SENILE DEMENTIA: OVERVIEW

Senile dementia is a disease caused by degeneration of the brain cells. It is different from normal senility in the elderly in that the patient’s brain function will gradually deteriorate resulting in progressive loss of memory and mental abilities, and noticeable personality changes.

Causes and Development

Dementia is always caused by an underlying disease or condition. Brain tissue is damaged, and functioning is diminished. The most common cause of dementia is Alzheimer’s disease, a progressive brain disorder causing deterioration in memory and thought processes.

Causes include:

- Alzheimer’s disease
- Vascular dementia, the second most common cause of dementia, accounting for up to 20% of all dementias
- Huntington disease, a progressive degenerative disease that causes dance-like movements and mental deterioration
- Atherosclerosis, or hardening of the arteries
- Multiple sclerosis, a disorder of the sheath that lines the brain and spinal cord
- HIV, the immunodeficiency disorder that leads to AIDS
• Parkinson’s disease, a degenerative disorder of part of the nervous system
• Creutzfeldt-Jakob disease, a rapidly progressing degenerative disorder of the nervous system causing problems with walking, talking, and the senses
• Pick’s disease, a disorder of the brain that causes slowly progressing dementia
• Viral or bacterial encephalitis, an inflammation of the brain
• Lewy body disease, a degenerative disease of the nervous system
• Normal pressure hydrocephalus, or increased cerebrospinal fluid in the brain
• Chronic subdural hematoma, or bleeding between the brain lining and brain tissue
• Brain tumor
• Wilson disease, a rare disease causing an accumulation of copper in the liver, brain, kidneys, and corneas
• Neurosyphilis, an infection of the nervous system by the syphilis bacteria, which causes weakness and mental deterioration
• Progressive supranuclear palsy, also known as Steele-Richardson-Olszewski syndrome, a rare disorder of late middle age that causes widespread neurological problems.

Certain abnormalities of a person’s metabolism or hormones may also be responsible for the development of dementia, including the following:
• Hypothyroidism, which means the thyroid gland is underactive
• Hyperthyroidism, which means the thyroid gland is overactive
• High-dose steroid abuse
• Deficiency, or low body levels, of vitamin B12
• Thiamine deficiency
• Deficiency of niacin, or vitamin B3
• Chronic alcohol abuse
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- Chronic exposure to metals, such as lead or mercury, and to dyes, such as aniline
- Medication side-effects or drug interactions.

In some of these cases, dementia can be reversed by removing the toxic agent or bringing vitamin levels back to normal.

**Signs and Symptoms**

Symptoms at the early stage include the following:
- Forgetting recent events (distant memories also fade as the disease progresses)
- Experiencing difficulty in reasoning, calculation, and accepting new things
- Becoming confused over time, place and direction
- Impaired judgment
- Changes in personality
- Becoming passive and losing initiative.

Symptoms at the middle stage include the following:
- Losing cognitive ability, such as the ability to learn, judge, and reason
- Becoming emotionally unstable, and easily losing temper or becoming agitated
- Needing help to simply live from day to day
- Confusing night and day; disturbing others’ normal sleeping time.

Symptoms at the later stage include the following:
- Losing all cognitive ability
- Becoming entirely incapable of self-care, including eating, bathing, and so on
- Neglecting personal hygiene
- Incontinence
- Losing weight gradually
- Walking unsteadily and becoming confined to bed.

**Treatment and Prevention**

Senile dementia that is caused by depression, poor nutrition, thyroid dysfunction, drug poisoning, alcoholism, and so on, can
often be corrected by treating the underlying problem. Alzheimer’s disease and multi-infarct dementia are degenerative diseases, and up to now there is no effective treatment. It is best to recognize the symptoms early and be diagnosed and assessed by a doctor. There are currently some medications available to slow the progress of Alzheimer’s disease.

If you recognize the symptoms of senile dementia in a family member, these steps should be taken:

- Consult your doctor to confirm the diagnosis.
- Join a family support group for senile dementia patients. This will help to ease the pressure of looking after the patient through sharing of experience.
- Take advantage of social services such as day care centers for the elderly.
- Explain your loved one’s illness to your relatives and neighbors to gain their understanding and support.
- Make alterations in your home environment to prevent accidents.
- Establish a daily routine for the patient to reduce his or her feelings of confusion.
- Have the patient wear a wrist bracelet labeled with his name and telephone number. Always have a recent photo of the patient at home so that it will help to find him if he or she gets lost.

There is up till now no effective way to prevent Alzheimer’s disease. However, multi-infarct dementia is caused by damaged blood vessels, and can be prevented through healthy living habits.

**MEMORY LOSS AND OTHER SYMPTOMS OF DEMENTIA**

While symptoms of dementia can vary greatly, at least two of the following core mental functions must be significantly impaired to be considered dementia:

- Memory
- Communication and language
- Ability to focus and pay attention
**Introduction**

- Reasoning and judgment
- Visual perception

People with dementia may have problems with short-term memory, keeping track of a purse or wallet, paying bills, planning and preparing meals, remembering appointments or traveling out of the neighborhood.

Many dementias are progressive, meaning symptoms start out slowly and gradually get worse. If you or a loved one is experiencing memory difficulties or other changes in thinking skills, don’t ignore them. Professional evaluation may detect a treatable condition. And even if symptoms suggest dementia, early diagnosis allows a person to get the maximum benefit from available treatments and provides an opportunity to volunteer for clinical trials or studies. It also provides time to plan for the future.

**Causes**

Dementia is caused by damage to brain cells. This damage interferes with the ability of brain cells to communicate with each other. When brain cells cannot communicate normally, thinking, behavior and feelings can be affected.

The brain has many distinct regions, each of which is responsible for different functions (for example, memory, judgment and movement). When cells in a particular region are damaged, that region cannot carry out its functions normally.

Different types of dementia are associated with particular types of brain cell damage in particular regions of the brain. For example, in Alzheimer’s disease, high levels of certain proteins inside and outside brain cells make it hard for brain cells to stay healthy and to communicate with each other. The brain region called the hippocampus is the center of learning and memory in the brain, and the brain cells in this region are often the first to be damaged. That’s why memory loss is often one of the earliest symptoms of Alzheimer’s.

While most changes in the brain that cause dementia are permanent and worsen over time, thinking and memory problems caused by the following conditions may improve when the condition is treated or addressed:
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- Depression
- Medication side effects
- Excess use of alcohol
- Thyroid problems
- Vitamin deficiencies.

Diagnosis of dementia

There is no one test to determine if someone has dementia. Doctors diagnose Alzheimer’s and other types of dementia based on a careful medical history, a physical examination, laboratory tests, and the characteristic changes in thinking, day-to-day function and behavior associated with each type. Doctors can determine that a person has dementia with a high level of certainty. But it’s harder to determine the exact type of dementia because the symptoms and brain changes of different dementias can overlap. In some cases, a doctor may diagnose “dementia” and not specify a type. If this occurs it may be necessary to see a specialist such as a neurologist or gero-psychologist.

Dementia treatment and care

Treatment of dementia depends on its cause. In the case of most progressive dementias, including Alzheimer’s disease, there is no cure and no treatment that slows or stops its progression. But there are drug treatments that may temporarily improve symptoms. The same medications used to treat Alzheimer’s are among the drugs sometimes prescribed to help with symptoms of other types of dementias. Non-drug therapies can also alleviate some symptoms of dementia.

Ultimately, the path to effective new treatments for dementia is through increased research funding and increased participation in clinical studies. Right now, volunteers are urgently needed to participate in more than 180+ actively enrolling clinical studies and trials about Alzheimer’s and related dementias.

Dementia risk and prevention

Some risk factors for dementia, such as age and genetics, cannot be changed. But researchers continue to explore the impact of other risk factors on brain health and prevention of dementia.
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Some of the most active areas of research in risk reduction and prevention include cardiovascular factors, physical fitness, and diet.

Cardiovascular risk factors: Your brain is nourished by one of your body’s richest networks of blood vessels. Anything that damages blood vessels anywhere in your body can damage blood vessels in your brain, depriving brain cells of vital food and oxygen. Blood vessel changes in the brain are linked to vascular dementia. They often are present along with changes caused by other types of dementia, including Alzheimer’s disease and dementia with Lewy bodies. These changes may interact to cause faster decline or make impairments more severe. You can help protect your brain with some of the same strategies that protect your heart – don’t smoke; take steps to keep your blood pressure, cholesterol and blood sugar within recommended limits; and maintain a healthy weight.

Physical exercise: Regular physical exercise may help lower the risk of some types of dementia. Evidence suggests exercise may directly benefit brain cells by increasing blood and oxygen flow to the brain.

Diet: What you eat may have its greatest impact on brain health through its effect on heart health. The best current evidence suggests that heart-healthy eating patterns, such as the Mediterranean diet, also may help protect the brain. A Mediterranean diet includes relatively little red meat and emphasizes whole grains, fruits and vegetables, fish and shellfish, and nuts, olive oil and other healthy fats.

DIAGNOSIS, TREATMENT, PREVENTION

If someone shows dementia symptoms, it is best to consult a doctor. Doctors will perform the required checks to understand whether the person has dementia. They will try to find out which diseases could be causing the symptoms.

Anyone can get dementia

Dementia can happen to persons of any race, gender, social class, and education status. Therefore everyone needs to be alert
about the symptoms of dementia in themselves and in people around them.

Many people think that intelligent and active persons won’t get dementia. People say, “Oh, I solve crosswords. I won’t get dementia.” This is not true. Many persons who got dementia had been leading physically and mentally active lives.

Also note that while dementia is more common among older persons, younger persons and middle-aged persons can also get dementia.

**Why early diagnosis is important**

Most persons do not notice early dementia symptoms. Or they ignore them. Take memory loss. Most people consider it a part of ageing. They do not tell their doctor about memory problems during normal health checkups. They do not consult a doctor if they have been forgetting things.

Or consider problems like confusion or disorientation. Or even apathy or major personality changes, like becoming abusive. These are not seen as problems that could be related to a disease.

Early diagnosis is useful because some causes of dementia symptoms can be reversed with treatment. Examples of reversible causes include Vitamin B12 deficiency, depression, stress, hormonal problems, and many others. So by taking the medicines, someone with a reversible dementia can get relief from the symptoms.

Early diagnosis is also useful for irreversible dementias. Some treatments are available for some types of dementia. These can reduce the severity of the symptoms in the early stages for some patients.

Initially patients face mild problems like memory loss, confusion, and disorientation. Simple tasks become difficult to do. They may feel different in strange ways. This worries them. They may wonder whether they are stupid or crazy. But they often hide their problems because they are embarrassed or scared. The problems get noticed only after serious mistakes are made, like a person wandering. Or family members see major changes in the person’s personality, and suspect a problem. There are many symptoms associated with dementia. Only some of these are seen
in early stages. But aware persons will notice these and consult doctors and get a diagnosis and maybe even treatment.

**Whom to approach**

People can tell the family doctor about the problems being faced. The doctor will do some initial checking. If needed, the doctor will direct them to a specialist.

Because of poor dementia awareness, many doctors do not know about enough about dementia. Family doctors may think that memory loss is because of age. They may think the changed behavior is a personality problem. They are more likely to miss dementia in younger persons.

Dementia diagnosis is usually done by a specialist. The specialist will perform tests and ask questions to understand the symptoms. This includes talking to the patient and family members. A “differential diagnosis” is done to see which disease is causing the symptoms. The patient may have more than one medical condition.

To consult a specialist, visit the neurology, geriatrics, or psychiatry department of a hospital. Doctors can be consulted at a hospital’s OPD (out patient department).

Some persons with symptoms may refuse to see a doctor. They can be suspicious. If you force them to see a doctor, they get angry. Talk to the doctor in the absence of the person. Ask the doctor to check the person for dementia as part of a normal health check-up. Sometimes volunteers make home visits to do an assessment. This can be used to decide on further medical follow-up.

**DIAGNOSIS OF DEMENTIA**

A dementia diagnosis is a “clinical” diagnosis given by the doctor (clinician). Patient history is very important for doing the diagnosis. Doctors gather information from the patient and family on the symptoms and their impact. They check the abilities of the patient to see if these have reduced a lot. They ask questions to know how fast the decline was. The patient’s medical data and current medicines are studied. Families must give the doctor all
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this information. They have to be ready to answer such questions. Doctors also make patients perform some tasks. These could include drawing something, answering questions about the news or general knowledge, asking them to remember something, walking on a straight line, etc. Doctors may use a “Mini Mental State Examination” (MMSE) test or a similar test to see the cognitive status of the patient. Local, adapted versions may also be used, such as the Hindi Mental Status Examination (HMSE). Only doctors are supposed to use such tests and interpret the results.

The diagnosis will also involve tests to check for additional medical problems. Examples of some common tests are blood tests for vitamin B12, thyroid hormones, and various deficiencies. Brain scans may be done. They help doctors see whether the brain has some damage, and which parts of the brain are active and which are not.

Doctors then put together all the data to see if the person has dementia. While family doctors may do some initial checking, the complete diagnosis is usually done by specialists in neurology, psychiatry, or geriatrics. If the dementia symptoms are serious, the doctor may say the patient has all-cause dementia. The doctor also tries to see which specific diseases are causing the symptoms. Examples are Alzheimer's, Lewy Body Dementia, Fronto-temporal dementia (FTD), vascular, etc. Often doctors give only a tentative diagnosis. They use terms like “possible Alzheimer's” or “probable Alzheimer's”. The reason is that a firm diagnosis of many dementias can only be given after someone dies and the brain is checked in an autopsy.

If the symptoms are mild, doctors may say the person has Mild Cognitive Impairment (MCI). MCI is not dementia. Some persons with MCI will develop dementia later. Others will stay at that same level, or may even improve. However because MCI sometimes develops into dementia, families have to remain alert about more decline to get another check-up.

Media reports sometimes give wrong information about the diagnosis procedure. Such reports may be based on research and not on approved diagnosis methods. Here are some clarifications:

• Genetic testing is not used for diagnosis.
• Blood tests are not yet used to diagnose Alzheimer’s Disease.
• Alzheimer’s Disease cannot be diagnosed twenty years before the symptoms appear. A diagnosis of pre-clinical Alzheimer’s Disease is not currently an approved way of diagnosing.

Confusion about the diagnosis process is mainly because of a proposed approach. Experts have suggested an approach using a three-stage model for Alzheimer’s Disease. The first stage is pre-clinical AD. Here the brain shows some changes, but the person has no dementia symptoms. The second stage is when there are mild symptoms, called “MCI due to Alzheimer’s Disease.” The third stage is called “dementia caused by Alzheimer’s Disease.” The proposed approach also includes two biomarkers. This proposed approach was first described in 2011. It has been described again in the 2015 Facts and Figures report. But these are still just “Proposed Criteria and Guidelines”. Doctors are not supposed to use them to diagnose patients. The report states: more research is needed before the proposed diagnostic criteria and guidelines can be used in clinical settings, such as in a doctor’s office.

PROBLEMS IN DIAGNOSIS (MISSED DIAGNOSIS, WRONG DIAGNOSIS)

Doctors may miss the dementia diagnosis. Or they may give a wrong or incomplete diagnosis. Here are some examples of problems in getting a correct and complete diagnosis:

• Symptoms are seen as being old age or changed character.: This mistake is very common. It happens more when persons are in early-stage dementia and symptoms are mild.

• Dementia is diagnosed as some other problem.: The typical dementia patient is an older person with memory loss. If a person is younger or does not have memory loss, the doctor may think the symptoms are because of some other problem. For example, FTD patients are often considered psychiatric patients. Or middle-aged persons with memory problems are told they are just having too much stress.
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- The dementia is called irreversible though the symptoms are because of a reversible problem. For example, a depressed person may get a dementia diagnosis. Or someone with thyroid problems is diagnosed as having Alzheimer’s Disease. Less known problems, like normal pressure hydrocephalus, can also be missed.
- A diagnosis mentions a wrong irreversible dementia. There are many irreversible diseases that cause dementia. Doctors may give a wrong diagnosis about which irreversible disease the patient has. One common problem is telling Lewy Body Dementia (LBD) patients they have Alzheimer’s Disease (AD). This mistake is harmful because some AD medicines can harm someone with LBD.
- Other serious medical problems may be missed. Persons may have more than one medical problems adding to the dementia symptoms. One problem may get diagnosed properly. But others may be missed. For example someone has LBD as well as AD, but gets diagnosed only for AD.

When the diagnosis is incomplete or wrong, the treatment is not proper. Medicine may not be given for a curable disease. Or a wrong medicine may be given, causing harm. Another thing is that new medical problems may develop after the initial diagnosis. However, the family may not go for additional checkups. Also, doctors may not check whether the patient now also has a new problem. So the new problem remains untreated.

To reduce such problems, families must know about dementia and diagnosis. They must give the full patient history to the doctor. They must be alert during the diagnosis. Sometimes a junior doctor gives a diagnosis without doing the full checkup. Families must ask questions. If they are not satisfied with the diagnosis, they should get a second opinion. Also, families should not think that someone has dementia just because the person has memory loss or other symptoms.

After the diagnosis

Doctors tell the family the diagnosis, but usually do not have the time to explain things repeatedly and in detail. They may not
discuss the non-medical care needed for the patient. Dementia lasts for many years and requires a lot of support. A few short visits to the doctor are not enough to learn about dementia and care. So patients and their families have to look for more sources and spend more time and effort to learn about dementia. Better information and counseling lets families plan better for dementia. Patients are able to continue an active and meaningful life for more time. For example, Terry Pratchett, the well-known fantasy writer, was diagnosed in 2007. He remained active till his death in 2015. Another example is Charles Kuen Kao, who was diagnosed in early 2004 and won the Nobel Prize for Physics in 2009.

Those who have just received a diagnosis of dementia may feel overwhelmed and uncertain about what to expect and how to proceed. An extremely useful set of resources for such persons is Dementia Mentors, a website designed to help persons with dementia stay active and connected. The site explains their goal as “To help those who are newly diagnosed and in the early stages of dementia.” and is intended for an international audience. Also, while the site aims at persons diagnosed with dementia, it is also very useful for family caregivers trying to understand and support persons with dementia.

Counselors may be available in hospitals, dementia associations, and support groups. There are online groups for various types of dementia. Getting in touch with others facing similar situations gives a better understanding of what to expect. Also, get information on the type of support available. There are also websites and books on these topics.

**TREATMENT AND RESEARCH**

Some conditions that cause dementia can be cured. But most types of dementia are irreversible and progressive. Unfortunately, medicines don’t help much. Media reports that dementia can be cured are misleading. Here is an overview of the current status of medicines.

- Many diseases can create dementia symptoms. Most research is on Alzheimer’s Disease, the commonest form
of dementia. But there are no disease-modifying therapies even for Alzheimer’s Disease. That is, no medicine can change how Alzheimer’s Disease damages the brain. Some medicines can help reduce symptoms like memory loss. But these do not work for all patients. Here is a quote from the 2015 Alzheimer’s Association report (USA):

…none of the treatments available today for Alzheimer’s disease slows or stops the damage to neurons that causes Alzheimer’s symptoms and eventually makes the disease fatal.

• Media reports often claim that alternate therapies and herbs can cure dementia. These are misleading. Some such therapies can even harm. Popular therapies mentioned are coconut oil, turmeric, cinnamon, etc.. The Alzheimer UK’s page, Science behind the headlines, discusses these therapies. A quote:

…while a study or many studies may show a benefit to a particular behaviour within the lab or in models of dementia, this does not mean that it will necessarily work in people or in the long-term way that we would like.

• Stem cell therapies cannot cure Alzheimer’s Disease. The Indian Govt has cautioned that untested techniques may harm patients. The Alzheimer’s Society, UK, has said in its position paper that no stem cell cure is currently available.

Medical research looks at three broad areas:

1. For normal people: how to prevent onset.
2. For persons where the dementia disease has started damaging the brain but symptoms are not yet visible: slow the progress of the brain damage. Keep delaying the onset of symptoms. (This stage is called the prodromal stage)
3. For persons clinically diagnosed with dementia: treat the symptoms to improve the quality of life. Slow the damage caused in the brain by the disease.

Interested persons can help by funding research. They can take part in drug trials, and in studies on lifestyle impact. Contact dementia associations and major neurology hospitals if you want to help.
PREVALENCE AND RISK FACTORS OF DEMENTIA

Researchers are trying to understand how various factors affect the brain, and how the brain can be kept healthy. The only clear correlation so far is that the probability of dementia increases with age. The Dementia India Report 2010 (PDF file) lists two types of risk factors:

Non-modifiable factors
- Age
- Family history +
- ApoE4 allele
- Female sex
- Depression
- Head trauma
- Mutation on 1,14,21 chromosome
- Down’s syndrome

Potentially modifiable factors
- Vascular Disease
- Hypertension
- Diabetes
- Dyslipidaemia
- Nutritional deficiency (Vit B)
- Smoking
- Alcohol
- Obesity
- Diet.

Reducing the risk of dementia

There is no definite way for an individual to make sure they will not get dementia. Media articles sometimes claim that people can prevent dementia if they do some particular activity or eat some particular food. That is not true. People can reduce their risk of dementia by making some changes in their lives, but they cannot be certain that they will never get dementia. It is also wrong to think that persons who get dementia were leading unhealthy or inactive lives. The World Alzheimer’s Report 2014:
Dementia and Risk Reduction says: There is no evidence strong enough at this time to claim that lifestyle changes will prevent dementia on an individual basis.

One action that can reduce the chance of dementia is taking care of vascular health. A useful mantra to remember is: "What is good for your heart is good for your brain”. This is also mentioned in the 2014 World Alzheimer’s Report.

Doctors suggest focusing on the modifiable risk factors. A healthy lifestyle is expected to reduce the chance of dementia. Here are some examples of what to do:

- Maintain a healthy weight and eating a healthy diet with lots of vegetables and fruits.
- Have high levels of physical activity.
- Maintain mental fitness by learning new things.
- Reduce risk of heart disease.
- Remain socially active.
Dementia

Dementia, also known as senility, is a broad category of brain diseases that cause a long term and often gradual decrease in the ability to think and remember that is great enough to affect a person’s daily functioning. Other common symptoms include emotional problems, problems with language, and a decrease in motivation. A person’s consciousness is usually not affected. A dementia diagnosis requires a change from a person’s usual mental functioning and a greater decline than one would expect due to aging. These diseases also have a significant effect on a person’s caregivers.

The most common type of dementia is Alzheimer’s disease, which makes up 50% to 70% of cases. Other common types include vascular dementia (25%), Lewy body dementia (15%), and frontotemporal dementia. Less common causes include normal pressure hydrocephalus, Parkinson’s disease, syphilis, and Creutzfeldt–Jakob disease among others. More than one type of dementia may exist in the same person. A small proportion of cases run in families. In the DSM-5, dementia was reclassified as a neurocognitive disorder, with various degrees of severity. Diagnosis is usually based on history of the illness and cognitive testing with medical imaging and blood work used to rule out other possible causes. The mini mental state examination is one commonly used cognitive test. Efforts to prevent dementia include trying to decrease risk factors such as high blood pressure, smoking, diabetes, and obesity. Screening the general population for the
disorder is not recommended. There is no cure for dementia. Cholinesterase inhibitors such as donepezil are often used and may be beneficial in mild to moderate disorder. Overall benefit, however, may be minor. For people with dementia and those who care for them many measures can improve their lives. Cognitive and behavioral interventions may be appropriate. Educating and providing emotional support to the caregiver is important. Exercise programs may be beneficial with respect to activities of daily living and potentially improve outcomes. Treatment of behavioral problems with antipsychotics is common but not usually recommended due to the little benefit and side effects, including an increased risk of death.

Globally, dementia affects 36 million people. About 10% of people develop the disorder at some point in their lives. It becomes more common with age. About 3% of people between the ages of 65–74 have dementia, 19% between 75 and 84 and nearly half of those over 85 years of age. In 2013 dementia resulted in about 1.7 million deaths up from 0.8 million in 1990. As more people are living longer, dementia is becoming more common in the population as a whole. For people of a specific age, however, it may be becoming less frequent, at least in the developed world, due to a decrease in risk factors. It is one of the most common causes of disability among the old. It is believed to result in economic costs of 604 billion USD a year. People with dementia are often physically or chemically restrained to a greater degree than necessary, raising issues of human rights. Social stigma against those affected is common.

SIGNS AND SYMPTOMS

The symptoms of dementia vary across types and stages of the diagnosis. The most common affected areas include memory, visual-spatial, language, attention and problem solving. Most types of dementia are slow and progressive. By the time the person shows signs of the disorder, the process in the brain has been happening for a long time. It is possible for a patient to have two types of dementia at the same time. About 10% of people with dementia have what is known as mixed dementia, which is usually a combination of Alzheimer’s disease and another type of dementia.
Dementia

such as frontotemporal dementia or vascular dementia. Additional psychological and behavioral problems that often affect people who have dementia include:

- Balance problems
- Tremor
- Speech and language difficulty
- Trouble eating or swallowing
- Memory distortions (believing that a memory has already happened when it has not, thinking an old memory is a new one, combining two memories, or confusing the people in a memory)
- Wandering or restlessness
- Perception and visual problems
- Behavioral and psychological symptoms of dementia (BPSD) almost always occur in all types of dementia. BPSDs may manifest as:
  - Agitation
  - Depression
  - Anxiety
  - Abnormal motor behavior
  - Elated mood
  - Irritability
  - Apathy
  - Disinhibition and impulsivity
  - Delusions (often believing people are stealing from them) or hallucinations
  - Changes in sleep or appetite.

When people with dementia are put in circumstances beyond their abilities, there may be a sudden change to crying or anger (a “catastrophic reaction”).

Depression affects 20–30% of people who have dementia, and about 20% have anxiety. Psychosis (often delusions of persecution) and agitation/aggression also often accompany dementia. Each of these must be assessed and treated independently of the underlying dementia.
Mild cognitive impairment

In the first stages of dementia, the signs and symptoms of the disorder may be subtle. Often, the early signs of dementia only become apparent when looking back in time. The earliest stage of dementia is called mild cognitive impairment (MCI). 70% of those diagnosed with MCI progress to dementia at some point. In MCI, changes in the person’s brain have been happening for a long time, but the symptoms of the disorder are just beginning to show. These problems, however, are not yet severe enough to affect the person’s daily function. If they do, it is considered dementia. A person with MCI scores between 27 and 30 on the Mini-Mental State Examination (MMSE), which is a normal score. They may have some memory trouble and trouble finding words, but they solve everyday problems and handle their own life affairs well.

Early stages

In the early stage of dementia, the person begins to show symptoms noticeable to the people around them. In addition, the symptoms begin to interfere with daily activities. The person usually scores between a 20 and 25 on the MMSE. The symptoms are dependent on the type of dementia a person has. The person may begin to have difficulty with more complicated chores and tasks around the house. The person can usually still take care of him or herself but may forget things like taking pills or doing laundry and may need prompting or reminders.

The symptoms of early dementia usually include memory difficulty, but can also include some word-finding problems (anomia) and problems with planning and organizational skills (executive function). One very good way of assessing a person’s impairment is by asking if he or she is still able to handle his/her finances independently. This is often one of the first things to become problematic. Other signs might be getting lost in new places, repeating things, personality changes, social withdrawal and difficulties at work.

When evaluating a person for dementia, it is important to consider how the person was able to function five or ten years earlier. It is also important to consider a person’s level of education.
Dementia

when assessing for loss of function. For example, an accountant who can no longer balance a checkbook would be more concerning than a person who had not finished high school or had never taken care of his/her own finances.

In Alzheimer’s dementia the most prominent early symptom is memory difficulty. Others include word-finding problems and getting lost. In other types of dementia, like dementia with Lewy bodies and fronto-temporal dementia, personality changes and difficulty with organization and planning may be the first signs.

**Middle stages**

As dementia progresses, the symptoms first experienced in the early stages of the dementia generally worsen. The rate of decline is different for each person. A person with moderate dementia scores between 6–17 on the MMSE. For example, people with Alzheimer’s dementia in the moderate stages lose almost all new information very quickly. People with dementia may be severely impaired in solving problems, and their social judgment is usually also impaired. They cannot usually function outside their own home, and generally should not be left alone. They may be able to do simple chores around the house but not much else, and begin to require assistance for personal care and hygiene other than simple reminders.

**Late stages**

People with late-stage dementia typically turn increasingly inward and need assistance with most or all of their personal care. Persons with dementia in the late stages usually need 24-hour supervision to ensure personal safety, as well as to ensure that basic needs are being met. If left unsupervised, a person with late-stage dementia may wander or fall, may not recognize common dangers around them such as a hot stove, may not realize that they need to use the bathroom or become unable to control their bladder or bowels (incontinent).

Changes in eating frequently occur. Caregivers of people with late-stage dementia often provide pureed diets, thickened liquids, and assistance in eating, to prolong their lives, to cause them to gain weight, to reduce the risk of choking, and to make feeding
the person easier. The person’s appetite may decline to the point that the person does not want to eat at all. He or she may not want to get out of bed, or may need complete assistance doing so. Commonly, the person no longer recognizes familiar people. He or she may have significant changes in sleeping habits or have trouble sleeping at all.

CAUSES

Reversible causes

There are four main causes of easily reversible dementia: hypothyroidism, vitamin B12 deficiency, Lyme disease, and neurosyphilis. All people with memory difficulty should be checked for hypothyroidism and B12 deficiency. For Lyme disease and neurosyphilis, testing should be done if there are risk factors for those diseases in the person.

Alzheimer’s disease

![Fig. Brain atrophy in severe Alzheimer's](image)

Alzheimer’s disease accounts for up to 50% to 70% of cases of dementia. The most common symptoms of Alzheimer’s disease are short-term memory loss and word-finding difficulties. People with Alzheimer’s disease also have trouble with visual-spatial areas (for example, they may begin to get lost often), reasoning, judgment, and insight. Insight refers to whether or not the person realizes he/she has memory problems.

Common early symptoms of Alzheimer’s include repetition, getting lost, difficulties keeping track of bills, problems with cooking
especially new or complicated meals, forgetting to take medication, and word-finding problems.

The part of the brain most affected by Alzheimer’s is the hippocampus. Other parts of the brain that show shrinking (atrophy) include the temporal and parietal lobes. Although this pattern suggests Alzheimer’s, the brain shrinkage in Alzheimer’s disease is very variable, and a scan of the brain cannot actually make the diagnosis. The relationship between undergoing anesthesia and AD is unclear.

Vascular dementia

Vascular dementia is the cause of at least 20% of dementia cases, making it the second most common cause of dementia. It is caused by disease or injury affecting the blood supply to the brain, typically involving a series of minor strokes. The symptoms of this dementia depend on where in the brain the strokes have occurred and whether the vessels are large or small. Multiple injuries can cause progressive dementia over time, while a single injury located in an area critical for cognition (i.e. hippocampus, thalamus) can lead to sudden cognitive decline.

On scans of the brain, a person with vascular dementia may show evidence of multiple strokes of different sizes in various locations. People with vascular dementia tend to have risk factors for disease of the blood vessels, such as tobacco use, high blood pressure, atrial fibrillation, high cholesterol or diabetes, or other signs of vascular disease such as a previous heart attack or angina.

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is a dementia that has the primary symptoms of visual hallucinations and “Parkinsonism.” Parkinsonism is a term that describes a person with features of Parkinson’s disease. This includes tremor, rigid muscles, and a face without emotion. The visual hallucinations in DLB are generally very vivid hallucinations of people and/or animals and they often occur when someone is about to fall asleep or just waking up. Other prominent symptoms include problems with attention, organization, problem solving and planning (executive function), and difficulty with visual-spatial function.
Again, imaging studies cannot necessarily make the diagnosis of DLB, but some signs are particularly common. A person with DLB often shows occipital hypoperfusion on SPECT scan or occipital hypometabolism on a PET scan. Generally, a diagnosis of DLB is straightforward and unless it is complicated, a brain scan is not always necessary.

**Frontotemporal dementia**

Frontotemporal dementia (FTD) is characterized by drastic personality changes and language difficulties. In all FTD, the person has a relatively early social withdrawal and early lack of insight into the disorder. Memory problems are not a main feature of this disorder.

There are three main types of FTD. The first has major symptoms in the area of personality and behavior. This is called behavioral variant FTD (bv-FTD) and is the most common. In bv-FTD, the person shows a change in personal hygiene, becomes rigid in their thinking, and rarely recognize that there is a problem, they are socially withdrawn, and often have a drastic increase in appetite. They may also be socially inappropriate. For example, they may make inappropriate sexual comments, or may begin using pornography openly when they had not before. One of the most common signs is apathy, or not caring about anything. Apathy, however, is a common symptom in many different dementias.

The other two types of FTD feature language problems as the main symptom. The second type is called semantic dementia or temporal variant dementia (TV-FTD). The main feature of this is the loss of the meaning of words. It may begin with difficulty naming things. The person eventually may also lose the meaning of objects as well. For example, a drawing of a bird, dog, and an airplane in someone with FTD may all appear just about the same. In a classic test for this, a patient is shown a picture of a pyramid and below there is a picture of both a palm tree and a pine tree. The person is asked to say which one goes best with the pyramid. In TV-FTD the person would not be able to answer that question.

The last type of FTD is called progressive non-fluent aphasia (PNFA). This is mainly a problem with producing speech. They
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have trouble finding the right words, but mostly they have a difficulty coordinating the muscles they need to speak. Eventually, someone with PNFA only uses one-syllable words or may become totally mute.

With both TV-FTD and PNFA the symptoms of behavior may be present, but milder and later than in bv-FTD. Imaging studies have shown shrinking of the frontal and temporal lobes of the brain.

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is a form of dementia that is characterized by problems with eye movements. Generally the problems begin with difficulty moving the eyes up and/or down (vertical gaze palsy). Since difficulty moving the eyes upward can sometimes happen in normal aging, problems with downward eye movements are the key in PSP. Other key symptoms of PSP include falls backwards, balance problems, slow movements, rigid muscles, irritability, apathy, social withdrawal, and depression. The person may also have certain “frontal lobe signs” such as perseveration, a grasp reflex and utilization behavior (the need to use an object once you see it). People with PSP often have progressive difficulty eating and swallowing, and eventually with talking as well. Because of the rigidity and slow movements, PSP is sometimes misdiagnosed as Parkinson’s disease.

On scans of the brain, the midbrain of people with PSP is generally shrunken (atrophied), but there are no other common brain abnormalities visible on images of the person’s brain.

Corticobasal degeneration

Corticobasal degeneration is a rare form of dementia that is characterized by many different types of neurological problems that get progressively worse over time. This is because the disorder affects the brain in many different places, but at different rates. One common sign is difficulty with using only one limb. One symptom that is extremely rare in any condition other than corticobasal degeneration is the “alien limb.” The alien limb is a limb of the person that seems to have a mind of its own, it moves without control of the person’s brain. Other common symptoms
include jerky movements of one or more limbs (myoclonus), symptoms that are different in different limbs (asymmetric), difficulty with speech that is due to not being able to move the mouth muscles in a coordinated way, numbness and tingling of the limbs and neglecting one side of the person’s vision or senses. In neglect, a person ignores the opposite side of the body from the one that has the problem. For example, a person may not feel pain on one side, or may only draw half of a picture when asked. In addition, the person’s affected limbs may be rigid or have muscle contractions causing strange repetitive movements (dystonia).

The area of the brain most often affected in corticobasal degeneration is the posterior frontal lobe and parietal lobe. Still, many other part of the brain can be affected.

Rapidly progressive

Creutzfeldt-Jakob disease typically causes a dementia that worsens over weeks to months, and is caused by prions. The common causes of slowly progressive dementia also sometimes present with rapid progression: Alzheimer’s disease, dementia with Lewy bodies, frontotemporal lobar degeneration (including corticobasal degeneration and progressive supranuclear palsy).

On the other hand, encephalopathy or delirium may develop relatively slowly and resemble dementia. Possible causes include brain infection (viral encephalitis, subacute sclerosing panencephalitis, Whipple’s disease) or inflammation (limbic encephalitis, Hashimoto’s encephalopathy, cerebral vasculitis); tumors such as lymphoma or glioma; drug toxicity (e.g., anticonvulsant drugs); metabolic causes such as liver failure or kidney failure; and chronic subdural hematoma.

Other conditions

There are many other medical and neurological conditions in which dementia only occurs late in the illness. For example, a proportion of patients with Parkinson’s disease develop dementia, though widely varying figures are quoted for this proportion. When dementia occurs in Parkinson’s disease, the underlying cause may be dementia with Lewy bodies or Alzheimer’s disease,
or both. Cognitive impairment also occurs in the Parkinson-plus syndromes of progressive supranuclear palsy and corticobasal degeneration (and the same underlying pathology may cause the clinical syndromes of frontotemporal lobar degeneration). Chronic inflammatory conditions of the brain may affect cognition in the long term, including Behçet’s disease, multiple sclerosis, sarcoidosis, Sjögren’s syndrome, and systemic lupus erythematosus. Although the acute porphyrias may cause episodes of confusion and psychiatric disturbance, dementia is a rare feature of these rare diseases.

Aside from those mentioned above, inherited conditions that can cause dementia (alongside other symptoms) include:

- Alexander disease
- Canavan disease
- Cerebrotendinous xanthomatosis
- Dentatorubral-pallidoluysian atrophy
- Epilepsy
- Fatal familial insomnia
- Fragile X-associated tremor/ataxia syndrome
- Glutaric aciduria type 1
- Krabbe's disease
- Maple syrup urine disease
- Niemann–Pick disease type C
- Neuronal ceroid lipofuscinosis
- Neuroacanthocytosis
- Organic acidemias
- Pelizaeus–Merzbacher disease
- Sanfilippo syndrome type B
- Spinocerebellar ataxia type 2
- Urea cycle disorders.

**Mild cognitive impairment**

Mild cognitive impairment means that the person exhibits memory or thinking difficulties, but those difficulties are not severe enough to meet criteria for a diagnosis of dementia. He or she should score between 25–30 on the MMSE. Around 70% of people
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with MCI go on to develop some form of dementia. MCI is generally divided into two categories. The first is one that is primarily memory loss (amnestic MCI). The second category is anything that is not primarily memory difficulties (non-amnestic MCI). People with primarily memory problems generally go on to develop Alzheimer’s disease. People with the other type of MCI may go on to develop other types of dementia.

Diagnosis of MCI is often difficult, as cognitive testing may be normal. Often, more in-depth neuropsychological testing is necessary to make the diagnosis. The most commonly used criteria are called the Peterson criteria and include:

• Memory or other cognitive (thought-processing) complaint by the person or a person who knows the patient well.
• The person must have a memory or other cognitive problem as compared to a person of the same age and level of education.
• The problem must not be severe enough to affect the person’s daily function.
• The person must not have dementia.

Fixed cognitive impairment

Various types of brain injury may cause irreversible cognitive impairment that remains stable over time. Traumatic brain injury may cause generalized damage to the white matter of the brain (diffuse axonal injury), or more localized damage (as also may neurosurgery). A temporary reduction in the brain’s supply of blood or oxygen may lead to hypoxic-ischemic injury. Strokes (ischemic stroke, or intracerebral, subarachnoid, subdural or extradural hemorrhage) or infections (meningitis and/or encephalitis) affecting the brain, prolonged epileptic seizures, and acute hydrocephalus may also have long-term effects on cognition. Excessive alcohol use may cause alcohol dementia, Wernicke’s encephalopathy, and/or Korsakoff’s psychosis.

Slowly progressive

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

Causes of dementia depend on the age when symptoms begin. In the elderly population (usually defined in this context as over 65 years of age), a large majority of dementia cases are caused by Alzheimer's disease, vascular dementia, or both. Dementia with Lewy bodies is another commonly exhibited form, which again may occur alongside either or both of the other causes. Hypothyroidism sometimes causes slowly progressive cognitive impairment as the main symptom, and this may be fully reversible with treatment. Normal pressure hydrocephalus, though relatively rare, is important to recognize since treatment may prevent progression and improve other symptoms of the condition. However, significant cognitive improvement is unusual.

Dementia is much less common under 65 years of age. Alzheimer's disease is still the most frequent cause, but inherited forms of the disorder account for a higher proportion of cases in this age group. Frontotemporal lobar degeneration and Huntington's disease account for most of the remaining cases. Vascular dementia also occurs, but this in turn may be due to underlying conditions (including antiphospholipid syndrome, CADASIL, MELAS, homocystinuria, moyamoya, andBinswanger's disease). People who receive frequent head trauma, such as boxers or football players, are at risk of chronic traumatic encephalopathy (also called dementia pugilistica in boxers).

In young adults (up to 40 years of age) who were previously of normal intelligence, it is very rare to develop dementia without other features of neurological disease, or without features of disease elsewhere in the body. Most cases of progressive cognitive disturbance in this age group are caused by psychiatric illness, alcohol or other drugs, or metabolic disturbance. However, certain genetic disorders can cause true neurodegenerative dementia at this age. These include familial Alzheimer's disease, SCA17 (dominant inheritance); adrenoleukodystrophy (X-linked); Gaucher's disease type 3, metachromatic leukodystrophy,
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Niemann-Pick disease type C, pantothenate kinase-associated neurodegeneration, Tay-Sachs disease, and Wilson’s disease (all recessive). Wilson’s disease is particularly important since cognition can improve with treatment.

At all ages, a substantial proportion of patients who complain of memory difficulty or other cognitive symptoms have depression rather than a neurodegenerative disease. Vitamin deficiencies and chronic infections may also occur at any age; they usually cause other symptoms before dementia occurs, but occasionally mimic degenerative dementia. These include deficiencies of vitamin B₁₂, folate, or niacin, and infective causes including cryptococcal meningitis, HIV, Lyme disease, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis, syphilis, and Whipple’s disease.

DIAGNOSIS

As seen above, there are many specific types and causes of dementia, often showing slightly different symptoms. However, the symptoms are very similar and it is usually difficult to diagnose the type of dementia by symptoms alone. Diagnosis may be aided by brain scanning techniques. In many cases, the diagnosis cannot be absolutely sure except with a brain biopsy, but this is very rarely recommended (though it can be performed at autopsy). In those who are getting older, general screening for cognitive impairment using cognitive testing or early diagnosis of dementia has not been shown to improve outcomes. However, it has been shown that screening exams are useful in those people over the age of 65 with memory complaints.

