There are many reasons why an individual chooses to provide care, including but not limited to:
  - The desire to keep the individual with Alzheimer's disease at **home**
  - The **proximity** to the person with Alzheimer's disease
  - The caregiver's perceived **obligation** to the person with Alzheimer's disease

Early Stage of Caregiving

- In the early stage of caregiving, the individual with Alzheimer's disease probably functions **independently**.
- Some of the primary caregiver tasks are providing **support** and companionship.
- It is also important to help the individual plan for the future in terms of **legal** documents, **finances**, and long-term **care** planning.

Caring for the Caregiver

- It is also very important for the caregiver of someone with Alzheimer's disease to take care of their **physical** and **mental** health as well.

Overview of ADLARITY eLearning Module

Study Guide

INTRODUCTION TO ADLARITY

ADLARITY FORMULATION

Introduction to ADLARITY

- ADLARITY (donepezil transdermal system) is a **once-weekly** transdermal formulation of **donepezil** that continuously delivers consistent medication doses through the skin over a 7-day period.
- The most **commonly** prescribed medications for Alzheimer's disease (AD) dementia are acetylcholinesterase inhibitors (AChEI).
- Of the available AChEIs, oral **donepezil** is the most widely prescribed.

ADLARITY Indication and Dosage Strengths

- ADLARITY is indicated for the treatment of **mild**, **moderate**, or **severe** dementia of the Alzheimer's type and is available in 2 dosage strengths: **5** mg/day and **10** mg/day.

Composition of ADLARITY Transdermal System

- ADLARITY is a rectangular patch with a **6-layer** laminate composition.

- The first layer of the Adlarity patch contains 2 parts: an overlay backing on **top** and an **adhesive** layer just below the overlay backing.
- Layer 2 is a **separating** layer between the overlay backing/adhesive layer above it and the drug matrix layer below it.
- Layer 3 is the drug matrix layer that contains **donepezil**.
- Layer 4 is a **microporous** membrane that separates the drug matrix layer above it from the contact adhesive layer below it. This microporous membrane controls the **rate** of donepezil delivery to the skin.
- Layer 5 is the contact **adhesive** layer that adheres the patch to the patient's skin.
- Layer 6: The release liner is **removed** before the patch is applied to the skin.

Rationale for Transdermal Delivery of Donepezil

- AChEIs, including donepezil, rivastigmine, and galantamine, **bind** to acetylcholinesterase (AChE) in neuronal synapses to exert a pharmacologic effect in patients with AD dementia.
- AChEIs prevent the breakdown of **acetylcholine**, a chemical messenger important for memory and learning.
- Preventing the breakdown of acetylcholine increases the concentration of acetylcholine in neuronal synapses, thereby **enhancing** cholinergic function.

Oral Administration of AChEIs

- Most AD medications are administered **orally**.
- GI Adverse Reactions: High doses of AChEI formulations may cause **gastrointestinal (GI)** adverse reactions, such as abdominal pain, nausea, vomiting, diarrhea, and anorexia.
- Medication Adherence: Orally administered AD dementia medications also may be associated with low rates of medication **adherence** because of memory loss.
    - A high incidence of **dysphagia** (difficulty swallowing) in patients with AD dementia can also reduce medication adherence.

Transdermal Administration of AChEIs

- For patients with AD dementia, there are several potential **advantages** with transdermal administration of AChEIs.

Greater Patient Compliance:

- Patients with dysphagia can **avoid** the need to swallow or chew a pill by receiving medication through a patch.
- In addition, caregivers who need to keep **track** of medication administration may find it easier to apply a patch to a patient once weekly than to administer oral medications daily.

Avoidance of First-Pass Metabolism:

- In transdermal AChEI administration the medication is absorbed directly into the **blood** through the skin and therefore bypasses first-pass metabolism in the GI tract and liver.
- By avoiding first-pass metabolism, there is a potential for **lower** medication doses to be administered to achieve a therapeutic effect, and lower doses may be associated with fewer **side effects**.

- The ADLARITY transdermal system provides a slow, steady, continuous release of **donepezil** through the skin.
- The transdermal formulation is designed to **avoid** medication absorption in the GI tract and associated GI AEs.
- Oral donepezil administration is associated with fluctuating plasma levels, whereas the slow, steady release of donepezil from the ADLARITY patch is associated with **consistent** plasma medication levels that maintain the level of medicine needed for effective treatment.