Normally, symptoms must be present for at least six months to support a diagnosis. Cognitive dysfunction of shorter duration is called delirium. Delirium can be easily confused with dementia due to similar symptoms. Delirium is characterized by a sudden onset, fluctuating course, a short duration (often lasting from hours to weeks), and is primarily related to a somatic (or medical) disturbance. In comparison, dementia has typically a long, slow onset (except in the cases of a stroke or trauma), slow decline of mental functioning, as well as a longer duration (from months to
Dementia

Some mental illnesses, including depression and psychosis, may produce symptoms that must be differentiated from both delirium and dementia. Therefore, any dementia evaluation should include a depression screening such as the Neuropsychiatric Inventory or the Geriatric Depression Scale. Physicians used to think that anyone who came in with memory complaints had depression and not dementia (because they thought that those with dementia are generally unaware of their memory problems). This is called pseudodementia. However, in recent years researchers have realized that many older people with memory complaints in fact have MCI, the earliest stage of dementia. Depression should always remain high on the list of possibilities, however, for an elderly person with memory trouble.

Changes in thinking, hearing, and vision are associated with normal ageing and can cause problems when diagnosing dementia due to the similarities.

Cognitive testing

There are some brief tests (5–15 minutes) that have reasonable reliability to screen for dementia. While many tests have been studied, presently the mini mental state examination (MMSE) is the best studied and most commonly used, albeit some may emerge as better alternatives. Other examples include the abbreviated mental test score (AMTS), the Modified Mini-Mental State Examination (3MS), the Cognitive Abilities Screening Instrument (CASI), the Trail-making test, and the clock drawing test. The MOCA (Montreal Cognitive Assessment) is a very reliable screening test and is available online for free in 35 different languages. The MOCA has also been shown somewhat better at detecting mild cognitive impairment than the MMSE.

Another approach to screening for dementia is to ask an informant (relative or other supporter) to fill out a questionnaire about the person’s everyday cognitive functioning. Informant questionnaires provide complementary information to brief cognitive tests. Probably the best known questionnaire of this sort is the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). The Alzheimer’s Disease Caregiver Questionnaire is another tool. It is about 90% accurate for Alzheimer’s and can be
completed online or in the office by a caregiver. On the other hand, the General Practitioner Assessment Of Cognition combines both, a patient assessment and an informant interview. It was specifically designed for the use in the primary care setting.

Clinical neuropsychologists provide diagnostic consultation following administration of a full battery of cognitive testing, often lasting several hours, to determine functional patterns of decline associated with varying types of dementia. Tests of memory, executive function, processing speed, attention, and language skills are relevant, as well as tests of emotional and psychological adjustment. These tests assist with ruling out other etiologies and determining relative cognitive decline over time or from estimates of prior cognitive abilities.

**Laboratory tests**

Routine blood tests are also usually performed to rule out treatable causes. These tests include vitamin B₁₂, folic acid, thyroid-stimulating hormone (TSH), C-reactive protein, full blood count, electrolytes, calcium, renal function, and liver enzymes. Abnormalities may suggest vitamin deficiency, infection, or other problems that commonly cause confusion or disorientation in the elderly. The problem is complicated by the fact that these cause confusion more often in persons who have early dementia, so that “reversal” of such problems may ultimately only be temporary. Testing for alcohol and other known dementia-inducing drugs may be indicated.

**Imaging**

A CT scan or magnetic resonance imaging (MRI scan) is commonly performed, although these tests do not pick up diffuse metabolic changes associated with dementia in a person that shows no gross neurological problems (such as paralysis or weakness) on neurological exam. CT or MRI may suggest normal pressure hydrocephalus, a potentially reversible cause of dementia, and can yield information relevant to other types of dementia, such as infarction (stroke) that would point at a vascular type of dementia. The functional neuroimaging modalities of SPECT and PET are more useful in assessing long-standing cognitive
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dysfunction, since they have shown similar ability to diagnose dementia as a clinical exam and cognitive testing. The ability of SPECT to differentiate the vascular cause (i.e., multi-infarct dementia) from Alzheimer’s disease dementias, appears superior to differentiation by clinical exam.

Recent research has established the value of PET imaging using carbon-11 Pittsburgh Compound B as a radiotracer (PIB-PET) in predictive diagnosis of various kinds of dementia, in particular Alzheimer’s disease. Studies from Australia have found PIB-PET 86% accurate in predicting which patients with mild cognitive impairment will develop Alzheimer’s disease within two years. In another study, carried out using 66 patients seen at the University of Michigan, PET studies using either PIB or another radiotracer, carbon-11 dihydrotetrabenazine (DTBZ), led to more accurate diagnosis for more than one-fourth of patients with mild cognitive impairment or mild dementia.

PREVENTION

Many prevention measures have been proposed, including lifestyle changes and medication, though none has been reliably shown effective. Among otherwise healthy older people, computerized cognitive training may improve memory. However it is not known if it prevents dementia.

MANAGEMENT

Except for the treatable types listed above, there is no cure. Cholinesterase inhibitors are often used early in the disorder course; however, benefit is generally small. Cognitive and behavioral interventions may be appropriate. Educating and providing emotional support to the caregiver is of importance as well. Exercise programs are beneficial with respect to activities of daily living and potentially improve dementia.

Psychological therapies

Psychological therapies for dementia include music therapy with unclear evidence, tentative evidence for reminiscence therapy, some benefit for cognitive reframing for caretakers, unclear
evidence for validation therapy, and tentative evidence for mental exercises, such as cognitive stimulation programs for people with mild to moderate dementia. Adult daycare centers as well as special care units in nursing homes often provide specialized care for dementia patients. Adult daycare centers offer supervision, recreation, meals, and limited health care to participants, as well as providing respite for caregivers. In addition, home care can provide one-on-one support and care in the home allowing for more individualized attention that is needed as the disorder progresses. Psychiatric nurses can make a distinctive contribution to people’s mental health.

Since dementia impairs normal communication due to changes in receptive and expressive language, as well as the ability to plan and problem solve, agitated behaviour is often a form of communication for the person with dementia. Actively searching for a potential cause, such as pain, physical illness, or overstimulation can be helpful in reducing agitation. Additionally, using an “ABC analysis of behaviour” can be a useful tool for understanding behavior in people with dementia. It involves looking at the antecedents (A), behavior (B), and consequences (C) associated with an event to help define the problem and prevent further incidents that may arise if the person’s needs are misunderstood.

Medications

No medications have been shown to prevent or cure dementia. Medications may be used to treat the behavioural and cognitive symptoms but have no effect on the underlying disease process. Acetylcholinesterase inhibitors, such as donepezil, may be useful for Alzheimer disease and dementia in Parkinson’s, DLB, or vascular dementia. The quality of the evidence however is poor and the benefit is small. No difference has been shown between the agents in this family. In a minority of people side effects include bradycardia and syncope.

As assessment for an underlying cause of the behavior is a needed before prescribing antipsychotic medication for symptoms of dementia. Antipsychotic drugs should be used to treat dementia only if non-drug therapies have not worked, and the person’s
actions threaten themselves or others. Aggressive behavior changes are sometimes the result of other solvable problems, that could make treatment with antipsychotics unnecessary. Because people with dementia can be aggressive, resistant to their treatment, and otherwise disruptive, sometimes antipsychotic drugs are considered as a therapy in response. These drugs have risky adverse effects, including increasing the patient’s chance of stroke and death. Generally, stopping antipsychotics for people with dementia does not cause problems, even in those who have been on them a long time.

N-methyl-D-aspartate (NMDA) receptor blockers such as memantine may be of benefit but the evidence is less conclusive than for AChEIs. Due to their differing mechanisms of action memantine and acetylcholinesterase inhibitors can be used in combination however the benefit is slight.

While depression is frequently associated with dementia, selective serotonin reuptake inhibitors (SSRIs) do not appear to affect outcomes. It is recommended that benzodiazepines such as diazepam be avoided in dementia due to the risks of increased cognitive impairment and falls. There is little evidence for the effectiveness in this population.

There is no solid evidence that folate or vitamin B12 improves outcomes in those with cognitive problems. Statins also have no benefit in dementia. Medications for other health conditions may need to be managed differently for a person who also has a diagnosis of dementia. The MATCH-D criteria can help identify ways that a diagnosis of dementia changes medication management for other health conditions. It is unclear if there is a link between blood pressure medication and dementia. There is a possibility that people may experience an increase in cardiovascular-related events if these medications are withdrawn.

Pain

As people age, they experience more health problems, and most health problems associated with aging carry a substantial burden of pain; therefore, between 25% and 50% of older adults experience persistent pain. Seniors with dementia experience the same prevalence of conditions likely to cause pain as seniors
without dementia. Pain is often overlooked in older adults and, when screened for, often poorly assessed, especially among those with dementia since they become incapable of informing others that they’re in pain. Beyond the issue of humane care, unrelieved pain has functional implications. Persistent pain can lead to decreased ambulation, depressed mood, sleep disturbances, impaired appetite, and exacerbation of cognitive impairment, and pain-related interference with activity is a factor contributing to falls in the elderly.

Although persistent pain in the person with dementia is difficult to communicate, diagnose, and treat, failure to address persistent pain has profound functional, psychosocial, and quality of life implications for this vulnerable population. Health professionals often lack the skills and usually lack the time needed to recognize, accurately assess, and adequately monitor pain in people with dementia. Family members and friends can make a valuable contribution to the care of a person with dementia by learning to recognize and assess their pain. Educational resources (such as the Understand Pain and Dementia tutorial) and observational assessment tools are available.

**Eating difficulties**

Persons with dementia may have difficulty eating. Whenever it is available as an option, the recommended response to eating problems is having a caretaker do assisted feeding for the person. A secondary option for people who cannot swallow effectively is to consider gastrostomy feeding tube placement as a way to give nutrition. However, in bringing person comfort and keeping functional status while lowering risk of aspiration pneumonia and death, assistance with oral feeding is at least as good as tube feeding. Tube-feeding is associated with agitation, increased use of physical and chemical restraints, and worsening pressure ulcers. Tube feedings may also cause fluid overload, diarrhea, abdominal pain, local complications, less human interaction, and may increase the risk of aspiration.

Benefits of this procedure in those with advanced dementia has not been shown. The risks of using tube feeding include agitation, the person pulling out the tube or otherwise being
physically or chemically immobilized to prevent them from doing this, or getting pressure ulcers. There is about a 1% fatality rate directly related to the procedure with a 3% major complication rate. The percentage of people at the end of their life with dementia using feeding tubes in the USA has dropped from 12% in 2000 to 6% as of 2014.

**Alternative medicine**

Aromatherapy and massage have unclear evidence. There have been studies on the efficacy and safety of cannabinoids in relieving behavioral and psychological symptoms of dementia. Omega-3 fatty acid supplements from plants or fish sources do not appear to benefit or harm people with mild to moderate Alzheimer’s disease. It is unclear if taking omega-3 fatty acid supplements can improve other types of dementia.

**Palliative care**

Given the progressive and terminal nature of dementia, palliative care can be helpful to patients and their caregivers by helping both people with the disorder and their caregivers understand what to expect, deal with loss of physical and mental abilities, plan out a patient’s wishes and goals including surrogate decision making, and discuss wishes for or against CPR and life support. Because the decline can be rapid, and because most people prefer to allow the person with dementia to make his or her own decisions, palliative care involvement before the late stages of dementia is recommended.

**EPIDEMIOLOGY**

The number of cases of dementia worldwide in 2010 was estimated at 35.6 million. Rates increase significantly with age, with dementia affecting 5% of the population older than 65 and 20–40% of those older than 85. Around two thirds of individuals with dementia live in low and middle income countries, where the sharpest increases in numbers are predicted. Rates are slightly higher in women than men at ages 65 and greater. In 2013 dementia resulted in about 1.7 million deaths up from 0.8 million in 1990.
History

Until the end of the 19th century, dementia was a much broader clinical concept. It included mental illness and any type of psychosocial incapacity, including conditions that could be reversed. Dementia at this time simply referred to anyone who had lost the ability to reason, and was applied equally to psychosis of mental illness, “organic” diseases like syphilis that destroy the brain, and to the dementia associated with old age, which was attributed to “hardening of the arteries.”

Dementia has been referred to in medical texts since antiquity. One of the earliest known accounts was written by the 7th century BC Greek physician and mathematician Pythagoras, who divided the human lifespan into six distinct phases, which were 0–6 (infancy), 7–21 (adolescence), 22–49 (young adulthood), 50–62 (middle age), 63–79 (old age), and 80- (advanced age). The last two he described as the “senium”, a period of mental and physical decay, and of the final phase being where “the scene of mortal existence closes after a great length of time that very fortunately, few of the human species arrive at, where the mind is reduced to the imbecility of the first epoch of infancy”. In 550 BC, the Greek Athenian statesman and poet Solon argued that the terms of a man’s will might be invalidated if he exhibited loss of judgement due to advanced age. Chinese medical texts made allusions to the condition as well, and the characters for “dementia” translate literally to “foolish old person”.

Aristotle and Plato from Ancient Greece spoke of the mental decay of advanced age, but apparently simply viewed it as an inevitable process that affected all old men, and which nothing could prevent. The latter stated that the elderly were unsuited for any position of responsibility because, “There is not much acumen of the mind that once carried them in their youth, those characteristics one would call judgement, imagination, power of reasoning, and memory. They see them gradually blunted by deterioration and can hardly fulfill their function.”

For comparison, the Roman statesman Cicero held a view much more in line with modern-day medical wisdom that loss of mental function was not inevitable in the elderly and “affected
only those old men who were weak-willed”. He spoke of how those who remained mentally active and eager to learn new things could stave off dementia. However, Cicero’s views on aging, although progressive, were largely ignored in a world that would be dominated by Aristotle’s medical writings for centuries. Subsequent physicians during the time of Roman Empire such as Galen and Celsus simply repeated the beliefs of Aristotle while adding few new contributions to medical knowledge.

Byzantine physicians sometimes wrote of dementia, and it is recorded that at least seven emperors whose lifespans exceeded the age of 70 displayed signs of cognitive decline. In Constantinople, there existed special hospitals to house those diagnosed with dementia or insanity, but these naturally did not apply to the emperors who were above the law and whose health conditions could not be publicly acknowledged.

Otherwise, little is recorded about senile dementia in Western medical texts for nearly 1700 years. One of the few references to it was the 13th-century friar Roger Bacon, who viewed old age as divine punishment for original sin. Although he repeated existing Aristotelian beliefs that dementia was inevitable after a long enough lifespan, he did make the extremely progressive assertion that the brain was the center of memory and thought rather than the heart.

Poets, playwrights, and other writers however made frequent allusions to the loss of mental function in old age. Shakespeare notably mentions it in some of his plays including *Hamlet* and *King Lear*.

Dementia in the elderly was called *senile dementia* or *senility*, and viewed as a normal and somewhat inevitable aspect of growing old, rather than as being caused by any specific diseases. At the same time, in 1907, a specific organic dementing process of early onset, called Alzheimer’s disease, had been described. This was associated with particular microscopic changes in the brain, but was seen as a rare disease of middle age because the first patient diagnosed with it was a 50-year-old woman.

During the 19th century, doctors generally came to believe that dementia in the elderly was the result of cerebral atherosclerosis, although opinions fluctuated between the idea
that it was due to blockage of the major arteries supplying the brain or small strokes within the vessels of the cerebral cortex. This viewpoint remained conventional medical wisdom through the first half of the 20th century, but by the 1960s was increasingly challenged as the link between neurodegenerative diseases and age-related cognitive decline was established. By the 1970s, the medical community maintained that vascular dementia was rarer than previously thought and Alzheimer’s disease caused the vast majority of mental impairments in old age. More recently however, it is believed that dementia is often a mixture of both conditions.

Much like other diseases associated with aging, dementia was comparatively rare before the 20th century, due to the fact that it is most common in people over 80, and such lifespans were uncommon in preindustrial times. Conversely, syphilitic dementia was widespread in the developed world until largely being eradicated by the use of penicillin after WWII. With significant increases in life expectancy following WWII, the number of people in developed countries over 65 started rapidly climbing. While elderly persons constituted an average of 3–5% of the population prior to 1945, by 2010 it was common in many countries to have 10–14% of people over 65 and in Germany and Japan, this figure exceeded 20%. Public awareness of Alzheimer’s Disease was greatly increased in 1994 when former US president Ronald Reagan announced that he had been diagnosed with the condition.

By the period of 1913–20, schizophrenia had been well-defined in a way similar to today, and also the term dementia praecox had been used to suggest the development of senile-type dementia at a younger age. Eventually the two terms fused, so that until 1952 physicians used the terms dementia praecox (precocious dementia) and schizophrenia interchangeably. The term precocious dementia for a mental illness suggested that a type of mental illness like schizophrenia (including paranoia and decreased cognitive capacity) could be expected to arrive normally in all persons with greater age. After about 1920, the beginning use of dementia for what we now understand as schizophrenia and senile dementia helped limit the word’s meaning to “permanent, irreversible mental deterioration”. This began the change to the more recognizable use of the term today.
In 1976, neurologist Robert Katzmann suggested a link between senile dementia and Alzheimer’s disease. Katzmann suggested that much of the senile dementia occurring (by definition) after the age of 65, was pathologically identical with Alzheimer’s disease occurring before age 65 and therefore should not be treated differently. He noted that the fact that “senile dementia” was not considered a disease, but rather part of aging, was keeping millions of aged patients experiencing what otherwise was identical with Alzheimer’s disease from being diagnosed as having a disease process, rather than simply considered as aging normally. Katzmann thus suggested that Alzheimer’s disease, if taken to occur over age 65, is actually common, not rare, and was the 4th or 5th leading cause of death, even though rarely reported on death certificates in 1976.

This suggestion opened the view that dementia is never normal, and must always be the result of a particular disease process, and is not part of the normal healthy aging process, per se. The ensuing debate led for a time to the proposed disease diagnosis of “senile dementia of the Alzheimer’s type” (SDAT) in persons over the age of 65, with “Alzheimer’s disease” diagnosed in persons younger than 65 who had the same pathology. Eventually, however, it was agreed that the age limit was artificial, and that Alzheimer’s disease was the appropriate term for persons with the particular brain pathology seen in this disorder, regardless of the age of the person with the diagnosis. A helpful finding was that although the incidence of Alzheimer’s disease increased with age (from 5–10% of 75-year-olds to as many as 40–50% of 90-year-olds), there was no age at which all persons developed it, so it was not an inevitable consequence of aging, no matter how great an age a person attained. Evidence of this is shown by numerous documented supercentenarians (people living to 110+) that experienced no serious cognitive impairment. There is some evidence that dementia is most likely to develop between the ages of 80–84 and individuals who pass that point without being affected have a lower chance of developing it. Women account for a larger percentage of dementia cases than men, although this can be attributed to their longer overall lifespan and greater odds of attaining an age where the condition is likely to occur.
Also, after 1952, mental illnesses like schizophrenia were removed from the category of organic brain syndromes, and thus (by definition) removed from possible causes of “dementing illnesses” (dementias). At the same, however, the traditional cause of senile dementia - “hardening of the arteries” - now returned as a set of dementias of vascular cause (small strokes). These were now termed multi-infarct dementias or vascular dementias.

In the 21st century, a number of other types of dementia have been differentiated from Alzheimer’s disease and vascular dementias (these two being the most common types). This differentiation is on the basis of pathological examination of brain tissues, symptomatology, and by different patterns of brain metabolic activity in nuclear medical imaging tests such as SPECT and PET scans of the brain. The various forms of dementia have differing prognoses (expected outcome of illness), and also differing sets of epidemiologic risk factors. The causal etiology of many of them, including Alzheimer’s disease, remains unclear, although many theories exist such as accumulation of protein plaques as part of normal aging, inflammation (either from bacterial pathogens or exposure to toxic chemicals), inadequate blood sugar, and traumatic brain injury.

**SOCIETY AND CULTURE**

Many countries consider the care of people living with dementia a national priority and invest in resources and education to better inform health and social service workers, unpaid caregivers, relatives, and members of the wider community. Several countries have national plans or strategies. In these national plans, there is recognition that people can live well with dementia for a number of years, as long as there is the right support and timely access to a diagnosis. The former British Prime Minister David Cameron has described dementia as being a “national crisis”, affecting 800,000 people in the United Kingdom.

In the United Kingdom, as with all mental disorders, where a person with dementia could potentially be a danger to themselves or others, they can be detained under the Mental Health Act 1983 for the purposes of assessment, care and treatment. This is a last
resort, and usually avoided if the patient has family or friends who can ensure care.

Driving with dementia could lead to severe injury or even death to self and others. Doctors should advise appropriate testing on when to quit driving. The United Kingdom DVLA (Driver & Vehicle Licensing Agency) states that people with dementia who specifically have poor short term memory, disorientation, or lack of insight or judgment are not fit to drive, and in these instances the DVLA must be informed so that the driving licence can be revoked. They do, however, acknowledge low-severity cases and those with an early diagnosis, and those drivers may be permitted to drive pending medical reports.

Many support networks are available to people with dementia and their families and caregivers. Several charitable organisations aim to raise awareness and campaign for the rights of people living with dementia. There is also support and guidance on assessing testamentary capacity in people who have dementia.

In 2015, Atlantic Philanthropies announced a $177 million gift aimed at understanding and reducing dementia. The recipient was Global Brain Health Institute, a program co-led by the University of California, San Francisco and Trinity College Dublin. This donation is the largest non-capital grant Atlantic has ever made, and the biggest philanthropic donation in Irish history.

**PREVENTION OF DEMENTIA**

Prevention of dementia is the attempt to avoid developing dementia. Although no cure for dementia is available, there are ways of decreasing the risk of developing dementia, including both lifestyle changes and medication. Efforts to prevent dementia include trying to decrease risk factors for vascular disease, including diabetes, high blood pressure, obesity, smoking and physical inactivity.

**Lifestyle**

**Mental activity**

“Use it or lose it” might be applied to the brain when it comes to dementia. Intellectual activities help keep the mind in shape in
later years. Activities such as reading, learning a new language, playing cards and board games and playing a musical instrument can postpone the onset and slow the progression of both Alzheimer’s and vascular dementia. The risk decrease is proportional to frequency of activity, with slower cognitive decline being associated with both late-life and early-life increased cognitive activity.

SMART Brain Aging is a cognitive rehabilitation program designed to improve brain function in elderly individuals who may have early memory loss, including Mild Cognitive Impairment MCI. The treatment was developed by Scottsdale, Arizona-based Clinical Neuropsychologist John DenBoer. This early stage dementia treatment has received media attention due to the positive results patients are experiencing as a result of the SMART Brain Aging Program. DenBoer is part of a growing community of neuropsychologists who believe regimented and personalized mental exercises can help slow the progress of dementia significantly.

Apart from spare time activities, a mentally demanding job may prevent dementia, especially during the thirties, forties and fifties. Mental activity may help to prevent dementia by building up a “brain reserve”: additional connections between neurons are created which are more resistant to the deterioration seen in dementia.

**Physical activity**

Since vascular dementia is the second most common form of dementia (after Alzheimer’s disease), reducing the risk of cerebrovascular disease also reduces the risk of dementia. Thus, physical exercise, having good blood cholesterol, healthy body weight and blood pressure lowers the risk of developing dementia. An active lifestyle can almost halve the risk compared to a sedentary one.

The effect of physical activity is not limited to vascular effects. Physical activity can give rise to new neurons in the brain, as well as releasing a substance that can protect them. The protein known as brain-derived neurotropic factor (BDNF) is known to be
Dementia

important in the development, survival and plasticity of neurons. Regular exercise can boost BDNF levels by 2-3 times.

Some studies say Alzheimer’s and other dementias may be caused by high blood pressure, since it can cause blood vessel damage through constriction.

Diet

Obesity increases the risk of any dementia and Alzheimer’s disease in particular. The effect of alcohol on the risk of dementia is a J curve: high alcohol consumption increases the risk of dementia while low alcohol consumption may be protective. However, low alcohol consumption may not protect against vascular dementia and overall cognitive decline. Moderate alcohol consumption can possibly reduce the risk of vascular disease and dementia because it can increase blood levels of HDL cholesterol and weakens blood-clotting agents such as fibrinogen, which offers some protection against heart attacks and small subclinical strokes that together can ultimately damage the brain.

The effects of omega-3 fatty acid in the prevention of dementia is uncertain. Vegetables and nuts may be of benefit, because of their high content of polyunsaturated fats. Non-fish meat, on the other hand, increases the risk of Alzheimer’s, because of its high content of saturated fat. However, consumption of fish should be limited due to concerns over mercury poisoning, which could exacerbate the symptoms of dementia.

Niacin (vitamin B₃) is also believed to prevent dementia as research shows those who have the highest levels of niacin in their blood, are believed to have the lowest risk of developing dementia or having cognitive decline. Niacin is involved with DNA synthesis and repair and also neural cell signaling, it improves circulation and reduces cholesterol levels. In order for niacin to have a positive effect on the brain, it is recommended that patients have 100 to 300 mg per day.

There is evidence for an association between cognitive decline, homocysteine (Hcy) status, and vitamin B status relating especially to B12 and also to vitamins B6 and B9. In particular, deficiency of vitamin B12 and/or of folate can cause an increase in Hcy plasma
levels, which in turn leads to toxic effects on the vascular and nervous systems. Vitamin D deficiency correlates with cognitive impairment and dementia; however, the value of vitamin D substitution in cognitive impairment remains doubtful.

**Sleep pattern**
More than nine hours of sleep per day (including daytime napping) may be associated with an increased risk of dementia. Lack of sleep may also increase risk of dementia by increasing beta-amyloid deposition.

**Personality and Mental Health**
Being neurotic increases the risk of developing Alzheimer’s, a type of dementia. Neuroticism is associated with increased brain atrophy and cognitive impairment in life, while conscientiousness has a protective effect by preventing brain atrophy.

**MEDICATION**

**Hypertension medications**
The etiology of vascular dementia includes hypertension, and thus, lowering blood pressure with antihypertensives may have a positive effect in the prevention of dementia, just as physical activity.

However, a study failed to demonstrate a link between high blood pressure and developing dementia. The study, published in the *Lancet Neurology* journal July 2008, found that blood pressure lowering medication did not reduce the incidence of dementia to a statistically significant degree. A prospective meta-analysis of the data from this study with other studies suggested that further research might be warranted.

**Anti-diabetic drugs**
Diabetes mellitus is a risk factor for vascular dementia, and is thus the risk is lowered with anti-diabetic drugs. Besides, Rosiglitazone (Avandia) improves memory and thinking ability for people with mild Alzheimer’s disease. The mechanism of the effect may be the ability of the drug to reduce insulin resistance.
Thus, less insulin needs to be released to achieve its metabolic effects. Insulin in the bloodstream is a trigger of amyloid beta-production, so decreased insulin levels decrease the level of amyloid beta. This leads to less formation of amyloid plaques seen in Alzheimer’s disease.

**Steroid hormones**

Estrogen may also help in the prevention of dementia but cannot help when dementia is already present and when cognitive function is already impaired. It increases cerebral blood flow and is an anti-inflammatory agent, enhancing activity at the neuronal synapses in the brain. It may also help to increase brain activation in regions that are affected by dementia which is mainly the hippocampus region. Recent evidence on the effects of estrogen do not allow for an unambiguous recommendation for estrogen supplementation and they indicate that the timing of estrogen supplementation may be important, with early postmenopausal use being preferable over its use later in life.

**NSAIDs**

Non-steroidal anti-inflammatory drugs (NSAIDs) can decrease the risk of developing Alzheimer’s and Parkinson’s diseases. The length of time needed to prevent dementia varies, but in most studies it is usually between 2 and 10 years. Research has also shown that it must be used in clinically relevant dosages and that so called “baby aspirin” doses are ineffective at preventing and treating dementia. Alzheimer’s disease causes inflammation in the neurons by its deposits of amyloid beta peptides and neurofibrillary tangles. These deposits irritate the body by causing a release of e.g. cytokines and acute phase proteins, leading to inflammation. When these substances accumulate over years they contribute to the effects of Alzheimer’s. NSAIDs inhibit the formation of such inflammatory substances, and prevent the deteriorating effects.

**Vaccine**

There is as yet no vaccine against dementia. It has been theorized that a vaccine could activate the body’s own immune system to combat the beta amyloid plaques in Alzheimer’s disease.
One problem to overcome is overreaction from the immune system, leading to encephalitis.

**COGNITIVE THERAPIES FOR DEMENTIA**

Psychological therapies for dementia are starting to gain some momentum. Improved clinical assessment in early stages of Alzheimer’s disease and other forms of dementia, increased cognitive stimulation of the elderly, and the prescription of drugs to slow cognitive decline have resulted in increased detection in the early stages. Although the opinions of the medical community are still apprehensive to support cognitive therapies in dementia patients, recent international studies have started to create optimism.

**Classification and efficacy of the different therapies**

Psychological therapies which are considered as a treatment for dementia include music therapy, reminiscence therapy, cognitive reframing for caretakers, validation therapy, and mental exercise. Interventions may be used in conjunction with pharmaceutical treatment and can be classified within behavior, emotion, cognition or stimulation oriented approaches. Research on efficacy is reduced.

**Behavioral interventions**

Behavioral interventions attempt to identify and reduce the antecedents and consequences of problem behaviors. This approach has not shown success in the overall functioning of patients, but can help to reduce some specific problem behaviors, such as incontinence. There is still a lack of high quality data on the effectiveness of these techniques in other behavior problems such as wandering.

**Emotion-oriented interventions**

Emotion-oriented interventions include reminiscence therapy, validation therapy, supportive psychotherapy, sensory integration or snoezelen, and simulated presence therapy. Supportive psychotherapy has received little or no formal scientific study, but some clinicians find it useful in helping mildly impaired patients
Dementia

adjust to their illness. Reminiscence therapy (RT) involves the discussion of past experiences individually or in group, many times with the aid of photographs, household items, music and sound recordings, or other familiar items from the past. Although there are few quality studies on the effectiveness of RT it may be beneficial for cognition and mood. Simulated presence therapy (SPT) is based on attachment theories and is normally carried out playing a recording with voices of the closests relatives of the patient. There is preliminary evidence indicating that SPT may reduce anxiety and challenging behaviors. Finally, validation therapy is based on acceptance of the reality and personal truth of another’s experience, while sensory integration is based on exercises aimed to stimulate senses. There is little evidence to support the usefulness of these therapies.

Cognition-oriented treatments

The aim of cognition-oriented treatments, which include reality orientation and cognitive retraining is the restoration of cognitive deficits. Reality orientation consists in the presentation of information about time, place or person in order to ease the understanding of the person about its surroundings and his place in them. On the other hand, cognitive retraining tries to improve impaired capacities by exercitation of mental abilities. Both have shown some efficacy improving cognitive capacities, although in some works these effects were transient and negative effects, such as frustration, have also been reported. Most of the programs inside this approach are fully or partially computerized and others are fully paper based such as the Cognitive Retention Therapy method.

Stimulation-oriented treatments

Stimulation-oriented treatments include art, music and pet therapies, exercise, and any other kind of recreational activities for patients. Stimulation has modest support for improving behavior, mood, and, to a lesser extent, function. Nevertheless, as important as these effects are, the main support for the use of stimulation therapies is the improvement in the patient daily life routine they suppose.
A study published in 2006 tested the effects of Cognitive Stimulation Therapy (CST) on the demented elderly’s quality of life. The researchers looked at the effect of CST on cognitive function, the effect of improved cognitive function on quality of life, then the link between the three (CST, cognition, and QoL). The study found an improvement in cognitive function from the CST treatment, as measured by the Mini Mental State Examination (MMSE) and the Alzheimer’s Disease Assessment Scale (ADAS-Cog), as well as an improvement in quality of life self-reported by the participants using the Quality of Life-AD measure. The study then used regression models to explain the correlation between the CST therapy and quality of life to see if the improved cognitive function was the primary mediating factor for the improved quality of life. The models supported the correlation and proposed that it was the improved cognition more than other factors (such as reduced depression symptoms and less anxiety) that led to the participants reporting back that they had a better quality of life (with significant improvements especially in energy level, memory, relationship with significant other, and ability to do chores.)

Another study that was done in 2010 by London College that tested the efficacy of the Cognitive Stimulation Therapy. Participants were tested using a Mini Mental State Examination to test their level of cognitive ability and see if they qualified as a demented patient to be included in the study. The participants had to have no other health problems allowing for the experiment to have accurate internal validity. The results clearly showed that those who were given the Cognitive Stimulation Therapy did significantly better on all memory tasks than those that did not receive the therapy. Out of the eleven memory tasks that were given ten of the memory tasks were improved by the therapeutic group. This is another study that supports the efficacy of CST, demonstrating that the elderly that have dementia greatly benefit from this treatment. Just like it was tested in the 2006 study, the improvement of the participants’ cognitive abilities can ultimately improve their daily lives since it helps with social influences being able to speak, remember words etc.
In July 2015 UK NHS trials were reported of a robot seal from Japan being in the management of distressed and disturbed behaviour in dementia patients. “Paro”, which has some artificial intelligence has the ability to “learn” and remember its own name. It can also learn the behaviour that results in a pleasing stroking response and repeat it. The robot was being evaluated in a joint project involving Sheffield Health and Social Care NHS Foundation Trust and the University of Sheffield.

PSYCHOLOGICAL APPROACHES TO THE MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS OF DEMENTIA

Out of 1632 total studies reviewed roughly 10% of them were included in the review. Objective was to determine the level of quality of the studies and the effectiveness of the results. Main theories of the studies explored were as follows.

• Reminiscence Therapy - using household materials, family pictures and old newspapers to stimulate memories and hopefully have the participant share their experiences.

  Results were dependent on reality orientation and were largely insignificant.

• Validation Therapy - Based on personal uniqueness, promotes validating feelings of unfinished conflicts.

  Results were inconclusive and insignificant.

• Reality Orientation Therapy - Uses reminders about information such as day, time and location.

  Results were insignificant.

• Cognitive Retention Therapy - Uses information processing.

  Results varied but were very positive in improving aspects of neuropsychiatric symptoms immediately and for many months after. Also improved mood, and delayed institutionalization.

• Other dementia-specific therapies - “individualized special instruction” and “self-maintenance therapy”

  Results may have been a product of environment but concluded an improvement to behavior and depression.
• Non-dementia-specific therapies - Included many different varieties of treatments. Most were inconclusive. Positive results were achieved using ‘life review, sensory stimulation’ and other personalized techniques.
  • Music Therapy - Helps reduce agitation and improve behavior during sessions and immediately after, however no long term benefits.
  • Snoezelen therapy - Possible improvement in disruptive behavior during sessions, effects are only apparent for a short time after.
  • Other sensory stimulation - Calming effects during sessions, no long term usefulness.
  • Simulated presence therapy - Possible reduction in agitation, no other real benefits.
  • Therapeutic activity programs - Results varied but overall were inconsistent and inconclusive with no real benefits.
  • Montessori activities - No changes realized.
  • Physical exercise - No changes realized.
  • Social interaction - Possible improvement in neuropsychiatric symptoms in some participants.
  • Decreased sensory stimulation - No real benefits.
  • Environmental Manipulation - Changing the visual environment, adding or removing mirrors, signposting, unlocking doors and other environmental manipulations such as group living.

Results showed a possible reduction in agitation and improvement with orientation, with no other real benefits.

• Other studies focused on psychoeducation of Staff and family members ability to manage behavioral problems.

Results showed individual education was more effective then groups in being useful to treat neuropsychiatric symptoms.

DEMENTIA PRAECOX

Dementia praecox (a “premature dementia” or “precocious madness”) is a chronic, deteriorating psychotic disorder characterized by rapid cognitive disintegration, usually beginning
in the late teens or early adulthood. Schizophrenia is the new word describing this disease. The term was first used in 1891 by Arnold Pick (1851–1924), a professor of psychiatry at Charles University in Prague. His brief clinical report described the case of a person with a psychotic disorder resembling hebephrenia. German psychiatrist Emil Kraepelin (1856–1926) popularised it in his first detailed textbook descriptions of a condition that eventually became a different disease concept and relabeled as schizophrenia. Kraepelin reduced the complex psychiatric taxonomies of the nineteenth century by dividing them into two classes: manic-depressive psychosis and dementia praecox. This division, commonly referred to as the Kraepelinian dichotomy, had a fundamental impact on twentieth-century psychiatry, though it has also been questioned.

The primary disturbance in dementia praecox is a disruption in cognitive or mental functioning in attention, memory, and goal-directed behaviour. Kraepelin contrasted this with manic-depressive psychosis, now termed bipolar disorder, and also with other forms of mood disorder, including major depressive disorder. He eventually concluded that it was not possible to distinguish his categories on the basis of cross-sectional symptoms.

Kraepelin viewed dementia praecox as a progressively deteriorating disease from which no one recovered. However, by 1913, and more explicitly by 1920, Kraepelin admitted that while there may be a residual cognitive defect in most cases, the prognosis was not as uniformly dire as he had stated in the 1890s. Still, he regarded it as a specific disease concept that implied incurable, inexplicable madness.

History

First use of the term

Dementia is an ancient term which has been in use since at least the time of Lucretius in 50 B.C.E. where it meant “being out of one’s mind”. Until the seventeenth century dementia referred to states of cognitive and behavioural deterioration leading to psychosocial incompetence. This condition could be innate or acquired and the concept had no reference to a necessarily
irreversible condition. It is the concept in this popular notion of psychosocial incapacity that forms the basis for the idea of legal incapacity.

By the eighteenth century, at the period when the term entered into European medical discourse, clinical concepts were added to the vernacular understanding such that dementia was now associated with intellectual deficits arising from any cause and at any age.

By the end of the nineteenth century the modern ‘cognitive paradigm’ of dementia was taking root. This holds that dementia is understood in terms of criteria relating to aetiology, age and course which excludes former members of the family of the demented such as adults with acquired head trauma or children with cognitive deficits.

Moreover, it was now understood as an irreversible condition and a particular emphasis was placed on memory loss in regard to the deterioration of intellectual functions.

The term *démence précoce* was used in passing to describe the characteristics of a subset of young mental patients by the French physician Bénédict Augustin Morel in 1852 in the first volume of his *Études cliniques*, and the term is used more frequently in his textbook *Traité des maladies mentales* which was published in 1860.

Morel, whose name will be forever associated with religiously inspired concept of degeneration theory in psychiatry, used the term in a descriptive sense and not to define a specific and novel diagnostic category.

It was applied as a means of setting apart a group of young men and women who were suffering from “stupor.” As such their condition was characterised by a certain torpor, enervation, and disorder of the will and was related to the diagnostic category of melancholia. He did not conceptualise their state as irreversible and thus his use of the term dementia was equivalent to that formed in the eighteenth century as outlined above.

While some have sought to interpret, if in a qualified fashion, the use by Morel of the term *démence précoce* as amounting to the “discovery” of schizophrenia, others have argued convincingly
that Morel’s descriptive use of the term should not be considered in any sense as a precursor to Kraepelin’s dementia praecox disease concept.

This is due to the fact that their concepts of dementia differed significantly from each other, with Kraepelin employing the more modern sense of the word and that Morel was not describing a diagnostic category. Indeed, until the advent of Pick and Kraepelin, Morel’s term had vanished without a trace and there is little evidence to suggest that either Pick or indeed Kraepelin were even aware of Morel’s use of the term until long after they had published their own disease concepts bearing the same name. As Eugène Minkowski succinctly stated, ‘An abyss separates Morel’s démence précoce from that of Kraepelin.’

Morel described several psychotic disorders that ended in dementia, and as a result he may be regarded as the first alienist or psychiatrist to develop a diagnostic system based on presumed outcome rather than on the current presentation of signs and symptoms. Morel, however, did not conduct any long-term or quantitative research on the course and outcome of dementia praecox (Kraepelin would be the first in history to do that) so this prognosis was based on speculation. It is impossible to discern whether the condition briefly described by Morel was equivalent to the disorder later called dementia praecox by Pick and Kraepelin.

**Time component**

Psychiatric nosology in the nineteenth-century was chaotic and characterised by a conflicting mosaic of contradictory systems. Psychiatric disease categories were based upon short-term and cross-sectional observations of patients from which were derived the putative characteristic signs and symptoms of a given disease concept.

The dominant psychiatric paradigms which gave a semblance of order to this fragmentary picture were Morelian degeneration theory and the concept of “unitary psychosis” (*Einheitspsychose*). This latter notion, derived from the Belgian psychiatrist Joseph Guislain (1797–1860), held that the variety of symptoms attributed to mental illness were manifestations of a single underlying disease
process. While these approaches had a diachronic aspect they lacked a conception of mental illness that encompassed a coherent notion of change over time in terms of the natural course of the illness and based upon an empirical observation of changing symptomatology.

In 1863, the Danzig-based psychiatrist Karl Ludwig Kahlbaum (1828–1899) published his text on psychiatric nosology *Die Gruppierung der psychischen Krankheiten* (*The Classification of Psychiatric Diseases*). Although with the passage of time this work would prove profoundly influential, when it was published it was almost completely ignored by German academia despite the sophisticated and intelligent disease classification system which it proposed.

In this book Kahlbaum categorized certain typical forms of psychosis (*vesania typica*) as a single coherent type based upon their shared progressive nature which betrayed, he argued, an ongoing degenerative disease process. For Kahlbaum the disease process of *vesania typica* was distinguished by the passage of the sufferer through clearly defined disease phases: a melancholic stage; a manic stage; a confusional stage; and finally a demented stage.

In 1866 Kahlbaum became the director of a private psychiatric clinic in Görlitz (Prussia, today Saxony, a small town near Dresden). He was accompanied by his younger assistant, Ewald Hecker (1843–1909), and during a ten-year collaboration they conducted a series of research studies on young psychotic patients that would become a major influence on the development of modern psychiatry.

Together Kahlbaum and Hecker were the first to describe and name such syndromes as dysthymia, cyclothymia, paranoia, catatonia, and hebephrenia. Perhaps their most lasting contribution to psychiatry was the introduction of the “clinical method” from medicine to the study of mental diseases, a method which is now known as psychopathology.

When the element of time was added to the concept of diagnosis, a diagnosis became more than just a description of a collection of symptoms: diagnosis now also defined by prognosis
(course and outcome). An additional feature of the clinical method was that the characteristic symptoms that define syndromes should be described without any prior assumption of brain pathology (although such links would be made later as scientific knowledge progressed). Karl Kahlbaum made an appeal for the adoption of the clinical method in psychiatry in his 1874 book on catatonia. Without Kahlbaum and Hecker there would be no dementia praecox.

Upon his appointment to a full professorship in psychiatry at the University of Dorpat (now Tartu, Estonia) in 1886, Kraepelin gave an inaugural address to the faculty outlining his research programme for the years ahead.

Attacking the “brain mythology” of Meynert and the positions of Griesinger and Gudden, Kraepelin advocated that the ideas of Kahlbaum, who was then a marginal and little known figure in psychiatry, should be followed. Therefore, he argued, a research programme into the nature of psychiatric illness should look at a large number of patients over time to discover the course which mental disease could take. It has also been suggested that Kraepelin’s decision to accept the Dorpat post was informed by the fact that there he could hope to gain experience with chronic patients and this, it was presumed, would facilitate the longitudinal study of mental illness.

**Quantitative component**

Understanding that objective diagnostic methods must be based on scientific practice, Kraepelin had been conducting psychological and drug experiments on patients and normal subjects for some time when, in 1891, he left Dorpat and took up a position as professor and director of the psychiatric clinic at Heidelberg University. There he established a research program based on Kahlbaum’s proposal for a more exact qualitative clinical approach, and his own innovation: a quantitative approach involving meticulous collection of data over time on each new patient admitted to the clinic (rather than only the interesting cases, as had been the habit until then).

Kraepelin believed that by thoroughly describing all of the clinic’s new patients on index cards, which he had been using
Diagnosis and Treatment of Senile Dementia

since 1887, researcher bias could be eliminated from the investigation process. He described the method in his posthumously published memoir:... after the first thorough examination of a new patient, each of us had to throw in a note [in a “diagnosis box”] with his diagnosis written on it. After a while, the notes were taken out of the box, the diagnoses were listed, and the case was closed, the final interpretation of the disease was added to the original diagnosis. In this way, we were able to see what kind of mistakes had been made and were able to follow-up the reasons for the wrong original diagnosis.

The fourth edition of his textbook, Psychiatrie, published in 1893, two years after his arrival at Heidelberg, contained some impressions of the patterns Kraepelin had begun to find in his index cards. Prognosis (course and outcome) began to feature alongside signs and symptoms in the description of syndromes, and he added a class of psychotic disorders designated “psychic degenerative processes”, three of which were borrowed from Kahlbaum and Hecker: dementia paranoides (a degenerative type of Kahlbaum’s paranoia, with sudden onset), catatonia (per Kahlbaum, 1874) and dementia praecox, (Hecker’s hebephrenia of 1871). Kraepelin continued to equate dementia praecox with hebephrenia for the next six years.

In the March 1896 fifth edition of Psychiatrie, Kraepelin expressed confidence that his clinical method, involving analysis of both qualitative and quantitative data derived from long term observation of patients, would produce reliable diagnoses including prognosis:

What convinced me of the superiority of the clinical method of diagnosis (followed here) over the traditional one, was the certainty with which we could predict (in conjunction with our new concept of disease) the future course of events. Thanks to it the student can now find his way more easily in the difficult subject of psychiatry.

Kraepelin’s influence on the next century

In the 1899 (6th) edition of Psychiatrie, Kraepelin established a paradigm for psychiatry that would dominate the following
century, sorting most of the recognized forms of insanity into two major categories: dementia praecox and manic-depressive illness. Dementia praecox was characterized by disordered intellectual functioning, whereas manic-depressive illness was principally a disorder of affect or mood; and the former featured constant deterioration, virtually no recoveries and a poor outcome, while the latter featured periods of exacerbation followed by periods of remission, and many complete recoveries.

The class, dementia praecox, comprised the paranoid, catatonic and hebephrenic psychotic disorders, and these forms were found in the Diagnostic and Statistical Manual of Mental Disorders until the fifth edition was released, in May 2013. These terms, however, are still found in general psychiatric nomenclature. The ICD-10 still uses “hebephrenic” to designate the third type.

**Change in prognosis**

In the seventh, 1904, edition of *Psychiatrie*, Kraepelin accepted the possibility that a small number of patients may recover from dementia praecox.

Eugen Bleuler reported in 1908 that in many cases there was no inevitable progressive decline, there was temporary remission in some cases, and there were even cases of near recovery with the retention of some residual defect.

In the eighth edition of Kraepelin’s textbook, published in four volumes between 1909 and 1915, he described eleven forms of dementia, and dementia praecox was classed as one of the “endogenous dementias”. Modifying his previous more gloomy prognosis in line with Bleuler’s observations, Kraepelin reported that about 26% of his patients experienced partial remission of symptoms. Kraepelin died while working on the ninth edition of *Psychiatrie* with Johannes Lange (1891–1938), who finished it and brought it to publication in 1927.

**Etiology**

Though his work and that of his research associates had revealed a role for heredity, Kraepelin realized nothing could be said with certainty about the aetiology of dementia praecox, and he left out speculation regarding brain disease or neuropathology
in his diagnostic descriptions. Nevertheless, from the 1896 edition onwards Kraepelin made clear his belief that poisoning of the brain, “auto-intoxication,” probably by sex hormones, may underlie dementia praecox – a theory also entertained by Eugen Bleuler. Both theorists insisted dementia praecox is a biological disorder, not the product of psychological trauma.

Thus, rather than a disease of hereditary degeneration or of structural brain pathology, Kraepelin believed dementia praecox was due to a systemic or “whole body” disease process, probably metabolic, which gradually affected many of the tissues and organs of the body before affecting the brain in a final, decisive cascade. Kraepelin, recognizing dementia praecox in Chinese, Japanese, Tamil and Malay patients, suggested in the eighth edition of *Psychiatrie* that, “we must therefore seek the real cause of dementia praecox in conditions which are spread all over the world, which thus do not lie in race or in climate, in food or in any other general circumstance of life...”

**Treatment**

Kraepelin had experimented with hypnosis but found it wanting, and disapproved of Freud’s and Jung’s introduction, based on no evidence, of psychogenic assumptions to the interpretation and treatment of mental illness.

He argued that, without knowing the underlying cause of dementia praecox or manic-depressive illness, there could be no disease-specific treatment, and recommended the use of long baths and the occasional use of drugs such as opiates and barbiturates for the amelioration of distress, as well as occupational activities, where suitable, for all institutionalized patients. Based on his theory that dementia praecox is the product of autointoxication emanating from the sex glands, Kraepelin experimented, without success, with injections of thyroid, gonad and other glandular extracts.

**Use of term spreads**

Kraepelin noted the dissemination of his new disease concept when in 1899 he enumerated the term’s appearance in almost twenty articles in the German-language medical press. In the early
years of the twentieth century the twin pillars of the Kraepelinian
dichotomy, dementia praecox and manic depressive psychosis,
were assiduously adopted in clinical and research contexts among
the Germanic psychiatric community.

German-language psychiatric concepts were always introduced
much faster in America (than, say, Britain) where émigré German,
Swiss and Austrian physicians essentially created American
psychiatry. Swiss-émigré Adolf Meyer (1866–1950), arguably the
most influential psychiatrist in America for the first half of the
20th century, published the first critique of dementia praecox in
But it was not until 1900 and 1901 that the first three American
publications regarding dementia praecox appeared, one of which
was a translation of a few sections of Kraepelin’s 6th edition of
1899 on dementia praecox.

Adolf Meyer was the first to apply the new diagnostic term
in America. He used it at the Worcester Lunatic Hospital in
Massachusetts in the fall of 1896. He was also the first to apply
Eugen Bleuler’s term “schizophrenia” (in the form of
“schizophrenic reaction”) in 1913 at the Henry Phipps Psychiatric
Clinic of the Johns Hopkins Hospital.

The dissemination of Kraepelin’s disease concept to the
Anglophone world was facilitated in 1902 when Ross Diefendorf,
a lecturer in psychiatry at Yale, published an adapted version of
the sixth edition of the Lehrbuch der Psychiatrie.

This was republished in 1904 and with a new version, based
on the seventh edition of Kraepelin’s Lehrbuch appearing in 1907
and reissued in 1912.

Both dementia praecox (in its three classic forms) and “manic-
depressive psychosis” gained wider popularity in the larger
institutions in the eastern United States after being included in the
official nomenclature of diseases and conditions for record-keeping
at Bellevue Hospital in New York City in 1903. The term lived on
due to its promotion in the publications of the National Committee
on Mental Hygiene (founded in 1909) and the Eugenics Records
Office (1910). But perhaps the most important reason for the
longevity of Kraepelin’s term was its inclusion in 1918 as an
official diagnostic category in the uniform system adopted for comparative statistical record-keeping in all American mental institutions, *The Statistical Manual for the Use of Institutions for the Insane*. Its many revisions served as the official diagnostic classification scheme in America until 1952 when the first edition of the *Diagnostic and Statistical Manual: Mental Disorders*, or DSM-I, appeared. Dementia praecox disappeared from official psychiatry with the publication of DSM-I, replaced by the Bleuler/Meyer hybridization, "schizophrenic reaction".

Schizophrenia was mentioned as an alternate term for dementia praecox in the 1918 *Statistical Manual*. In both clinical work as well as research, between 1918 and 1952 five different terms were used interchangeably: dementia praecox, schizophrenia, dementia praecox (schizophrenia), schizophrenia (dementia praecox) and schizophrenic reaction. This made the psychiatric literature of the time confusing since, in a strict sense, Kraepelin’s disease was not Bleuler’s disease. They were defined differently, had different population parameters, and different concepts of prognosis.

The reception of dementia praecox as an accepted diagnosis in British psychiatry came more slowly, perhaps only taking hold around the time of World War I. There was substantial opposition to the use of the term “dementia” as misleading, partly due to findings of remission and recovery.

Some argued that existing diagnoses such as “delusional insanity” or “adolescent insanity” were better or more clearly defined. In France a psychiatric tradition regarding the psychotic disorders predated Kraepelin, and the French never fully adopted Kraepelin’s classification system. Instead the French maintained an independent classification system throughout the 20th century. From 1980, when DSM-III totally reshaped psychiatric diagnosis, French psychiatry began to finally alter its views of diagnosis to converge with the North American system. Kraepelin thus finally conquered France via America.

**From dementia praecox to schizophrenia**

Due to the influence of alienists such as Adolf Meyer, August Hoch, George Kirby, Charles Macphie Campbell, Smith Ely Jelliffe
and William Alanson White, psychogenic theories of dementia praecox dominated the American scene by 1911. In 1925 Bleuler’s schizophrenia rose in prominence as an alternative to Kraepelin’s dementia praecox. When Freudian perspectives became influential in American psychiatry in the 1920s schizophrenia became an attractive alternative concept. Bleuler corresponded with Freud and was connected to Freud’s psychoanalytic movement, and the inclusion of Freudian interpretations of the symptoms of schizophrenia in his publications on the subject, as well as those of C.G. Jung, eased the adoption of his broader version of dementia praecox (schizophrenia) in America over Kraepelin’s narrower and prognostically more negative one.

The term “schizophrenia” was first applied by American alienists and neurologists in private practice by 1909 and officially in institutional settings in 1913, but it took many years to catch on. It is first mentioned in The New York Times in 1925. Until 1952 the terms dementia praecox and schizophrenia were used interchangeably in American psychiatry, with occasional use of the hybrid terms “dementia praecox (schizophrenia)” or “schizophrenia (dementia praecox)”.

**Diagnostic manuals**

Editions of the Diagnostic and Statistic Manual of Mental Disorders since the first in 1952 had reflected views of schizophrenia as “reactions” or “psychogenic” (DSM-I), or as manifesting Freudian notions of “defense mechanisms” (as in DSM-II of 1969 in which the symptoms of schizophrenia were interpreted as “psychologically self-protected”). The diagnostic criteria were vague, minimal and wide, including either concepts that no longer exist or that are now labeled as personality disorders (for example, schizotypal personality disorder). There was also no mention of the dire prognosis Kraepelin had made. Schizophrenia seemed to be more prevalent and more psychogenic and more treatable than either Kraepelin or Bleuler would have allowed.

**Conclusions**

As a direct result of the effort to construct Research Diagnostic Criteria (RDC) in the 1970s that were independent of any clinical
diagnostic manual, Kraepelin’s idea that categories of mental disorder should reflect discrete and specific disease entities with a biological basis began to return to prominence. Vague dimensional approaches based on symptoms—so highly favored by the Meyerians and psychoanalysts—were overthrown. For research purposes, the definition of schizophrenia returned to the narrow range allowed by Kraepelin’s dementia praecox concept. Furthermore, after 1980 the disorder was a progressively deteriorating one once again, with the notion that recovery, if it happened at all, was rare. This revision of schizophrenia became the basis of the diagnostic criteria in DSM-III (1980). Some of the psychiatrists who worked to bring about this revision referred to themselves as the “neo-Kraepelinians”.
Advances in the understanding of the pathophysiology of dementing illnesses have changed the management of patients with these disorders from a conservative, symptomatic approach to a more biologically and medically specific one.

The mainstay of management is still symptomatic: treatment of behavioral disturbances, environmental manipulations to support function, and counseling with respect to safety issues. The future promises disease-specific and, hopefully, disease-modifying treatments.

In the past, a rudimentary, and nearly always negative, work-up was conducted to rule out a “reversible” cause of dementia, leaving “senile dementia” as a default diagnosis. When no disease-specific treatments were available, that approach had a certain logic, but it is no longer adequate.

A more precise diagnosis is required for effective management and accurate prognosis.

As an example, a practitioner who misdiagnoses “senile dementia” in a patient with progressive memory problems and visual hallucinations, overlooking very mild parkinsonism, might initiate treatment of hallucinations with haloperidol.

This apparently sensible symptomatic treatment exposes the patient, who most likely has dementia with Lewy bodies (DLB), to severe and even life-threatening deterioration.
DEMENTIA - TREATMENT OVERVIEW

Some cases of dementia are caused by medical conditions that can be treated, and treatment can restore some or all mental function. But most of the time, dementia cannot be reversed.

Treatment when dementia can be reversed

Sometimes treating the cause of dementia helps the dementia. For example, the person might:

- Take vitamins for a deficiency of vitamin B12.
- Take thyroid hormones for hypothyroidism.
- Have surgery to remove a brain tumor or to reduce pressure on the brain.
- Stop or change medicines that are causing memory loss or confusion.
- Take medicines to treat an infection, such as encephalitis.
- Take medicine to treat depression.
- Get treatment for reversible conditions caused by AIDS.

Palliative care

Palliative care is a kind of care for people who have a serious illness. It’s different from care to cure the illness. Its goal is to improve a person’s quality of life—not just in body but also in mind and spirit.

ENVIRONMENTAL MODIFICATIONS

Modifying the environment can increase safety and comfort while decreasing agitation. Home modifications for safety include removal or lock-up of hazards such as sharp knives, dangerous chemicals, and tools.

Child-proof latches may be used to limit access. Bed rails and bathroom safety rails can be important safety measures as well.

Another example is lowering the hot water temperature, which reduces the risk of burning or disabling the stove and/or using stove childproof knobs may be necessary to prevent cooking accidents.
Medication

Medication can be prescribed to reduce dementia symptoms. There are a number of drugs available today for improving brain function. Typically, anti-dementia or other psychotropic drugs are prescribed.

The more recent anti-dementia agents belong to the so-called acetylcholinesterase inhibitors. Acetylcholine is one of the chemical substances that allow brain cells to communicate with one another, the so-called neurotransmitters. Research suggests that acetylcholine is reduced in the brain of AD patients. These kinds of drugs prevent acetylcholine being eliminated too quickly, prolonging its ability to conduct chemical messages between brain cells. It could be shown in clinical trials that, with these kinds of drugs, the deterioration of the disease could be delayed by at least 12 months. Apart from preserving and partially improving mental capacities, and coping with daily activities, a delayed onset of behavioural disturbances and a reduction in caring time could also be demonstrated.

Psychotropic drugs can be used as a supportive therapy in the treatment of behavioural problems in dementia. For instance, antipsychotic medications (typically used to treat disorders like schizophrenia) can be effective in reducing persistent aggression, and in patients who have been unresponsive to non-pharmacological approaches, and where there is a risk of harm to themselves or others; however, such treatments should be used on a short-term up to six weeks rather than a systematic basis.

Anti-anxiety medications (typically used to treat anxiety disorders) can also be prescribed to help treating agitation and restlessness. Likewise, antidepressant medication can be prescribed to alleviate symptoms of depression. Treating depression symptoms is particularly important, as depression makes it harder for a person with dementia to remember things and enjoy life. It also adds to the difficulty of caring for someone with dementia. Significant improvements can be made by treating depression, as the patient’s mood and their ability to participate in activities may be improved. In general, medications should be administered very cautiously to patients with dementia and in the lowest possible
effective doses, to minimise side effects. Supervision of taking medications is generally required. With each of these medications, there are associated side effects and risks. Therefore, a careful risk-benefit evaluation should be conducted before treatment initiation and on a regular basis throughout treatment. However, one must bear in mind that these medications do not cure dementia or reverse someone’s symptoms. There is no evidence that life is prolonged by taking medications. Rather, these medications can help some patients functioning better for a longer period of time.

Psychosocial intervention for Alzheimer’s disease patients

Psychosocial interventions can be beneficial to patients suffering from AD. Such treatments generally fall under four categories:

- Behaviour-oriented therapies are used most often with patients who exhibit behaviours that are difficult to manage. The therapies consist of changing environmental factors thought to affect the patients and to reduce the patients’ behavioural problems. There is some evidence for the benefits of such therapies, but additional clinical trials are necessary.

- Emotion-oriented therapies include options like psychotherapy. They are often used to address issues of memory loss and to improve mood and behaviour.

- Cognition-oriented therapies include reality orientation, cognitive retraining and skills focusing on cognitive deficits. This type of treatment provides some improvements, but they are generally short-term.

- Stimulation-oriented therapy includes therapies related to pleasurable activities, such as art, music or exercise. Some data demonstrates its relative effectiveness in reducing behavioural problems.

Other therapies

Other therapies may also help persons with dementia with activities of daily living. Physical therapy may improve mobility by teaching patients to use canes or walkers properly and showing them how to get in and out of chairs or beds. Aroma, music,
reminiscence, or occupational therapy, as well as art activities, may be beneficial and have a calming or rewarding effect for the person with dementia.

Finally, a growing number of herbal remedies, vitamins and other dietary supplements are promoted as treatments for AD and related diseases. They can be appealing to some people as they come from natural ingredients. Although many of these remedies may be possible treatment options, using these drugs as an alternative to or in addition to physician-prescribed therapy raise legitimate concerns. For instance, the efficacy, tolerability and safety of these products are not established and need to undergo further scientific testing. Further, they may not be manufactured consistently by all vendors or always contain the ingredients listed on the label. Moreover, herbal and nutritional supplements can interact with prescribed medications in harmful ways. Therefore, no supplement should be taken without first consulting a physician or informing the doctor treating the dementia patient.

Apart from treating the specific symptoms of dementia, it is important to observe the general state of health because a good general condition improves the feeling of well-being and might prevent or delay the onset of the disease.

**HOW IS DEMENTIA TREATED?**

Most types of dementia cannot be cured and will gradually cause more severe problems. But there are important exceptions, including dementia caused by vitamin and thyroid hormone deficiencies, which can be treated with supplements.

Some causes can be treated surgically – for example, some brain tumours, excess fluid on the brain (hydrocephalus) or head injury. For types of dementia that involve degeneration of nerve and brain tissue, you can take action to prevent further damage. It’s possible to do this by reducing dementia risk factors, such as by managing high blood pressure, high cholesterol, type 1 diabetes and stopping smoking.

For dementia that currently cannot be cured, some types of medicine may prevent symptoms getting worse for a period of time. These medicines are usually given to people in the early and
middle stages of the disease, to try to maintain or improve their independence. It is fairly common for people with dementia to have depression. If you have dementia and depression, your GP may consider prescribing an antidepressant medication, or get you an appointment with a psychiatrist who specialises in working with older people.

Perhaps the most important type of treatment for anyone with dementia is the care and support they receive from healthcare professionals, family and friends. If you or a loved one have been diagnosed with dementia, you should start planning the future care that will be required.

Discuss the options, such as Power of Attorney, with the people concerned – your family, your GP and your local authority. The Alzheimer’s Society is also a valuable source of information and support. It has branches in England, Ireland and Wales. Finally, there are things you or your loved one can do to maintain memory, independence and function when you have dementia.

**Medicines to treat dementia**

A number of medications have been shown to be effective in treating mild, moderate and severe dementia. Depending on the particular type of dementia, the severity of the condition, or any other issues observed by the doctor, you may be prescribed medications. However, not everyone will benefit from these drugs.

*Aricept (donepezil) and other acetylcholinesterase inhibitors*

Acetylcholinesterase inhibitors (such as galantamine, and rivastigmine) are used to treat mild to moderate Alzheimer’s disease. They can also be used to treat dementia with Lewy bodies, and can be particularly effective at treating hallucinations. Common side effects of acetylcholinesterase inhibitors include nausea and vomiting, but these usually get better after two weeks of taking the medication. Acetylcholinesterase inhibitors can sometimes slow down your heartbeat, so you may need to have an electrocardiogram (ECG) both before and during treatment. An ECG is a procedure that records the rhythms and electrical activity of your heart.
Memantine hydrochloride

Memantine is a medicine that works by blocking the effects of a chemical in the brain. It is used to treat severe Alzheimer’s disease, but can also be given to people with moderate symptoms if they don’t respond well to acetylcholinesterase inhibitors.

Antipsychotics

Antipsychotics are medicines that are sometimes used to treat people who’s behaviour is disruptive – for example, they tend to become aggressive or agitated. They are normally used for a short period of time and with caution, because they can increase the risk of cardiovascular problems, cause drowsiness and tend to make other symptoms of dementia worse. There is some evidence that antipsychotics can cause a range of serious side effects for people who have dementia with Lewy bodies. These include:

- rigidity
- immobility
- inability to communicate

In most cases, antipsychotics are only used when there are severe symptoms of challenging and disruptive behaviour that pose harm. Before being given antipsychotic drugs, the benefits and risks of treatment should be fully discussed between health and care professionals, family carers, and, if possible, with the person being prescribed the drugs. If antipsychotics are used, they will be prescribed at the lowest possible dose and for the shortest possible time. The health of anyone taking antipsychotics needs to be carefully monitored.

Antidepressants

Depression is an issue for many people with dementia, perhaps linked with frustrations caused by the condition. Depression can sometimes make the memory of a person with dementia worse. Antidepressants may be prescribed.

PSYCHOLOGICAL TREATMENTS FOR DEMENTIA

Psychological treatments do not slow down the progression of dementia, but they can help with the symptoms.
Cognitive stimulation and reality orientation therapy

Cognitive stimulation involves taking part in activities and exercises designed to improve memory, problem-solving skills and language ability. Reality orientation therapy reduces feelings of mental disorientation, memory loss and confusion, while improving self-esteem.

Evidence suggests that cognitive stimulation can improve thinking and memory skills in people with dementia. It is currently the only psychological treatment directly recommended by the National Institute for Health and Care Excellence (NICE) to help people with mild or moderate dementia. Reality orientation may also be beneficial in some cases, but the benefits can be small and are often only apparent with continued effort.

Validation therapy

Validation therapy focuses on dementia from an emotional, rather than factual, perspective. It is based on the principle that even the most confused behaviour has some meaning for the person. For example, if someone with dementia becomes agitated at a certain point every day because they believe their mother is going to come and pick them up, telling them that their mother is no longer alive could cause them to become more agitated and distressed.

With validation therapy, the response to this situation might involve not correcting the person and accepting their concerns, but talking to them about the issue and gradually steering the conversation in another direction. In theory, this should reduce their distress, while acknowledging that their thoughts and feelings have meaning for them. However, while validation therapy may sometimes be used as part of the treatment of someone with dementia, there is not enough evidence about the effectiveness of this approach to be certain whether it is beneficial.

Behavioural therapy

Behavioural therapy tries to find reasons for difficult behaviour. Different strategies are adopted to try to change that behaviour. For example, a person with dementia may have a history of wandering out of their home or care centre because they feel
restless. Therefore, encouraging them to take part in regular physical exercise may help to decrease their restlessness.

Behavioural therapy can be used to treat many of the behavioural problems that are associated with dementia, such as depression, aggression and delusional thinking. Behavioural therapy is often given by a trained friend or relative (usually the main family carer), or by an employed carer, but is supervised by a healthcare professional.

**DRUG TREATMENTS FOR ALZHEIMER’S DISEASE**

There are no drug treatments that can cure Alzheimer’s disease or any other common type of dementia. However, medicines have been developed for Alzheimer’s disease that can temporarily alleviate symptoms, or slow down their progression, in some people. This factsheet explains how the main drug treatments for Alzheimer’s disease work, how to access them, and when they can be prescribed and used effectively. Drug treatment for Alzheimer’s disease is important, but the benefits are small, and drugs should only be one part of a person’s overall care. Non-drug treatments, activities and support are just as important in helping someone to live well with Alzheimer’s disease.

Many drugs have at least two names. The generic name identifies the substance. The brand name varies depending on the company that manufactures it. For example, a familiar painkiller has the generic name paracetamol and is manufactured under brand names such as Panadol and Calpol, among others. Occasionally, a drug with a very well-known generic name (such as paracetamol) will also be manufactured and sold using just this name.

**What are the main drugs used?**

There are two types of medication used to treat Alzheimer’s disease: acetylcholinesterase inhibitors (often shortened to just ‘cholinesterase inhibitors’) and NMDA receptor antagonists. The two types work in different ways. These are explained below.

- The generic names for the cholinesterase inhibitors are donepezil, rivastigmine and galantamine:
Donepezil was originally patented as the brand name Aricept, but is more widely available now as just generic donepezil.

Rivastigmine was patented as Exelon and is now also available as other brands, as well as generic rivastigmine.

Galantamine was patented as Reminyl and is now also available as generic galantamine and the brands Reminyl XL, Acumor XL, Galsy XL and Gatalin XL.

• The NMDA receptor antagonist is memantine. It was originally patented as Ebixa and is now also available as generic memantine. Other UK brand names for memantine include Maruxa and Nemdatine.

How do they work?

**Cholinesterase inhibitors (donepezil, rivastigmine and galantamine)**

In the brain of a person with Alzheimer’s disease, there are lower levels of a chemical called acetylcholine. Acetylcholine helps to send messages between certain nerve cells. In Alzheimer’s there is also a loss of the nerve cells that use acetylcholine. Falling acetylcholine levels and progressive loss of these nerve cells are linked to worsening symptoms.

Donepezil, rivastigmine and galantamine all prevent an enzyme called acetylcholinesterase from breaking down acetylcholine in the brain. As a result, an increased concentration of acetylcholine leads to increased communication between nerve cells. This may temporarily alleviate or stabilise some symptoms of Alzheimer’s disease. All three cholinesterase inhibitors work in a similar way, but one might suit a certain individual better than another, particularly in terms of side effects experienced.

Guidance on the use of drugs in the NHS is issued by the National Institute for Health and Care Excellence (NICE). NICE reviews drugs and decides whether they represent good enough value for money to be available as part of NHS treatment. Drugs considered by NICE will also have been through the UK or European licensing process for new medicines. This means the
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medicine has been tested and met rigorous standards of safety, quality and effectiveness. The licence will be granted for treatment of a particular health condition. For the cholinesterase inhibitors, the NICE guidance (2011) suggests that the cheapest drug (currently donepezil) should generally be tried first.

**Memantine**

The action of memantine is different from that of donepezil, rivastigmine and galantamine. Glutamate is another chemical that helps to send messages between nerve cells. Glutamate is released in excessive amounts when brain cells are damaged by Alzheimer’s disease. This causes the brain cells to be damaged further. Memantine protects brain cells by blocking the effects of excess glutamate.

**Are these drugs effective for everyone with Alzheimer’s disease?**

**Donepezil, rivastigmine and galantamine**

The guidance from NICE (2011) recommends that donepezil, rivastigmine or galantamine is offered as part of NHS care for people with mild-to-moderate Alzheimer’s disease. There is good evidence (strongest for donepezil) that these cholinesterase inhibitors also help people with more severe Alzheimer’s disease.

Between 40 and 70 per cent of people with Alzheimer’s disease benefit from taking a cholinesterase inhibitor. In cases where the treatment shows benefit, symptoms improve temporarily (for between six and 12 months in most cases) and then gradually worsen over the following months. People taking a cholinesterase inhibitor can experience: reduced anxiety; improvements in motivation, memory and concentration; and improved ability to continue daily activities (eg personal care, shopping, dressing).

It is not clear whether the cholinesterase inhibitors also bring benefits for behavioural changes such as agitation or aggression. Trials in this area have given mixed results.

**Memantine**

The NICE guidance (2011) recommends use of memantine as part of NHS care for severe Alzheimer’s disease. NICE also
Diagnosis and Treatment of Senile Dementia

recommends memantine for people with moderate Alzheimer’s disease who cannot take the cholinesterase inhibitor drugs (this is usually because of side effects). Memantine is licensed for the treatment of moderate-to-severe Alzheimer’s disease. In people in the middle and later stages of the disease, it can slow down the progression of symptoms, including disorientation and difficulties carrying out daily activities. There is some evidence that memantine may also help with symptoms such as delusions, aggression and agitation.

Are there any side effects?

Generally, cholinesterase inhibitors and memantine can be taken without too many side effects. Not everyone experiences the same side effects, or has them for the same length of time (if they have them at all). The most frequent side effects of donepezil, rivastigmine and galantamine are loss of appetite, nausea, vomiting and diarrhoea. Other side effects include muscle cramps, headaches, dizziness, fatigue and insomnia. Side effects can be less likely for people who start treatment by taking the lower prescribed dose for at least a month.

The side effects of memantine are less common and less severe than for the cholinesterase inhibitors. They include dizziness, headaches, tiredness, raised blood pressure and constipation. It is important to discuss any side effects with the doctor and/or the pharmacist. None of these drugs are addictive.

How are these drugs prescribed?

NICE guidance (2011) states that, in the first instance, these drugs can only be prescribed by a specialist in dementia care. This will often be a consultant old-age psychiatrist, geriatrician or neurologist. A GP will generally refer a person with suspected dementia to a memory service for a specialist assessment. A consultant-led team at the clinic will carry out a series of tests to determine whether the person has dementia and, if so, which type.

If the diagnosis is Alzheimer’s disease, the consultant will offer the drugs and write the first prescription. (In some parts of the country arrangements allow for the consultant to write to the GP to ask them to start prescribing.) Once the person has started
on the drugs and is stable at the optimum dose, the specialist will usually ask the GP to take over routine prescribing. The person will then generally have regular reviews of how well their medication is working, either with a specialist at the memory clinic or with the GP.

**Are these drugs effective for other types of dementia?**

The cholinesterase inhibitors were developed specifically to treat Alzheimer’s disease. There has been relatively little research into whether they (or memantine) are helpful for people with other types of dementia. There is evidence that the cholinesterase inhibitors are effective in people with dementia with Lewy bodies, and dementia due to Parkinson’s disease. Rivastigmine is licensed for Parkinson’s disease dementia. Acetylcholine levels are often even lower in people with dementia with Lewy bodies than in those with Alzheimer’s disease.

NICE guidelines recommend that a cholinesterase inhibitor is offered to a person with dementia with Lewy bodies or Parkinson’s disease dementia if they have distressing symptoms (e.g. hallucinations) or challenging behaviours (e.g. agitation, aggression).

Several trials have looked at the treatment of vascular dementia with a cholinesterase inhibitor or memantine. The benefits for either are very small (if any), and seen mainly for mental abilities of people with a combination of both Alzheimer’s disease and vascular dementia (known as mixed dementia). NICE guidelines recommend cholinesterase inhibitors for treatment of mixed dementia when Alzheimer’s is the main cause, but not for the treatment of pure vascular dementia.

From the few trials carried out, there is no good evidence that the cholinesterase inhibitors or memantine are of benefit for people with frontotemporal dementia, including Pick’s disease. In some people they may make symptoms worse. These drugs are not licensed for frontotemporal dementia and will not generally be prescribed for it.

**Taking the drugs**

NICE guidelines (2011) say the specialist should seek the views of the carer on the condition of the person with dementia,
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before treatment and during follow-up appointments. They should also seek the views of the person with dementia.

The person should take the drugs as prescribed and the doctor should try to ensure this is done. The person may benefit from using a pill box with different compartments for each day of the week, containing the prescribed dose. The pharmacist may be able to supply drugs pre-packed like this.

If the person misses a dose of any of these drugs, they should take it as soon as they remember, as long as it is on the same day. If it is the next day, the person should not take two tablets, but should simply continue with their normal dose.

Doses vary. Usually a person with Alzheimer’s disease will start on a low dose, which will be increased later to make the treatment more effective. Some people may not be able to take the highest dose because of side effects. The doctor will prescribe the best dose for each individual. Information about doses is given below.

- **Donepezil** is available in 5mg or 10mg tablets. It is taken once a day, usually at bedtime. Treatment is started at 5mg a day and then increased to 10mg a day after one month if necessary. The maximum licensed total daily dose is 10mg.

- **Rivastigmine** comes in capsules or a solution to drink. It is taken twice a day, with morning and evening meals. People start with 3mg a day in two divided doses, which will usually increase (at intervals of at least two weeks) to between 6mg and 12mg a day. The maximum licensed total daily dose for oral rivastigmine is 12mg. Rivastigmine patches are also available. These deliver daily doses of 4.6mg, 9.5mg or 13mg, with fewer side effects than the capsules. Patches are suited to people who struggle with taking medication by mouth; they are popular with carers. Only one patch should be applied at any one time and it should be put on different parts of the skin each time, to avoid the person getting a rash.

- **The recommended starting dose for galantamine** is 8mg each day for four weeks, increasing to 16mg a day for
another four weeks, and then kept at a dose of between 16 and 24mg daily. Galantamine is made in a variety of forms including a 4mg/ml (twice-daily) oral solution, and tablets of 8mg and 12mg. Slow-release (XL) capsules are available in doses of 8mg, 16mg and 24mg. These are popular because they only need to be taken once a day. The maximum licensed total daily dose for galantamine is 24mg.

- Memantine comes in two forms: as 10mg and 20mg tablets, and as 10mg oral drops. The 10mg tablets can be broken in half (into 5mg doses) and taken with or without food. The recommended starting dose is 5mg a day, increasing every week by 5mg, up to 20mg a day after four weeks. The maximum licensed total daily dose for memantine is 20mg.
- It is important that the person takes the doses that have been prescribed.

Questions to ask the doctor when starting the drugs

It is important that someone who has been prescribed one of these drugs understands what it does and how to take it.

The following are things that they may wish to ask the doctor about. It can help for the person with dementia or their carer to write down these questions, and any answers the doctor gives.

- Why have I been prescribed this drug specifically?
- What are the potential benefits of taking this drug?
- How long will it be before I see a result?
- If I get side effects, should I stop taking the drug immediately?
- What will happen if I stop taking the drug suddenly?
- Can I drink alcohol while taking the drug?
- How might this drug affect other medical conditions?
- What changes in health should I report immediately?
- How often will I need to visit the clinic or surgery?
- If this drug doesn’t suit me, can I try another drug?
Stopping treatment

Medication should be reviewed regularly, and continued for as long as the benefits outweigh any side effects. If the person with Alzheimer’s decides to stop taking a drug, they should speak to the doctor first if possible, or as soon as they can after stopping treatment. Treatment may also be stopped by agreement with the doctor if the person becomes unable to take the medicines in the prescribed way, even with support. If someone stops taking their prescribed drug, their condition may get worse more quickly. If someone has stopped and thinks they should restart their medication, it is important that they contact their doctor as soon as possible.

For someone who is taking a cholinesterase inhibitor, a decision will need to be made when their Alzheimer’s disease becomes severe. There is now good evidence that cholinesterase inhibitors continue to bring benefits even when someone’s Alzheimer’s is severe. Many doctors therefore continue to prescribe a cholinesterase inhibitor for severe Alzheimer’s until the above criteria for stopping treatment are met, if ever. The issue of whether to add memantine to the cholinesterase inhibitor for someone with severe Alzheimer’s disease (known as combination treatment) is less clear cut. The two drugs work in different ways and there is research evidence that, for someone who is already on donepezil, adding memantine might bring additional benefit. However, NICE guidance (2011) does not recommend combination treatment.

NICE guidance: a summary

In 2011, NICE issued revised guidance recommending that people with Alzheimer’s disease (or mixed dementia in which Alzheimer’s is the main cause) should have increased access to the available drugs.

The current NICE guidance on drug treatments for Alzheimer’s disease recommends that people in the mild-to-moderate stages of the disease should be given treatment with donepezil, galantamine or rivastigmine, including individuals with both Alzheimer’s disease and learning disabilities. The NICE guidance (2011) further recommends that memantine should be prescribed
Treatment of Dementia

as part of NHS care for people with severe Alzheimer’s disease, or for those with moderate disease who cannot take the cholinesterase inhibitor drugs. NICE also says that, when considering drug treatment, how severe someone’s dementia has become should not be measured by scores on mental ability tests (eg the Mini Mental State Examination (MMSE)) alone, but by a broader view of the person’s condition. This is to avoid an arbitrary decision to stop drug treatment, such as when the person’s MMSE score has crossed a threshold from moderate to severe or because they have gone into a care home.

NICE guidelines allow people with dementia with Lewy bodies or Parkinson’s disease dementia to be offered a cholinesterase inhibitor if their non-cognitive symptoms (eg hallucinations, agitation) are causing distress or leading to challenging behaviour. The consultant will decide whether these treatments are appropriate for a particular individual.

In relation to the Alzheimer’s disease drugs, NICE makes the following recommendations:

• Treatment is started by a doctor who specialises in the care of people with dementia.
• People who are started on one of the drugs are checked regularly, usually by a specialist team unless shared care arrangements with primary care are in place.
• The check-up includes an assessment of the person’s mental abilities, behaviour and ability to cope with daily life.
• The views of the carer on the person’s condition are discussed at the start of drug treatment and at check-ups.
• Treatment is continued as long as it is judged to be having a worthwhile effect.
• Where a cholinesterase inhibitor is given, the least expensive of the three drugs (currently donepezil) is prescribed first. However, if donepezil is not suitable for the person, another cholinesterase inhibitor could be chosen.

MEDICINES FOR DEMENTIA

Medicines for dementia are used to help with symptoms that affect thinking and memory. They are also used to help with
symptoms that affect mood and how someone behaves. These medicines do not cure dementia and they may only work for some people. They also may only work for a short time (6-12 months). Medicines for dementia are always started by a doctor who specialises in treating dementia. Like all medicines, they may cause a number of side-effects - for example, diarrhoea, feeling sick (nausea) and being sick (vomiting). But, for most people, any side-effects go away after a few weeks.

What is dementia?

Dementia is a condition of the brain which causes a gradual loss of mental ability. This includes problems with memory, understanding, judgement, thinking and language. In addition, other problems commonly develop, such as changes in personality and changes in the way a person interacts with others in social situations. As dementia progresses, a person’s ability to look after themselves from day to day may also become affected.

There are several causes of dementia. It can be caused by various diseases or disorders which affect the parts of the brain involved with thought processes. Most cases are caused by Alzheimer’s disease. Some of the other types of dementia are:

- Vascular dementia. This is due to problems with the blood vessels in the brain. Brain damage is called by a stroke or a series of tiny mini-strokes.
- Dementia with Lewy bodies (DLB). A type of dementia where abnormal proteins called Lewy bodies are found in the brain.
- Dementia with Parkinson’s disease.
- Frontotemporal dementia. A type of dementia where specific parts of the brain only are affected.
- Mixed dementia.

What are medicines for dementia?

Medicines for dementia are used firstly as a treatment to help with symptoms that affect thinking and memory (cognitive symptoms). Secondly, they are used as treatment to help with symptoms that affect mood and how someone behaves (non-
cognitive symptoms). They do not cure dementia. There are four medicines available in the UK which can be prescribed for dementia. These are donepezil, rivastigmine, galantamine and memantine. They are available as tablets, liquids, tablets that dissolve in water, or patches. They come in various brand names.

In addition, there are a number of other medicines that may be prescribed to people who have dementia. For example:

- An antidepressant may be advised if depression is suspected. Depression is common in people with dementia and may be overlooked.
- Aspirin and other medicines to treat the risk factors for stroke and heart disease may be appropriate for some people. This is especially the case for those with vascular dementia.
- Sleeping tablets are sometimes needed if difficulty sleeping is a persistent problem.
- A tranquilliser or an antipsychotic medicine is sometimes prescribed as a last resort for people with dementia who become easily agitated.

The rest of this leaflet only discusses the use of donepezil, rivastigmine, galantamine and memantine.

**How do medicines for dementia work?**

Medicines for dementia work by increasing the levels of certain chemicals in the brain. Donepezil, rivastigmine and galantamine belong to a group of medicines called acetylcholinesterase inhibitors. They work by increasing the level of acetylcholine. This is a chemical in the brain that is low in people with Alzheimer’s disease. Memantine works in a different way to acetylcholinesterase inhibitors. It reduces the amount of a brain chemical called glutamate. It is thought that this may help to slow down the damage to brain cells affected by Alzheimer’s disease.

**When are medicines for dementia usually prescribed?**

Your GP will usually refer you to a doctor who specialises in treating dementia, to confirm that you have dementia. The specialist will then decide if you should have treatment. This decision to start treatment and which treatment to start depends on various
things. These include what has caused your dementia, what your symptoms are and how severe your dementia is. Dementia is usually classed as being mild, moderate or severe.

**Which medicine for dementia is usually prescribed?**

Your specialist will decide which treatment is right for you. There are national guidelines for people with dementia that can help your specialist decide which treatment to choose. One of the following is usually recommended: donepezil, galantamine and rivastigmine for people with mild or moderate Alzheimer’s disease, providing that:

- The medicine is started by a specialist in the care of people with dementia.
- A person receiving treatment has regular reviews and assessments of their condition.

Memantine can be considered as a treatment option for:

- People who have moderate Alzheimer’s disease and who, for some reason, cannot take, or are intolerant to, the acetylcholinesterase inhibitor medicines.
- People who have severe Alzheimer’s disease.

These medicines are not usually used for people with other types of dementia. However, rivastigmine can be used for people with mild-to-moderately severe dementia who also have Parkinson’s disease. So, doctors may suggest this medicine for this group of people. Also, an acetylcholinesterase inhibitor medicine may sometimes be suggested for people with DLB who have problems with challenging or disruptive behaviour (non-cognitive symptoms).

**How well do medicines for dementia work?**

It is thought that about half the people treated with a cholinesterase inhibitor will see an improvement in symptoms that affect thinking and memory. Whether they help with other symptoms such as aggression and agitation has still not been confirmed. The improvement in symptoms is usually only seen for about 6-12 months. For memantine, some studies have shown that it can slow down the progression of symptoms in some cases.
How should I take these medicines?

It is usual to start with a low dose. This is then increased over a period of weeks to a target treatment dose. The dose is increased slowly because when you first start taking these medicines you may develop some unpleasant side-effects - for example, diarrhoea, feeling sick (nausea) and being sick (vomiting). Most people who develop side-effects find that after a period of time they go away. If you are tolerating a low dose well, your doctor will increase your dose, if needed. How often the dose is increased depends upon which medicine you are taking. For example, if you are taking galantamine, the dose is increased every four weeks. If you are taking rivastigmine tablets, the dose is increased every two weeks.