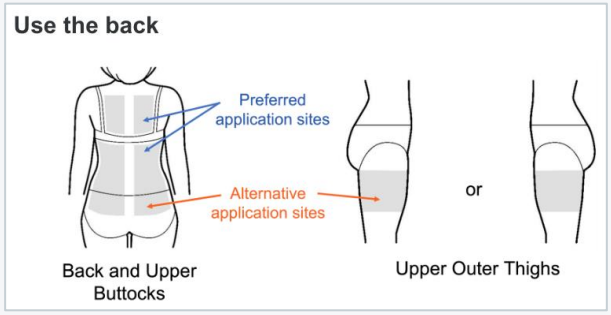
USE OF ADLARITY

Adlarity Dosage

- Recommended Dosage:
  - The recommended starting dosage of ADLARITY is **one** 5 mg/day transdermal system applied to the skin once **weekly**.
  - After 4 to 6 weeks, the dosage may be increased to the maximum recommended dosage of ADLARITY **10** mg/day once **weekly**.
  - Doses of ADLARITY **higher** than 10 mg/day have not been evaluated.
- Switching to ADLARITY From Donepezil Tablets or Donepezil ODT
  - Patients treated with donepezil 5 mg or 10 mg **tablets** may be switched to ADLARITY.
  - A patient who is being treated with a total daily dose of **5** mg of oral donepezil can be switched to the once-weekly 5 mg/day ADLARITY **patch**.
    - Patients may be switched **immediately** to the once-weekly 10 mg/day patch if the patient has been on 5 mg oral donepezil for at least 4 to 6 weeks.
  - A patient who is being treated with a total daily dose of 10 mg of **oral** donepezil can be switched to the once-weekly **10** mg/day ADLARITY patch.

ADLARITY Administration

- Timing: each ADLARITY transdermal system (ie, patch) is designed to continuously deliver donepezil for **7** days (1 week).
    - At the end of 7 days, the used transdermal system is **removed**, and a new transdermal system is applied.
    - Only **1** transdermal system should be applied at a time.
- Missed Dose: If an ADLARITY patch falls off or a dose is missed, a new patch should be applied **immediately**, and then this patch should be replaced 7 days later to start a new 1-week cycle.
- Application: ADLARITY is intended for **transdermal** use on **intact** skin.
    - The **recommended** application site is the back (avoiding the spine).
    - If needed, the upper buttocks or upper outer thigh may be used.



- Change **site** of patch application weekly
    - Do not use the same application site for at least **2 weeks (14 days)** after removal of a patch from that location.
- ADLARITY adhesion is maintained in **wet** conditions; therefore, ADLARITY use does not need to be interrupted due to bathing or hot weather.
- ADLARITY Storage:
    - **Refrigeration** of patches is required (36°F to 46°F)
    - Patches should not be **frozen**
    - The pouch containing the ADLARITY patch should be removed from the refrigerator and allowed to reach **room** temperature before removing the new transdermal system for application

UNMET NEEDS IN THE TREATMENT OF AD dementia

Treatment Challenges in Patients with AD dementia

Introduction:

- There are several treatment **challenges** for patients with AD dementia and their caregivers.
- Oral AChEIs are associated with **adverse reactions** that may limit the dose of medication that a patient can tolerate or result in discontinuation of a medication.
- In addition, taking an orally administered medication may be **difficult** for some patients with AD dementia.
- Oral administration of AChEIs results in fluctuating plasma medication levels that may be associated with an **increased** likelihood of adverse reactions when plasma levels are high or reduced **efficacy** when plasma levels are low.

Adverse Reactions Associated With Oral Donepezil:

- Although oral donepezil treatment improves **symptoms** in patients with AD dementia, it is associated with GI, CNS, and other adverse reactions.
    - The most common adverse reactions (defined as those occurring at a frequency of ≥ 5% and twice the placebo rate) are **predicted** by the cholinergic effects of donepezil.
    - These include **nausea**, diarrhea, insomnia, **vomiting**, muscle cramps, fatigue, and anorexia.
- In general, adverse reactions with oral donepezil occurred **more** frequently in female and older patients.
- Adverse reactions associated with donepezil are often **transient** and resolve during continued treatment without the need for dose **modification**.
- However, the **GI** adverse reactions of donepezil can be particularly bothersome for some patients, which may potentially prevent the AChEI dose from being increased to achieve optimal medication effectiveness and/or result in medication discontinuation.