What is the usual length of treatment?

Medicines for dementia are usually only continued for as long as they are thought to be having a worthwhile effect on symptoms.

What about side-effects?

Medicines for dementia cause side-effects in some people. However, if side-effects do occur, they are usually minor and often go away after a few months.

The most common side-effects of anticholinesterase inhibitors include:

- Diarrhoea.
- Muscle cramps.
- Feeling tired (fatigue).
- Feeling sick (nausea).
- Being sick (vomiting).
- Not sleeping well (insomnia).
- Headache.
- Being incontinent of urine.

Other less common side-effects include:

- Symptoms of the common cold.
- Loss of appetite.
- Mental health disorders.
• Fainting and seizures.
• Dizziness.
• A thumping heart (palpitations).
• Flushing or sweating.
• Rash.
• Itching.

Memantine may cause:
• Dizziness.
• Headache.
• Feeling out of breath.
• Constipation.
• Drowsiness.
• High blood pressure.

Other less common side-effects include:
• Vomiting.
• Blood clots (thrombosis).
• Heart problems.
• Confusion.
• Feeling tired.
• Seeing things or hearing things which are not real (hallucinations).
• Problems with walking.

The above is not an exhaustive list but highlights the more common possible side-effects. For a full list of side-effects see the information leaflet that comes with the medicine.

**Who cannot take medicines for dementia?**

In general, most people are able to take these medicines. Caution may be needed in people with certain medical problems. For example, people with severe liver or kidney problems may not be able to take them, or they may need a lower dose. Care also needs to be taken in people who have had fits in the past.

**How to use the Yellow Card Scheme**

If you think you have had a side-effect to one of your medicines you can report this on the Yellow Card Scheme. The Yellow Card
Scheme is used to make pharmacists, doctors and nurses aware of any new side-effects that medicines or any other healthcare products may have caused. If you wish to report a side-effect, you will need to provide basic information about:

- The side-effect.
- The name of the medicine which you think caused it.
- The person who had the side-effect.
- Your contact details as the reporter of the side-effect.

**VASCULAR DEMENTIA TREATMENT & MANAGEMENT**

**Medical Care**

The mainstay of management of vascular dementia is the prevention of new strokes. This includes administering antiplatelet drugs and controlling major vascular risk factors. Aspirin has also been found to slow the progression of vascular dementia. Recent guidelines from the American Psychiatric Association provide both treatment principles and possible specific therapies.

Drug treatment is primarily used to prevent further worsening of vascular dementia by treating the underlying disease such as hypertension, hyperlipidemia, and diabetes mellitus. Antiplatelet agents are indicated. Pentoxifylline and, to a more limited extent, ergoloid mesylates (Hydergine), may be useful for increasing cerebral blood flow. In the European Pentoxifylline Multi-Infarct Dementia Study, which is a double-blinded, placebo-controlled, multicenter study, treatment with pentoxifylline was found to be beneficial for patients with multi-infarct dementia. Significant improvement was observed in the scales used for assessing intellectual and cognitive function.

Neuroprotective drugs such as nimodipine, propentofylline, and posatirelin are currently under study and may be useful for vascular dementia. Nicardipine is a dihydropyridine calcium channel blocker that was studied on the treatment of cognitive deterioration of vascular origin. Preliminary studies showed decrease in cognitive deterioration in patients with cerebrovascular disease. Increasing evidence supports the involvement of the
cholinergic system in vascular dementia, similar to that seen in Alzheimer dementia. However, no cholinesterase inhibitors have been approved to date for the treatment of vascular dementia, despite positive results in clinical trials with this medication.

The general management of dementia includes appropriate referral to community services, judgment and decision-making regarding legal and ethical issues (e.g., driving, competency, advance directives), and consideration of caregiver stress. Agitation and psychosis are common in older adults with dementia and are challenging to manage. Relatively few studies have examined the use of antidepressants for the treatment of agitation and psychosis in dementia; however, the selective serotonin reuptake inhibitors (SSRIs) sertraline and citalopram appear to be associated with a reduction in symptoms of agitation when compared with placebo. Both appear to be reasonably well tolerated when compared with placebo, typical antipsychotics, and atypical antipsychotics. However, more studies are needed to determine if SSRIs, trazodone, or other antidepressants are safe and effective treatments for agitation and psychosis in dementia.

**MONTESSORI METHOD IS BECOMING A POPULAR TREATMENT FOR DEMENTIA**

Developed in the early 20th century, the Montessori method of teaching holds that when you’re working with children, you must consider their needs and capabilities in concert. What do they like to do? What are they able to do? The balancing act the teacher performs centers on not challenging the students – you don’t want them to get frustrated and give up – but rather, making the task a little beyond their comfort zone, so they still have the opportunity to learn and improve. The same is true for those with Alzheimer’s.

**Connecting the Montessori Method to Alzheimer’s**

One way to think about why the Montessori method is gaining traction with Alzheimer’s caregivers is this: Montessori teachers create lessons and activities specifically designed to engage the senses. The more ways students are given to connect with the world they’re learning about for the first time, the more
brains become engaged, which means more opportunities for the new information to become long-term memory. The Montessori method of caregiving has a very similar goal: engaging the senses in order to help Alzheimer’s and dementia patients and loved ones rediscover the world around them. Providing the most effective care means maximizing the opportunities these patients have to reconnect with a world they’re losing access to. Researchers and caregivers are increasingly finding that sensory experiences created through physical activities and art or music therapy, gives loved ones with Alzheimer’s positive emotions that they may have lost the ability to experience.

Though a patient may become withdrawn or paranoid as dementia advances, in many cases, their long-term memories will be largely well-preserved. The Montessori method is about providing ways to connect with those memories. Presenting a loved one with fresh flowers and an empty vase may give him or her a way to step out of a sense of isolation and into a beautiful spring day, because the experience of putting the flowers in the vase is enough to powerfully call forth the memory of cutting fresh flowers, for instance.

The positive attitudes and personal touch that are hallmarks of the Montessori method help caregivers maximize their loved ones’ opportunities to reconnect with pleasant events of the past, and to re-experience the accompanying positive emotions.

**How Caregivers Can Put the Montessori Method into Play**

Dr. Cameron Camp, a psychologist in applied gerontology, discovered that the Montessori method could be adapted into the basis of a new approach to dementia care. Dr. Camp states the problem this way: “How can we connect with the person who is still here?” One answer to this question is to use the Montessori approach to re-engage the types of memory that are spared by dementia, including motor memory such as how to dress and how to eat. An example of a skills-building activity that Dr. Camp employs involves Alzheimer’s patients using a slotted spoon to dig in a tub of dry rice for objects that are buried beneath the surface. When they find a “treasure,” the rice falls through the
slots, leaving the object on the spoon. In the process, their brains are re-learning the motor skills that are necessary to feed yourself.

“We want to flip the system on its ear,” Dr. Camp says, “to change people’s expectations about what people with dementia are capable of. Our job is to allow this person to be present — to help them, wherever they are in the journey of dementia, to be connected with a community and contribute to the best of their ability.”

Let’s take a look at different ways caregivers can put Montessori into practice.

1. Prep tables with materials for activities such as puzzles, sorting exercises and other games.
2. Lay out a basket of clean towels to fold.
3. Have a basket of clean socks that need to be matched and folded.
4. Put out a bin of plastic plumbing tubes that can be connected and put together.
5. For advanced dementia patients who may take comfort in holding dolls, a series of dolls and doll clothes can make for a pleasurable activity.
6. For those who enjoy cooking or baking, a safe kitchen environment and baking ingredients.

What we’re increasingly learning is that dementia patients can come to not only enjoy the process of participating in something they used to regularly do, but also come away with a definite sense of accomplishment that can help improve their quality of life.
Epidemiology of Dementia

Dementia is a syndrome resulting from acquired brain disease and characterized by progressive deterioration in memory and other cognitive domains (e.g., language, judgment, abstract thinking, and executive functioning). Although the cognitive profiles of individuals diagnosed with dementia vary somewhat by etiology, the degree of deterioration represents a decline from previous levels of functioning and is sufficient to interfere with social and occupational functioning.

The cognitive decline associated with dementia affects an individual’s ability to comprehend and produce linguistic information. Additionally, behavioral problems that develop as a result of the neuropathology (e.g., paranoia, hallucinations, and repetitiousness) may interfere with communication.

The cognitive and behavioral symptoms of dementia are differentiated from those of

- delirium, an acute state of confusion associated with temporary, but reversible, cognitive impairments;
- age-related memory decline;
- other conditions that have inconsistent symptoms or are temporary and/or treatable, including
  - infections (e.g., urinary tract infection [UTI], meningitis, syphilis),
  - toxicity (e.g., drug-induced dementia, toxic metal exposure),
pseudodementia due to psychiatric disorders (e.g., depression, generalized anxiety disorder, schizophrenia, mania, conversion disorders).

In contrast to these conditions, the symptoms associated with dementia continue to progress in severity until death. Neurodegenerative diseases that result in dementia include

- Alzheimer’s disease,
- Lewy body disease,
- vascular pathology (e.g., multi-infarct dementia),
- frontotemporal lobar degeneration (e.g., Pick’s disease and primary progressive aphasia),
- Huntington’s disease,
- Parkinson’s disease.

Other conditions that result in dementia due to progressive changes in brain function include

- Wernicke-Korsakoff syndrome secondary to chronic alcohol abuse,
- traumatic brain injury (TBI),
- chronic traumatic encephalopathy due to repeated trauma (e.g., dementia pugilistica),
- chemotherapy ,
- multiple sclerosis,
- human immunodeficiency virus (HIV).

**Primary Versus Secondary Dementia**

Primary dementias are those—like Alzheimer’s disease (AD), multi-infarct dementia, and dementia with Lewy bodies—in which the dementia itself is the major sign of an organic brain disease not directly related to any other organic illness. Secondary dementias are those caused by, or closely related to, some other recognizable disease, such as HIV, head injury, multiple sclerosis, or chronic alcohol abuse.

**Mild Cognitive Impairment**

There is evidence that neuropathological changes occur well in advance of clinical manifestations of Alzheimer’s dementia ,
and subtle cognitive deficits occur up to 9 years prior to the diagnosis. These and similar findings have led to the concept of mild cognitive impairment (MCI), described as a transitional stage between normal aging (i.e., age-associated memory impairment) and dementia. Individuals diagnosed with MCI are at greater risk of developing dementia; early identification of MCI might enable the use of cognitive interventions to slow the progression of decline (Qualls, 2005).

MCI is consistent with the diagnostic category, Mild Neurocognitive Disorder, defined in the Diagnostic and Statistical Manual of Mental Disorders-5th edition. The clinical criteria for diagnosing MCI are

• subjective complaints or concerns about cognitive changes corroborated by an informant,
• impairment in one or more cognitive domains relative to age and educational level (preferably documented by standardized testing),
• essentially normal activities of daily living (although some may require greater effort or use of compensatory strategies),
• absence of dementia—changes are mild with no significant social or occupational impairment.

**Early Onset**

Dementia is typically associated with the elderly population. However, dementia can affect younger individuals. Early-onset dementia (EOD) refers to dementias that occur before the age of 65.

Differential diagnosis of EOD is complicated by the fact that symptoms may be more variable in younger patients than in the elderly, due to different etiologies and a lack of awareness about the condition, even among health care professionals. In addition, some causes of EOD are curable, which makes the need for timely and accurate diagnosis even more crucial.

The needs of younger individuals with dementia are different from those of individuals with late-onset dementia. EOD often affects individuals who are working and have dependent families
and significant financial responsibilities, and services and supports for these individuals are complex and require input from a multidisciplinary team. Early diagnosis allows for early treatment, access to appropriate supports, and long-term preparation and planning for the family.

**Relationship Between Hearing Loss and Dementia**

Approximately one third of Americans between the ages of 65 and 74 and nearly half of those over the age of 75 have hearing loss (National Institute on Deafness and Other Communication Disorders [NIDCD], 2010). Many older adults will have both hearing impairment and cognitive loss, and, together, these losses will affect communication, social participation, and quality of life.

Lin et al. (2013) found that individuals with baseline hearing loss had greater rates of cognitive decline over time than individuals with normal hearing. Further investigation is needed to clarify this relationship and to determine whether or not hearing loss is a risk factor for dementia. One hypothesis is that when a hearing loss is present, greater cognitive resources are dedicated to auditory processing, leaving fewer resources for other cognitive processes, like working memory. Recent research suggests the possibility of a shared etiological pathway responsible for both hearing loss and dementia. It is important for clinicians to differentiate between hearing loss and cognitive impairment and to identify when one or both of these conditions are present.

**INCIDENCE AND PREVALENCE**

Estimates of the prevalence of dementia vary considerably by the age group on which the estimates are based. Prevalence among those age 85 and above, for example, is likely to be considerably higher than estimates based on those age 65 and above. In addition, prevalence data are often categorized more broadly or more narrowly than “dementia.” The Centers for Disease Control and Prevention, for example, cites prevalence data for specific causes of dementia, typically Alzheimer’s disease, while the National Institutes of Health (NIH) subsumes dementia under the category of Serious Mental Illness. Data on the prevalence of Alzheimer’s indicate increasing prevalence. Starting at age 65, the risk of
developing the disease doubles every 5 years. By age 85 years and older, between 25% and 50% of people will exhibit signs of Alzheimer's disease. Up to 5.3 million Americans currently have Alzheimer's disease. By 2050, the number is expected to more than double due to the aging of the population. Alzheimer's disease is the sixth leading cause of death in the United States and is the fifth leading cause among persons age 65 and older.

A recent meta-analysis found global prevalence of dementia from all causes to be between 5% and 7% of adults age 60+. Two recent studies of dementia prevalence have shown some indication that prevalence may be declining. In one, prevalence surveys of adults age 65+ were conducted almost 2 decades apart. After controlling for differences in the patient populations, the researchers found that the 2008 cohort had significantly lower prevalence of dementia. The second study took a slightly different approach. Those researchers assessed two cohorts of patients. One cohort was born in 1905 and was assessed in 1998 at age 93. The second cohort was born 10 years later, in 1915, and was assessed in 2010 at age 95. The 1915 cohort was found to have significantly lower prevalence of dementia. Both research teams concluded that the likely explanation was improved primary prevention of causes such as stroke.

Neither of the research teams found changes in the prevalence of Alzheimer's specifically, and it should also be noted that one study was conducted in the United Kingdom and the other in Denmark, so it cannot necessarily be concluded that primary prevention efforts in the United States have been similarly successful.

A limited number of studies have examined the prevalence of dementia among racial and ethnic groups. Differences in sampling methods and definitions of dementia, as well as difficulties controlling for variables such as level of education and bias in assessment batteries, limit the generalizability of results. However, results from individual studies suggest that the incidence and prevalence of dementia varies across racial and ethnic groups.

The Aging, Demographics, and Memory Study (ADAMS) used a nationally representative Health and Retirement Survey to
estimate the prevalence of Alzheimer’s disease (AD) and other dementias in the United States.

Results were analyzed to determine the overall prevalence of dementia, as well as the relationship between dementia and variables such as education, gender, race (African American or Caucasian), and Apolipoprotein E (APOE) genotype.

Controlling for education, gender, and APOE genotype, researchers found that African Americans were at a greater risk for dementia than Caucasians, although this difference was not statistically significant.

**Signs and Symptoms**

- Signs and Symptoms
- Social Cognition and Behavior
- Impact of Cognitive Changes.

The symptoms of dementia can be different depending on the diagnosis and the stage of the disease. Although late-stage signs and symptoms may be similar across etiologies, characteristic early symptoms can vary considerably. For example, individuals with frontotemporal dementia and Huntington’s disease experience behavior changes and depression; those with primary progressive aphasia experience gradual loss of language function but relatively well-preserved memory; and individuals with Binswanger’s disease (a type of vascular dementia) experience stroke-related neurological symptoms, including dysarthria and dysphagia. Cultural values, views of the aging process, and beliefs relative to cognitive decline may influence a family’s decisions about therapeutic services and may at times inhibit or delay seeking help until symptoms are beyond early or mild stages.

**Signs and Symptoms**

In general, individuals with dementia experience a gradual loss of memory and other cognitive functions. As the disease progresses, early symptoms intensify, eventually affecting the ability to communicate effectively and function independently. Examples of common signs and symptoms of dementia are listed below.
Attention

Common attention deficits include
- being easily distracted,
- having difficulty attending, unless input is restricted/simplified,
- experiencing decreased information-processing speed—thinking/processing takes longer than usual.

Learning and Memory

Common learning and memory deficits include
- episodic memory deficits, including difficulty remembering specific autobiographical events, situations, and experiences;
- short-term/working memory deficits—rapid forgetting of information recently seen or heard;
- difficulty acquiring and remembering new information (e.g., appointments or events, new routines).

Reasoning and Executive Functioning

Common reasoning and executive functioning deficits include
- difficulty setting goals and planning, including reliance on others to plan activities and/or make decisions;
- poor judgment and impaired reasoning and problem-solving abilities, such as making decisions without regard to safety;
- difficulty multi-tasking and handling complex tasks—need to focus on one task at a time;
- difficulty responding to feedback, self-monitoring, and correcting one’s own errors;
- lack of inhibition;
- lack of mental flexibility.

Perceptual Abilities

Common perceptual deficits include
- difficulty completing previously familiar activities or navigating in familiar environments;
inability to recognize familiar people, common objects, sounds, etc.;
inability to find objects in direct view, independent of visual acuity.

**Language**

Common language deficits include
- less concise (empty) discourse with fewer ideas;
- economy of utterances and stereotypy of speech;
- repetitious/perseverative language (e.g., asking the same question repeatedly);
- word-finding difficulties, including long latencies, paraphasias, and word substitutions;
- difficulty recalling names of family and friends;
- tangential language;
- circumlocution;
- grammatical errors, including omission or incorrect use of articles, prepositions, auxiliary verbs, etc.;
- use of jargon and loss of meaningful speech;
- difficulty following and maintaining conversation;
- in bilingual patients, errors in selecting and maintaining appropriate language during conversation;
- regression to primary language in bilingual patients (Mendez, Perryman, Fontón, Cummings, 1990);
- language comprehension deficits;
- difficulty following multi-step commands;
- impaired ability to compose meaningful written language;
- reading comprehension difficulties.

**SOCIAL COGNITION AND BEHAVIOR**

Common social cognition and behavior deficits include
- inappropriate behavior outside of socially acceptable range,
- inability to read facial expressions and other social cues,
- loss of empathy,
- mood fluctuations, including agitation and crying,
Epidemiology of Dementia

• restlessness,
• depression,
• negative reaction to questioning,
• combativeness/hostility/aggressiveness,
• compulsive or obsessive behaviors,
• erratic or strange behaviors,
• loss of initiative/motivation,
• paranoia and delusions of persecution.

IMPACT OF COGNITIVE CHANGES

Communication

Cognition and language are intrinsically and reciprocally related in both development and function. An impairment of language may disrupt one or more cognitive processes (e.g., attention, perception, memory, and executive functioning) and, similarly, an impairment of one or more cognitive processes may disrupt language and affect the individual’s ability to communicate effectively.

Individuals who forget what they have recently heard, seen, or thought may have difficulty following a conversation; they often lose track of the topic, miss the point, and/or repeat themselves. With more significant memory decline, individuals may become disoriented to time and place and have difficulty remembering recent events. Verbal output may be reduced and less substantive, and they may become less efficient in expressing information. Attention, executive functioning, and processing deficits can affect the ability to actively engage in conversation, keep track of topic changes, and process information accurately and in a timely manner.

Feeding And Swallowing

In addition to the effects of neuromuscular and/or motor planning deficits associated with some conditions, the cognitive decline associated with dementia can impact feeding and swallowing. Individuals with dementia may forget to eat meals, initiate eating less often, or take in less food and drink than they
normally would during meals, due to distractions in the environment. Reduced intake may eventually compromise nutrition. In addition, individuals with dementia may not attend to food in the mouth or may not remember to chew and initiate a swallow, placing them at risk for choking and aspiration pneumonia.

CAUSES

Cognitive Reserve

Most dementias are the result of neuropathology resulting from diffuse degeneration in cortical and/or subcortical structures and neural pathways, and/or chemical changes that affect neural functioning. Examples of structural changes include neurofibrillary tangles and neuritic plaques, commonly associated with Alzheimer’s disease. Neural pathways (connections between neurons) responsible for memory and new learning are also lost. Examples of chemical changes include cholinergic deficits within the subcortical structures, as in Alzheimer’s disease, or chemical imbalances associated with metabolic disorders.

Alzheimer’s disease is the most common cause of dementia, accounting for approximately 70% of all cases, and the risk of acquiring Alzheimer’s is higher if an individual has a first-order relative with the disease. Vascular dementia is widely considered the second most common cause, accounting for approximately 17%. The remaining cases are accounted for by dementia with Lewy bodies, Parkinson’s disease, frontotemporal lobar dementia, and mixed dementia types.

Cognitive Reserve

The concept of cognitive reserve was introduced to account for the observation that there does not appear to be a direct relationship between the severity of brain damage or pathology and the degree of disruption in performance. It is applicable to most situations in which disruption to brain functioning occurs, including traumatic brain injury and dementia.

Models of cognitive reserve postulate that increased brain reserve capacity or more efficient cognitive processing allows
some individuals to cope with brain insult better than others. Individual differences in cognitive reserve can stem from genetic differences or differences in life experiences, including educational and occupational experiences and involvement in leisure activities.

In addition to lifestyle factors, lifelong bilingualism has been proposed as a factor contributing to cognitive reserve. In studies comparing bilingual and monolingual individuals, bilinguals demonstrated onset of dementia symptoms approximately 4 to 5 years later than monolinguals. The cognitive demands of bilingualism may contribute to an increased cognitive reserve in much the same way as other stimulating activities. These results cannot be generalized to individuals who are not fully bilingual.

ROLES AND RESPONSIBILITIES

Interprofessional Collaboration

Speech-language pathologists (SLPs) play a central role in the screening, assessment, diagnosis, and treatment of persons with dementia.

The professional roles and activities in speech-language pathology include clinical/educational services (diagnosis, assessment, planning, and treatment), prevention and advocacy, and education, administration, and research.

Appropriate roles for SLPs include

- identifying risk factors for dementia, taking into account variability among individuals from different racial and ethnic backgrounds and culturally and linguistically diverse populations;
- providing prevention information to individuals and groups known to be at risk for dementia, as well as to individuals working with those at risk;
- educating other professionals, third-party payers, and legislators on the needs of persons with dementia and the role of SLPs in diagnosing and managing cognitive communication and swallowing disorders associated with dementia;
• educating caregivers about possible communication difficulties and providing strategies to facilitate effective communication;
• screening individuals who present with language and communication difficulties, including hearing screening;
• determining the need for further assessment and/or referral for other services;
• conducting a culturally and linguistically appropriate comprehensive assessment across the SLP scope of practice, including assessment of cognitive-communication functioning and swallowing;
• diagnosing cognitive-communication disorders of dementia across the course of the underlying disease complex;
• assessing, diagnosing, and treating swallowing disorders associated with dementia;
• referring to an audiologist to rule out hearing loss and balance problems;
• referring to other professionals to rule out other conditions, determine etiology, and facilitate access to comprehensive services;
• making decisions about the management of cognitive-communication deficits associated with dementia;
• developing treatment plans for maintaining cognitive-communication and functional abilities at the highest level throughout the underlying disease course;
• treating the cognitive aspects of communication, including attention, memory, sequencing, problem solving, and executive functioning;
• selecting culturally and linguistically appropriate techniques for direct intervention;
• gathering and reporting treatment outcomes;
• monitoring cognitive-communicative status to ensure appropriate intervention and support;
• providing indirect intervention through the individual’s caregivers and environmental modification;
Epidemiology of Dementia

- providing counseling to persons with dementia and their families regarding communication-related issues and providing information about the nature of dementia and its course;
- consulting and collaborating with other professionals, family members, caregivers, and others to facilitate program development and to provide supervision, evaluation, and/or expert testimony, as appropriate;
- remaining informed of research in the area of dementia and helping advance the knowledge base related to the nature and treatment of dementia;
- advocating for individuals with dementia and their families at the local, state, and national levels;
- serving as an integral member of an interdisciplinary team working with individuals with dementia and their families/caregivers;
- serving as a case manager, coordinator, or team leader to ensure appropriate and timely delivery of a comprehensive management plan;
- providing quality control and risk management.

As indicated in the Code of Ethics, SLPs who serve this population should be specifically educated and appropriately trained to do so. Given the relationship between cognition and communication, practitioners who serve individuals with dementia require knowledge and skills in both areas, including specific knowledge of cognitive-communication disorders associated with dementia, to fulfill the aforementioned roles.

Most common dementia-associated diseases are progressive in nature, and SLPs have an ethical responsibility to provide appropriate services that will benefit the individual and maximize cognitive-communication functioning at all stages of the disease process.

Interprofessional Collaboration

SLPs collaborate with many other disciplines in caring for individuals with dementia. Referral and collaboration between members of the team, particularly during the assessment process
and treatment planning, are important to help ensure quality service for individuals affected by communication and cognitive disorders. Coordinating assessment can prevent overlap in test selection. Ultimately, the focus of collaborative efforts must be on the clinical utility of information and how professionals with complementary knowledge and skills can affect functional outcomes for patients in a beneficial manner.

**ASSESSMENT**

The diagnosis of dementia is made by a medical team. The role of the speech-language pathologist (SLP) is to assess cognitive-communication deficits related to dementia (e.g., memory problems; disorientation to time, place, and person; difficulty with language comprehension and expression) and to identify cultural, environmental, and linguistic factors that impede functioning.

The SLP determines the most appropriate assessment protocol based on the stage of dementia and the individual’s communication needs. In addition, when selecting cognitive-communication screening instruments and subsequent tests for comprehensive evaluation, the clinician considers the cultural and linguistic background of the client, using tests that have normative samples of culturally and ethnically diverse groups when available. Standard scores should not be reported, if the normative sample is not representative of the individual being assessed.

**Screening**

Screening for cognitive impairment is conducted by an SLP or other member of the interdisciplinary care team for individuals with any condition that increases their risk for cognitive-communicative problems, including hearing loss. Many standardized instruments with demonstrated reliability for screening of dementia are available. These instruments typically assess orientation to time, place, and person. Other tests (e.g., story recall/story retelling) assess episodic memory and can be useful for screening for early dementia.

Prior to screening for cognitive-communication disorders associated with dementia, it is important to consider the impact
of sensory impairment, depression, and current medications on cognitive functioning. If screening reveals cognitive impairment, individuals are referred to an SLP for a comprehensive evaluation of communicative function. Referral for other examinations or services are made as needed.

**Hearing Loss**

Hearing loss is common among older adults, and many individuals have untreated hearing loss and do not wear hearing aids or make use of other hearing technologies. Audiometric hearing screening and otoscopic inspection for impacted cerumen are to be conducted prior to cognitive-communication screening.

Traditional behavioral tests of hearing (e.g., pure tone and speech audiometry) are generally successful in the early stages of dementia, although modifications such as simplifying directions, using pulse tones, slowing presentation of speech stimuli, providing reminders to respond, and responding with “yes” instead of raising a finger or pressing a button may be needed. During the later stages of dementia, more objective tests (e.g., otoacoustic emissions or auditory steady state response) may be necessary to obtain estimated thresholds, as may be modifications of assessment procedures for those patients who do not condition to standard tasks.

If the individual fails the hearing screening, a referral is made to an audiologist for a comprehensive assessment. If an individual has a diagnosed hearing loss and wears hearing aids, hearing aids are inspected to ensure that they are in working order and worn by the individual during cognitive-communication screening. The use of assistive listening technology should be employed when hearing aids are not being used.

**Visual Impairment**

If visual deficits are suspected, the individual is referred for vision testing prior to completing cognitive-communication screening. Prescription eye glasses, as needed, are to be worn during screening, and adequate lighting used in the test (and treatment) environment.
Depression

Depression is common in individuals with dementia and can adversely affect test performance. Cognitive changes associated with depression so resemble the cognitive changes associated with dementia that depressive symptoms are often referred to as “pseudodementia.” If signs and symptoms of depression are present, the individual is referred to a neuropsychologist or clinical psychologist experienced with geriatric depression.

Medications

Prior to screening, the SLP considers the effects of prescription drugs on cognitive-communicative function. Polypharmacy, or the concurrent use of several medications, is common among older adults who have multiple medical conditions, and some medications may exacerbate cognitive problems. Questions about the effects of medication use on cognitive-communication functioning can be answered by a pharmacist knowledgeable in geriatric pharmacy.

COMPREHENSIVE ASSESSMENT

Individuals suspected of having cognitive-communication problems are referred for a comprehensive assessment of language and communication. SLPs often conduct these assessments in collaboration with neuropsychologists. Assessment may include clinical observations in the home or long-term care setting.

Assessment is conducted to identify and describe

- underlying strengths and weaknesses related to cognition, language, and social/behavioral factors that affect communication performance;
- effects of cognitive-communication impairments on the individual’s activities and participation in ideal settings, everyday contexts, and employment settings;
- contextual factors that serve as barriers to or facilitators of successful communication and participation for individuals with cognitive-communication impairment;
- the impact on quality of life for the individual and the impact on his or her family/caregivers.
Assessment may result in
- diagnosis of a cognitive-communication disorder;
- clinical description of the characteristics of a cognitive-communication disorder;
- statement of prognosis for improved outcomes;
- recommendations for intervention and support;
- identification of the effectiveness of intervention and supports;
- referral for other assessments or services.

A comprehensive assessment is sensitive to cultural and linguistic diversity and addresses the components within the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF) framework, including body structures/functions, activities/participation, and contextual factors. Assessment should occur in the language(s) used by the person with dementia.

Assessment can be static (i.e., using procedures designed to describe current levels of functioning within relevant domains) and/or dynamic (i.e., an ongoing process using hypothesis-testing procedures to identify potentially successful intervention and support procedures). When dementia is caused by a progressive disease, periodic reevaluation (e.g., yearly) and adjustment of care plans become essential to meet changing needs.

Assessment typically includes
- relevant case history, including medical status, education, occupation, and socioeconomic, cultural, and linguistic background;
- review of auditory, visual, motor, cognitive, and emotional status;
- patient/client and family reports of goals and preferences, as well as domains and contexts of concern;
- standardized and nonstandardized methods selected with consideration for ecological validity:
  - observation and description of the individual’s processing of various types of information under ideal conditions and in the context of various activities and
settings (e.g., ability to attend to, perceive, organize, and remember verbal and nonverbal information to reason and to solve problems);

- observation and description of the individual’s executive or self-regulatory control over cognitive, language, and social skills functioning (e.g., ability to set goals, plan, initiate and inhibit, self-monitor and self-evaluate, solve problems, and think and act strategically);

- analysis of the cognitive and communication demands of relevant social, academic, and/or vocational tasks and identification of possible facilitative effects in modification of those tasks;

- identification of the communication and support competencies of relevant people in the environment and possible facilitative effects of modification of their support behaviors;

- identification of the individual’s potential for effective compensatory behaviors and associated motivational barriers and facilitators;

- follow-up services to monitor cognitive-communication status and ensure appropriate intervention and support for individuals with identified cognitive-communication disorders.

**Assessment of Swallowing**

A comprehensive assessment includes a swallowing screening or, if indicated, a swallowing assessment. An estimated 45% of individuals with dementia residing in an institution have dysphagia, and dysphagia is more prevalent in patients with Alzheimer’s disease than in normal elderly individuals.

This increased prevalence may be associated with a diminished sense of smell and cognitive changes associated with the progression of dementia.

Swallowing assessment with individuals with dementia involves evaluation of

- the oral mechanism;
• the patient’s ability to comprehend and use compensatory strategies;
• the individual’s oral preparatory, oral, pharyngeal, and esophageal phases;
• the individual’s recognition of food and utensils;
• environmental impacts, including the appearance of the food, lighting, and distractions;
• food and liquid trials with a variety of temperatures, textures, tastes, postures, and strategies and consideration for the individual’s food preferences;
• the potential impact of the individual’s prescribed medications on swallowing function;
• the influence of cognitive factors on feeding and swallowing.

An instrumental evaluation may be performed to determine safety and identify effective treatment techniques or strategies, if the patient is able to respond appropriately and tolerate the procedure. The instrumental evaluation may provide additional information about the oral and pharyngeal bolus transit, airway protection, the impact of bolus texture and size, and appropriate pacing.

**Assessment Measures**

There are a number of assessment tools that produce a valid characterization of cognitive-communication strengths and weaknesses—including language comprehension and expression and integrity of working, declarative, and procedural memory systems—and that have been standardized on individuals with dementia. The severity level of dementia in the individual being tested is factored into test selection. Some tests are too difficult for the individual with severe dementia and do not yield useful information, because the individual fails most or all of the items.

**Assessment in Long-Term Care Facilities**

Passage of the Omnibus Budget Reconciliation Act in 1987 mandated evaluation of the physical and psychological status of residents in long-term care facilities at the time of admission and
periodically thereafter. The required evaluation, known as the Minimum Data Set (MDS), includes questions about the ability of residents to hear, comprehend, and produce language. Although the law does not require that judgments about hearing and communicative function be made by SLPs, the inclusion of these questions on the MDS helped establish a role for SLPs with long-term care residents.

**TREATMENT**

- Caregivers and Communication Partners
- Treatment Options
- Feeding and Swallowing Treatment
- Treatment For Hearing Loss
- End-of-Life Issues
- Service Delivery

Treatment for the cognitive-communication deficits associated with dementia addresses the specific needs of the individual, taking into consideration the stage of the illness. Most common dementia-associated diseases are progressive in nature, and speech-language pathologists (SLPs) have an ethical responsibility to provide appropriate services that will benefit the individual and maximize cognitive-communication functioning at all stages of the disease process. Interventions that enhance activity and participation through modification of contextual factors may be warranted even if the prognosis for improved body structure/function is limited.

SLPs consider the individual’s age, education, premorbid information, social history, present social context, cultural and linguistic background, and vocational status (current or premorbid) in formulating realistic and functional treatment goals within the bounds of the cognitive-communication disorder and with consideration for the progressive nature of the disease. Goals are often set based on the individual’s current level of functioning, which can be determined using standardized functional rating scales.

Decisions about goals and treatment options are made in collaboration with clients, families/caregivers, and other health
professionals. Clinicians can work directly with the individual who has dementia or indirectly through environment modifications, caregiver training, or the development of therapeutic routines and activities.

Treatment also involves providing information and guidance to the individual, family/caregiver(s), and other significant persons about the nature of the disorder and the course of treatment. Treatment occurs in the language(s) used by the person with dementia either by a bilingual SLP or with the use of trained interpreters, when necessary.

Demographic shifts and immigration patterns have led to increased diversity among the elderly population and their caregivers in the United States. Cultural influences and familial expectations regarding roles may impact long-term care decisions, who makes these decisions, and the value of treatment and intervention.

Although SLPs are autonomous professionals, successful intervention with individuals with cognitive-communication disorders often requires the collaborative involvement of other professionals. SLPs work collaboratively with neuropsychologists and other professional colleagues (e.g., audiologists), families, employers, and others who provide support to individuals with cognitive-communication disorders. SLPs (working within their scope of practice and at their individual level of competence) are uniquely qualified to treat communication disorders associated with cognitive impairments.

Consistent with the World Health Organization (WHO) framework, intervention is designed to

- capitalize on strengths and address weaknesses related to underlying structures and functions that affect communication,
- facilitate the individual's activities and participation by assisting the person to acquire new skills and strategies,
- modify contextual factors that serve as barriers and enhance facilitators of successful communication and participation, including development and use of appropriate accommodations.
Because of the progressive nature of most dementia-associated illnesses, clinicians must determine whether individuals with dementia have the potential to benefit from cognitive-communication interventions. Positive prognostic factors are identified that demonstrate the feasibility of the proposed intervention.

Depending on assessment results, intervention addresses

- processing of various types of information under ideal conditions and in the context of various activities and settings;
- executive or self-regulatory skills (e.g., setting goals, planning, initiating and inhibiting, self-monitoring and self-evaluating, problem solving, thinking and acting strategically);
- use of effective compensatory behaviors and communication techniques and strategies;
- audiology services as needed for identified hearing loss (e.g. hearing aids, hearing assistive technology);
- cognitive and communication demands of relevant social, academic, and/or vocational tasks to facilitate performance of those tasks;
- communication and support competencies of relevant people in the environment.

CAREGIVERS AND COMMUNICATION PARTNERS

Those who provide care to individuals with dementia, including both professionals and family members, are faced with a number of challenges that can ultimately affect their own health and wellbeing. The changes in communication functioning brought about by cognitive decline can significantly affect day-to-day communication, resulting in considerable frustration. Research focused on individuals with AD suggests that training caregivers about dementia and teaching them to use strategies to enhance communication effectiveness may contribute to increased caregiver understanding of communication breakdowns; more successful conversational exchanges; and improved quality of life for the individual with dementia.
Epidemiology of Dementia

Treatment Options

The goal of cognitive-communication treatment is to maximize the individual’s quality of life and communication success, using whichever approach or combination of approaches meets the needs and values of that individual.

The following are brief descriptions of both general and specific treatments for persons with cognitive-communication disorders associated with dementia. Some treatment approaches are considered compensatory, and some are considered restorative in nature. Compensatory treatment approaches focus on teaching methods and skills to compensate for or overcome deficits that are not amenable to retraining. Restorative treatments involve direct therapy aimed at improving or restoring impaired function(s) through retraining. Where available, links to evidence and expert opinion regarding the intervention are provided. This list is not exhaustive nor does inclusion of any specific treatment approach imply endorsement by ASHA.

Assistive Technology (including hearing assistive technology)

Assistive technology (AT) is a generic term that includes assistive, adaptive, and rehabilitative devices and services for individuals with disabilities. An assistive technology device is any item, piece of equipment, or system—whether commercial, modified, or customized—that is used to increase, maintain, or improve the functional capabilities of a person with disabilities. Hearing Assistive Technology Systems (HATS) are available for individuals who currently use hearing technology, such as hearing aids and cochlear implants. HATS are also available for those with hearing loss that is untreated. Personal amplifiers and FM systems and other technology can enhance face-to-face communication. There are several commercially available and emerging assistive technologies that, with further interdisciplinary research and modifications, may have potential applications to dementia care.

Cognitive Stimulation Therapy

Cognitive stimulation therapy (CST) focuses on actively stimulating and engaging individuals with dementia by using
theme-based activities in an optimal learning environment (typically, in a small-group setting).

**Environmental Modifications**

Environmental modifications are changes or adaptations to the environment to improve communication skills in individuals with dementia. Modifications are aimed at optimizing the cognitive, visual, and auditory aspects of the environment and include improving lighting, reducing glare, and reducing visual clutter; minimizing background noise and noise reverberation; and providing cues (e.g., signs that incorporate text and simple graphics) and displaying personal items to improve memory, awareness, and orientation.

**External Memory Aids**

External memory aids are aimed at helping individuals with memory problems in their day-to-day activities. They include electronic and non-electronic devices, as well as environmental adjustments. Examples include personal digital assistants (PDAs), message boards, clocks, and pictures.

**Memory-Training Programs**

Memory-training programs focus on improving/re-training memory skills using techniques such as spaced retrieval, errorless learning, procedural memory stimulation, vanishing cues, and didactic approaches.

**Montessori-Based Treatment**

Montessori-based treatments use principles developed by Maria Montessori (2008), including using real-life materials, designing activities that are of interest to the individual, allowing learning to progress in sequence, minimizing the risk of failure and maximizing the chance of success, and breaking down activities into component parts and practicing these one at a time.

**Reality Orientation (RO)**

Reality Orientation (RO) is a technique to reduce confusion and improve quality of life for individuals with dementia by providing orienting information (e.g., time, place, or person) to
reinforce understanding and awareness of the environment. Information is repeated at regular intervals throughout the day.

**Reminiscence Therapy (RT)**

Reminiscence Therapy (RT) is an intervention approach that uses the life history and experience of an individual to improve his or her sense of well-being. RT programs typically involve the discussion of past activities, events, and experiences—using tangible prompts, such as photographs, familiar items, and music from the past. The customized nature and individual focus of reminiscence therapy make it an intervention particularly well suited for individuals from diverse backgrounds.

**Simulated Presence Therapy (SimPres)**

Simulated presence therapy (SIMPRES) is an emotion-oriented approach aimed at reducing levels of anxiety and challenging behaviors by playing audio recordings of the voices of close relatives of the individual. SIMPRES has been used to improve well-being (e.g., decrease agitation and withdrawal behaviors) in individuals with Alzheimer’s disease who have adequate hearing and have retained communication skills.

**Validation Therapy**

Validation therapy is an approach that involves validating or accepting the values, beliefs, and reality of the person with dementia to help reduce stress and provide opportunities for the individual to communicate his or her feelings; validation therapy was developed by Naomi Feil (1982) for individuals with cognitive impairment and dementia.

**FEEDING AND SWALLOWING TREATMENT**

Individuals progressing through different stages of dementia may demonstrate difficulty feeding and swallowing. For example, individuals with moderately severe cognitive decline often demonstrate difficulty using a knife; individuals with severe cognitive decline may demonstrate difficulties discriminating between utensils; and individuals with very severe cognitive decline may be easily overwhelmed and require cues to locate food on the
plate and to swallow. Swallowing function may also be affected by reduced muscle strength and coordination. Once appropriate feeding and swallowing strategies, postures, and consistencies have been identified, the clinician can train caregivers to provide feeding support and cuing as appropriate.

**Diet Modifications**

Diet modifications consist of altering the viscosity, texture, temperature, or taste of a food or liquid to facilitate safety and ease of swallowing. Typical modifications may include thickening liquids or softening, chopping, or pureeing solid foods. Taste or temperature of a food may be altered to provide additional sensory input for swallowing, and preferences of the individual are considered to the extent feasible. The nutritional needs of the individual and the safety of medical treatments (e.g., swallowing vitamin supplements or drinking thin liquids) are also considered before making modifications. A referral to a dietician is made as necessary.

**Postural Changes**

Positioning techniques involve adjusting an individual’s posture or position during feeding. These techniques aim to protect the airway and offer safe transit of food and liquid. No single posture will provide improvement to all patients/clients; rather, the general goal is to establish central alignment and stability for safe feeding.

**Tube Feeding**

Tube feeding includes supplemental or alternative avenues of intake (e.g., nasogastric tube [NG], transpyloric tube placed in the duodenum or jejunum, or gastrostomy-G-tube placed into the stomach or GJ-tube placed into the jejunum). These approaches may be used if the individual’s swallowing safety and efficiency cannot reach a level of adequate function or does not support nutrition and hydration adequately. In these instances, the swallowing and feeding team considers whether the individual will need the supplemental or alternative source for a short or extended period of time to determine the optimum tube feeding
selection to best meet the individual’s needs. Alternative feeding does not preclude the need for feeding-related treatment.

**TREATMENT FOR HEARING LOSS**

The presence of dementia should not preclude fitting with a hearing aid; however, ongoing support may be necessary to ensure compliance with hearing aid use. Although there is no current evidence that hearing aids can improve cognition in persons with dementia, problem behaviors (e.g., repeating questions, negative statements, forgetting, restlessness, pacing, “hearing things”) can be improved with the use of amplification. In addition, elderly patients fitted with hearing aids during the early stages of hearing loss may retain cognitive function better than those who postpone fitting of hearing aids.

Given the relationship between hearing loss and dementia and the co-occurrence of hearing loss and dementia in aging adults, audiologists play a significant role in the treatment of these individuals. In addition to assessing the need for HATS, hearing aids, and cochlear implants, audiologists educate family members and caregivers on strategies to improve communication at home (e.g., improving listening environments) and provide ongoing counseling and support in the use of technology.

**End-of-Life Issues**

Speech-language pathologists (SLPs) working with individuals with dementia may be presented with a patient nearing the end of life. These patients introduce complex clinical and ethical issues around feeding and communication that impact the role of the SLP and other health care professionals.

The goal of intervention with patients at this stage is not rehabilitative, but facilitative or palliative. The SLP may be asked to participate in team decision making regarding the use of alternative nutrition, such as tube feeding, and may develop an alternative communication strategy, if appropriate, that will allow the individual to express his or her wants and needs more effectively. The expected outcome of intervention is not necessarily to improve abilities, but to allow the individual to use the abilities
he or she still possesses to interact with family and friends and/or enjoy favorite foods, if that is the patient’s wish.

The pattern of functional decline in individuals at the end of life varies, depending on a person’s diagnosis. In dementia, the decline may be inconsistent over a long period of time. SLPs need to understand the process of dying to understand the emotional and psychological issues faced by their patients and patients’ family members. The wishes of the patient and family are paramount when considering end-of-life issues, and the role of the SLP extends only as far as the patient or family wishes. What the SLP may think is best for the patient clinically may not always be accepted as best for the patient’s quality of life. The document, 2004-2005 Ethics, Rights, and Responsibilities Standards of the Joint Commission on Accreditation of Healthcare Organizations, addresses this issue in Standard RI.2.80.

Views of the natural aging process and acceptance of disability vary by culture. Cultural views and preferences may not be consistent with medical approaches typically used in the U.S. health care system, but must be recognized and respected. The clinician approaches clinical interactions with cultural humility and demonstrates sensitivity to social and cultural influences when sharing potential treatment recommendations and outcomes.

**EPIDEMIOLOGY**

**Global picture**

The World Health Organization (WHO) predicts that by 2025, about 75% of the estimated 1.2 billion people aged 60 years and older will reside in developing countries. It is estimated that the number of people living with dementia will almost double every 20 years to 42.3 million in 2020 and 81.1 million in 2040. The rate of growth will be the highest (around 336%) in India, China, South Asia, and western Pacific regions, 235-393% in Latin America and Africa, and the lowest (100%) in developed regions. Based on 2001 global population, about 24.3 million have dementia and 4.6 million incident or new cases are added yearly. As per global burden of disease study by WHO and World Bank, dementia contributes 4.1% of all disability-adjusted life years (DALYs).
Prevalence of dementia in India

Prevalence rates (PRs) [Table 1] from different regions of India differ widely. The rate may possibly be related to adoption of different methodology, screening instruments, defining criteria, multiethnicity, and multicultural and environmental factors. The prevalence of dementia of rural population in South India and that in North India showed a widely varying rate from 3.39 to 0.84%, respectively. There are few urban studies from several regions of India showing similar varying rates: From 2.44 to 4.1% in West India, 1.83% in North India, 0.8-1.28% in East India, and 3.6% in South India. The differences may be true considering the multiethnic, multicultural, and environmental differences. Utilizing a common protocol and undertaking multicentric study on dementia prevalence and incidence may overlook distinctive differences across regions.

Mild cognitive impairment

Mild cognitive impairment (MCI) is a transitional phase between normal aging and dementia. Understanding (MCI) is important, and many cases may progress to dementia, though some may revert to normal cognition. Very few studies on MCI have been carried out in India. One of these was a community-based study and another was a clinic-based study. The community prevalence of MCI in India is about 14.89% (95% CI: 12.19-17.95%) and that of multi-domain type (8.85%) was higher than amnestic type (6.04%). Interestingly, this data is comparable to a study from a developed country. Another longitudinal study from India has recorded a conversion rate of MCI to dementia, which is similar to western countries and varies from 8 to 14%. It might indicate the dynamic factors for conversion of MCI to dementia are possibly the same in developed and developing countries. In the clinic-based study, out of 194 referral cases with cognitive dysfunction, 65.5% cases had dementia based on clinical, neuropsychological, and imaging evidences and about 22.14% cases had MCI.

Stroke dementia

Increasing stroke prevalence and incidence has led to the expectation that stroke dementia will be higher in India. Recently,
a prospective community study from East India documented PR of post-stroke dementia at 13.88% (95% CI: 9.91-18.90%). The prevalence was higher than the rate calculated from a meta-analysis of the studies on stroke dementia worldwide (overall rate 7.4%; 95% CI: 4.8-10.0%). Higher rate in the above study may be due to inclusion of pre-stroke dementia subjects. In a clinic-based study from South India, the pattern of vascular damage and underlying vascular risk factors were documented among subjects with vascular dementia (VaD). Out of the different patterns, subcortical, cortical-subcortical, strategic infarcts, and cortical dementia were documented in 52.4%, 26.2%, 14.3%, and 7.1% of cases, respectively.

Incidence of Dementia in India

Long-term study on dementias and cognitive dysfunction are few from India. One study from North India on Alzheimer disease (AD) has shown an incidence of 4.7 per 1000 person-years as compared to 17.5 per 1000 person-years in Monongahela valley, USA. Both were sister studies with similar methodology, but differing in life expectancy and literacy of the studied samples. Another incidence study in Dogra population of North India documented an incidence rate of 5.34 per 1000 person-years.

The study on stroke dementia has also documented an annual progression rate of 3.53% of stroke survivors into dementia, indicating that 1 out of every 28 stroke survivors become demented each year. Thus, it is estimated that one-third of stroke survivors will become demented if they remain alive for a decade after stroke. Chance of having dementia becomes more pronounced when they have recurrent and thrombotic stroke.

Mortality of Dementia

The study from India, conducted in South India, investigated predictors of mortality among older people living in the community. Mortality risk was 2.3 times more for older people with dementia and linearly correlated with the severity of cognitive impairment. Similarly, another study has shown higher mortality by 2.65 times in patients with post-stroke dementia than in stroke survivors without cognitive dysfunction.
RISK FACTORS OF DEMENTIA

The traditional risk factors of dementia are advancing age, illiteracy, addiction, hypertension, diabetes, poor socioeconomic status, trauma, familial or genetic factors, nutritional factors, and stroke.

A study from West India has documented advancing age, poor literacy level, low socioeconomic status, and positive family history as the risk factors for dementia. On the other hand, marriage was found to be protective in the same study. Marriage is possibly linked to health and economic benefit. Married individuals tend to have better physical health and psychological well-being, and a lower mortality risk. Chandra et al. speculated, based on their study of elderly rural persons from North India, that the risk factors for cognitive dysfunction not amounting to dementia were nutritional deficiencies and certain common infectious diseases. The neurologic factors which may be resultant of nutritional disturbances were history of impaired consciousness due to head injury or seizure disorders, gait disturbances, diminished tendon reflexes suggestive of neuropathy, and presence of at least one primitive reflex indicating diffuse forebrain dysfunction. A study from South India has documented family history of dementia as a risk factor for AD and smoking and hypertension as the risk factors for VaD. From East India, a community study has shown that the risk factors for MCI were hypertension, diabetes mellitus, and smoking which included both inhalant and chewing tobacco, as compared to the control population. Among the stroke survivors, stroke dementia is commoner among the elderly and in those with cortical atrophy. Recurrent stroke and thrombotic stroke were the other risk factors for stroke dementia.

Protective Factor

Animal studies have shown the protective effect of curcumin, a yellow curry paste (turmeric) which is almost consumed universally by Indians. It has antioxidant and anti-inflammatory effects and decreases amyloid protein synthesis. Possibility of lower prevalence of dementia among Indians may be related to this dietary protective factor in the diet.
HIV Infection and Dementia

HIV is an important cause of cognitive dysfunction among young and middle-aged persons. One study from South India documented cognitive dysfunction in about 60.5% of HIV subjects. Prevalence of AIDS dementia is however lower among Indian (approx. 2%) is much lower than Americans (15-30%). This has been related to “TAT” protein which is stable in Indian variants of HIV C type virus than in western countries. This also indicates existence of protective factor in Indian environment and probably needs to be probed further.

Genetics of Dementia in India

ApoE gene polymorphism has important association with dementia and has been confirmed in both clinic- and community-based studies. In the western countries, APOE gene has been shown to be increasingly associated with dementia. Frequency of APOE4 gene polymorphism (ApoE genotypes with at least one e-4 allele) is less common in the Indian population (around 0.07). However, a clinic-based study from South India confirmed the increased frequency of ApoE4 in patients with dementia (0.18), especially among those with AD (0.21), and also in VaD. The frequency was higher than that reported in the other rural community-based study from North India (0.15 in all dementias) and the hospital-based study. A study from Central India has shown positive influence of presenilin gene (PS1, allele 1) and ApoE gene e-4 alleles, increasing the susceptibility for degenerative dementia as compared to VaD. APOE4 polymorphism does not influence the magnitude of clinical and functional deficits. Other than AD group, VaD group has also shown higher frequency of APOE4 alleles (0.17), though the study from urban northern India has shown higher positivity of APOE4 allele among VaD patients (0.34) than among AD patients (0.29). Occasional cases of familial dementia have been recorded, but no genetic report of established mutation in presenilin 1 and presenilin 2 has been published. A family of autopsy-proved AD has been documented. We have not encountered and found any report on specific mutation of known genes of AD dementia. In a study on 81 patients with frontotemporal lobe degeneration, microtubular associated protein
gene, progranulin gene, and APOE genes have been found to play limited roles in the pathogenesis among Indian population as compared to European and North American populations.

**NEUROPATHOLOGY OF DEMENTIA**

Since autopsy is optional in India for non-medicolegal cases, there is dearth of reports on the pathology of brain in subjects with dementia. It is a serious deterrent in validating the antemortem diagnosis of dementia and its subtypes. However, a study on the pathological finding of aging brain has been carried out in West India and this was compared with similar studies from a center in USA, utilizing the same methodology. Mean brain weight of Indian sample was lower and mean diffuse plaque density was higher. Differences in mean density and counts of neurofibrillary tangles and neuritic plaques were not statistically significant. This is at variance with the expected lower AD-related lesion burden based on the clinical/epidemiological studies, suggesting lower prevalence of AD in India.

**Problems in Recognizing early Dementia Cases in Indian Context**

In Indian social scenario, forgetfulness in the elderly is often recognized as normal variation of aging. When it is recognized, it is often in advanced stages. Commonly, the responsibility of household instrumental activities such as marketing, office work, monetary transaction, etc., is shouldered in next generation family members. Consequently, milder problems remain unrecognized. Another important hurdle is to get proper and chronological history. Being a multilingual country with significant proportion of illiterate people, formulating and validating different evaluation scales is a challenging task.

**Dementia Subtype and Indian Perspective**

Subtyping of dementia has been carried out in many studies from India. Community-based studies have shown that the frequency of AD varied from 0.34 to 1.5% above 60 years of age. However, clinic-based studies have one advantage that they are well investigated. A clinic-based study from South India found
AD in 38.3%, VaD in 25.4%, frontotemporal dementia (FTD) in 18.7%, diffuse Lewy body disease (DLB) in 8.9%, and mixed dementia in 8.6% of the patients. Prevalence of overall dementia and its subtype from India is 2.7% [95% CI (1.4-4.0%); AD, 1.3% (0.8-1.8%); VaD, 1.1% (0.2-1.9)].

Proportionately VaD is higher in Asian countries than in western countries. In clinically diagnosed dementia cases, 75% were AD and 13% were VaD from a North American country. The mean age at presentation in India is about 66.3 years, about one decade younger than in developed countries. The proportion of patients with early-onset dementia was high (49.9%), compared to 7-30% in developed countries.

This may be related to younger age of Indian population as compared to western population or ethnically related. The two clinic-based studies from two regions have shown subjects with dementia showing similarity in age group, but differing in subtypes and etiologies, indicating possible contribution by varied environmental factors and possible referral bias.

Thus, the two studies evaluated the cases based on clinical, biochemical, radiological, and neuropsychological assessment. Significant finding was the noticeably lower frequency of AD from Central India. One of the explanations was that frequency of mixed dementia might be overestimated in this study. Possibly many of the cases might be categorized as degenerative dementia if autopsy could be performed.

A study on early-onset dementia (d<65 years) from East India documented higher frequency of possible AD (30%), followed by FTD (27%), VaD (20%), Huntington disease (HD) (4%), and miscellaneous causes in 11% of cases. Higher frequency of family history was noted in 30% of cases with AD, 20% in FTD, 5% in VaD, 75% in HD, and 25% in Parkinson’s disease (PD) with dementia. Thus, the study may indicate higher influence of possibly genetic factors in early-onset cases. Besides, this study also emphasizes that AD is the predominant type of dementia even in early-onset cases, though in those below 50 years, FTD was the commonest variety.
Behavioral and Psychological Symptoms of Dementia

Overall, the patients can present in two ways, either with cognitive deterioration or with behavior and psychological symptoms of dementia (BPSD), and thus can present to either neurologist or psychiatrist. Rarely, degenerative dementias, particularly AD subtype, may present with unusual clinical phenomenon such as visual disturbances.

Though cognitive symptoms are the main focus for diagnosis and management of dementia, recent years have seen growing importance of BPSD particularly from the point of management, caregiver’s burden, quality of life, and outcome of dementia. However, most of the studies have been carried out in developed countries. Recently some studies have also been done in the developing countries including India by the 10/66 group. This group reported that at least one BPSD was present in 70.9% of cases and the commonest psychiatric abnormalities were depressive syndrome (43.8%) followed by anxiety neurosis (14.2%) and schizophreniform/paranoid psychosis (10.9%). In contrast, a community study from North America documented that 61% had exhibited one or more mental or behavioral disturbances in the past month. Apathy (27%), depression (24%), and agitation/aggression (24%) were most common in subjects with dementia. Thus, higher depression in developing countries may be related to cultural and socioeconomic influences. A recent community study from western India has documented varied BPSD such as irritability (15.1%), agitation (9.3%), apathy (8.1%), hallucination (8.1%), depression (7%), disinhibition (5.8%), and somatic symptoms such as poor sleep (5.8%), poor appetite (2.3%), and suspiciousness (2.3%). Pattern of BPSD differs depending on the subtypes of dementia. A study from West India recorded that AD patients have significantly more delusions, hallucinations, anxieties and phobias, and caregiver distress than patients with VaD. Another study from South India had found that over 96% patients of dementia had one or more BPSD and certain delusions such as delusion of theft or that one’s house is not his own. Similarly, in a study from South India, the neuropsychiatric symptoms between AD, VaD, and FTD were compared and it was observed that
aberrant motor behavior, disinhibition, and appetitive/eating behavior differentiated FTD from AD and VaD. No significant difference was found between AD and VaD. Mean total psychopathology scores increased in tandem with dementia severity regardless of dementia type. In another study from East India, higher frequency of utilization behavior in subjects with FTD was noted and the actual underlying cause was not known. It may be related to the pattern of degeneration in frontal lobe with secondary release phenomenon of underlying repetitive behavior. Interestingly, one European study had found more psychiatric symptoms in FTD cases and all were diagnosed as primary psychiatric disorders at the onset. It emphasizes early need of recognition of BPSD.

Neuroimaging

Study on functional neuroimaging pattern in patients with dementia showed similar picture as standard literature. AD has been found to be the most frequent form of dementia. However, a significantly higher proportion of frontal lobe involvement was noted in the Indian population, as compared to global literature. No occipital cortex extension was found in Indian patients. In another community-based study, magnetic resonance imaging (MRI) has shown increase in prevalence of infarcts and more extensive white matter change indicating possible vascular changes. Frontal lobe atrophy was dominant in FTD cases. In 74.5% of cases with AD, both gray and white matter involvement was noticed. Only prominent cortical gray matter involvement was noted in a small number of cases of AD (8.1%) and VaD (7.7%). This report indicates that dementia subtyping based on neuroimaging is not reliable.

Awareness

Interestingly, systematic study on awareness about dementia is infrequent. The awareness about dementia is poor among common people and also general practitioners. One study from India has recorded that dementias are considered as neglect by family members. Dementia subjects are often stigmatized. Poor awareness leads to poor recognition, resulting in delayed diagnosis
and sometimes catastrophic situation may arise. There is little help from health service sectors which do not provide the needed information and support for carers and family members. Print media and electronic media have started to raise awareness among the general public in India. Alzheimer Related Disorder Society of India is taking part in this process through its different chapters nationally.

**Caregiver Burden in India**

The caregivers have to bear the brunt of the dementia patients and BPSD is the most important factor predicting the caregiver burden in dementia. In India, the majority of the caregivers are women in 70% of cases, and are mostly wives, daughters, and daughters-in-law. The principal sources of caregiver strain are BPSD and incontinence. Strain is exacerbated by the lack of supportive response from local health services and of family support resulting from adverse behaviors from other family members, and they suffer significant mental strains indicating clear need for support and more education. A study from Goa, West India has shown that community-based interventions have considerable potential to improve the quality of life of the caregivers and the subjects with dementia. Home-based care is preferred to daycare program for the caregivers of persons with dementia. The study has shown that the use of locally available, low-cost human resources in tune with socio-culturally acceptable method is feasible and leads to significant improvement in caregiver’s mental health and burden of care.

**Socio-Cultural Context of Dementia: Kerala Model**

Kerala, an advanced state in terms of literacy and human development index, has undergone rapid urbanization and modernization in 80s and 90s of the last century. As a result, there is exodus of earning member for economic reason. Traditionally in Indian culture, the elderly persons are taken care of by the next generation family members. Urbanization leads to disruption of joint family due to migration and older people are left in rural communities with meager or absence of family support in many cases. Thus, demographic changes characterized by increasing
elderly population and modernization have led to negative
influence of people with dementia. In such a situation, non-
governmental organizations have come in the forefront. They are
attempting to arrange awareness program and daycare and
homecare centers for the patients as well as for the caregivers. In
this state, many institutions have been set up to take care of
patients with dementia.

**EPIDEMIOLOGY**

**Frequency**

Vascular dementia is the second most common cause of
dementia in the United States and Europe, but it is the most
common form in some parts of Asia.

The prevalence rate of vascular dementia is 1.5% in Western
countries and approximately 2.2% in Japan. In Japan, vascular
dementia accounts for 50% of all dementias that occur in individuals
older than 65 years.

In Europe, vascular dementia and mixed dementia account
for approximately 20% and 40% of cases, respectively.

In Latin America, 15% of all dementias are vascular.

In community-based studies in Australia, the prevalence rate
for vascular and mixed dementia is 13% and 28%, respectively.

The prevalence rate of dementia is 9 times higher in patients
who have had a stroke than in controls. One year after a stroke,
25% of patients develop new-onset dementia. Within 4 years
following a stroke, the relative risk of incident dementia is 5.5%.

The prevalence of vascular dementia is higher in men than in
women.
Risk Factors for Dementia

Research has identified many risk factors associated with dementia. It’s impossible to eliminate every single one; after all we can’t avoid age, which is the most significant. While it is possible to develop dementia early in life, the chances of doing so increase dramatically with age. One in 50 people between the ages of 65 and 70 have a form of dementia, compared to one in five people over the age of 80.

RISK FACTORS FOR DEMENTIA

The following risk factors can increase a person’s chance of developing one or more kinds of dementia. Some of these factors can be modified, while others cannot.

Age. The risk goes up with advanced age.

Alcohol use. Most studies suggest that drinking large amounts of alcohol increases the risk of dementia, while drinking a moderate amount may be protective.

Atherosclerosis. The accumulation of fats and cholesterol in the lining of arteries, coupled with an inflammatory process that leads to a thickening of the vessel walls (known as atherosclerosis), can hinder blood from getting to the brain, which can lead to stroke or another brain injury. For example, high levels of low-density lipoprotein can raise the risk for vascular dementia. High LDL levels also have been linked to AD.

Diabetes. People with diabetes appear to have a higher risk for dementia, although the evidence for this association is modest.
Poorly controlled diabetes, however, is a well-proven risk factor for stroke and cardiovascular disease-related events, which in turn increase the risk for vascular dementia.

Down syndrome. Many people with Down syndrome develop early-onset AD, with signs of dementia by the time they reach middle age.

Genetics. One’s likelihood of developing a genetically linked form of dementia increases when more than one family member has the disorder. But in some cases, such as with CADASIL, having just one parent who carries a mutation increases the risk of inheriting the condition. In other instances, genetic mutations may underlie dementias in specific populations. For example, a mutation of the gene TREM2 has been found to be common among people with a form of very early onset frontotemporal dementia that runs in Turkish families.

Hypertension. High blood pressure has been linked to cognitive decline, stroke, and types of dementia that affect the white matter regions of the brain.

Mental illness. Depression has been associated with mild mental impairment and cognitive function decline.

Smoking. Smokers are prone to diseases that slow or stop blood from getting to the brain.

**MEDICAL RISK FACTORS FOR DEMENTIA**

Risk factors associated with dementia include the following:

**Atherosclerosis**

Atherosclerosis is the thickening and hardening of artery walls due to plaque buildup. Plaque is made of cholesterol, fat, calcium, and other substances in the blood. This buildup can narrow your arteries and interfere with the flow of blood to your brain. This impairs the ability of your brain cells to function properly. This can ultimately lead to the death of these brain cells and their connections to other brain cells.

**Cholesterol**

A high level of LDL cholesterol increases your risk of
developing vascular dementia. This may be due to the association between atherosclerosis and high cholesterol.

**Homocysteine**

This amino acid naturally circulates in your blood and is a building block of protein. A high level of homocysteine is a risk factor for a number of diseases, including:

- Alzheimer’s disease
- vascular dementia
- cognitive impairment
- stroke.

**Diabetes**

Diabetes may be associated with an increased risk of developing both AD and vascular dementia. Diabetes is also a risk factor for atherosclerosis and stroke. Both of these can contribute to vascular dementia.

**Psychological and experiential factors**

Psychological and experiential factors may be a risk factor for dementia as well. For example, if you tend to socially isolate yourself or don’t regularly engage in cognitively stimulating activities, you may be at an increased risk of developing AD.

**Mild cognitive impairment (MCI)**

MCI can be thought of as a stage between normal forgetfulness and dementia. However, if you have MCI, it doesn’t mean you’ll develop Alzheimer’s. But most cases of Alzheimer’s start with MCI. Symptoms for MCI include:

- memory loss greater than expected for your age
- memory deficiency is great enough to be noticed and measured
- continued independence because the deficiency isn’t enough to compromise your ability to care of yourself and conduct normal activities.

**Down syndrome**

By middle age, most people with Down syndrome have the
Diagnosis and Treatment of Senile Dementia

plaques and tangles of Alzheimer’s disease. Many also develop dementia.

GENETIC AND LIFESTYLE RISK FACTORS FOR DEMENTIA

Age

The risk of developing Alzheimer’s disease, vascular dementia, and several other dementias increases as you age. In the United States, one in nine people over the age of 65 has Alzheimer’s, about five million people, according to the Alzheimer’s Association. One in three seniors dies with Alzheimer’s or another form of dementia.

Genetics

Many forms of dementia have a genetic component and it often runs in families. In addition, certain mutations in specific genes have been identified as increasing the risk for developing dementia.

Smoking

A study in the JAMA Neurology journal found that smoking may significantly increase your risk of mental decline and dementia. If you smoke, you have a higher risk of atherosclerosis and other types of vascular disease. These diseases may contribute to the increased risk of dementia.

Alcohol use

Drinking large amounts of alcohol also increases your risk of developing a type of dementia known as Korsakoff syndrome. Symptoms of Korsakoff syndrome include:

• difficulty learning new information
• short-term memory loss
• long-term memory gaps.

Outlook

Many risk factors are involved in developing dementia, including medical conditions, lifestyle choices, genetics, and old
Risk Factors for Dementia

age. If you have a high risk for developing dementia, see your
doctor about how you can prevent it and any lifestyle changes that
may help.

CARDIOVASCULAR RISK FACTORS

Brain infarcts, heart disease and mid-life hypertension increase
the risk of Alzheimer’s disease and Vascular dementia. Smoking
has also been identified as a risk factor.

Diabetes

A recent study found that having diabetes increases the risk
of developing Alzheimer’s disease by 65%. This risk can be reduced
by careful management of diabetes with medications that maintain
blood glucose levels within a healthy range.

High cholesterol

Cholesterol is essential to brain function – it is a component
of cell membranes (structures that enclose nerve cells), and it is
required for the repair and establishment of new connections
between nerve cells. However, studies have shown that, high
cholesterol in mid-life and late-life can increase the risk of
Alzheimer’s disease. Subsequent studies have indicated that
cholesterol lowering drugs may lower the risk of developing
Alzheimer’s disease.

High homocysteine levels

Homocysteine is a by-product of many metabolic reactions
occurring in our body. Some studies have found that high
homocysteine levels are associated with an increased risk of
Alzheimer’s disease and other dementias. Adequate intake of
vitamin B and folate can help reduce homocysteine levels.

Some risk factors predisposing to dementia are associated
with genetic inheritance or previous life events, for example:

Genes associated with Alzheimer’s disease

One gene (Apolipoprotein E) has been associated with an
increased risk of late onset Alzheimer’s disease while three
additional genes (Amyloid Precursor Protein, Presenilin 1 and
Presenilin 2) are associated with early onset Alzheimer’s disease. Apolipoprotein E (ApoE) carries and delivers cholesterol to the nerve cells which use it for the repair and establishment of new connections. There are three common variants of the ApoE gene. The ApoE 3 variant is the most common, the ApoE 4 variant is thought to increase the risk of Alzheimer’s disease while the ApoE 2 variant appears to have a protective influence.

Mutations in the Amyloid Precursor Protein (APP), Presenilin 1 and Presenilin 2 cause the inherited form of Alzheimer’s disease. However, a majority Alzheimer’s disease cases appear to be sporadic and only a small number of cases are known to be inherited.

The APP gene makes a protein that is present on the surface of nerve cells and may help them grow and move. The presenilin 1 and 2 genes make proteins that are required for the correct functioning of the APP protein. Mutations in any one of these genes can cause the APP protein to be cut off from the surface of nerve cells. When this happens APP tends to accumulate in amyloid plaques which are a hallmark of Alzheimer’s disease.

**Family history**

A family history of dementia increases one’s risk of developing dementia. This is probably due to genetic factors that have not yet been discovered.

**Head injury**

A study of World War II veterans indicated that moderate to severe head injury increased risk of developing Alzheimer’s disease and other dementias. Another study found that this risk is further increased if the head injury resulted in loss of consciousness.

**ENVIRONMENTAL OR NON-GENETIC RISK FACTORS FOR ALZHEIMER’S DISEASE**

In contrast to the advances made in our understanding of genetic risk factors in Alzheimer’s disease, identification of non-genetic or environmental risk factors has been slower. Non-inherited risk factors are likely to be important, as monozygotic
twin concordance rates reach only 40%. Different ethnic groups living in similar environments show comparable prevalence rates, again suggesting a role for environmental factors. Studies, which are often beset with methodological problems, have produced repeatedly conflicting results. Interpretation is further hampered by multiple interactions between different factors. Apolipoprotein E (ApoE) status in particular appears to modulate the influence of several environmental risk factors.

**Age**

With the exception of increasing age, none of the evidence for non-genetic risk factors is universally accepted. After 65 years of age, the incidence and prevalence of Alzheimer’s disease doubles every 5 years. It is reasoned that older individuals have longer exposure to putative environmental and genetic influences. However, Alzheimer’s disease in advanced age is not inevitable; differences in distribution and density of senile plaques and neurofibrillary tangles exist between patients and age-matched controls. Recent work suggests that the acceleration of incidence rates for Alzheimer’s disease slows down in very old age (although there is no evidence of a rate decline), the corollary thus being that Alzheimer’s disease is age-related rather than age-dependent.

**Gender and hormonal effects**

Even when controlling for differences in longevity, several studies have found that women are at increased risk for Alzheimer’s disease. This is complicated by the observation that men have a greater risk of developing vascular dementia, which may lessen the likelihood of developing pure Alzheimer’s disease. Gender-related differences in risk could be at least partly ascribed to hormonal factors, as several studies suggest that oestrogen replacement can prevent or delay the onset of Alzheimer’s disease. A 16-year follow-up of nearly 500 women found that hormone replacement therapy produced a 54% reduction in risk of Alzheimer’s disease. However, a recent trial exploring the value of therapeutic oestrogen in subjects with Alzheimer’s disease was unable to demonstrate any improvement in cognition or disease progression. Oestrogen may be implicated in Alzheimer’s disease
in several ways, for example, via reduction in \(\beta\)-amyloid deposition, improvement in cerebral blood flow, neuroprotection or suppression of ApoE.

**Oxidative and inflammatory stress**

Increased levels of oxidative stress are a biochemical feature of Alzheimer’s disease. Trials of the antioxidants vitamin E and selegiline showed a delay in nursing home placement compared with patients receiving placebo. However, there was no effect on cognition. Oxidative changes may constitute a response rather than a cause. The same may apply to the described inflammatory changes within the Alzheimer brain. It is hypothesised that \(\beta\)-amyloid excites an immune response via microglial cell activation. Anti-inflammatory drugs may inhibit this response and delay nerve cell damage. Several studies have reported that intake of non-steroidal anti-inflammatory drugs (NSAIDs) is negatively associated with the risk of developing Alzheimer’s disease. As with all case-control studies, confounding bias may weaken interpretations. Alzheimer’s disease patients may be less likely to receive NSAIDs because they are less able to complain of pain. In the central nervous system, cyclooxygenase-2 (COX-2) is present both in neurons and in reactive microglial cells. Therefore, COX-2 inhibition may favourably affect neuronal function as well as inflammation. Clinical trials involving selective COX-2 inhibitors in Alzheimer’s disease are underway.

**Vascular risk factors**

Several case-control studies have reported an inverse relationship between smoking and risk of Alzheimer’s disease. Studies based on prevalent patients may be flawed, as smoking may cause the death of subjects before they enter the age group where susceptibility to Alzheimer’s disease is more pronounced. Results from a pooled analysis of incident patients demonstrated increased risk of Alzheimer’s disease in current and former smokers. Positive relationships between Alzheimer’s disease and other vascular risk factors, including insulin-dependent diabetes, vascular disease, hypertension and electrocardiogram ischaemia, have also been reported. Fish consumption, an important source
of $\omega$-3 polyunsaturated fatty acids, was inversely related to dementia, and in particular to Alzheimer’s disease, in the Rotterdam incident analysis.

Positive, negative and neutral associations have been noted between blood pressure levels and Alzheimer’s disease, although a recent clinical trial has revealed the potential preventive effect of antihypertensive treatment on the incidence of dementia, especially of Alzheimer’s disease.

**Head trauma**

The dementia pugilistica of boxers is associated with pathological changes similar to those of Alzheimer’s disease. This led to the hypothesis that previous head injury increased the risk of subsequent Alzheimer’s disease. Studies of head trauma have been hampered by recall bias, as relatives of affected patients may be more likely to remember previous events than those of healthy controls. A recent meta-analysis failed to implicate head trauma as a risk factor for Alzheimer’s disease.

**Education**

Poor education has been cited as a risk factor for Alzheimer’s disease, especially in males. Better education may reflect greater cognitive capacity and reserve, thus deferring the onset of the illness. Similar arguments apply to head size and dementia risk. It is unclear whether it is education obtained in childhood or the life-time acquisition of knowledge (thus implicating challenging occupations) that is protective. Assuming the latter, a trial of cognitive training in individuals at risk of dementia is currently running in the USA.

**Chemical exposure**

Solvents and heavy metals have been implicated as possible aetiological factors. In theory, high levels of iron could encourage free radical formation and oxidant stress. Current research into genetic polymorphisms within iron-handling genes may yield useful results. The involvement of both lead and solvents is generally discounted. The well-publicised relationship between Alzheimer’s disease and aluminium is difficult to assess.
Epidemiological studies were initiated in response to the observation of aluminium within plaques and tangles. Moreover, aluminium can cause abnormal phosphorylation of tau, a major component of the neurofibrillary tangle. Aluminium is ubiquitous and caution is needed when interpreting positive associations based on population exposure to high aluminium levels in drinking water. Studies concerning the role of aluminium compounds in antacids and antiperspirants have generally yielded negative results. As events at Camelford, England (where large quantities of aluminium sulphate were allowed to contaminate the water supply) indicate, aluminium is potentially neurotoxic. It is much less clear whether aluminium is responsible for the chronic neurodegeneration of Alzheimer’s disease. Only large-scale prospective analysis can help to resolve the issue.

**Depression**

The frequent coexistence of dementia and depression has stimulated speculation that associations exist between the two conditions. Prospective studies have again yielded opposing results. Depressive symptoms have been shown to increase the risk of subsequent cognitive decline. This has been tempered by research suggesting that depression is merely an early manifestation, rather than a predictor, of Alzheimer’s disease. High levels of cortisol may be associated with depression, and indeed stress, and may also cause neuronal death.

**Parental age**

Both old and young maternal ages have been found by different studies to increase the risk of subsequent Alzheimer’s disease in offspring – the role of paternal age is even less clear.

**RISK FACTORS FOR VASCULAR DEMENTIA**

Research into dementia has concentrated on Alzheimer’s disease, and much progress has been made in revealing possible genetic and neuropathological mechanisms. However, over the past few years there has been renewed interest in vascular dementia, the only preventable type of dementia. This highlights the importance of identifying potential modifiable risk factors.
Unlike Alzheimer’s disease, which is primarily a cortical dementia, and progressive supranuclear palsy, Parkinson’s disease and Huntington’s disease, which are all subcortical, vascular dementia can be cortical (e.g., large cortical infarcts), subcortical (e.g., lacunar states, or Binswagers) or both cortical and subcortical.

The prevalence of dementia would appear to be constant worldwide, but the type of dementia varies from country to country. Alzheimer’s disease is generally accepted as the most common type of dementia in the Western world, whereas vascular dementia is more common in Asian countries.

Vascular dementia accounts for 24–48% of dementing illnesses in older people, with an incidence of 6–10 in 10,000 per year in those aged over 70 years. Prevalence varies from 1.2% to 4.2% of those aged 65 years or above, increasing with age. There would appear to be a slight male preponderance. The average duration of the illness is 5 years and survival is less than that for Alzheimer’s disease.

Clinical diagnosis requires the presence of: (a) dementia; (b) cerebrovascular disease; and (c) a temporal relation between vascular disease and dementia.

There has been difficulty in establishing agreed criteria for diagnosis, definition and assessment of subjects, and much of the uncertainty stems from diagnostic issues. Furthermore, problems arise owing to the common co-occurrence of Alzheimer’s disease and vascular dementia. To improve the sensitivity and specificity of the clinical diagnosis of vascular dementia, two sets of criteria have been developed over the past 5 years by the State of California Alzheimer’s Disease Diagnostic and Treatment Centers (ADDTC) and the National Institute of Neurological Disorders and Stroke (NINDS), with support from the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN). The NINDS-AIREN criteria, expressly developed for research purposes, have a high specificity, making them most useful tool in this area.

**Demographic risk factors**

It is widely accepted that advancing age is a risk factor for stroke and thereby vascular dementia, as are male gender and race/ethnicity.
Vascular risk factors

The diagnosis of vascular dementia is associated with a history of cerebrovascular disorders, therefore some risk factors are the same as for stroke.

**Stroke**

Dementia after stroke is particularly associated with lacunar infarcts, left-hemispheric lesions and infarcts in the left-posterior and left-anterior cerebral territories.

One year after stroke, the probability of new-onset dementia is 5.4% in patients over 60 years of age and 10.4% in patients over 90 years. Four years after a first lacunar infarct, 23% of patients develop dementia, that is, 4-12 times more than controls.

In one study, the prevalence of dementia after ischaemic stroke in patients aged 60 or over was 26.3%, that is, 9.4-fold higher than that of a stroke-free control group, after adjusting for age and level of education. This, however, included patients who were suffering from dementia prior to stroke. In this study, stroke was the underlying cause of dementia in 56.1%, while in 36.4% it was presumed to be owing to the cumulative effects of stroke and Alzheimer’s disease, as suggested by a pre-stroke history of functional impairment.

The increased incidence of dementia after stroke suggests that cognitive decline is not only a direct consequence of the damage to the brain caused by stroke, but that there are additional processes related to the occurrence of stroke and the development of dementia. Approximately one-third of cases cannot be explained by the sequelae of stroke or hypoxic or ischaemic disorders.

**Hypertension**

Hypertension is the most important remediable risk factor for stroke (especially lacunar infarction) and vascular dementia. There is substantial evidence to suggest that elevated blood pressure earlier in life is a risk factor for dementia in later life. Late-life cognitive impairment can be associated with normal or low-normal blood pressure. Thus, blood pressure may be an important early-life predictor of dementia, and control of blood pressure may
prevent or delay dementia onset. Alternatively, mild systolic blood pressure increase in patients with vascular dementia could have beneficial effects.

The Vascular Dementia arm of the Systolic Hypertension in Europe trial investigated whether antihypertensive drug treatment could reduce the incidence of dementia. The results showed that treatment was associated with a lower incidence of dementia. If 1000 hypertensive patients were treated with antihypertensive drugs for 5 years, 19 cases of dementia might be prevented. It may be that antihypertensive agents have actions other than blood-pressure lowering (e.g. endothelial arterial wall modification), which add to their ability to slow the progression of dementia or cognitive impairment. The Cochrane Library is conducting a review of effectiveness of antihypertensives in dementia.

**Diabetes**

Along with hyperlipidaemia, diabetes is associated with a reduction in cerebral perfusion due to microangiopathy, often resulting in lacunar infarctions.

**Lipids**

Elevated levels of low-density lipoproteins, in particular, have been shown to be an independent risk factor for the development of dementia with stroke. However, no relationship has been found between lipid levels and the risk of probable Alzheimer’s disease, suggesting that dyslipidaemia may be most relevant to the occurrence of dementia with a vascular component.

**Smoking**

Smoking has been shown to be a risk factor by Meyer *et al* (1988), whereas the Canadian Study of Health and Aging did not show any association, a possible explanation being that there could be a decreased survival of smokers.

**Cerebral white-matter lesions**

Cerebral white-matter lesions refer to a state of demyelination in the subcortical structures of the brain and arteriosclerotic changes of the small penetrating arteries and arterioles in the white matter.
These are seen more frequently in vascular dementia than in other dementias or in normal, cognitively intact elderly subjects. White-matter changes are associated with risk factors for stroke and are themselves independent predictors of post-stroke dementia. Cerebral white-matter lesions on magnetic resonance imaging in association with the classic cardiovascular risk factors – stroke/myocardial infarction, factor VIIc, fibrinogen level and, in those over 65 years of age, hypertension and plasma cholesterol – have been associated with lower tests of cognitive function and significantly associated with lower scores on tests of subjective mental decline. In patients with first-ever lacunar infarction, mortality, stroke recurrence, risk of dementia and risk of dependence are significantly higher in patients with white-matter changes. Other vascular risk factors are history of myocardial infarction and atrial fibrillation.

Non-vascular risk factors

Occupational exposure

Interestingly, the Canadian Study of Health and Aging also showed an elevated odds ratio for vascular dementia in patients who had occupational exposure to pesticides and fertilisers and liquid plastics or rubbers. These should be studied in more detail as, again, they are potentially preventable causes of vascular dementia.

Alcohol

Several studies have shown an increased risk of vascular dementia in patients with a history of alcohol misuse, but not all report this. This warrants further study, as it is potentially preventable.

Other non-vascular risk factors

Psychological stress early in life, poor formal education and blue-collar occupation have been associated with a higher incidence of vascular dementia.

Genetic factors

Several rare genetic diseases have been associated with stroke
and subsequent vascular dementia. These include autosomal dominant hereditary cerebral haemorrhage with amyloidosis - Dutch type and familial vascular encephalopathies, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Several studies have shown an increased risk of stroke or coronary heart disease in patients with the ApoE polymorphism, a known genetic risk factor for Alzheimer’s disease. This may suggest a shared pathogenic relationship and unifying explanation. Alzheimer’s disease patients also have some degree of vascular changes and one-fifth have vascular lesions, which probably contributes to their cognitive decline. The link between stroke and Alzheimer’s disease seems to be higher than that expected by chance and may reduce the period of preclinical Alzheimer’s disease.

Furthermore, ApoE could influence the pathogenesis of dementia with stroke through its effects on lipid metabolism and atherosclerosis. In summary, there are many risk factors for vascular dementia, most of which are shared in common with stroke. As vascular dementia is the only preventable type of dementia, it is important that these risk factors are identified early in life to reduce not only stroke risk, but risk of dementia.

**GENETIC RISK FACTORS FOR DEMENTIA**

Alzheimer’s disease is the most common form of dementia, and the fact that the vast majority of genetic risk investigations are concerned with Alzheimer’s disease reflects this. In familial disease, risk to first-degree relatives has been estimated to range from 24% to over 50% at the age of 90 years. Concordance rates in monozygotic twins have been reported to be 40-50%. Early-onset families show an autosomal dominant mode of inheritance with age-related penetrance, and mutations in one of at least three genes have been shown to confer this susceptibility. The three genes in question are those encoding the amyloid precursor protein (APP) gene on chromosome 21, presenilin 1 (PS-1) on chromosome 14 and presenilin 2 (PS-2) on chromosome 1. Late-onset families show a more complicated mode of inheritance, which, like sporadic
disease, probably indicates the involvement of a number of genetic and other factors.

One stratagem for identifying genetic risk factors is to type deoxyribonucleic acid (DNA) polymorphisms in genes that may be involved in the pathogenesis of that disease. Polymorphisms in DNA are the existence of differences in the DNA sequence at a particular locus. These are more frequent than mutations and can be found in the DNA of both controls and disease subjects.