Challenges With Oral Administration of AD Dementia Medications:

- Administration of oral medications to patients with AD dementia are associated with 2 key challenges: **dysphagia** (difficulty swallowing) and treatment **adherence**.
- **Tolerability** challenges associated with AChEIs along with dysphagia and impaired memory can all impact the ability of patients with AD dementia to experience optimal effectiveness of orally administered AChEIs.

ADLARITY Path to Approval

CLINICAL DEVELOPMENT OF ADLARITY

The Challenges in Developing a Transdermal Delivery System

- Medication formulated in a transdermal delivery system has to **permeate** the various layers of skin to reach the systemic circulation.
- Permeation involves **penetration** of drug molecules from one layer of skin (ie, epidermis) into subsequent layers (ie, dermis).
- After medication molecules reach the blood vessels in the dermis, they are **absorbed** into the systemic circulation.
- Low Rate of Permeability: One challenge of donepezil transdermal delivery is that the medication molecule has a **low** rate of permeability through the skin.
    - The addition of permeation enhancers to transdermal donepezil delivery systems was associated with skin **irritation** problems.
- Solid Medication Crystals: Another issue with transdermal donepezil delivery is that solid medication crystals can form over time in **stored** patches.
    - These solid crystals led to **reduced** patch adhesion to skin and an uneven skin permeation rate for donepezil in previous transdermal delivery systems.
- The need for transdermal medication delivery of donepezil led to the development of ADLARITY using **Corplex™** technology.

Corplex Technology

- ADLARITY utilizes Corium's **proprietary** Corplex technology.
- Corium's Corplex system is a novel commercial-stage platform technology designed to broadly enable the **transdermal** delivery of small molecules, such as donepezil, that have not previously been amenable to transdermal delivery.
- This technology is a **matrix-type** patch designed to consistently deliver donepezil over a 7-day period.
- In a matrix-type transdermal delivery system, the medication is **dissolved** in a liquid or gel-based reservoir.
- Corplex technology allows the donepezil medication molecule to be delivered through the skin with a **low** rate of skin irritation.
- The ADLARITY patch is designed to **continuously** deliver donepezil, leading to plasma levels that remain within the therapeutic window for the medication.

Path to FDA Approval

- FDA approval of ADLARITY was based on a New Drug Application (NDA) that followed the **505(b)(2)** regulatory pathway.
- Because donepezil was previously approved as Aricept, the FDA agreed that a 505(b)(2) NDA was **acceptable**.
- Demonstration of **bioequivalence** between the ADLARITY 10 mg/day patch and oral donepezil 10 mg once daily was the basis of the FDA's approval.
- Using the 505(b)(2) pathway, Corium was able to rely on previously completed Aricept clinical studies that demonstrated donepezil **effectiveness**.
- These clinical studies in patients with mild to moderate dementia of the Alzheimer's type and moderate to severe dementia of the Alzheimer's type are reviewed in the **ADLARITY PI**.
- The ADLARITY PI includes adverse reaction data from an ADLARITY **pharmacokinetic (PK)** study and also adverse reaction data from clinical studies of **oral** donepezil.
- The ADLARITY clinical development program was performed in **healthy** volunteers and not in patients with AD.

ADLARITY PHARMACOKINETIC STUDIES

Overview

- An ADLARITY 10 mg/day patch is considered **bioequivalent** to oral donepezil 10 mg taken once daily.
    - *Bioequivalence* means that 2 medications have the **same** biologic effects.
- PK studies are used to evaluate the **plasma** concentrations of a medication (such as donepezil) over time following medication administration.
- PK studies determine what the **body** does to the drug, including:
    - **Absorption** of the drug into the body
    - Distribution of the drug **throughout** the body
    - **Metabolism** of the drug by the body
    - Excretion of the drug **from** the body

Pivotal Bioequivalence Study

- Objective: The objective of the pivotal bioequivalence study was to **compare** the bioequivalence of ADLARITY 10 mg/day and oral Aricept 10 mg once daily in healthy adults.
- Study Design: The pivotal bioequivalence study was a phase 1, **open-label**, randomized, 3-period, 3-treatment, crossover PK study in **healthy** volunteers
  - During the first treatment period, each volunteer received **ADLARITY** 5 mg/day for 5 weeks (meaning that 1 patch was applied each week for 5 weeks).
  - Volunteers were then **randomized** to receive each of the other 2 treatments in random order, either ADLARITY 10 mg/day for 5 weeks followed by Aricept 10 mg tablet orally once daily for 5 weeks or Aricept 10 mg tablet orally once daily followed by ADLARITY 10 mg/day for 5 weeks.
- Assessment of Bioequivalence: Bioequivalence was evaluated by comparing plasma concentration–time **profiles** of donepezil after administration of the commercial formulation of ADLARITY 5 mg/day and 10 mg/day with oral administration of Aricept tablets 10 mg once daily.
  - These PK data were used to demonstrate the **bioequivalence** of ADLARITY 10 mg/day to Aricept 10 mg once daily based on FDA criteria for bioequivalence of 2 medications.
- Results: Results of the pivotal bioequivalence study **demonstrated** bioequivalence of ADLARITY 10 mg/day to Aricept 10 mg once daily.
  - Bioequivalence of the ADLARITY **5 mg/day** dosage strength was also demonstrated.

Bioequivalence of ADLARITY Application at Alternative Body Sites

- Objective: The objective of this PK study was to compare the bioequivalence of ADLARITY 10 mg/day applied to the **thigh** versus the back and the buttock versus the **back**.
- Study Design: This was a randomized, **open-label**, 3-way crossover PK study of 66 healthy adult volunteers.
  - Each volunteer received ADLARITY 10 mg/day applied to the back, upper buttocks, or upper outer thigh in **random** order.
  - Each 7-day treatment period was separated by a 35-day **washout** period (ie, no ADLARITY patch was applied during the washout period).
  - In this study, thigh and buttock application are considered the **test** condition and back application is considered the **reference** condition.

- Results:
  - ADLARITY application to the upper buttock and the back were **not** bioequivalent.
  - ADLARITY application to the upper outer thigh and the back were **not** bioequivalent.

Bioequivalence of ADLARITY Application in the Prescence or Absence of Heat

- Objective: The objective of this PK study was to compare the bioequivalence of ADLARITY 5 mg/day applied to the back in the presence and absence of a **heating pad**.
- Study Design: This study was a **randomized**, open-label, 2-way **crossover** study of 24 healthy adults.
  - Each volunteer was randomized to wear an ADLARITY 5 mg/day patch for 1 week in the **presence** or **absence** of a heating pad and then **crossed over** to the other treatment condition for 1 week.
  - There was a 35-day washout period between the 2 treatment conditions.
- Results: The mean plasma donepezil concentration-versus-time profiles were **similar** with or without applied heat.
  - Small, transient increases in plasma donepezil concentrations were observed during the heat sessions, but the overall results indicated plasma exposure to donepezil was not **statistically** significantly different in the presence and absence of heat.
  - ADLARITY 5 mg/day applied in the presence of heat was **bioequivalent** to ADLARITY 5 mg/day applied in the absence of heat.

ADLARITY Adhesion

- The ADLARITY clinical development program also included evaluations of **patch** adhesion during the studies.

DONEPEZIL CLINICAL STUDIES IN MILD, MODERATE, AND SEVERE DEMENTIA OF THE ALZHEIMER'S TYPE

- The **effectiveness** of donepezil as a treatment for mild, moderate, and severe dementia of the Alzheimer's type was demonstrated in 2 randomized, double-blind, placebo-controlled clinical investigations of donepezil tablets in patients with AD, including a 30-week study and a 15-week study.
- Outcome Measures: In each study, the effectiveness of donepezil treatment was evaluated using a **dual-outcome** assessment that included assessment of both the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview-Based Impression of Change with the use of caregiver information (CIBIC-plus).

- ADAS-COG: The cognitive subscale of the ADAS-cog was used to assess the ability of donepezil to **improve** cognitive performance in patients with dementia of the Alzheimer's type.
- CIBIC-PLUS: The CIBIC-plus was used to assess the overall **clinical** effect of donepezil.