Although most reported genetic risk factors remain controversial, the ApoE õ4 allele has been identified as a risk factor for Alzheimer’s disease in most populations. Individuals who possess the õ4 allele are approximately four times more likely to suffer from Alzheimer’s disease than those without it, and this risk increases with õ4 dose. ApoE õ4 also reduces the age at which one can expect to develop the disease. However, possession of ApoE õ4 is neither necessary nor sufficient for disease initiation, and this has prompted a search for other genetic factors that may influence risk for Alzheimer’s disease.

An intronic polymorphism in the early-onset gene for PS–1 was reported to increase the risk of sporadic Alzheimer’s disease, but this finding was not universally replicated. A form of vascular dementia, CADASIL, has been linked to the human Notch3 gene. The gene product has been shown to interact with human PS–1, possibly a common pathway for neurodegeneration and dementia.

Other research groups have concentrated on receptors for ApoE, reasoning that if ApoE conferred increased risk then polymorphisms in ApoE receptors may modify that risk. A polymorphism in very low-density lipoprotein receptor (VLDL-R) was reported to increase risk in a Japanese Alzheimer’s disease population, and this was confirmed in a Scottish Alzheimer’s disease population, but other studies could not replicate this finding. Our group has reported an increased risk for Alzheimer’s disease in Northern Ireland associated with a different genotype of VLDL–R from that originally reported by the Japanese group, reflecting the different population origins. Another ApoE receptor, the low-density lipoprotein receptor-related protein (LRP), was shown to increase risk for Alzheimer’s disease in some studies.
The identity of this molecule as a risk factor was further enhanced by the identification of a region of chromosome 12 near to the LRP locus as possibly being involved in familial Alzheimer’s disease aetiology. However, other groups, including ours, failed to confirm this association.

Alpha-2 macroglobulin (A2M), a ligand for LRP and a serum pan-protease inhibitor, has also been shown in some studies to increase risk of Alzheimer’s disease. It resides close to LRP on the short arm of chromosome 12 and is also in the region of the locus linked to familial Alzheimer’s disease. As in the previous case, other groups, including our own, failed to replicate this finding. Polymorphisms in another protease inhibitor, α-1 antichymotrypsin (AACT), have been linked with risk of Alzheimer’s disease. This molecule, like ApoE, is a component of amyloid plaques, which increased its candidature as a risk factor. However, this also proved controversial.

Variations in the mitochondrial genome have been estimated to account for up to 20% of late-onset Alzheimer’s disease cases. Polymorphisms in several genes, such as the COI and COII subunits of the cytochrome C oxidase complex, have been associated with increased risk of Alzheimer’s disease. Mutations in mitochondrial genes have also been implicated in the aetiology of Parkinson’s disease. Point mutations in genes encoding sub-units of NADH-ubiquinone oxoreductase have been proposed to lead to increased susceptibility to oxidative damage and neurodegeneration.

Parkinson’s disease shares other susceptibility loci with Alzheimer’s disease. One of these is the oestrogen receptor gene. This gene is a well-known, although not widely replicated, risk factor for Alzheimer’s disease. Recently, a Japanese group reported that one allele of a polymorphism in this gene increased the risk of both Alzheimer’s disease and Parkinson’s disease. Mutations in the α-synuclein gene are also thought to increase the risk of both diseases. Another gene that appears to be involved in the pathogenesis of both Parkinson’s disease and Alzheimer’s disease is the tau gene on chromosome 17. Mutations in this gene are now known to cause frontal temporal dementia with parkinsonism.
linked to chromosome 17 (FTDP-17). Clinically, this syndrome is very similar to Alzheimer’s disease, although the frontal lobe abnormalities do not match the Alzheimer’s disease phenotype. FTDP-17 has also been confused with Pick’s disease.

In the search for genetic risk factors for both Alzheimer’s disease and vascular dementia, generalised vascular disease genetic risk factors have also been examined. Recently, our group in collaboration with groups from London and Cardiff reported that the I allele of a common insertion (I)/deletion (D) polymorphism in the angiotensin-converting enzyme (ACE) was associated with increased risk of Alzheimer’s disease.

This finding has since been replicated in a US population, enhancing the candidacy of ACE as a risk factor for Alzheimer’s disease. The results of studies on vascular dementia have not been as fruitful.

Of the few reports in the literature, most are contradictory with no clear candidate risk factor for this disease identified so far. However, given the effect that molecular genetics has had on complex diseases, especially Alzheimer’s disease, the identification of definitive genetic risk factors for other forms of dementia cannot be too far off.

PREPARING FOR YOUR APPOINTMENT

If you’ve had a stroke, your first conversations about your symptoms and recovery will likely take place in the hospital. If you’re noticing milder symptoms, you may decide you want to talk to your doctor about changes in your thought processes, or you may seek care at the urging of a family member who arranges your appointment and goes with you.

You may start by seeing your primary care doctor, but he or she is likely to refer you to a doctor who specializes in disorders of the brain and nervous system (neurologist).

Because appointments can be brief, and there’s often a lot of ground to cover, it’s a good idea to be well-prepared for your appointment. Here’s some information to help you get ready and know what to expect from your doctor.
Risk Factors for Dementia

What you can do

- Be aware of any pre-appointment restrictions. When you make your appointment, ask if you need to fast for blood tests or if you need to do anything else to prepare for diagnostic tests.
- Write down all of your symptoms. Your doctor will want to know details about what's causing your concern about your memory or mental function. Make notes about some of the most important examples of forgetfulness, poor judgment or other lapses you want to mention. Try to remember when you first started to suspect that something might be wrong. If you think your difficulties are getting worse, be ready to describe it.
- Take along a family member or friend, if possible. Corroboration from a relative or trusted friend can play a key role in confirming that your difficulties are apparent to others. Having someone along can also help you recall all the information provided during your appointment.
- Make a list of your other medical conditions. Your doctor will want to know if you're currently being treated for diabetes, high blood pressure, heart disease, past strokes or any other conditions.
- Make a list of all your medications, including over-the-counter drugs and vitamins or supplements.

Because time with your doctor is limited, writing down a list of questions will help you make the most of your appointment. If you're seeing your doctor regarding concerns about vascular dementia, some questions to ask include:

- Do you think I have memory problems?
- Do you think my symptoms are due to circulation problems in my brain?
- What tests do I need?
- Do I need to see a specialist? What will that cost? Will my insurance cover it?
- If my diagnosis is vascular dementia, will you or another doctor manage my ongoing care? Can you help me get a plan in place to work with all my doctors?
• Are treatments available?
• Is there a generic alternative to any medicine you may prescribe?
• Are there any clinical trials of experimental treatments I should consider?
• What should I expect to happen over the long term?
• Will my symptoms affect how I manage my other health conditions?
• Do I need to follow any restrictions?
• Do you have any brochures or other printed material I can take home with me? What websites and support resources do you recommend?

In addition to the questions you’ve prepared ahead of time, don’t hesitate to ask your doctor to clarify anything you don’t understand.

What to expect from your doctor

Your doctor is also likely to have questions for you. Being ready to respond may free up time to focus on any points you want to talk about in-depth. Your doctor may ask:

• What kinds of thinking problems and mental lapses are you having? When did you first notice them?
• Are they steadily getting worse, or are they sometimes better and sometimes worse? Have they suddenly gotten worse?
• Has anyone close to you expressed concern about your thinking and reasoning?
• Have you started having problems with any long-standing activities or hobbies?
• Do you feel any sadder or more anxious than usual?
• Have you gotten lost lately on a driving route or in a situation that’s usually familiar to you?
• Have you noticed any changes in the way you react to people or events?
• Do you have any change in your energy level?
Risk Factors for Dementia

• Are you currently being treated for high blood pressure, high cholesterol, diabetes, heart disease or stroke? Have you been treated for any of these in the past?
• What medications are you taking?
• Are you taking any vitamins or supplements?
• Do you drink alcohol? How much?
• Do you smoke?
• Have you noticed any trembling or trouble walking?
• Are you having any trouble remembering your medical appointments or when to take your medication?
• Have you had your hearing and vision tested recently?
• Did anyone else in your family ever have trouble with thinking or remembering things as they got older? Was anyone ever diagnosed with Alzheimer’s disease or dementia?

TESTS AND DIAGNOSIS

Doctors can nearly always determine that you have dementia, but there’s no specific test that confirms you have vascular dementia. Your doctor will make a judgment about whether vascular dementia is the most likely cause of your symptoms based on the information you provide, your medical history for stroke or disorders of the heart and blood vessels, and results of tests that may help clarify your diagnosis.

Lab tests

If your medical record doesn’t include recent values for key indicators of the health of your heart and blood vessels, your doctor will test your:

• Blood pressure
• Cholesterol
• Blood sugar

He or she may also order tests to rule out other potential causes of memory loss and confusion, such as:

• Thyroid disorders
• Vitamin deficiencies
Neurological exam

Your doctor is likely to check your overall neurological health by testing your:

- Reflexes
- Muscle tone and strength, and how strength on one side of your body compares with the other side
- Ability to get up from a chair and walk across the room
- Sense of touch and sight
- Coordination
- Balance

Brain imaging

Images of your brain can pinpoint visible abnormalities caused by strokes, blood vessel diseases, tumors or trauma that may cause changes in thinking and reasoning. A brain-imaging study can help your doctor zero in on more likely causes for your symptoms and rule out other causes.

Brain-imaging procedures your doctor may recommend to help diagnose vascular dementia include:

- Computerized tomography (CT) scan. For a CT scan, you’ll lie on a narrow table that slides into a small chamber. X-rays pass through your body from various angles, and a computer uses this information to create detailed cross-sectional images (slices) of your brain. This test is painless and takes about 20 minutes.

  A CT scan can provide information about your brain’s structure; tell whether any regions show shrinkage; and detect evidence of strokes, mini strokes (transient ischemic attacks), blood vessel changes or tumors. Sometimes you’ll receive an intravenous (IV) injection of a contrast agent that will help highlight certain brain tissues.

- Magnetic resonance imaging (MRI). An MRI uses radio waves and a strong magnetic field to produce detailed images of your brain. You lie on a narrow table that slides into a tube-shaped MRI machine, which makes loud banging noises while it produces images.
The entire procedure can take an hour or more. MRIs are painless, but some people feel claustrophobic inside the machine and are disturbed by the noise. MRIs can provide even more detail than CT scans about strokes, mini strokes and blood vessel abnormalities.

**Carotid ultrasound**

This procedure uses high-frequency sound waves to determine whether your carotid arteries — which run up through either side of your neck to supply blood to brain — show signs of narrowing as a result of plaque deposits or structural problems. Your test may include a Doppler ultrasound, which shows the movement of blood through your arteries in addition to structural features.

**Neuropsychological tests**

This type of exam assesses your ability to:

- Speak, write and understand language
- Work with numbers
- Learn and remember information
- Develop a plan of attack and solve a problem
- Respond effectively to hypothetical situations.

Neuropsychological tests sometimes show characteristic results for people with different types of dementia. People with vascular dementia may have an exceptionally hard time analyzing a problem and developing an effective solution. They may be less likely to have trouble learning new information and remembering than are people with Alzheimer’s unless their blood vessel problems affect specific brain regions important for memory. However, there’s often a lot of overlap in exam results for people with vascular dementia and people who have Alzheimer’s disease.

**TREATMENTS AND DRUGS**

**Controlling underlying conditions and risk factors**

Controlling conditions that affect the underlying health of your heart and blood vessels can sometimes slow the rate at which vascular dementia gets worse, and may also sometimes prevent
further decline. Depending on your individual situation, your 
doctor may prescribe medications to:

- Lower your blood pressure
- Reduce your cholesterol level
- Prevent your blood from clotting and keep your arteries 
clear
- Help control your blood sugar if you have diabetes.

**Alzheimer’s medications**

The Food and Drug Administration (FDA) has not approved 
any drugs specifically to treat changes in judgment, planning, 
memory and other thought processes caused by vascular dementia. 
However, certain medications approved by the FDA to treat these 
symptoms in Alzheimer’s disease may also help people with 
vascular dementia to the same modest extent they help those with 
Alzheimer’s. Doctors may prescribe one or both types of the 
following Alzheimer’s drugs:

- Cholinesterase inhibitors — including donepezil (Aricept),
galantamine (Razadyne) and rivastigmine (Exelon) — work 
by boosting levels of a brain cell chemical messenger 
involved in memory and judgment. Side effects can include 
nausea, vomiting, muscle cramps and diarrhea.
- Memantine (Namenda) regulates another brain cell 
chemical messenger important for information processing, 
storage and retrieval. Side effects can include headache, 
constipation, confusion and dizziness.

**MODIFIABLE RISK FACTORS**

**Risk factors for both Alzheimer’s disease and cardiovascular diseases**

High cholesterol levels in the blood, high blood pressure, 
diabetes, smoking and obesity are the major modifiable risk factors 
for cardiovascular diseases, including heart disease and stroke. 
The risk factors for cardiovascular disease represent risk factors 
for both Alzheimer’s disease and vascular dementia. These 
cardiovascular risk factors are more common in older age groups.
Smoking

Cigarette smoking is causally related to a wide range of diseases including many forms of cancer, cardiovascular disease and diabetes. The evidence is strong and consistent that smokers (vs. non-smokers or ex-smokers) are at a 45% higher risk of developing Alzheimer’s disease. They are also at a higher risk of developing vascular dementia (although the evidence is not quite as strong) and even other forms of dementia. Also, ex-smokers reduce their risk by not smoking. This is an encouraging finding for dementia prevention, suggesting, as with other adverse impacts of smoking, that the increased risk of dementia can be avoided by quitting smoking.

High blood pressure

People who have high blood pressure (hypertension) in midlife are on average more likely to develop dementia compared to those with normal blood pressure. High blood pressure affects the heart, the arteries and blood circulation so it increases the risk of developing Alzheimer’s disease, particularly vascular dementia. Research has shown that treating high blood pressure with physical activity and better diet can bring the risk down and if this is not successful, with appropriate medications.

Diabetes

Research has shown that type 2 diabetes in midlife is associated with increased risk of dementia, Alzheimer’s disease, vascular dementia and cognitive impairment. In fact, people who have type 2 diabetes are, on average, twice as likely to develop dementia compared to those without diabetes.

High cholesterol

People with high total cholesterol levels in midlife are on average more likely to develop dementia compared to those with normal total cholesterol. Research has shown that people who have their high cholesterol treated with drugs called “statins” have a lower risk of dementia. So treating high cholesterol is important for both heart and brain health. High cholesterol is an
important risk factor for hypertension and diabetes and also contributes independently to cardiovascular risk.

**Obesity and lack of physical activity**

Both obesity and lack of physical activity are important risk factors for diabetes and high blood pressure, and should, therefore, also be taken into consideration. Obesity in midlife may increase the risk of dementia and Alzheimer’s disease and, for that reason, should also be addressed.

**OTHER RISK FACTORS**

**Alcohol**

Alcohol is ranked fifth among the most important risk factors for death and disability worldwide and it has been implicated as a causal factor for more than 200 diseases and injuries, including major non-communicable diseases such as liver cirrhosis, some cancers and cardiovascular disease.

People who drink moderate amounts of alcohol have the lowest risk of developing dementia. Those who don’t drink any alcohol at all have a slightly higher risk. Those who drink excessively have the highest risk.

**Low levels of formal education**

Research shows that education lowers the risk of dementia. The quality and quantity of education, that protects against dementia, remains to be clarified.

**Depression**

People who experience depression in later life or have a history of depression may also develop dementia. However, the relationship between depression and dementia is still unclear. Many researchers believe that depression is a risk factor for dementia, whereas others believe it may be an early symptom of the disease.

**Head injuries**

People who experience severe or repeated head injuries are
Risk Factors for Dementia

at increased risk of developing dementia. It is possible that deposits
that form in the brain as a result of the injury may be linked to
the onset of dementia.

NON-MODIFIABLE RISK FACTORS

Age

Alzheimer’s disease is not a normal part of aging but age is
the strongest known risk factor for Alzheimer’s disease. But this
does not mean that most people develop the disease as they age.
Most do not. Some younger people, in their 40s or 50s, are diagnosed
with the young (early) onset form of the disease. After the age of
65, the risk of developing Alzheimer’s disease doubles
approximately every five years. The older you become, the higher
the risk – 1 in 20 Canadians over age 65 and 1 in 4 of those over
age 85 have Alzheimer’s disease. It is well-established that aging
can impair the body’s self-repair mechanisms, including in the
brain. And, many of the cardiovascular risk factors increase with
age, such as high blood pressure, heart disease, and high cholesterol.

Family history and genetics

Most Alzheimer’s disease does not run in families and is
described as “sporadic”. Rare cases of Alzheimer’s disease are
inherited or ‘familial’.

Familial Alzheimer’s disease

Familial Alzheimer’s disease accounts for less than 5% of all
cases of Alzheimer’s disease. This form of the disease runs in
families. If a person has familial Alzheimer’s disease, each of his/
her children has an increased chance of inheriting the disease-causing
gene and developing Alzheimer’s disease.

Familial Alzheimer’s disease is due to changes or alterations
in specific genes that can be directly passed on from parent to
child. Three familial Alzheimer’s disease risk genes have been
discovered so far: the PS1, PS2, and APP genes. If you have an
alteration in any one of these genes, you will have a greater chance
of developing young (early) onset familial Alzheimer’s disease.
Researchers are searching for other genes that might be associated with familial Alzheimer’s disease.

**Sporadic Alzheimer’s disease**

The most common form of Alzheimer’s disease is called sporadic Alzheimer’s disease. Sporadic Alzheimer’s disease is due to a complex combination of our genes, our environment, and our lifestyle. The single greatest risk factor for developing sporadic Alzheimer’s disease is aging. Most cases begin after age 60-65 years.

**Gender**

There has been some debate that women may be more likely to develop Alzheimer’s disease than men. The international evidence has not consistently shown this to be true. More research is required to determine if other factors than age may heighten a women’s chances of developing Alzheimer’s disease.

**Other**

Other medical conditions that can increase a person’s chances of developing dementia include Parkinson’s disease, multiple sclerosis, chronic kidney disease and HIV. Down syndrome and some other learning disabilities also increase a person’s risk of dementia.

**EPIDEMIOLOGY AND RISK FACTORS OF DEMENTIA**

Dementia refers to a syndrome that is characterised by progressive deterioration of cognitive functions. Neuropsychiatric symptoms, such as apathy, agitation, and depression, are also common. With increasing loss of function, a patient is gradually robbed of his or her independence. Eventually, placement in a nursing home may be necessary. Patients with dementia usually survive 7–10 years after onset of symptoms. Dementia places a tremendous burden not only on caregivers, but also on society, and has already been established as one of the major challenges of this century.
Epidemiology refers to the medical science that studies frequencies of disease. Measures of frequency that are often used in epidemiology are prevalence and incidence. The concept of prevalence refers to the number of patients with a disease at a certain moment in time, whereas measures of incidence reflect the number of new cases over time. Although important for health care planners, the knowledge of frequency of disease in itself is not the goal of epidemiology.

Rather, the aim is to gain insight into the mechanisms that cause disease, eventually to be able to cure or prevent disease. Therefore, frequencies are studied in relation to determinants, or risk factors. Although marked as “the epidemic of our century”, still surprisingly little is known about the epidemiology of dementia. In this chapter, a brief overview will be given of the epidemiology and risk factors of dementia. Furthermore, we comment on some specific methodological problems associated with studies in dementia.

**Syndrome And Disease**

The syndrome of dementia may be caused by various underlying diseases, each characterised by a specific constellation of signs and symptoms in combination with a presumed underlying substrate of neuropathology. Alzheimer’s disease (AD) is the most prevalent cause of dementia. It is a neurodegenerative disorder, generally assumed to be caused by neuritic plaques and neurofibrillary tangles accumulating in the brain. The second most prevalent cause of dementia is vascular dementia (VaD), which may be caused by various types of vascular pathology in the brain, such as “large vessel” (large territorial or strategical infarctions) and “small vessel” (lacunes and white matter hyperintensities) disease. Other frequent causes of dementia include frontotemporal lobar degeneration and dementia with Lewy bodies. It is often difficult (if not impossible) to reliably distinguish between subtypes of dementia (we will come back to this subject in the section on methodological issues). Therefore, epidemiological studies often focus on dementia as a whole, sometimes giving separate numbers for the two most important subtypes—AD and VaD.
Prevalence

Prevalence is defined as the proportion of a population that has disease at a specific point in time. Prevalence estimates vary highly between studies. These variations may be due to variations in study population—that is, reflect real differences. For example, age is the most important risk factor for dementia. Differences in age between populations will result in different estimates of prevalence.

Alternatively, and just as plausible, is the assumption that differences in prevalence estimates are caused by methodological differences, such as study design and diagnostic procedure. One solution to obtain more certainty about the value of prevalence is to combine data from multiple studies in a meta-analysis. Meta-analyses have two advantages. First, small differences due to methodological differences between studies level out. Secondly, and more importantly, the analysis is based on a far larger sample than a single study could ever realise, resulting in more precise estimates.

Pooled estimates of prevalence

In 2000, prevalence data from 11 European population based studies were pooled to obtain stable estimates of prevalence of dementia in the elderly (> 65 years). Age standardised prevalence was 6.4% for dementia (all causes), 4.4% for AD, and 1.6% for VaD. Prevalence of dementia was higher in women than in men and nearly doubled with every five year increase in age: 0.8% in the group age 65-69 years and 28.5% at age 90 years and older. Of all dementia cases, 54% suffered AD. Prevalence of AD showed the steepest increase with age, from 0.6% in the group age 65-69 years to 22.2% in the group aged 90 years and older. VaD accounted for 16% of cases, and prevalence increased with age from 0.3% (65-69 years) to 5.2% (90+ years). More recently, prevalence rates for dementia were compared among 12 population based European studies. Crude prevalence rates varied between 5.9% (Italy, the Counselice study) and 9.4% (the Netherlands, Rotterdam study). Again, an almost exponential increase with age and a female excess—mostly after age 75—was described.
Dementia with young onset

Most studies on prevalence of dementia focus on subjects aged over 65 years. Although age is well established as its most important risk factor, dementia may also affect people under the age of 65. Few data exist on the prevalence of dementia in younger people. A recent study in the UK was designed to determine the prevalence of dementia in people under the age of 65 in a large catchment area (total population of 567 500 people) and use these figures to estimate the number of younger people affected by dementia in the UK. The prevalence of dementia in those aged 30–64 was 54 per 100 000. For those aged 45–64, the prevalence was 98 per 100 000. Like the studies mentioned above describing prevalence over the age of 65, there was a strong age dependency: from the age of 35 years onwards, the prevalence of dementia approximately doubled with every five year increase in age. In contrast with studies describing populations over 65, males seem at a higher risk to become demented before they reach the age of 65 than females.

Extrapolating these figures nationally suggests that there are well over 18 000 people with dementia under the age of 65 in the UK. At 34%, AD was also the most prevalent cause of dementia among younger people, although with less prominence than at old age. The relative prevalence of VaD (18%) roughly equals the prevalence at old age. Frontotemporal dementia (12%) and alcohol related dementia (10%) were relatively more prevalent among the younger population than among elderly populations. These figures underline the fact that, although relatively uncommon, dementia does develop in younger subjects, and it should always be part of the differential diagnosis in patients with cognitive complaints. Furthermore, these data also highlight the differences between dementia in younger people and dementia in older people, with frontotemporal dementia and alcohol related dementia being relatively common causes of dementia in the younger age group.

“When I’m sixty four”

Nearly 40 years ago, The Beatles launched a famous song which included the words “Will you still need me, will you still
feed me when I’m 64”. At that time Paul McCartney, looking at his 64 year old father, wondered how life would be at 64—considered “old” at that time apparently—probably also being afraid for age related diseases, such as dementia. In the coming decades, the financial and emotional burden placed by dementia on the working age population will rise notably. As the age distribution of the western population shifts, the rapid increase of the prevalence of dementia with increasing age means that both the number of affected individuals and the affected proportion of the total population are increasing. This will be especially prominent in Europe, where the median age of the population is higher than in all other parts of the world. Based on several meta-analyses of epidemiological studies and the population projections of the United Nations, the number of prevalent cases in Europe in the year 2000 was about seven million. Within the next 50 years, this number is estimated to more than double to well over 16 million patients with dementia. Not only will the number of patients with dementia increase; in the same time span, the working age population will considerably decrease in number. While in the year 2000, there was a ratio of 69 working age persons to one demented person, this ratio will decrease to 21:1 in 2050.

In this paragraph, an overview of the prevalence of dementia has been given. Prevalence is determined by both the number of new cases over a given period of time, and by the duration of survival once patients have the disease. Death results in a decrease of prevalence; therefore, diseases that quickly lead to death may have low prevalence, even if they occur frequently, while diseases with long survival have higher prevalence, even if they occur with lower frequency. From the above it follows that studies based on prevalent cases yield associations that reflect the determinants of survival with disease just as much as the causes of disease. This can result in misleading situations—for example, if a new treatment would positively influence the course of dementia by lengthening survival (although not curing the disease), this would result in a higher prevalence. In such a situation, the paradoxical situation may occur that this medication would be positively associated with the prevalence of dementia, and so be misconstrued as a
Risk Factors for Dementia

causative agent. For this reason incidence, rather than prevalence, is the desired measure of disease frequency.

Incidence

Incidence refers to the number of new cases over a given period of time. The observed number of new cases depends on the evaluated duration of follow up. To be able to compare studies with varying duration of follow up, incidences per year are usually given. Furthermore, within a given study, length of follow up time may differ between subjects. To profit from all the available information, the length of time at risk is determined for every person. The total length of follow up time is obtained after summing all person-times, and represented as the number of person-years of follow up. Most studies on incidence report incidence rates that are calculated as the number of new cases divided by the person-years at risk. Incidence rates are usually represented as number of new cases per 1000 person-years.

Pooled estimates of incidence

In the same collaborative effort that pooled prevalence data of European studies, data on incidence of dementia of eight population based European studies were compared and pooled. In total, there were 42,996 person-years of follow up with 835 new dementia cases. Of these, 60–70% were diagnosed with AD and 15–20% with VaD. Incidence rates of dementia increased exponentially with age from 2.4 per 1000 person-years in the 65–69 age group, to 70.2 per 1000 person-years in the 90+ age group. Rates among women were higher, especially above the age of 80. The rates continued to increase with age in women, whereas the increase reached a plateau in men at age 85. For AD, findings were comparable, with pooled incidence rates increasing from 1.2 per 1000 person-years among 65–69 year olds to 53.5 among subjects over 90 years old.

Will we be all demented at the age of 140?

The question of whether the incidence rates reach a plateau at a certain age is important, as an exponential increase in incident AD would suggest that the disease is an inevitable consequence
of aging, whereas convergence to a fixed value or a decline could suggest that an element of the population has reduced vulnerability, owing perhaps to genetic or environmental factors. Results with respect to incidence increasing with age have been conflicting, with some studies suggesting an ongoing increase with advancing age, whereas other studies suggest that incidence rates reach a plateau after a certain age. This issue is difficult to resolve, however, as the oldest age groups are always underrepresented, resulting in less precise estimations. The Cache County in Utah, USA, is known for the longevity of its inhabitants. The relatively large proportion of extremely old individuals provides the opportunity to give reliable estimates of incident dementia among the oldest old. There were 185 new cases of dementia (123 AD) among 3308 participants who contributed 10,541 person-years of follow up. The incidence of dementia increased with advancing age from 2 per 1000 person-years in the group aged \( \geq 68 \), to peak with 122 per 1000 person-years in the 90–92 age group, and decline in the 93+ age group (110 per 1000 person-years). The incidence of dementia was higher in females over the age of 80. If incidence rates would indeed plateau at a certain age, then the future public health burden of dementia and AD, albeit still enormous, might be less than previously projected.

**Variation across regions?**

Incidence rates have been found to vary between studies. Methodological issues partly account for these differences, but it is also conceivable that the variable estimates reflect real geographical differences. There are substantial differences in possible risk factors for dementia between regions. Such chronic disease risk factor variation is thought to be responsible for the wide variation seen in other diseases of older age such as cancer and cardiovascular disease (for example, differences between North and South Europe). Given the available evidence for risk factors of dementia and the pronounced variation in vascular risk factors across regions, there could be parallel variation in the incidence of dementia. In fact, the pooled analysis of eight European studies mentioned above suggests a geographical dissociation, with higher incidence rates being found among the oldest old of northwestern
countries than among southern countries. To assess variation in incidence within country, the Medical Research Council cognitive function and ageing study (MRC CFAS) compared incidence rates among five sites with different risk patterns and mortality rates. As reported before, incidence was observed to rise with age, particularly above the age of 75, and continued to increase for both males and females into the oldest age groups. However, there was no convincing evidence for variation across sites, and incidence rates did not reflect the variations in the prevalence of possible risk factors in these sites.

RISK FACTORS

The estimates of frequency of dementia are important by themselves, as they underline the extent of the health care problem as created by dementia. Although important for health care planners, the frequency of disease in itself is not the most important issue. Rather, we need to gain insight into the mechanisms that cause dementia, to be able to develop therapeutic agents that can slow down or even cure these diseases. Risk factors are studied to find out the basic mechanisms leading to dementia. By influencing these risk factors we hope to be able to modify the course of the disease.

Studies on risk factors for dementia have mainly focused on AD, as it is the most frequent cause of dementia. Age is the most well known risk factor for dementia. Studies of prevalence and incidence of dementia and AD have consistently shown an almost exponential increase with advancing age, in that estimates of both prevalence and incidence double with every five year increase in age. In addition, female sex has repeatedly been shown to be associated with an increased risk of AD, especially at old age. Other risk factors for AD include genetic and vascular factors.

Genetic risk factors

Only a small proportion of all individuals with dementia suffers from a familial form of dementia, caused by an autosomal dominant mutation. Mutations in several genes (including Aβ precursor protein, presenilin 1, and presenilin 2) have been shown to cause AD, but these genetic forms of AD account for less than
5% of all cases. The largest proportion of AD cases is therefore “sporadic”. However, genetic factors also seem to influence non-familial cases of AD. The “common disease/common variant” hypothesis postulates that common disorders, such as AD, are also governed by common DNA variants. These variants significantly increase disease risk but are neither necessary nor sufficient to actually cause a specific disorder. Rather, these risk genes display intricate patterns of interaction with each other as well as with non-genetic variables, modifying the risk for a disease. To date, only one such factor has been identified in AD. The apolipoprotein E gene presents in three allelic forms (α2, α3, and α4), of which the α4 allele is a risk factor for AD. APOE α4 itself is neither necessary nor sufficient to cause AD, but instead operates as a genetic risk modifier. The well known effect of age on AD is modified by APOE, as age of onset is lower in APOE α4 positives. In addition, it has been suggested that APOE interacts with vascular risk factors.

Vascular risk factors

There is abundant evidence that vascular factors play a role in AD. Vascular risk factors such as hypertension, diabetes mellitus, smoking, and heart disease all have been shown to be associated with AD. Explanations for these associations include: (1) the coincidence of common disorders in the elderly; (2) vascular and cerebrovascular disease precipitating AD; (3) an additive or synergistic (AD + vascular) pathogenesis of dementia; and (4) misclassification of vascular dementia as AD. At this moment, the question about the primary and secondary pathology in AD is unlikely to be answered. The mechanisms linking vascular risk factors to AD remain unclear. Atherosclerosis has been postulated as one common mechanism mediating the association between AD and various vascular risk factors. However, statistical models have failed to demonstrate an important mediating role for atherosclerosis as one common factor. Either the measures of extracranial atherosclerosis are not suitable as proxies for intracranial atherosclerosis, or there are other mechanisms whereby cardiovascular risk factors are associated with AD.
METHODOLOGICAL ISSUES

A brief overview has been given of the current knowledge of prevalence, incidence, and risk factors of dementia. Although progress in understanding dementia is being made, the basic mechanisms causing the majority of dementias are still not known, and satisfying therapeutic options are as yet not available. Studies of dementia are hampered by certain methodological issues inherent to the disorder. These methodological issues may influence the results of studies and be partly responsible for variability in results across studies. Without intending to give a complete overview of the methodological issues associated with the study of dementia, we would like to address briefly four important issues here.

Diagnostic procedure

The most important problem with respect to studying dementia and AD is defining the outcome. As yet, there is no single diagnostic test for AD or most of the other types of dementia. The diagnosis of AD is based on clinical criteria, and can be graded as possible, probable, or definite. Several sets of criteria are available, of which the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRDA), dating from 1984, are the most commonly used. The diagnostic work-up of dementia is time and cost intensive. In large population based studies, it is impossible to assess every subject with a complete diagnostic work-up. Using medical records to identify cases would lead to an underestimation of the number of individuals with dementia, as many of the cases of dementia are never diagnosed in a formal setting.

Therefore, large population based studies usually employ a stepwise approach to identify cases. Most studies use one of two possible stepwise approaches. (1) All subjects are assessed using a screening test. Only those performing below a certain cut off level receive an extensive assessment. A drawback of this approach is the low sensitivity of screening tests. Subjects who are demented but score above cut-off on the screening test are missed. These
may include mild cases, and individuals with good cognitive reserve due to, for example, high educational level. (2) A subsample, stratified by certain characteristics such as age, sex, and performance on a screening test, receives an extensive diagnostic assessment. Results are extrapolated to the entire sample. Inherent to this approach is the fact that not all cases will receive an extensive assessment, which may result in lack of precision. The use of different criteria to diagnose dementia, and the variable approaches to operationalise these criteria in large samples, can result in highly varying estimates of frequency. The difficulty of diagnosing mild dementia can lead to an additional problem in incidence studies, as cases that are very mild and therefore not recognised at baseline may be wrongly counted as incident cases at follow up, resulting in biased estimates.

**Insidious onset**

A second—and related—methodological problem inherent to dementia is the insidious onset of the disorder. Neuropathological changes, eventually leading to the clinical syndrome of dementia, may start as early as decades before the disease becomes clinically overt. In analogy with the gradually accumulating neuropathology, the transition from healthy to demented is also gradual, rather than abrupt. The moment when dementia is diagnosed is in fact arbitrary. Moreover, the artificial dichotomisation between healthy and demented does not do justice to the continuum of cognitive (dys)function.

The concept of mild cognitive impairment (MCI) has been developed to account for the transitional phase between healthy and demented. However, introducing concepts like MCI only shifts the problem, as the borders between healthy and MCI and between MCI and demented remain just as arbitrary and unclear. A possible solution would be to discard the arbitrary distinction between normal and demented, and instead use a continuous outcome, such as a test of cognitive function.

This would have several advantages. First, costs and time can be saved as the extensive diagnostic work-up is not necessary anymore. Second, by abolishing the artificial dichotomisation into
normal and demented, the continuum of cognitive decline is done more justice. This approach also provides the opportunity to study progression of decline within demented individuals.

**Biomarkers**

A third issue reflects the complex relationship between the syndrome of dementia and the underlying diseases. When we talk of AD, we refer to the syndrome that is characterised by progressive memory problems, which usually has an insidious onset, etc. However, at the moment the diagnosis of AD is made, we assume to know the underlying neuropathological substrate—that is, neuritic plaques and neurofibrillary tangles. We assume to know this, because during lifetime, it is impossible to directly measure neuropathology. In fact, post-mortem studies have shown that this assumption in many cases is wrong. In a report of the MRC CFAS of the first 209 subjects (48% demented) who came to necropsy, Alzheimer-type pathology and vascular pathology were equally common, and both correlated with cognitive decline. Most subjects had mixed pathology. Approximately one third of clinically demented patients did not fulfil neuropathological criteria for definite AD, whereas an equally large proportion of non-demented elderly subjects did fulfil these criteria. Neuropathologically, the distinction between different types of dementia, and even between demented and non-demented, seems to be very difficult. The question arises that if it is useful to make clinical distinctions between subtypes of dementia, neuropathology may not even exist. A step towards directly measuring disease, rather than clinical phenotype, would be to take biomarkers as outcome of studies. Both neuroimaging and cerebrospinal fluid can provide useful surrogate markers that give a more direct impression of the pathology. In this way, the possibility of different types of pathology coexisting within one subject is appreciated. For example, magnetic resonance imaging (MRI) measures suggestive of Alzheimer-type pathology and vascular pathology can be evaluated simultaneously.

**Cross sectional versus longitudinal studies**

Studies with a longitudinal design are preferred over studies with a cross sectional design for several reasons. It is conceivable
that information about risk factors may be systematically different between patients and controls. Patient data must come from a proxy, who might recall the medical history differently than a proxy of a control or the control himself. In addition, prevalence is determined by both the number of new cases over a given period of time, and by the duration of survival once patients have the disease. In analogy, findings of cross sectional studies can reflect the contribution a risk factor makes to developing dementia as well as to surviving after the dementia starts.

Another important issue in this respect is that risk factors may change over time. The impact of environmental factors, such as smoking, diet, physical activity, and vascular disease, may change over time both within an individual and across birth cohorts. Risk factors such as blood pressure change with ageing. Furthermore, the disease, once it has started, may in turn influence the risk factor. For example, the diet of a demented individual may change, when the person forgets to eat his or her meals on a regular basis. Therefore, the relationship between a risk factor and disease may differ depending on the age the risk factor is measured relative to the outcome.

The age related changes in risk factors make causal inferences as to the development of dementia difficult. Studies of blood pressure in relation to dementia form a good example of how the relationship between risk factors and dementia may be influenced by the moment when the risk factor is measured. There have been conflicting reports, with some studies suggesting that low blood pressure is associated with dementia, whereas others report the opposite, namely that high blood pressure is a risk factor for dementia. Important in this respect is that blood pressure has been shown to decrease as a consequence of dementia. It is therefore important that this risk factor (blood pressure) is measured before the disease process starts. However, by the age most ageing studies begin — that is, 65 years old — individuals have already experienced the initial neuropathologic changes that eventually lead to dementia. As soon as the disease process has started (this may be years, possibly decades, before the dementia becomes overt), it is too late to measure risk factors, as the disease may have started.
Risk Factors for Dementia

to influence the risk factor itself. Therefore, it seems as though risk factors should be measured as early as possible. By now, there are several studies with more than 20 years of follow up. These studies, measuring midlife risk factors to predict late life dementia, have shed some light on the perceived incongruence in earlier studies. In fact, the conflicting reports with respect to the effect of blood pressure on the development of dementia may be entirely explained by the moment of measuring the risk factor. Cross sectional studies suggest that low blood pressure is associated with dementia. Studies measuring blood pressure during midlife have consistently shown that midlife hypertension is associated with late life dementia.

TIPS FOR LIVING A BRAIN-HEALTHY LIFESTYLE

A range of lifestyle and health strategies may keep your brain healthy and reduce your risk of developing dementia.

Exercise your brain

Any activity that involves thinking and learning can improve your brain health and help protect against dementia. Evidence suggests that greater benefit comes from more complex and challenging mental activities. The more brain activities you do, the more frequently you do them and the more complex the activity, the lower your risk of dementia is likely to be. The best activities are those that you enjoy – boredom and frustration are not good for your brain. The types of activities include:

• enjoying hobbies like painting, woodwork, sewing or writing
• doing a short course
• doing a jigsaw, crossword, number or word puzzle
• learning to dance, play an instrument or speak a new language
• going to the theatre, movies, museum, gallery or a concert.

Stay socially engaged

Regular and enjoyable interactions with friends, family and others may help reduce your risk of dementia. There are many ways to interact with others, but some suggestions include:
• dancing – enjoy it with others, get some great exercise and use your brain and body to learn new moves
• travelling – also enjoyed with others and usually involving a lot of walking or other physical activities
• volunteering with a local group or your favourite charity
• walking with friends or family
• joining a group such as a book club or walking group
• organising games nights with friends
• taking dancing or singing lessons
• catch up with friends and talk to your neighbour

**Avoid excess alcohol consumption**

Drinking an excessive amount of alcohol can damage your brain and increase your risk of dementia. Long-term excessive alcohol consumption can cause brain damage and lead to a condition called alcohol-related dementia. It may also increase the risk of Alzheimer’s disease and other dementias.

If you do drink alcohol, do so in moderation. Follow the *Australian guidelines to reduce health risks from drinking alcohol*. The guidelines recommend no more than two standard drinks per day for both men and women. Every drink above this level increases your lifetime risk of a number of conditions, including dementia.

Some evidence suggests that drinking in moderation might decrease the risk of dementia slightly more than not drinking alcohol at all. Alcohol can increase health risks for people with some conditions, or if they are taking certain medications. More research is needed in this area, so ask your doctor if you have any questions. Your doctor can give advice about how much alcohol is safe for you and help you to reduce your drinking if you are consuming too much. Your doctor can write you a low-risk drinking prescription (with an individual plan to help you reduce your drinking), prescribe medications or refer you to specialist help if needed.

**Enjoy a brain healthy diet**

Research suggests the foods that are good for your heart and body may also be good for brain health and protect against
dementia. Australian dietary guidelines provide advice about what to include, and avoid, in your healthy diet.

Based on current evidence, nutritionists recommend that you:

- Eat a variety of foods, including fruits and vegetables, to ensure adequate nutrient intake.
- Reduce your intake of saturated fats by choosing fish, lean red meat, chicken without skin and reduced-fat dairy products. Limit butter, deep fried foods, pastries, cakes and biscuits.
- Choose unsaturated fats such as olive, canola, sunflower and safflower oils.
- Consider including foods rich in omega-3 fats in your diet, such as soy, canola and flaxseed oils, and fish.

**Stay physically active**

People who are physically active have a lower risk of heart disease and stroke. These conditions are both associated with an increased risk of developing dementia.

Research suggests that even small amounts of exercise (including simple exercise like walking) seem to be good for brain health and protects against dementia. Any physical activity you can build into your daily routine will help.

The *National physical activity and sedentary behaviour guidelines for Australian adults* recommends at least 30 minutes of moderate-intensity physical activity on most, preferably all, days to achieve health benefits. For general fitness, the most important types of activity are aerobic training, resistance or weight training, and flexibility exercises.

The type and amount of exercise you are able to do will depend on your age, physical capability, level of fitness and any medical conditions you have. Make sure to get advice from your doctor on what is the best program of activity for you. If you’ve been inactive, start slowly and gradually build up as you get fitter.

Examples of activities include:

- brisk walking
- cycling
The National physical activity and sedentary behaviour guidelines for Australian adults suggest that you:

- are active every day in as many ways as you can
- think of movement as an opportunity, not an inconvenience
- incorporate movement and activity into your normal daily routine
- are active with a friend or family member
- choose activities you enjoy
- if you can, enjoy regular vigorous exercise for extra health and fitness.

Your doctor can advise you on what type and level of physical activity is best for you. They can write you a physical activity prescription and provide regular follow-up to help you maintain your program.

**Look after your heart**

Research shows that people who have high blood pressure, high cholesterol, diabetes, or are obese, particularly around middle age, have a greater risk of developing dementia later in life. Leaving these conditions untreated can lead to damaged blood vessels in the brain, which in turn damages brain cells and leads to impaired thinking functions. Although there are no guarantees that keeping your heart healthy will prevent dementia, you will give yourself the best chance of avoiding or delaying dementia.

Promisingly, studies have shown that the treatment of high blood pressure reduces that risk. Other studies indicate that treating high cholesterol and diabetes may also reduce the risk of developing dementia, although more research is needed in this area.

It is recommended you have regular check-ups to assess your:

- blood pressure – effective long-term treatment of high blood pressure can reduce dementia risk, so all adults, especially once they reach middle age, should have their
blood pressure regularly checked by their doctor

• body weight – research shows that people who are obese in midlife are more likely to develop dementia compared to those of normal body weight so, to reduce the risk of dementia, all adults should try to maintain a healthy body weight

• cholesterol – even mildly elevated cholesterol is associated with increased risk of dementia, so it is important to do everything you can to keep your cholesterol in the healthy range

• blood sugar levels – high blood sugar is an indicator of type 2 diabetes that can increase your risk of dementia

• smoking – is a risk factor for dementia so, if you smoke, try to quit and avoid other people’s smoke.

To reduce your risk of dementia, you should have regular check-ups with your doctor, especially at midlife, and always follow the advice of your doctor.

Protect your head against injury

Head injury, particularly severe injury (causing unconsciousness for an extended period of time) is a risk factor for the development of Alzheimer’s disease. Avoid head injury by taking care as a pedestrian, wearing seat belts in cars, and using protective headgear when cycling or for high-risk activities.

BIOLOGICAL RISK FACTORS

Prevention of dementia

Ageing

Age is the most important known risk factor for AD. The risk of developing the disease doubles every five years over age 65. Dementia may occur at any age, although rarely below the age of 60. Although age is the most significant risk factor that we know about, dementia is not an inevitable part of ageing.

Family history of dementia

Some genetic risk factors have been identified so far, but only
a small proportion of AD cases can be explained by specific gene mutations. The risk of dementia and AD has been shown to be increased among people with a family history of dementia, but contradictory results exist as well. Life table analyses have shown a cumulative risk of dementia to first-degree relatives of AD cases of approximately 50% by age 90, while relatives of purported control subjects had a much lower cumulative risk. Studies of AD among twin pairs over age 70 provide the strongest support for genetic causation. Monozygotic twin pairs show higher concordance rates for AD than dizygotic twin pairs.

**Genetic factors**

Genes may be related to disease in two ways: through autosomal-dominant mutations, in themselves sufficient to cause the disease alternatively, gene variations (polymorphisms) may indirectly increase disease risk without being sufficient in themselves to cause the disorder. This latter group are referred to as susceptibility genes. Familial AD refers to small numbers of cases (at least 5% of all cases), in which there is a clear pattern of autosomal dominant inheritance. Such clear patterns usually are associated with an age of onset before 60 years of age. The disease usually starts in the 40’s and 50’s. These mutations have principally concerned early onset AD, and only explain a small proportion (less than 1%) of total cases. Some susceptibility genes are also currently being studied, of which polymorphisms of the apolipoprotein E gene have received the most attention, with earliest clinical reports suggesting it to be present in about 90% of late onset cases (which occur predominantly after 60 years old and do not have an apparent autosomal dominant mode of inheritance). Meta-analysis of recent epidemiological studies has shown that while ApoE e4 is more common in all forms of AD than in controls, it is specifically related to the late onset rather than the early onset variant. ApoE e4 is thus seen to be mostly strongly associated with late onset familial cases of AD. Having one copy of the ApoE e4 gene increases a person’s risk of developing AD by up to four times. Someone with two copies of ApoE e4, one from each parent, has a 10 times greater risk and earlier age of onset than individuals who inherited one e4 allele, but only
about 2% of the population have two copies of e4. The most common form of the gene is e3. About 60% of the population have two copies of ApoE e3 and are at average risk, which, means that about half will develop the disease by their late 80s.

About one in six people has at least one copy of ApoE e2. This form of the gene delays the onset and decreases the risk of AD. The lowest risk is for people who have two copies of ApoE e2. It is important to recognise that this gene affects risk and is not a predictor of whether someone will develop AD. Although ApoE e4 increases the risk of developing the disease it does not make it certain.

Many people who develop AD do not have an ApoE e4 gene, and some with the e4 type do not develop the disease. It is now recognized that ApoE is not the ‘cause’ of AD, but rather an important link in a biological chain of events, AD itself appearing less like a single disease process and more the result of the failure of diverse neuronal compensatory and repair mechanisms to deal with multiple ageing-related aggressions. An interactive effect with ApoE in AD has now been demonstrated in relation to a number of other risk factors so that the ApoE e4 carriers might be more vulnerable to various adverse environmental factors e.g. physical inactivity, saturated fat intake, alcohol drinking, diabetes, high BP and low B12/folate.

Gender

It has been suggested that the prevalence of AD is higher in women than in men. It is not clear whether this difference is due to biology, to the fact that women tend to live longer or to their behaviour. On the other hand, studies from provide evidence against a sex difference in the risk of AD. Vascular dementia is more common in men than women across all age groups. This may be because risk factors for vascular dementia, such as high blood pressure and heart disease, are more common in men. Overall, 66% of people with dementia are female. However, the proportion varies with age group: women account for only 37% of people with dementia between 65 and 69, but 79% of people with dementia aged 90 and above.
ENVIRONMENTAL/NUTRITIONAL RISK FACTORS

Prevention of dementia

Alcohol drinking

Cognitive impairment is frequently observed in heavy drinkers and visuomotor capacity, memory or abstract thinking is affected in those individuals. Excessive alcohol consumption can lead to alcohol-related brain damage and severe loss of short-term memory, and is responsible for alcoholic dementia, also named Korsakoff’s syndrome. This disease is associated with the lack of vitamin B1, frequently associated with malnutrition in heavy drinkers. It is assumed that light to moderate alcohol consumption may lower the risk of cognitive decline and dementia. The health benefit may be mediated by a protective effect against vascular disease, as moderate alcohol consumption lowers the risk of stroke as well as subclinical infarcts and white matter disease on brain imaging. Binge drinking in midlife is associated with an increased risk of dementia. There is evidence that risk of dementia increased with rising alcohol consumption for those people who carried the ApoE e4 allele. One possible explanation could be that individuals with the e4 allele have less effective neural repair mechanisms and thus would be more susceptible to the deleterious effects of alcohol. On the other hand, resveratrol, a polyphenol may partly be responsible for the beneficial effects of wine, especially of red wine. It has complex physiological effects via gene modulation: antioxidative, cytoprotective and anti-inflammatory. The impact of alcohol consumption on the incidence of MCI and its progression to dementia has been studied recently. Patients with MCI who were moderate drinkers, i.e. those who consumed less than 1 drink/day (approximately 15g of alcohol), had a lower rate of progression to dementia than abstainers.

There seems to be a J-shaped association between alcohol intake and a variety of adverse health outcomes, including coronary heart disease, diabetes, hypertension, congestive heart failure, stroke, dementia, Raynaud’s phenomenon, and all-cause mortality. Light to moderate alcohol consumption (up to 1 drink daily for women and 1 or 2 drinks daily for men) is associated with
Risk Factors for Dementia

Cardioprotective benefits, whereas increasingly excessive consumption results in proportional worsening of outcomes. Other studies have shown that a history of heavy drinking or alcohol abuse might be associated with an increased occurrence of dementia and Alzheimer’s disease.

There is insufficient evidence to promote alcohol to nondrinkers as a means of reducing dementia risk. As there is still debate whether the positive effects of moderate alcohol consumption are due to methodological artefacts, e.g. the fact that people who do not drink at all are more ill in general. Abstinent people might have deliberately stopped alcohol consumption due to severe chronic illness like past alcohol addiction.

Smoking

The interaction between smoking and dementia is complex. Smoking is a clear risk factor for cardiovascular disease and stroke. In prospective population based cohort studies like the Rotterdam study, smoking was a risk factor for AD. Overall in this study, smoking doubled AD (relative risk 2.3). The risk was much higher in individuals without an APOE4 allele. A recent collaborative population-based study in Europe confirmed that smoking is associated with higher rates of cognitive decline in elderly subjects without dementia; higher cigarette-year consumption was correlated with a significantly higher rate of decline. Older family and case-control studies have found that smoking has a protective effect against developing Alzheimer’s disease. In contrast, others have argued that the results reported by case-control studies were a consequence of survival bias rather than a true protective effect of smoking. Thus, any lower rates of Alzheimer’s disease among smokers may have little or nothing to do with any protective quality of smoking. Interestingly, findings from several studies have shown that there is an increased risk of dementia and Alzheimer’s disease associated with smoking in those without an APOE e4 allele.

Mediterranean diet

Adherence to a so-called “Mediterranean diet”, i.e. a diet containing more fish than (red) meat, more vegetables and fruit
than carbohydrates and moderate amounts of wine, (MeDi) may affect not only risk for Alzheimer’s disease (AD) but also subsequent disease course: Higher adherence to the MeDi is associated with lower mortality in AD. The gradual reduction in mortality risk for higher adherence to this diet suggests a possible dose-response effect.

**W-3 fatty acids and fish intake**

Elderly people who eat seafood or fish at least once a week are at lower risk of developing dementia. Daily consumption of fruit and vegetables was associated with a decreased risk of all cause dementia. Weekly consumption of fish seems to be associated with a reduced risk of all cause dementia but only among ApoE epsilon 4 non-carriers Regular use of omega-3 rich oils seems to be associated with a decreased risk of borderline significance for all cause dementia. Regular consumption of omega-6 rich oils not compensated by consumption of omega-3 rich oils or fish seems to be associated with an increased risk of dementia among ApoE epsilon 4 non-carriers. Frequent consumption of fruit and vegetables, fish, and omega-3 rich oils may decrease the risk of dementia and Alzheimer’s disease, especially among ApoE epsilon 4 non-carriers.

Although consumption of lean fried fish doesn’t seem to have a protective effect, consumption of fatty fish more than twice per week is associated with a reduction in risk of dementia by 28% in comparison to those who eat fish less than once per month. This effect seems to be selective to those without the epsilon4 allele.

However, until data from randomised trials become available for analysis, there is no good evidence to support the use of dietary or supplemental omega 3 PUFA for the prevention of cognitive impairment or dementia.

**Homocystein, Folate (Folic Acid) and Vitamin B12**

Plasma total homocysteine has emerged as a major vascular risk factor. Homocysteine is a sulfur amino acid in the blood whose metabolism is closely related to that of the vitamins folate, B6, and B12. Too much of it can damage blood vessels and it has also been linked with dementia. Folate and other B vitamins, including vitamins B6 and B12 help process and lower levels of
homocysteine. Fortified cereals, green leafy vegetables, orange juice, yeast extract and liver are all good sources of folate. There is evidence that having too little folate may contribute to the cognitive impairment of some older people’s brains. This may result in reversible damage or possible increase in the risk of AD and vascular dementia. Low levels of folate and vitamin B12 might be related to an increased risk of Alzheimer’s disease. The results from a prospective, observational study indicated that an increased plasma total homocysteine level is an independent risk factor for the development of dementia and AD. But there is no evidence currently that folate or vitamin B12 deficiency is associated with the neuropathologic hallmarks of AD. It is not yet known whether increasing your intake of folate either through diet or by taking supplements will reduce the risk of developing dementia.

**Antioxidants/Vitamin C and E**

One hypothesis that accounts for both the heterogeneous nature of AD and the fact that ageing is the most obvious risk factor is that free radicals are involved. The probability of this involvement is supported by the fact that neurons are extremely sensitive to attacks by destructive free radicals. Free radicals are a by-product that occurs when the body uses oxygen. They are harmful and can cause damage inside the cells of the body. Environmental factors such as cigarette smoke or pollution can increase the level of free radicals in the body. Antioxidants are the body’s defence system against free radicals, as they mop up these destructive molecules. The danger from free radical damage increases with age. Some researchers think that the destructive effect of free radicals may be one of the causes of brain cell death in Alzheimer’s disease. This has led to interest in whether increasing antioxidant intake through diet or vitamin supplements could provide any protection against Alzheimer’s disease. It seems that patients taking vitamin E supplement might have a slower progression of AD than patients taking placebo. In studies, neither supplemental dietary nor total intake of carotens and vitamin C and E was associated with a decreased risk of AD. In the Honolulu-Asia Aging Study (HAAS), men had been followed for research purposes for more than 30 years. It showed that midlife dietary intake of beta-carotene,
falvonoids, and vitamin E and C was not related to the incidence of dementia and its subtypes in late life. Others have investigated the association between the intake of antioxidants from food and the risk of AD.

The results from a population-based cohort study with a mean follow-up period of six years suggested that high intake of vitamin C and vitamin E from food might be associated with a lower incidence of Alzheimer’s disease. They found that those who had the highest intake of vitamin E had a 43% lower risk of developing Alzheimer’s disease compared with the people who had the lowest intake. There was a slight association between high intake of vitamin C and risk of Alzheimer’s disease. The results from the Chicago Health and Aging project showed that those with the highest intake of vitamin E from food, but not from vitamin supplements, had a 70% lower risk of developing Alzheimer’s disease. This reduced risk was only found in those people who did not have the ApoE e4 gene. Vitamin C did not seem to offer any protection.

THE PSYCHOLOGICAL RISK FACTORS FOR DEMENTIA

Are cynical people more likely to develop dementia? According to a new study in Neurology, the journal of the American Academy of Neurology, the answer is “yes”. The study, said to be the first to exclusively examine the link between cynicism and dementia, is just one of many to explore the psychological risk factors for Alzheimer’s and other dementias.

One of the most well-known of these long-term studies comes from David A. Bennett, director of the Rush Alzheimer’s Disease Center at Rush Medical College in Chicago, Illinois. Bennett’s study, along with a number of subsequent investigations, established that neuroticism, depression, social isolation and other social traits are all risk factors for Alzheimer’s and other forms of dementia.

On the flip side, advanced education, organizational skills, conscientiousness and other positive traits have been shown to offer protection against dementia and cognitive decline.
Mitigate Psychological Risk Factors

A natural predisposition towards cynicism or depression is not a dementia life sentence. There are a number of ways that individuals can build their brains and increase their cognitive reserve, regardless of their psychological risk factors. Since our brains are constantly changing in response to the environment, a lifetime of social, occupational and educational engagement can strengthen the brain against future decline. Moreover, individuals suffering from depression can (and should) seek treatment—if recognized and treated, depression is a risk factor often associated with potentially reversible cognitive impairment.

Negative Psychological Risk Factors Cause Cognitive Impairment and Dementia

Many of the negative psychological risk factors linked to dementia are associated with stress—or, more precisely, distress. While stress is always in our environment, distress only occurs when we have a negative psychological response to stress. When this happens, our blood is flooded with stress hormones (cortisol), which are toxic to the brain cells responsible for memory and learning.

We all walk through stressful environments daily, but people who are cynical, neurotic or depressed are constantly experiencing a distressed response to these environments.

Another common thread? These negative psychological risk factors are often bundled—for example, a depressed person is more likely to develop a cynical attitude and social isolation can lead to or worsen existing depression.

Knowledge Inform Drug Discovery to Prevent Cognitive Decline

We may be able to use this knowledge to research and develop a drug that blocks the effects of the stress hormone cortisol on the hippocampal region of the brain, where memory and learning happen. Researchers have already identified molecules that can block the cortisol receptor and mitigate the effect of cortisol on the brain.
The Alzheimer’s Drug Discovery Foundation has funded a number of studies investigating stress blocking compounds. These drugs could mitigate the negative biological effects of excess stress on the brain and protect populations with an increased risk for developing Alzheimer’s and other dementias.

Drugs used to treat depression may also hold promise for Alzheimer’s patients. Recent research suggests that the antidepressant citalopram (Celexa™) may inhibit the growth of beta-amyloid plaques. Citalopram belongs to a class of antidepressant drugs known as selective serotonin reuptake inhibitors (SSRIs) that function by increasing serotonin levels in the brain.
Alzheimer’s Disease:
Histopathological, Neurochemical
and Molecular Biological Aspects

ALZHEIMER’S DISEASE

Alzheimer’s disease (AD), also known as just Alzheimer’s, is a chronic neurodegenerative disease that usually starts slowly and gets worse over time. It is the cause of 60% to 70% of cases of dementia. The most common early symptom is difficulty in remembering recent events (short-term memory loss). As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self care, and behavioural issues. As a person’s condition declines, they often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death. Although the speed of progression can vary, the average life expectancy following diagnosis is three to nine years.

The cause of Alzheimer’s disease is poorly understood. About 70% of the risk is believed to be genetic with many genes usually involved. Other risk factors include a history of head injuries, depression, or hypertension. The disease process is associated with plaques and tangles in the brain. A probable diagnosis is based on the history of the illness and cognitive testing with medical imaging and blood tests to rule out other possible causes.
Initial symptoms are often mistaken for normal ageing. Examination of brain tissue is needed for a definite diagnosis. Mental and physical exercise, and avoiding obesity may decrease the risk of AD. There are no medications or supplements that decrease risk.

No treatments stop or reverse its progression, though some may temporarily improve symptoms. Affected people increasingly rely on others for assistance, often placing a burden on the caregiver; the pressures can include social, psychological, physical, and economic elements. Exercise programmes are beneficial with respect to activities of daily living and can potentially improve outcomes. Treatment of behavioural problems or psychosis due to dementia with antipsychotics is common but not usually recommended due to there often being little benefit and an increased risk of early death.

In 2015, there were approximately 48 million people worldwide with AD. It most often begins in people over 65 years of age, although 4% to 5% of cases are early-onset Alzheimer’s which begin before this. It affects about 6% of people 65 years and older. In 2010, dementia resulted in about 486,000 deaths. It was first described by, and later named after, German psychiatrist and pathologist Alois Alzheimer in 1906. In developed countries, AD is one of the most financially costly diseases.

Signs and symptoms

**Stages of Alzheimer’s disease**

- Effects of ageing on memory but not AD
  - Forgetting things occasionally
Alzheimer's Disease: Histopathological, Neurochemical...

- Misplacing items sometimes
- Minor short-term memory loss
- Not remembering exact details.

Early stage Alzheimer’s
- Not remembering episodes of forgetfulness
- Forgets names of family or friends
- Changes may only be noticed by close friends or relatives
- Some confusion in situations outside the familiar

Middle stage Alzheimer’s
- Greater difficulty remembering recently learned information
- Deepening confusion in many circumstances
- Problems with sleep
- Trouble knowing where they are

Late stage Alzheimer’s
- Poor ability to think
- Problems speaking
- Repeats same conversations
- More abusive, anxious, or paranoid

The disease course is divided into four stages, with a progressive pattern of cognitive and functional impairment.

**Pre-dementia**

The first symptoms are often mistakenly attributed to ageing or stress. Detailed neuropsychological testing can reveal mild cognitive difficulties up to eight years before a person fulfils the clinical criteria for diagnosis of AD. These early symptoms can affect the most complex activities of daily living. The most noticeable deficit is short term memory loss, which shows up as difficulty in remembering recently learned facts and inability to acquire new information.

Subtle problems with the executive functions of attentiveness, planning, flexibility, and abstract thinking, or impairments in semantic memory (memory of meanings, and concept relationships) can also be symptomatic of the early stages of AD. Apathy can be observed at this stage, and remains the most persistent
neuropsychiatric symptom throughout the course of the disease. Depressive symptoms, irritability and reduced awareness of subtle memory difficulties are also common. The preclinical stage of the disease has also been termed mild cognitive impairment (MCI). This is often found to be a transitional stage between normal ageing and dementia. MCI can present with a variety of symptoms, and when memory loss is the predominant symptom, it is termed “amnestic MCI” and is frequently seen as a prodromal stage of Alzheimer’s disease.

Early

In people with AD, the increasing impairment of learning and memory eventually leads to a definitive diagnosis. In a small percentage, difficulties with language, executive functions, perception (agnosia), or execution of movements (apraxia) are more prominent than memory problems. AD does not affect all memory capacities equally. Older memories of the person’s life (episodic memory), facts learned (semantic memory), and implicit memory (the memory of the body on how to do things, such as using a fork to eat or how to drink from a glass) are affected to a lesser degree than new facts or memories.

Language problems are mainly characterised by a shrinking vocabulary and decreased word fluency, leading to a general impoverishment of oral and written language. In this stage, the person with Alzheimer’s is usually capable of communicating basic ideas adequately. While performing fine motor tasks such as writing, drawing or dressing, certain movement coordination and planning difficulties (apraxia) may be present, but they are commonly unnoticed. As the disease progresses, people with AD can often continue to perform many tasks independently, but may need assistance or supervision with the most cognitively demanding activities.

Moderate

Progressive deterioration eventually hinders independence, with subjects being unable to perform most common activities of daily living. Speech difficulties become evident due to an inability to recall vocabulary, which leads to frequent incorrect word
substitutions (paraphasias). Reading and writing skills are also progressively lost. Complex motor sequences become less coordinated as time passes and AD progresses, so the risk of falling increases. During this phase, memory problems worsen, and the person may fail to recognise close relatives. Long-term memory, which was previously intact, becomes impaired.

Behavioural and neuropsychiatric changes become more prevalent. Common manifestations are wandering, irritability and labile affect, leading to crying, outbursts of unpremeditated aggression, or resistance to caregiving. Sundowning can also appear.

Approximately 30% of people with AD develop illusionary misidentifications and other delusional symptoms. Subjects also lose insight of their disease process and limitations (anosognosia). Urinary incontinence can develop. These symptoms create stress for relatives and carers, which can be reduced by moving the person from home care to other long-term care facilities.

**Advanced**

During the final stages, the patient is completely dependent upon caregivers. Language is reduced to simple phrases or even single words, eventually leading to complete loss of speech. Despite the loss of verbal language abilities, people can often understand and return emotional signals. Although aggressiveness can still be present, extreme apathy and exhaustion are much more common symptoms. People with Alzheimer’s disease will ultimately not be able to perform even the simplest tasks independently; muscle mass and mobility deteriorate to the point where they are bedridden and unable to feed themselves. The cause of death is usually an external factor, such as infection of pressure ulcers or pneumonia, not the disease itself.

**CAUSE**

The cause for most Alzheimer’s cases is still mostly unknown except for 1% to 5% of cases where genetic differences have been identified. Several competing hypotheses exist trying to explain the cause of the disease:
Genetics

The genetic heritability of Alzheimer’s disease (and memory components thereof), based on reviews of twin and family studies, range from 49% to 79%. Around 0.1% of the cases are familial forms of autosomal (not sex-linked) dominant inheritance, which have an onset before age 65. This form of the disease is known as early onset familial Alzheimer’s disease. Most of autosomal dominant familial AD can be attributed to mutations in one of three genes: those encoding amyloid precursor protein (APP) and presenilins 1 and 2. Most mutations in the APP and presenilin genes increase the production of a small protein called Aβ42, which is the main component of senile plaques. Some of the mutations merely alter the ratio between Aβ42 and the other major forms—particularly Aβ40—without increasing Aβ42 levels. This suggests that presenilin mutations can cause disease even if they lower the total amount of Aβ produced and may point to other roles of presenilin or a role for alterations in the function of APP and/or its fragments other than Aβ. There exist variants of the APP gene which are protective.

Most cases of Alzheimer’s disease do not exhibit autosomal-dominant inheritance and are termed sporadic AD, in which environmental and genetic differences may act as risk factors. The best known genetic risk factor is the inheritance of the ε4 allele of the apolipoprotein E (APOE). Between 40 and 80% of people with AD possess at least one APOEε4 allele. The APOEε4 allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes. Like many human diseases, environmental effects and genetic modifiers result in incomplete penetrance. For example, certain Nigerian populations do not show the relationship between dose of APOEε4 and incidence or age-of-onset for Alzheimer’s disease seen in other human populations. Early attempts to screen up to 400 candidate genes for association with late-onset sporadic AD (LOAD) resulted in a low yield. More recent genome-wide association studies (GWAS) have found 19 areas in genes that appear to affect the risk. These genes include: CASS4, CELFI, FERMT2, HLA-DRB5, INPP5D, MEF2C, NME8, PTK2B, SORL1, ZCWPW1, SIC24A4, CLU,
PICALM, CR1, BIN1, MS4A, ABCA7, EPHA1, and CD2AP. Mutations in the TREM2 gene have been associated with a 3 to 5 times higher risk of developing Alzheimer’s disease. A suggested mechanism of action is that when TREM2 is mutated, white blood cells in the brain are no longer able to control the amount of beta amyloid present.

**Cholinergic hypothesis**

The oldest, on which most currently available drug therapies are based, is the *cholinergic hypothesis*, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective. Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid, leading to generalised neuroinflammation.

**Amyloid hypothesis**

In 1991, the *amyloid hypothesis* postulated that extracellular amyloid beta (Aβ) deposits are the fundamental cause of the disease. Support for this postulate comes from the location of the gene for the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit at least the earliest symptoms of AD by 40 years of age.

Also, a specific isoform of apolipoprotein, APOE4, is a major genetic risk factor for AD. Whilst apolipoproteins enhance the breakdown of beta amyloid, some isoforms are not very effective at this task (such as APOE4), leading to excess amyloid buildup in the brain.

Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer’s-like brain pathology with spatial learning deficits. An experimental vaccine was found to clear the amyloid plaques in early human trials, but it did not have any significant effect on dementia.

Researchers have been led to suspect non-plaque Aβ oligomers (aggregates of many monomers) as the primary pathogenic form...
of Aβ. These toxic oligomers, also referred to as amyloid-derived diffusible ligands (ADDLs), bind to a surface receptor on neurons and change the structure of the synapse, thereby disrupting neuronal communication.

One receptor for Aβ oligomers may be the prion protein, the same protein that has been linked to mad cow disease and the related human condition, Creutzfeldt–Jakob disease, thus potentially linking the underlying mechanism of these neurodegenerative disorders with that of Alzheimer’s disease. One study found possible evidence of human to human transmission.

In 2009, this theory was updated, suggesting that a close relative of the beta-amyloid protein, and not necessarily the beta-amyloid itself, may be a major culprit in the disease. The theory holds that an amyloid-related mechanism that prunes neuronal connections in the brain in the fast-growth phase of early life may be triggered by ageing-related processes in later life to cause the neuronal withering of Alzheimer’s disease.

N-APP, a fragment of APP from the peptide’s N-terminus, is adjacent to beta-amyloid and is cleaved from APP by one of the same enzymes. N-APP triggers the self-destruct pathway by binding to a neuronal receptor called death receptor 6 (DR6, also known as TNFRSF21). DR6 is highly expressed in the human brain regions most affected by Alzheimer’s, so it is possible that the N-APP/DR6 pathway might be hijacked in the ageing brain to cause damage. In this model, beta-amyloid plays a complementary role, by depressing synaptic function.

**Tau hypothesis**

The tau hypothesis proposes that tau protein abnormalities initiate the disease cascade. In this model, hyperphosphorylated tau begins to pair with other threads of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies. When this occurs, the microtubules disintegrate, destroying the structure of the cell’s cytoskeleton which collapses the neuron’s transport system. This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells.
Other hypotheses

A neurovascular hypothesis has been proposed which states that poor functioning of the blood brain barrier may be involved. The cellular homeostasis of biometals such as ionic copper, iron, and zinc is disrupted in AD, though it remains unclear whether this is produced by or causes the changes in proteins.

These ions affect and are affected by tau, APP, and APOE, and their dysregulation may cause oxidative stress that may contribute to the pathology.

The quality of some of these studies has been criticised, and the link remains controversial. The majority of researchers do not support a causal connection with aluminium.

Smoking is a significant AD risk factor. Systemic markers of the innate immune system are risk factors for late-onset AD. There is tentative evidence that exposure to air pollution may be a contributing factor to the development of Alzheimer’s disease.

An infection with Spirochetes (a bacterium) in gum disease may cause dementia and may be involved in the pathogenesis of Alzheimer’s disease.

Retrogenesis is a medical hypothesis about the development and progress of Alzheimer’s disease proposed by Barry Reisberg in the 1980s.

The hypothesis is that just as the fetus goes through a process of neurodevelopment beginning with neurulation and ending with myelination, the brains of people with AD go through a reverse neurodegeneration process starting with demyelination and death of axons (white matter) and ending with the death of grey matter.

Likewise the hypothesis is, that as infants go through states of cognitive development, people with AD go through the reverse process of progressive cognitive impairment.

Reisberg developed the caregiving assessment tool known as “FAST” (Functional Assessment Staging Tool) which he says allows those caring for AD patients to identify the stages of disease progression and that provides advice about the kind of care needed at each stage.
PATHOPHYSIOLOGY

Histopathologic image of senile plaques seen in the cerebral cortex of a person with Alzheimer’s disease of presenile onset. Silver impregnation.

There is cortical atrophy in Alzheimer’s Disease, associated with loss of gyri and sulci in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus.

Neuropathology

Alzheimer’s disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus. Degeneration is also present in brainstem nuclei like the locus coeruleus. Studies using MRI and PET have documented reductions in the size of specific brain regions in people with AD as they progressed from mild cognitive impairment to Alzheimer’s disease, and in comparison with similar
images from healthy older adults. Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD. Plaques are dense, mostly insoluble deposits of beta-amyloid peptide and cellular material outside and around neurons. Tangles (neurofibrillary tangles) are aggregates of the microtubule-associated protein tau which has become hyperphosphorylated and accumulate inside the cells themselves. Although many older individuals develop some plaques and tangles as a consequence of ageing, the brains of people with AD have a greater number of them in specific brain regions such as the temporal lobe. Lewy bodies are not rare in the brains of people with AD.

Biochemistry
Enzymes act on the APP (amyloid precursor protein) and cut it into fragments. The beta-amyloid fragment is crucial in the formation of senile plaques in AD.

Alzheimer’s disease has been identified as a protein misfolding disease (proteopathy), caused by plaque accumulation of abnormally folded amyloid beta protein, and tau protein in the brain. Plaques are made up of small peptides, 39–43 amino acids in length, called amyloid beta (Aβ). Aβ is a fragment from the larger amyloid precursor protein (APP). APP is a transmembrane protein that penetrates through the neuron’s membrane. APP is critical to neuron growth, survival, and post-injury repair. In Alzheimer’s disease, gamma secretase and beta secretase act together in a proteolytic process which causes APP to be divided into smaller fragments. One of these fragments gives rise to fibrils of amyloid beta, which then form clumps that deposit outside neurons in dense formations known as senile plaques.

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

**Disease mechanism**

Exactly how disturbances of production and aggregation of the beta-amyloid peptide give rise to the pathology of AD is not known. The amyloid hypothesis traditionally points to the accumulation of beta-amyloid peptides as the central event triggering neuron degeneration. Accumulation of aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell’s calcium ion homeostasis, induces programmed cell death (apoptosis). It is also known that Aβ selectively builds up in the mitochondria in the cells of Alzheimer’s-affected brains, and it also inhibits certain
enzyme functions and the utilisation of glucose by neurons. Various inflammatory processes and cytokines may also have a role in the pathology of Alzheimer’s disease. Inflammation is a general marker of tissue damage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response. There is increasing evidence of a strong interaction between the neurons and the immunological mechanisms in the brain. Obesity and systemic inflammation may interfere with immunological processes which promote disease progression.

Alterations in the distribution of different neurotrophic factors and in the expression of their receptors such as the brain-derived neurotrophic factor (BDNF) have been described in AD.

DIAGNOSIS

PET scan of the brain of a person with AD showing a loss of function in the temporal lobe

Alzheimer’s disease is usually diagnosed based on the person’s medical history, history from relatives, and behavioural observations. The presence of characteristic neurological and neuropsychological features and the absence of alternative conditions is supportive. Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single-photon emission computed tomography (SPECT)
or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia. Moreover, it may predict conversion from prodromal stages (mild cognitive impairment) to Alzheimer’s disease.

Assessment of intellectual functioning including memory testing can further characterise the state of the disease. Medical organisations have created diagnostic criteria to ease and standardise the diagnostic process for practising physicians. The diagnosis can be confirmed with very high accuracy post-mortem when brain material is available and can be examined histologically.

Criteria

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRDA, now known as the Alzheimer’s Association) established the most commonly used NINCDS-ADRDA Alzheimer’s Criteria for diagnosis in 1984, extensively updated in 2007. These criteria require that the presence of cognitive impairment, and a suspected dementia syndrome, be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD. A histopathologic confirmation including a microscopic examination of brain tissue is required for a definitive diagnosis. Good statistical reliability and validity have been shown between the diagnostic criteria and definitive histopathological confirmation. Eight cognitive domains are most commonly impaired in AD—memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities. These domains are equivalent to the NINCDS-ADRDA Alzheimer’s Criteria as listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) published by the American Psychiatric Association.

Techniques

Neuropsychological tests such as the mini-mental state examination (MMSE) are widely used to evaluate the cognitive impairments needed for diagnosis. More comprehensive test arrays are necessary for high reliability of results, particularly in the earliest stages of the disease. Neurological examination in early
AD will usually provide normal results, except for obvious cognitive impairment, which may not differ from that resulting from other diseases processes, including other causes of dementia.

Further neurological examinations are crucial in the differential diagnosis of AD and other diseases. Interviews with family members are also utilised in the assessment of the disease. Caregivers can supply important information on the daily living abilities, as well as on the decrease, over time, of the person’s mental function.

A caregiver’s viewpoint is particularly important, since a person with AD is commonly unaware of his own deficits. Many times, families also have difficulties in the detection of initial dementia symptoms and may not communicate accurate information to a physician.

Supplemental testing provides extra information on some features of the disease or is used to rule out other diagnoses. Blood tests can identify other causes for dementia than AD—causes which may, in rare cases, be reversible. It is common to perform thyroid function tests, assess B12, rule out syphilis, rule out metabolic problems (including tests for kidney function, electrolyte levels and for diabetes), assess levels of heavy metals (e.g. lead, mercury) and anaemia. (It is also necessary to rule out delirium).

Psychological tests for depression are employed, since depression can either be concurrent with AD, an early sign of cognitive impairment, or even the cause.

PREVENTION

At present, there is no definitive evidence to support that any particular measure is effective in preventing AD. Global studies of measures to prevent or delay the onset of AD have often produced inconsistent results. Epidemiological studies have proposed relationships between certain modifiable factors, such as diet, cardiovascular risk, pharmaceutical products, or intellectual activities among others, and a population’s likelihood of developing AD. Only further research, including clinical trials, will reveal whether these factors can help to prevent AD.
Medication

Although cardiovascular risk factors, such as hypercholesterolaemia, hypertension, diabetes, and smoking, are associated with a higher risk of onset and course of AD, statins, which are cholesterol lowering drugs, have not been effective in preventing or improving the course of the disease.

Long-term usage of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced likelihood of developing AD. Evidence also support the notion that NSAIDs can reduce inflammation related to amyloid plaques. No prevention trial has been completed. They do not appear to be useful as a treatment. Hormone replacement therapy, although previously used, may increase the risk of dementia.

Lifestyle

People who engage in intellectual activities such as reading, playing board games, completing crossword puzzles, playing musical instruments, or regular social interaction show a reduced risk for Alzheimer’s disease. This is compatible with the cognitive reserve theory, which states that some life experiences result in more efficient neural functioning providing the individual a cognitive reserve that delays the onset of dementia manifestations. Education delays the onset of AD syndrome, but is not related to earlier death after diagnosis. Learning a second language even later in life seems to delay getting Alzheimer disease. Physical activity is also associated with a reduced risk of AD.

Diet

People who eat a healthy, Japanese, or Mediterranean diet have a lower risk of AD. A Mediterranean diet may improve outcomes in those with the disease. Those who eat a diet high in saturated fats and simple carbohydrates (mono- and disaccharide) have a higher risk. The Mediterranean diet’s beneficial cardiovascular effect has been proposed as the mechanism of action.

Conclusions on dietary components have at times been difficult to ascertain as results have differed between population-based
studies and randomised controlled trials. There is limited evidence that light to moderate use of alcohol, particularly red wine, is associated with lower risk of AD. There is tentative evidence that caffeine may be protective. A number of foods high in flavonoids such as cocoa, red wine, and tea may decrease the risk of AD.

Reviews on the use of vitamins and minerals have not found enough consistent evidence to recommend them. This includes vitamin A, C, E, selenium, zinc, and folic acid with or without vitamin B₁₂. Additionally, vitamin E is associated with health risks. Trials examining folic acid (B9) and other B vitamins failed to show any significant association with cognitive decline. Omega-3 fatty acid supplements from plants and fish, and dietary docosahexaenoic acid (DHA), do not appear to benefit people with mild to moderate Alzheimer’s disease.

Curcumin as of 2010 has not shown benefit in people even though there is tentative evidence in animals. There is inconsistent and unconvincing evidence that ginkgo has any positive effect on cognitive impairment and dementia. As of 2008 there is no concrete evidence that cannabinoids are effective in improving the symptoms of AD or dementia; however, some research looks promising.

MANAGEMENT

There is no cure for Alzheimer’s disease; available treatments offer relatively small symptomatic benefit but remain palliative in nature. Current treatments can be divided into pharmaceutical, psychosocial and caregiving.

Medications

Five medications are currently used to treat the cognitive problems of AD: four are acetylcholinesterase inhibitors (tacrine, rivastigmine, galantamine and donepezil) and the other (memantine) is an NMDA receptor antagonist. The benefit from their use is small. No medication has been clearly shown to delay or halt the progression of the disease.

Reduction in the activity of the cholinergic neurons is a well-known feature of Alzheimer’s disease. Acetylcholinesterase
inhibitors are employed to reduce the rate at which acetylcholine (ACh) is broken down, thereby increasing the concentration of ACh in the brain and combating the loss of ACh caused by the death of cholinergic neurons. There is evidence for the efficacy of these medications in mild to moderate Alzheimer’s disease, and some evidence for their use in the advanced stage. Only donepezil is approved for treatment of advanced AD dementia. The use of these drugs in mild cognitive impairment has not shown any effect in a delay of the onset of AD. The most common side effects are nausea and vomiting, both of which are linked to cholinergic excess. These side effects arise in approximately 10–20% of users, are mild to moderate in severity, and can be managed by slowly adjusting medication doses. Less common secondary effects include muscle cramps, decreased heart rate (bradycardia), decreased appetite and weight, and increased gastric acid production.

Glutamate is a useful excitatory neurotransmitter of the nervous system, although excessive amounts in the brain can lead to cell death through a process called excitotoxicity which consists of the overstimulation of glutamate receptors. Excitotoxicity occurs not only in Alzheimer’s disease, but also in other neurological diseases such as Parkinson’s disease and multiple sclerosis. Memantine is a noncompetitive NMDA receptor antagonist first used as an anti-influenza agent. It acts on the glutamatergic system by blocking NMDA receptors and inhibiting their overstimulation by glutamate. Memantine has been shown to have a small benefit in the treatment of Alzheimer’s disease. Reported adverse events with memantine are infrequent and mild, including hallucinations, confusion, dizziness, headache and fatigue. The combination of memantine and donepezil has been shown to be “of statistically significant but clinically marginal effectiveness”.

Atypical antipsychotics are modestly useful in reducing aggression and psychosis in people with Alzheimer’s disease, but their advantages are offset by serious adverse effects, such as stroke, movement difficulties or cognitive decline. When used in the long-term, they have been shown to associate with increased mortality. Stopping antipsychotic use in this group of people appears to be safe.
Huperzine A while promising, requires further evidence before it use can be recommended.

**Psychosocial intervention**

Psychosocial interventions are used as an adjunct to pharmaceutical treatment and can be classified within behaviour-, emotion-, cognition- or stimulation-oriented approaches. Research on efficacy is unavailable and rarely specific to AD, focusing instead on dementia in general.

Behavioural interventions attempt to identify and reduce the antecedents and consequences of problem behaviours. This approach has not shown success in improving overall functioning, but can help to reduce some specific problem behaviours, such as incontinence. There is a lack of high quality data on the effectiveness of these techniques in other behaviour problems such as wandering.

Emotion-oriented interventions include reminiscence therapy, validation therapy, supportive psychotherapy, sensory integration, also called snoezelen, and simulated presence therapy. Supportive psychotherapy has received little or no formal scientific study, but some clinicians find it useful in helping mildly impaired people adjust to their illness. Reminiscence therapy (RT) involves the discussion of past experiences individually or in group, many times with the aid of photographs, household items, music and sound recordings, or other familiar items from the past. Although there are few quality studies on the effectiveness of RT, it may be beneficial for cognition and mood. Simulated presence therapy (SPT) is based on attachment theories and involves playing a recording with voices of the closest relatives of the person with Alzheimer’s disease. There is partial evidence indicating that SPT may reduce challenging behaviours. Finally, validation therapy is based on acceptance of the reality and personal truth of another’s experience, while sensory integration is based on exercises aimed to stimulate senses. There is no evidence to support the usefulness of these therapies.

The aim of cognition-oriented treatments, which include reality orientation and cognitive retraining, is the reduction of cognitive deficits. Reality orientation consists in the presentation of
information about time, place or person to ease the understanding of the person about its surroundings and his or her place in them. On the other hand, cognitive retraining tries to improve impaired capacities by exercitation of mental abilities. Both have shown some efficacy improving cognitive capacities, although in some studies these effects were transient and negative effects, such as frustration, have also been reported.

Stimulation-oriented treatments include art, music and pet therapies, exercise, and any other kind of recreational activities. Stimulation has modest support for improving behaviour, mood, and, to a lesser extent, function. Nevertheless, as important as these effects are, the main support for the use of stimulation therapies is the change in the person’s routine.

Caregiving

Since Alzheimer’s has no cure and it gradually renders people incapable of tending for their own needs, caregiving essentially is the treatment and must be carefully managed over the course of the disease.

During the early and moderate stages, modifications to the living environment and lifestyle can increase patient safety and reduce caretaker burden. Examples of such modifications are the adherence to simplified routines, the placing of safety locks, the labelling of household items to cue the person with the disease or the use of modified daily life objects. If eating becomes problematic, food will need to be prepared in smaller pieces or even pureed. When swallowing difficulties arise, the use of feeding tubes may be required. In such cases, the medical efficacy and ethics of continuing feeding is an important consideration of the caregivers and family members. The use of physical restraints is rarely indicated in any stage of the disease, although there are situations when they are necessary to prevent harm to the person with AD or their caregivers.