30-week Study

- Objective: The objective of the 30-week study was to compare the **effectiveness** of donepezil tablets 5 mg once daily or 10 mg once daily with placebo in patients with mild, moderate, or severe dementia of the Alzheimer's type.
- Study Design: A total of 473 patients were **randomized** to receive once-daily doses of donepezil 5 mg, donepezil 10 mg, or placebo tablets.
  - Patients randomized to receive donepezil 10 mg once daily received 5 mg once daily for the first week before increasing to 10 mg once daily to **avoid** acute cholinergic effects
  - The 30-week study was divided into a **24**-week double-blind active treatment phase (ie, patients received donepezil 5 mg once daily, donepezil 10 mg once daily, or placebo) followed by a **6**-week single-blind placebo washout period (ie, all patients received placebo)
- Results:
  - ADAS-cog scores: After **24** weeks of treatment, the mean differences in the ADAS-cog change scores for donepezil compared with placebo patients were 2.8 points for donepezil 5 mg once daily and 3.1 points for donepezil 10 mg once daily.
    - Both differences between donepezil and placebo were statistically **significant**.
    - Although the treatment effect size may appear to be slightly greater for donepezil 10 mg once daily than for donepezil 5 mg once daily, there was **no** statistically significant difference between the 2 donepezil dosage regimens.
    - Following 6 weeks of placebo washout, the ADAS-cog scores for patients who had received either donepezil 5 mg once daily or 10 mg once daily were **indistinguishable** from the ADAS-cog scores for patients who had received only placebo for 30 weeks.
      - This suggests that the beneficial effects of donepezil **wane** during the 6 weeks following treatment discontinuation, indicating that improvements in the ADAS-cog that were measured during the first 24 weeks of the study represent **symptom** improvement rather than a change in the underlying disease.

- CIBIC-plus: The differences between donepezil and placebo were both statistically **significant**.
    - However, there was no statistically significant difference between the 2 donepezil dosage **strengths**.

15-week Study

- Objective: The objective of the 15-week study was to compare the **effectiveness** of donepezil tablets 5 mg once daily or 10 mg once daily with placebo in patients with mild, moderate, and severe dementia of the Alzheimer's type.
- Study Design:
    - Patients were **randomized** to receive once-daily doses of donepezil 5 mg, donepezil 10 mg, or placebo tablets
    - Patients randomized to receive donepezil 10 mg once daily received 5 mg once daily for the first week before increasing to 10 mg once daily to **avoid** acute cholinergic effects
    - The 15-week study was divided into a **12**-week double-blind active treatment phase (ie, patients received donepezil 5 mg once daily, donepezil 10 mg once daily, or placebo) followed by a 3-week single-blind placebo **washout** period (ie, all patients received placebo)
- Results:
    - ADAS-cog scores: After **12** weeks of treatment, the mean differences in ADAS-cog change scores for donepezil compared with placebo patients were 2.7 points for donepezil 5 mg once daily and 3.0 points for donepezil 10 mg once daily.
        - Both differences between donepezil and placebo were statistically **significant**.
        - Although the treatment effect size may appear to be slightly greater for donepezil 10 mg once daily than for 5 mg once daily, there was no statistically significant **difference** between the 2 donepezil dosage regimens.
        - Following 3 weeks of placebo washout, ADAS-cog scores for patients who had received donepezil 5 mg once daily or 10 mg once daily **increased**, indicating that donepezil discontinuation resulted in a **loss** of its treatment effect.
    - CIBIC-plus: The differences between donepezil and placebo were both statistically **significant**.

Conclusions

- The 2 randomized controlled studies in patients with mild, moderate, and severe dementia of the Alzheimer's type demonstrated that the higher dose of donepezil 10 mg once daily did **not** provide a statistically significantly greater clinical benefit than donepezil 5 mg once daily.
- However, additional data analyses suggested that donepezil 10 mg once daily might provide additional **benefit** for some patients.

DONEPEZIL CLINICAL STUDIES IN MODERATE TO SEVERE DEMENTIA OF THE ALZHEIMER'S TYPE

- The **effectiveness** of donepezil as a treatment for patients with moderate to severe AD was demonstrated in 2 randomized, double-blind, placebo-controlled clinical investigations of Aricept (donepezil tablets) in patients with AD.

Swedish 6-month Study

- Objective: The objective of the 6-month study was to compare the effectiveness of donepezil 10 mg once daily with **placebo** in patients with moderate to severe AD.
- Study Design:
  - A total of 248 patients were randomized to receive once-daily doses of donepezil 10 mg or placebo tablets for **6** months
  - Patients randomized to receive donepezil 10 mg once daily received 5 mg once daily for the first **28** days before increasing to 10 mg once daily to **avoid** acute cholinergic effects
  - By the end of the 6-month study, **90.5%** of donepezil patients were receiving the 10 mg once-daily dose
- Results:
  - SIB: At 6 months of treatment, the mean difference in SIB change scores for donepezil compared with placebo patients was **5.9** points.
    - Donepezil treatment resulted in statistically significantly greater clinical **improvement** than placebo.
  - ADCS-ADL-severe: At 6 months of treatment, the mean difference in the ADCS-ADL-severe change scores for donepezil compared with placebo patients was **1.8** points.
    - Donepezil treatment was statistically significantly greater improvement in daily **function** than placebo.

Japanese 24-week Study

- Objective: The objective of the 24-week study was to compare the effectiveness of donepezil tablets 5 or 10 mg once daily with placebo in Japanese patients with **severe** AD dementia.
- Study Design:
  - Patients were randomized to receive once-daily doses of donepezil 5 mg, donepezil 10 mg, or placebo tablets for **24** weeks
  - Patients randomized to receive donepezil were to receive their assigned doses by **titration** during a 6-week period, beginning with 3 mg once daily to avoid acute cholinergic effects
- Results: After 24 weeks of treatment, statistically **significant** differences were observed between the donepezil 10 mg once-daily dose and placebo on both the SIB and CIBIC-plus.
  - A statistically significant difference between the donepezil 5 mg once-daily dose and placebo was observed on the **SIB** but not on the **CIBIC-plus**.

SAFETY DATA FOR ADLARITY

Overview

- Adverse reactions and application-site reactions associated with ADLARITY were assessed in **healthy**, human volunteers who enrolled in the pivotal bioequivalence study of ADLARITY, not in patients with AD dementia.
- The most common adverse reactions in the ADLARITY PI are from clinical studies of **Aricept** (oral donepezil) in patients with AD dementia.

ADLARITY Adverse Reactions in Pivotal Bioequivalence PK Study

- The pivotal PK study that was used to establish the **bioequivalence** of ADLARITY 10 mg/day to orally administered Aricept 10 mg once daily also evaluated adverse reactions.
- The most common adverse reactions listed in the Highlights section of the ADLARITY PI (>5% with donepezil tablets and twice the placebo rate) are **nausea**, diarrhea, insomnia, vomiting, muscle cramps, **fatigue**, and anorexia.
- GI Adverse Events: Overall, the types of adverse reactions reported by healthy volunteers receiving the ADLARITY patch in the pivotal bioequivalence PK study were **consistent** with those reported by patients with AD dementia receiving oral donepezil therapy in clinical trials.

- However, ADLARITY 10 mg/day was associated with a **lower** incidence of all GI AEs compared with oral donepezil 10 mg once daily in healthy volunteers.
- In the pivotal bioequivalence study in healthy adults, the incidence of all GI AEs was ~**3.5** times lower with ADLARITY 10 mg/day than with oral donepezil 10 mg once daily.
- The incidence of nausea was ~**15** times lower, and the incidences of vomiting, diarrhea, and constipation were also lower.

- CNS Adverse Events: ADLARITY 10 mg/day was also associated with a **lower** incidence of CNS AEs compared with oral donepezil 10 mg once daily, including dizziness and somnolence.

Application-site Reactions With Adlarity

- In the pivotal bioequivalence PK study, an investigator-rated skin **irritation** scale was used to capture cases of skin irritation after ADLARITY removal.
- Skin irritation was observed, including erythema (64.6%), papules (16.0%), and edema (0.4%), following the removal of 268 ADLARITY 10 mg/day transdermal systems; none of the ADLARITY transdermal systems were **discontinued** because of skin irritation.
- All application-site AEs were reported as **mild**.
- In a clinical study investigating the skin-sensitizing potential of ADLARITY in 229 healthy adults, **4** cases of potential sensitization were observed (4/229 = 1.7%).

Adverse Reactions Leading to Discontinuation in Donepezil Clinical Trials

- Clinical Trials of Patients With Mild to Moderate AD dementia: Patient discontinuation rates from controlled clinical trials of donepezil tablets due to adverse reactions for donepezil 5 mg once daily were **comparable** to discontinuation rates for placebo (~ 5% of patients in both groups).
    - However, the discontinuation rate for patients who received 7-day escalations of donepezil tablets from 5 mg once daily to 10 mg once daily was **higher** (13%).

Clinical Trials of Patients With Severe AD dementia

- In patients with severe AD dementia, patient **discontinuation** rates from controlled donepezil clinical trials due to adverse reactions were ~ 12% donepezil compared with 7% for placebo patients.