As the disease progresses, different medical issues can appear, such as oral and dental disease, pressure ulcers, malnutrition, hygiene problems, or respiratory, skin, or eye infections. Careful management can prevent them, while professional treatment is
needed when they do arise. During the final stages of the disease, treatment is centred on relieving discomfort until death, often with the help of hospice.

**Feeding tubes**

People with Alzheimer’s disease (and other forms of dementia) often develop problems with eating, due to difficulties in swallowing, reduced appetite or the inability to recognise food. Their carers and families often request they have some form of feeding tube. However, there is no evidence that this helps people with advanced Alzheimer’s to gain weight, regain strength or improve their quality of life. In fact, their use might carry an increased risk of aspiration pneumonia, use of physical restraints, and increased risk of pressure ulcers.

**PROGNOSIS**

The early stages of Alzheimer’s disease are difficult to diagnose. A definitive diagnosis is usually made once cognitive impairment compromises daily living activities, although the person may still be living independently. The symptoms will progress from mild cognitive problems, such as memory loss through increasing stages of cognitive and non-cognitive disturbances, eliminating any possibility of independent living, especially in the late stages of the disease.

Life expectancy of the population with the disease is reduced. The mean life expectancy following diagnosis is approximately six years. Fewer than 3% of people live more than fourteen years. Disease features significantly associated with reduced survival are an increased severity of cognitive impairment, decreased functional level, history of falls, and disturbances in the neurological examination. Other coincident diseases such as heart problems, diabetes or history of alcohol abuse are also related with shortened survival. While the earlier the age at onset the higher the total survival years, life expectancy is particularly reduced when compared to the healthy population among those who are younger. Men have a less favourable survival prognosis than women.

The disease is the underlying cause of death in 68% of all cases. Pneumonia and dehydration are the most frequent
immediate causes of death brought by AD, while cancer is a less frequent cause of death than in the general population.

**EPIDEMIOLOGY**

Two main measures are used in epidemiological studies: incidence and prevalence. Incidence is the number of new cases per unit of person–time at risk (usually number of new cases per thousand person-years); while prevalence is the total number of cases of the disease in the population at any given time.

Regarding incidence, cohort longitudinal studies (studies where a disease-free population is followed over the years) provide rates between 10 and 15 per thousand person–years for all dementias and 5–8 for AD, which means that half of new dementia cases each year are AD. Advancing age is a primary risk factor for the disease and incidence rates are not equal for all ages: every five years after the age of 65, the risk of acquiring the disease approximately doubles, increasing from 3 to as much as 69 per thousand person years. There are also sex differences in the incidence rates, women having a higher risk of developing AD particularly in the population older than 85. The risk of dying from Alzheimer’s disease is 26% higher among the non-Hispanic white population than among the non-Hispanic black population, whereas the Hispanic population has a 30% lower risk than the non-Hispanic white population.

Prevalence of AD in populations is dependent upon different factors including incidence and survival. Since the incidence of AD increases with age, it is particularly important to include the mean age of the population of interest. In the United States, Alzheimer prevalence was estimated to be 1.6% in 2000 both overall and in the 65–74 age group, with the rate increasing to 19% in the 75–84 group and to 42% in the greater than 84 group. Prevalence rates in less developed regions are lower. The World Health Organization estimated that in 2005, 0.379% of people worldwide had dementia, and that the prevalence would increase to 0.441% in 2015 and to 0.556% in 2030. Other studies have reached similar conclusions. Another study estimated that in 2006, 0.40% of the world population (range 0.17–0.89%; absolute number
26.6 million, range 11.4–59.4 million) were afflicted by AD, and that the prevalence rate would triple and the absolute number would quadruple by 2050. It may contribute to 60% to 70% of cases of dementia.

**History**

The ancient Greek and Roman philosophers and physicians associated old age with increasing dementia. It was not until 1901 that German psychiatrist Alois Alzheimer identified the first case of what became known as Alzheimer’s disease, named after him, in a fifty-year-old woman he called Auguste D. He followed her case until she died in 1906, when he first reported publicly on it. During the next five years, eleven similar cases were reported in the medical literature, some of them already using the term Alzheimer’s disease.

For most of the 20th century, the diagnosis of Alzheimer’s disease was reserved for individuals between the ages of 45 and 65 who developed symptoms of dementia. The terminology changed after 1977 when a conference on AD concluded that the clinical and pathological manifestations of presenile and senile dementia were almost identical, although the authors also added that this did not rule out the possibility that they had different causes. This eventually led to the diagnosis of Alzheimer’s disease independent of age. The term *senile dementia of the Alzheimer type* (SDAT) was used for a time to describe the condition in those over 65, with classical Alzheimer’s disease being used to describe those who were younger. Eventually, the term Alzheimer’s disease was formally adopted in medical nomenclature to describe individuals of all ages with a characteristic common symptom pattern, disease course, and neuropathology.

**Society and culture**

**Social costs**

Dementia, and specifically Alzheimer’s disease, may be among the most costly diseases for society in Europe and the United States, while their costs in other countries such as Argentina, and South Korea, are also high and rising. These costs will probably
increase with the ageing of society, becoming an important social problem. AD-associated costs include direct medical costs such as nursing home care, direct nonmedical costs such as in-home day care, and indirect costs such as lost productivity of both patient and caregiver. Numbers vary between studies but dementia costs worldwide have been calculated around $160 billion, while costs of Alzheimer’s disease in the United States may be $100 billion each year.

The greatest origin of costs for society is the long-term care by health care professionals and particularly institutionalisation, which corresponds to 2/3 of the total costs for society. The cost of living at home is also very high, especially when informal costs for the family, such as caregiving time and caregiver’s lost earnings, are taken into account.

Costs increase with dementia severity and the presence of behavioural disturbances, and are related to the increased caregiving time required for the provision of physical care. Therefore, any treatment that slows cognitive decline, delays institutionalisation or reduces caregivers’ hours will have economic benefits. Economic evaluations of current treatments have shown positive results.

**Caregiving burden**

The role of the main caregiver is often taken by the spouse or a close relative. Alzheimer’s disease is known for placing a great burden on caregivers which includes social, psychological, physical or economic aspects. Home care is usually preferred by people with AD and their families. This option also delays or eliminates the need for more professional and costly levels of care. Nevertheless, two-thirds of nursing home residents have dementias.

Dementia caregivers are subject to high rates of physical and mental disorders. Factors associated with greater psychosocial problems of the primary caregivers include having an affected person at home, the carer being a spouse, demanding behaviours of the cared person such as depression, behavioural disturbances, hallucinations, sleep problems or walking disruptions and social isolation. Regarding economic problems, family caregivers often
give up time from work to spend 47 hours per week on average with the person with AD, while the costs of caring for them are high. Direct and indirect costs of caring for an Alzheimer’s patient average between $18,000 and $77,500 per year in the United States, depending on the study.

Cognitive behavioural therapy and the teaching of coping strategies either individually or in group have demonstrated their efficacy in improving caregivers’ psychological health.

Notable cases

Because Alzheimer’s disease is common, many notable people have developed it. Well-known examples are former United States President Ronald Reagan and Irish writer Iris Murdoch, both of whom were the subjects of scientific articles examining how their cognitive capacities deteriorated with the disease. Other cases include the retired footballer Ferenc Puskás, former Prime Ministers Harold Wilson (United Kingdom) and Adolfo Suárez (Spain), Indian politician George Fernandes, actress Rita Hayworth, actor Charlton Heston, actor-director Robert Loggia, actor-writer Gene Wilder, the author Harnett Kane, Nobel laureate Charles K. Kao, novelist Terry Pratchett, director Jacques Rivette, and politician and activist Sargent Shriver.

RESEARCH DIRECTIONS

As of 2014, the safety and efficacy of more than 400 pharmaceutical treatments had been or were being investigated in over 1,500 clinical trials worldwide, and approximately a quarter of these compounds are in Phase III trials, the last step prior to review by regulatory agencies.

One area of clinical research is focused on treating the underlying disease pathology. Reduction of beta-amyloid levels is a common target of compounds (such as apomorphine) under investigation. Immunotherapy or vaccination for the amyloid protein is one treatment modality under study. Unlike preventative vaccination, the putative therapy would be used to treat people already diagnosed. It is based upon the concept of training the immune system to recognise, attack, and reverse deposition of
amyloid, thereby altering the course of the disease. An example of such a vaccine under investigation was ACC-001, although the trials were suspended in 2008. Another similar agent is bapineuzumab, an antibody designed as identical to the naturally induced anti-amyloid antibody. Other approaches are neuroprotective agents, such as AL-108, and metal-protein interaction attenuation agents, such as PBT2. A TNFα receptor-blocking fusion protein, etanercept has showed encouraging results.

In 2008, two separate clinical trials showed positive results in modifying the course of disease in mild to moderate AD with methylthioninium chloride, a drug that inhibits tau aggregation, and dimebon, an antihistamine. The consecutive phase-III trial of dimebon failed to show positive effects in the primary and secondary endpoints. Work with methylthioninium chloride showed that bioavailability of methylthioninium from the gut was affected by feeding and by stomach acidity, leading to unexpectedly variable dosing. A new stabilised formulation, as the prodrug LMTX, is in phase-III trials (in 2014).

The herpes simplex virus HSV-1 has been found in the same areas as amyloid plaques. This suggested the possibility that AD could be treated or prevented with antiviral medication. Studies of antivirals in cell cultures have shown promising results. Preliminary research on the effects of meditation on retrieving memory and cognitive functions have been encouraging. A 2015 review suggests that mindfulness-based interventions may prevent or delay the onset of mild cognitive impairment and Alzheimer’s disease. Rare cases of possible transmission between people are being studied, e.g. to growth hormone patients.

Fungal infection of AD brain has also been described. This hypothesis was proposed by the microbiologist L. Carrasco when his group found statistical correlation between disseminated mycoses and AD. Further work revealed that fungal infection is present in different brain regions of AD patients, but not in the control individuals. A fungal infection explains the symptoms observed in AD patients. The slow progression of AD fits with the chronic nature of some systemic fungal infections, which can be asymptomatic and thus, unnoticed and untreated. The fungal
hypotheses is also compatible with some other established AD hypotheses, like the amyloid hypothesis, that can be explained as an immune system response to an infection in the CNS, as found by R. Moir and R. Tanzi in mouse and worm models of AD.

**Imaging**

Of the many medical imaging techniques available, single photon emission computed tomography (SPECT) appears to be superior in differentiating Alzheimer’s disease from other types of dementia, and this has been shown to give a greater level of accuracy compared with mental testing and medical history analysis. Advances have led to the proposal of new diagnostic criteria.

PiB PET remains investigational, but a similar PET scanning radiopharmaceutical called florbetapir, containing the longer-lasting radionuclide fluorine-18, has recently been tested as a diagnostic tool in Alzheimer’s disease, and given FDA approval for this use.

Amyloid imaging is likely to be used in conjunction with other markers rather than as an alternative. Volumetric MRI can detect changes in the size of brain regions. Measuring those regions that atrophy during the progress of Alzheimer’s disease is showing promise as a diagnostic indicator. It may prove less expensive than other imaging methods currently under study.

In 2011 An FDA panel voted unanimously to recommend approval of florbetapir, which is currently used in an investigational study. The imaging agent can help to detect Alzheimer’s brain plaques, but will require additional clinical research before it can be made available commercially.

**Early diagnosis**

Emphasis in Alzheimer’s research has been placed on diagnosing the condition before symptoms begin. A number of biochemical tests have been developed to attempt earlier detection. One such test involves the analysis of cerebrospinal fluid for beta-amyloid or tau proteins, both total tau protein and phosphorylated tau protein concentrations.
The biochemistry of Alzheimer’s disease (AD), one of the most common causes of adult dementia, is not yet very well understood. AD has been identified as a protein misfolding disease due to the accumulation of abnormally folded amyloid beta protein in the brains of Alzheimer’s patients. Amyloid beta, also written Aβ, is a short peptide that is an abnormal proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. The presenilins are components of proteolytic complex involved in APP processing and degradation.

Amyloid beta monomers are soluble and contain short regions of beta sheet and polyproline II helix secondary structures in
solution, though they are largely alpha helical in membranes; however, at sufficiently high concentration, they undergo a dramatic conformational change to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils. These fibrils deposit outside neurons in dense formations known as senile plaques or neuritic plaques, in less dense aggregates as diffuse plaques, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy or congophilic angiopathy.

AD is also considered a tauopathy due to abnormal aggregation of the tau protein, a microtubule-associated protein expressed in neurons that normally acts to stabilize microtubules in the cell cytoskeleton. Like most microtubule-associated proteins, tau is normally regulated by phosphorylation; however, in AD patients, hyperphosphorylated tau accumulates as paired helical filaments that in turn aggregate into masses inside nerve cell bodies known as neurofibrillary tangles and as dystrophic neurites associated with amyloid plaques. Although little is known about the process of filament assembly, it has recently been shown that a depletion of a prolyl isomerase protein in the parvulin family accelerates the accumulation of abnormal tau.

Neuroinflammation is also involved in the complex cascade leading to AD pathology and symptoms. Considerable pathological and clinical evidence documents immunological changes associated with AD, including increased pro-inflammatory cytokine concentrations in the blood and cerebrospinal fluid. Whether these changes may be a cause or consequence of AD remains to be fully understood, but inflammation within the brain, including increased reactivity of the resident microglia towards amyloid deposits, has been implicated in the pathogenesis and progression of AD.

Neuropathology

At a macroscopic level, AD is characterized by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus.
Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in AD brains. Plaques are dense, mostly insoluble deposits of protein and cellular material outside and around neurons. Tangles are insoluble twisted fibers that build up inside the nerve cell. Though many older people develop some plaques and tangles, the brains of AD patients have them to a much greater extent and in different brain locations.

**Biochemical characteristics**

Alzheimer’s disease has been identified as a protein misfolding disease, or proteopathy, due to the accumulation of abnormally folded Amyloid-beta proteins in the brains of AD patients.

Although AD shares pathophysiological mechanisms with prion diseases, it should be noted that AD is not transmissible like prion diseases. Amyloid-beta, also written Aβ, is a short peptide that is a proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. The presenilins are components of a proteolytic complex involved in APP processing and degradation. Although amyloid beta monomers are harmless, they undergo a dramatic conformational change at sufficiently high concentration to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils that deposit outside neurons in dense formations known as *senile plaques* or *neuritic plaques*, in less dense aggregates as *diffuse plaques*, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy or congophilic angiopathy.

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Levels of the neurotransmitter acetylcholine are reduced. Levels of the neurotransmitters serotonin, norepinephrine, and
somatostatin are also often reduced. Glutamate levels are usually elevated.

**Disease mechanism**

Although the gross histological features of AD in the brain are well characterized, three major hypotheses have been advanced regarding the primary cause. The oldest hypothesis suggests that deficiency in cholinergic signaling initiates the progression of the disease. Two alternative misfolding hypotheses instead suggest that either tau protein or amyloid beta initiates the cascade. While researchers have not identified a clear causative pathway originating from any of the three molecular hypotheses to explain the gross anatomical changes observed in advanced AD, variants of the amyloid beta hypothesis of molecular initiation have become dominant among the three possibilities.

**Cholinergic hypothesis**

The oldest hypothesis is the “cholinergic hypothesis”. It states that Alzheimer’s begins as a deficiency in the production of acetylcholine, a vital neurotransmitter. Much early therapeutic research was based on this hypothesis, including restoration of the “cholinergic nuclei”. The possibility of cell-replacement therapy was investigated on the basis of this hypothesis. All of the first-generation anti-Alzheimer’s medications are based on this hypothesis and work to preserve acetylcholine by inhibiting acetylcholinesterases (enzymes that break down acetylcholine). These medications, though sometimes beneficial, have not led to a cure. In all cases, they have served to only treat symptoms of the disease and have neither halted nor reversed it. These results and other research have led to the conclusion that acetylcholine deficiencies may not be directly causal, but are a result of widespread brain tissue damage, damage so widespread that cell-replacement therapies are likely to be impractical. More recently, cholinergic effects have been proposed as a potential causative agent for the formation of plaques and tangles leading to generalized neuroinflammation.

More recent hypotheses center on the effects of the misfolded and aggregated proteins, amyloid beta and tau. The two positions...
are lightheartedly described as “ba-ptist” and “tau-ist” viewpoints in one scientific publication. Therein, it is suggested that “Tau-ists” believe that the tau protein abnormalities initiate the disease cascade, while “ba-ptists” believe that beta amyloid deposits are the causative factor in the disease.

**Tau hypothesis**

The hypothesis that tau is the primary causative factor has long been grounded in the observation that deposition of amyloid plaques does not correlate well with neuron loss. A mechanism for neurotoxicity has been proposed based on the loss of microtubule-stabilizing tau protein that leads to the degradation of the cytoskeleton. However, consensus has not been reached on whether tau hyperphosphorylation precedes or is caused by the formation of the abnormal helical filament aggregates. Support for the tau hypothesis also derives from the existence of other diseases known as tauopathies in which the same protein is identifiably misfolded. However, a majority of researchers support the alternative hypothesis that amyloid is the primary causative agent.

**Amyloid hypothesis**

The amyloid hypothesis is initially compelling because the gene for the amyloid beta precursor APP is located on chromosome 21, and patients with trisomy 21 - better known as Down syndrome - who thus have an extra gene copy almost universally exhibit AD-like disorders by 40 years of age. The traditional formulation of the amyloid hypothesis points to the cytotoxicity of mature aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell’s calcium ion homeostasis and thus inducing apoptosis. This hypothesis is supported by the observation that higher levels of a variant of the beta amyloid protein known to form fibrils faster *in vitro* correlate with earlier onset and greater cognitive impairment in mouse models and with AD diagnosis in humans. However, mechanisms for the induced calcium influx, or proposals for alternative cytotoxic mechanisms, by mature fibrils are not obvious.

A more recent and broadly supported variation of the amyloid hypothesis identifies the cytotoxic species as an intermediate
misfolded form of amyloid beta, neither a soluble monomer nor a mature aggregated polymer but an oligomeric species, possibly toroidal or star-shaped with a central channel that may induce apoptosis by physically piercing the cell membrane. This ion channel hypothesis postulates that oligomers of soluble, non-fibrillar Aβ form membrane ion channels allowing unregulated calcium influx into neurons. A related alternative suggests that a globular oligomer localized to dendritic processes and axons in neurons is the cytotoxic species.

Relevantly, the cytotoxic-fibril hypothesis presented a clear target for drug development: inhibit the fibrillization process. Much early development work on lead compounds has focused on this inhibition; most are also reported to reduce neurotoxicity, but the toxic-oligomer theory would imply that prevention of oligomeric assembly is the more important process or that a better target lies upstream, for example in the inhibition of APP processing to amyloid beta.

**Soluble intracellular (o)Aβ42**

Two research papers published in 2009 have shown that oligomeric (o)Aβ42 (specific toxic species of Aβ), when in soluble intracellular form, acutely inhibit synaptic transmission, a pathophysiology that characterizes AD (especially in early stages), by activating casein kinase 2.

**Isoprenoid changes**

A 1994 study showed that the isoprenoid changes in Alzheimer’s disease differ from those occurring during normal aging and that this disease cannot, therefore, be regarded as a result of premature aging. During aging the human brain shows a progressive increase in levels of dolichol, a reduction in levels of ubiquinone, but relatively unchanged concentrations of cholesterol and dolichyl phosphate. In Alzheimer’s disease, the situation is reversed with decreased levels of dolichol and increased levels of ubiquinone. The concentrations of dolichyl phosphate are also increased, while cholesterol remains unchanged. The increase in the sugar carrier dolichyl phosphate may reflect an increased rate of glycosylation in the diseased brain and the increase in the
endogenous anti-oxidant ubiquinone an attempt to protect the brain from oxidative stress, for instance induced by lipid peroxidation. These findings appear to have been supported by a trial conducted at the Brain Sciences Institute at Swinburne University in Melbourne, Australia, reported in 2006, that confirmed certain neurocognitive effects of the polyprenol preparation Ropren identified previously in Russia (polyprenols are metabolised into dolichols in the body).

**Glucose consumption**

The human brain is one of the most metabolically active organs in the body and metabolizes a large amount of glucose to produce cellular energy in the form of adenosine triphosphate (ATP). Despite its high energy demands, the brain is relatively inflexible in its ability to utilize substrates for energy production and relies almost entirely on circulating glucose for its energy needs. This dependence on glucose puts the brain at risk if the supply of glucose is interrupted, or if its ability to metabolize glucose becomes defective. If the brain is not able to produce ATP, synapses cannot be maintained and cells cannot function, ultimately leading to impaired cognition.

Imaging studies have shown decreased utilization of glucose in the brains of Alzheimer’s disease patients early in the disease, before clinical signs of cognitive impairment occur. This decrease in glucose metabolism worsens as clinical symptoms develop and the disease progresses. Studies have found a 17%-24% decline in cerebral glucose metabolism in patients with Alzheimer’s disease, compared with age-matched controls. Numerous imaging studies have since confirmed this observation.

Abnormally low rates of cerebral glucose metabolism are found in a characteristic pattern in the Alzheimer’s disease brain, particularly in the posterior cingulate, parietal, temporal, and prefrontal cortices. These brain regions are believed to control multiple aspects of memory and cognition. This metabolic pattern is reproducible and has even been proposed as a diagnostic tool for Alzheimer’s disease. Moreover, diminished cerebral glucose metabolism (DCGM) correlates with plaque density and cognitive deficits in patients with more advanced disease.
Diminished cerebral glucose metabolism (DCGM) may not be solely an artifact of brain cell loss since it occurs in asymptomatic patients at risk for Alzheimer’s disease, such as patients homozygous for the epsilon 4 variant of the apolipoprotein E gene (APOE4, a genetic risk factor for Alzheimer’s disease), as well as in inherited forms of Alzheimer’s disease.

Given that DCGM occurs before other clinical and pathological changes occur, it is unlikely to be due to the gross cell loss observed in Alzheimer’s disease.

In imaging studies involving young adult APOE4 carriers, where there were no signs of cognitive impairment, diminished cerebral glucose metabolism (DCGM) was detected in the same areas of the brain as older subjects with Alzheimer’s disease. However, DCGM is not exclusive to APOE4 carriers. By the time Alzheimer’s has been diagnosed, DCGM occurs in genotypes APOE3/E4, APOE3/E3, and APOE4/E4. Thus, DCGM is a metabolic biomarker for the disease state.

**Insulin signaling**

Interestingly, a connection has been established between Alzheimer’s disease and diabetes during the past decade, as insulin resistance, which is a characteristic hallmark of diabetes, has also been observed in brains of subjects suffering from Alzheimer’s disease. Neurotoxic oligomeric amyloid-β species decrease the expression of insulin receptors on the neuronal cell surface and abolish neuronal insulin signaling. It has been suggested that neuronal gangliosides, which take part in the formation of membrane lipid microdomains, facilitate amyloid-β-induced removal of the insulin receptors from the neuronal surface. In Alzheimer’s disease, oligomeric amyloid-β species trigger TNF-α signaling. c-Jun N-terminal kinase activation by TNF-α in turn activates stress-related kinases and results in IRS-1 serine phosphorylation, which subsequently blocks downstream insulin signaling. The resulting insulin resistance contributes to cognitive impairment. Consequently, increasing neuronal insulin sensitivity and signaling may constitute a novel therapeutic approach to treat Alzheimer’s disease.
CRITERIA FOR THE PATHOLOGICAL DIAGNOSIS OF ALZHEIMER DISEASE

Of all pathological features described above, amyloid plaques and NFTs are the most characteristic of AD and, understandably, the criteria for the pathological diagnosis of AD rely on their amount and/or distribution.

The first pathological criteria for the diagnosis of AD were based on the highest density of total amyloid plaques (both diffuse and neuritic) in any cortical field, adjusted for age so that the older the patient at death, the greater the density required for diagnosis. The presence of NFTs was not required and diffuse plaques—relatively frequent in nondemented elderly people—had the same consideration as neuritic plaques. Although meritorious, these criteria were soon abandoned because, despite a very high sensitivity to diagnose AD dementia, they lacked sufficient specificity. In 1991, the Consortium to Establish a Registry for Alzheimer Disease (CERAD) proposed more specific diagnostic criteria by emphasizing the importance of neuritic plaques over diffuse plaques. CERAD criteria use a semiquantitative score of the density of neuritic plaques in the most severely affected region of the isocortex (frontal, temporal, or parietal) and the patient’s age at death to obtain an age-related plaque score. This score is then integrated with clinical information regarding the presence or absence of dementia to establish one of three levels of certainty that dementia is explained by the AD pathological changes: possible, probable, and definite. A diagnosis of AD is made if the criteria for probable or definite AD are met. Although higher than that of Khachaturian criteria, the specificity of CERAD criteria proved to be still insufficient because they did not incorporate the scoring of the severity of NFTs. By contrast, the use of Braak and Braak staging of NFTs alone—with the isocortical stages V and VI as criteria of definite AD—showed a high specificity at the expense of a low sensitivity.

Current pathological criteria for AD were defined in 1997 by a workshop of the National Institute of Aging and the Reagan Institute. The NIA-RI consensus recommendations combine the CERAD semiquantitative score of neuritic plaques and the Braak
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and Braak staging of NFTs to distinguish three probabilistic diagnostic categories: (1) high likelihood, if there are frequent neuritic plaques (CERAD definite) and abundant isocortical NFTs (Braak stage V/VI); (2) intermediate likelihood, if there are moderate neuritic plaques (CERAD probable) and NFTs are restricted to limbic regions (Braak III/IV), and (3) low likelihood, if there are infrequent neuritic plaques (CERAD possible) and NFTs are restricted to the entorhinal cortex and/or hippocampus (Braak I/II). A diagnosis of AD is made when the criteria for intermediate or high likelihood of AD are met and the patient had a clinical history of dementia (NIA-RI Consensus 1997). Because experience has revealed infrequent cases with many AD pathological lesions but no or few cognitive symptoms (and vice versa) and these circumstances were not addressed by the NIA-RI consensus workgroup, these diagnostic criteria are currently under review.

Both CERAD and NIA-RI criteria also incorporated the assessment of other pathologies, particularly vascular and Lewy body diseases, already recognizing the high prevalence of mixed pathologies underlying dementia in elderly people, a circumstance well documented by more recent longitudinal community-based clinicopathological studies (MRC CFAS 2001; Schneider et al. 2007). Thus, in many practical instances, the CERAD criteria for “possible AD” and the NIA-RI criteria for “intermediate probability of AD” are not only based on a moderate amount and distribution of AD pathology but also on the coexistence of vascular or Lewy body pathology with sufficient severity to contribute to the patient’s dementia.

NEUROPATHOLOGY OF MILD COGNITIVE IMPAIRMENT AND EARLY ALZHEIMER DISEASE

Clinicopathological correlation studies have taught us that at the moment of the clinical diagnosis, patients with AD-type dementia often already have a Braak stage V or VI of neurofibrillary degeneration and a substantial and widespread synaptic and neuronal loss. To anticipate the clinical diagnosis of AD before the stage of full-blown dementia, a new clinical construct was needed.
Petersen et al. proposed the concept of “mild cognitive impairment” (MCI) as a new diagnostic entity for the transition between normal aging and AD dementia. Patients with MCI have already some cognitive complaints that are detectable with the appropriate cognitive tests and represent a decline from a previous higher baseline level but that, unlike the definition of dementia, do not interfere with their activities of daily life. Importantly, MCI patients have an increased risk of developing dementia, which has been reported between 10% and 15% per year.

Autopsy studies on MCI patients are scarce but they have reproducibly found a stage of AD pathology intermediate between cognitively intact subjects and demented patients, particularly regarding neurofibrillary degeneration, that is consistent with the idea of a transition phase between normal aging and definite AD. Specifically, MCI patients usually have a moderate number of neuritic plaques and a limbic stage of NFTs (Braak stage III or IV), fitting into the NIA-RI category of intermediate likelihood of AD (sufficient to cause dementia) and providing a pathological validation for this clinical construct. Along the same lines, patients with a Clinical Dementia Rating score of 0.5 (equivalent to MCI or very mild AD) have already a $H^30\%$ of neuron loss in the entorhinal cortex compared to cognitively intact controls (CDR = 0), but still no evident neuronal loss in the superior temporal sulcus. Moreover, electron microscopy studies have shown that MCI patients also have an intermediate number of synapses between nondemented controls and mild AD patients in the hippocampus, further indicating that many individuals with the clinical symptoms of MCI have early AD. Of note, a paradoxical, presumably compensatory, up-regulation in the density of presynaptic glutamatergic boutons has been reported in the frontal cortex of MCI patients compared to nondemented controls and mild AD patients.

Although AD was the most common pathological diagnosis underlying MCI in the above case series, it should be noted that there was a high degree of pathological heterogeneity underlying the clinical diagnosis of MCI, with vascular disease, Lewy body disease, argyrophilic grain disease, and hippocampal sclerosis as
major concurrent or alternative pathologies. In addition, in the largest study a high proportion (up to 25%) of MCI patients had no pathology at autopsy. Finally, no significant pathological differences have been observed between the amnestic and the nonamnestic subtypes of MCI nor in their pathological outcome after conversion to dementia.

ALZHEIMER NEUROPATHOLOGY IN “NORMAL AGING”

Longitudinal prospective clinicopathological studies in nondemented elderly people have revealed that up to 45% of nondemented elderly would meet the NIA-RI criteria for AD had they been demented, usually the intermediate likelihood category of these criteria, and rarely the high likelihood category. Moreover, the pattern of regional distribution of pathological changes in nondemented controls matches that of AD patients. Thus, mounting evidence from clinicopathological studies support the view that AD is a continuous spectrum between asymptomatic lesions in cognitively normal elderly and dementia, with MCI as a transition phase between these two ends.

The apparent dissociation between AD pathology and cognitive status in some elderly people is remarkable because these so-called “high-pathology nondemented controls” or “individuals with asymptomatic AD” seem to be resilient to the neurotoxic effects of amyloid plaques and NFTs and to contradict the aforementioned positive correlation between NFT burden and cognitive decline. Understanding the biochemical and morphological substrates of this resilience to cognitive decline in the presence of abundant AD pathology might be crucial to discover new therapeutic targets for the disease. As expected from the highly significant clinicopathological correlations of synaptic and neuronal loss in AD, high-pathology controls have preserved synaptophysin levels compared to AD patients with a similar burden of plaques and NFTs, and they do not seem to have significant neuronal loss, not even in vulnerable regions such as the entorhinal cortex and the hippocampus. Moreover, they have lower levels of neuroinflammatory markers than pathology-
matched AD patients. This resistance to AD pathology has also been related to a nucleolar, nuclear, and cell body hypertrophy of the hippocampal and cortical neurons, suggestive of a compensatory metabolic activation to face the neurotoxic effects of AD lesions. In keeping with these pathological reports, a MRI-neuropathological correlation study revealed larger brain and hippocampal volumes in high-pathology controls than in pathology-matched demented patients, further supporting the preservation of both neurons and synapses.

**OVERLAP OF AD WITH LEWY BODY DISEASE**

Alzheimer disease and Parkinson’s disease (PD) are the leading causes of dementia and movement disorders in the aging population. It is estimated that over 10 million people live with these devastating neurological conditions in the United States. It is estimated that over 10 million people live with these devastating neurological conditions in the United States, and that this country alone will see a 50% annual increase of AD and PD by the year 2025.

PD and AD are two distinct clinicopathological entities. While in AD, abnormal accumulation of misfolded Aβ protein in the neocortex and limbic system is thought to be responsible for the neurodegenerative pathology, intracellular accumulation of α-synuclein has been centrally implicated in the pathogenesis of PD. In AD, Aβ protein accumulates in the intracellular and extracellular space, leading to the formation of plaques, whereas intracellular polymerization of phosphorylated cytoskeletal molecules such as tau results in the formation of neurofibrillary tangles. In PD, intracellular accumulation of α-synuclein—an abundant synaptic terminal protein—results in the formation of characteristic inclusions called Lewy bodies (LBs). The new consortium criteria for the classification of Lewy body diseases (LBD) recognizes two clinical entities, the first denominated dementia with LBs (DLB) and the second PD dementia (PDD). While in patients with DLB, the clinical presentation is of dementia followed by parkinsonism, in patients with PDD the initial signs are of parkinsonism followed by dementia. Interestingly, the brains of patients with DLB and
PDD display very similar pathology, with the exception that recent studies have shown extensive deposition of A\(\beta\) and \(\alpha\)-synuclein in the striatum and hippocampus in DLB compared to only \(\alpha\)-synuclein in PDD cases. Because of the implications for the management and treatment of parkinsonism and dementia in patients with PD and DLB, loss of dopaminergic neurons in the midbrain and cholinergic cells in the nucleus basalis of Meynert have been characterized in detail. Although the severity of the neuronal loss within these subcortical regions might explain some of the neurological deficits in patients with PD and DLB, the neuronal populations responsible for the more complex cognitive and psychiatric alterations have not been completely characterized. Abnormal accumulation of \(\alpha\)-synuclein in the CA2-3 region of the hippocampus, insula, amygdala and cingulate cortex has been shown to be an important neuropathological feature.

Remarkably, despite being initially considered distinct clinicopathological conditions, several studies have now confirmed that the clinical features and the pathology of AD and PD can overlap. Approximately 25% of all patients with AD develop parkinsonism, and about 50% of all cases of PD develop AD-type dementia after 65 years of age. Moreover, 70% of patients with sporadic AD display the formation of \(\alpha\)-synuclein-positive LB-like inclusions in the amygdala and limbic structures. Similarly, in patients with familial AD (FAD) and Down syndrome, LB-like pathology and parkinsonism have been reported. Last, as mentioned above, the single most important neuropathological finding that distinguishes PDD from DLB is the presence of A\(\beta\) deposits in the striatum and in the hippocampus.

A number of studies provide extensive support for an interaction between pathogenic pathways in AD and LBD and argue against a coincidental concurrence of both disorders (i.e., merely because of their high prevalence in the elderly). FAD cases with presenilin mutations that present with significant LB pathology strongly support an interaction between A\(\beta\) and \(\alpha\)-synuclein. Although plaques, tangles and LBs are useful neuropathological and diagnostic markers of these disorders, the initial injury that results in the cognitive and movement alterations...
is likely the damage of the synaptic terminals in selected circuitries. Several lines of investigation support the notion that oligomeric forms of Aβ and α-synuclein, rather than the polymers and fibrils associated with plaques and LBs, accumulate in the neuronal membranes and lead to the characteristic synaptic pathology. Some studies have shown that underlying interactions between α-synuclein and Aβ play a fundamental role in the pathogenesis of LBD. Specifically, Aβ promotes the oligomerization and toxic conversion of α-synuclein, Aβ exacerbates the deficits associated with α-synuclein accumulation, Aβ and α-synuclein colocalize in membrane and caveolar fractions, and Aβ stabilizes α-synuclein multimers that might form channel-like structures in the membrane. Both lysosomal leakage and oxidative stress appear to be involved in the process of neurotoxicity and pathological interactions between Aβ and α-synuclein.

Therefore, it is possible that the combined effects of α-synuclein and Aβ might lead to synaptic damage and selective degeneration of neurons in the neocortical, limbic, and subcortical regions. A more precise mapping of the neuronal populations affected in these regions is needed to understand the cellular basis for the characteristic cognitive dysfunction in PDD and DLB and to develop new treatments for these conditions.

**ORGANOPHOSPHATE INDUCED OXIDATIVE STRESS AND ALZHEIMER’S DISEASE**

Organophosphates induced free radical generation linked with enhanced oxidative stress in humans has been suggested as one of the key mechanism of their neurotoxic alterations. The amyloid β protein is found to be an important factor to enhance oxidative stress linked with increased levels of lipid peroxidation products including malondialdehyde, 4-hydroxynonenal (HNE) and acrolein. These toxic products, formed as a result of oxidative stress alter the cellular structure and physiological function of the brain and leads to neurodegenerative diseases, including Alzheimer’s disease. The involvement of lipids, inflammatory mediators in the production and accumulation of β-amyloid and enhanced oxidative stress in Alzheimer’s disease has also been
reported. We have also reviewed and suggested that the generation of reactive oxygen and nitrogen species as a result of pesticide exposure could damage the lipid membrane and alter the composition of lipid rafts leading to various brain related disorders.

On the other hand the accumulation of transition metals including iron further involve in the generation of free radicals through the process of Fenton’s reaction. Docosahexenoic (DHA), dietary essential polyunsaturated fatty acids (PUFA), another target in oxidative damage has been found to link with the cognitive decline and neuronal dysfunction in Alzheimer’s disease.

The alterations in the brain lipid profile, including phospholipids, sphingomyelin, ceramide and ganglioside could modulate the signaling cascade and neural function, leading to neurological disorders, including Alzheimer’s disease. Further altered levels of sphingomyelins and ceramides in Alzheimer’s disease brains have been reported as a result of sphingomyelin hydrolysis.

**Organophosphate Induced Neuronal Loss via Apoptosis**

Acetyl cholinesterase (AChE), an enzyme involved in the synaptic transmission is the prime target of action of organophosphates. They inhibit the activity of AChE in an irreversible manner and caused over accumulation of the levels of acetylcholine at the synaptic junction leading to desensitization of receptors and finally paralysis and cell death.

Mitochondrial dysfunction and oxidative metabolism are considered to be the key mechanism for organophosphates induced apoptosis and in the pathogenesis of Alzheimer’s disease. Mitochondria play a vital role in apoptotic pathways, as it contains decisive apoptotic factors, including cytochrome C in their intermembranous space.

Once the cytochrome C release into the cytosol, it initiates the activation of caspase-cascade mechanisms of apoptosis. The anti-apoptotic protein family, such as Bcl-2 and Bcl-xL strictly regulate the release of cytochrome C and maintain the ratio between Bcl2/Bax. The decrease in the ratio of Bcl2/Bax due to oxidative stress initiates the release of cytochrome C and activation of caspase-
cascade and leads to the apoptosis. The activation of caspases provides a crucial factor in the implementation of mitochondria mediated apoptosis.

Enhanced oxidative stress following exposure to monocrotophos in rats has been found to affect mitochondrial complex I, II and IV associated with decreased production of ATP. The over activation of apoptotic factors in central nervous system can contribute to the neuronal cell death and may cause neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases. Several studies have suggested that the toxicological response of organophosphates and its compounds may cause neuronal apoptosis linked with organophosphate induced delayed neuropathy (OPIDN).

The alteration in lipid rafts composition may also initiate the neurodegeneration and apoptosis through various pathways including aggregation of amyloid beta. Increased expression of apoptotic proteins including Bax, JNK, c-jun, ERK1/2, MAP kinases and decreased expression of anti-apoptotic proteins such as p38 MAP kinase, Bcl-2, Bcl-xL have been reported in the organophosphate induced neurotoxicity reported that exposure to chlorpyrifos may induce apoptosis in primary cortical neurons cultured from embryonic day 17 or newborn rats independently of AChE inhibition.

They further suggested that the activation of the ERK1/2 and JNK MAP kinases involve in apoptotic and activation of the p38 MAP kinase in antiapoptotic mechanism in cortical neurons following exposure to chlorpyrifos. Exposure to organophosphates enhanced the levels of intracellular calcium, which triggered the activation of calpains in nerve tissues.

This activated calpains may further activate the cyclin-dependent kinase 5 (Cdk5) and involved in the neuronal cell death. The detailed mechanism of neuronal apoptosis. Exposure to organophosphates, including monocrotophos, dichlorvos, chlorfenvinphos, chlorpyrifos, malathion, quinalphos etc. have been found to disrupt the balance of antioxidant and pro-oxidant in the brain and linked with enhanced oxidative stress. Increased lipid peroxidation in brain regions and cerebro-spinal fluid of rats
has been reported following exposure to malathion. Exposure of triazophos in rats has been found to cause increased lipid peroxidation associated with decreased mRNA and protein expression of brain derived neurotrophic factor (BDNF) and reduced glutathione in hippocampus suggesting the role of oxidative stress in the toxicity of triazophos. Further evidences also indicated that the generation of reactive nitrogen species through activated astrocytes and oxidative stress are involved in various neurodegenerative diseases, including Alzheimer’s disease, ischemia, epilepsy etc..

**Organophosphate induced Inflammation and Alzheimer’s disease**

The role of inflammation in the etiology and pathogenesis of Alzheimer’s disease has been suggested. The activation of these inflammatory cytokines occurs due to the enhanced oxidative stress, which may involve in the process of neurodegeneration in Alzheimer’s diseases. The role of microglia in Alzheimer’s disease has been suggested due to the presence of plaque associated microglia that exhibits a reactive phenotype.

The inflammatory response is primarily expressed by the activation of glial cells, macrophages and oligodendrocytes in the brain associated with the triggering of pro-inflammatory cytokines including interleukin (IL)-1β, IL-18 and IL-33 and linked with the infection, autoimmunity, neuroinflammation and associated disorders.

These activated microglias are involved in the process of apoptosis and neuronal death via the secretion of various proinflammatory molecules and cytokines (IL-1, IL-6 and TNF-α) and also facilitate the production and deposition of amyloid in the brain have demonstrated that dichlorvos exposure in rats can activate microglial cells and cause apoptosis through the upregulation of pro-inflammatory molecules like nitric oxide, TNF-α, and IL-1β.

The microglial apoptosis has also been found to be associated with the increased expression of Bax in mitochondria, cytochrome c release from mitochondria, and caspase-3 activation. The role of
inflammasomes in the pathophysiology of neuroinflammation and neurodegenerative diseases including dementia, memory and cognitive dysfunctions has been reported in the last decades. Also the role of inflammasomes in the etiologies of Alzheimer’s disease has been suggested. The roles of DNA methylation and hydroxymethylation in the development and potential treatment of AD have also been reported in their review has suggested that oxidative stress, neuroinflammation, microtubule alterations, synthesis of beta amyloid, calcium dyshomeostasis and mitochondrial dysfunction all are contributing factors in organophosphate induced neurological diseases.

**Prevention and Suggestions**

The risk of human exposure to organophosphates is enhanced several times in developing countries due to the irregularities in safety measures. Due to the high risk of neurotoxic impact of these organophosphate compounds on human health, especially on developing children, it deserves the attention of regulatory agencies and prevention authorities.

There is a need to develop the protective measures for agricultural workers and other individuals occupationally exposed to these pesticides. The industrial manufacturers should have to use proper safety measures and also aware the workers, users and general public about their harmful consequences through improper handling and uses.

There should be trainings and workshops on these pesticides, including organophosphates to awareness and educate the users in agricultural sectors and public health programs. The research should be continued in the area of developing substitute of these toxic compounds for their use in agriculture and public health. Specific biomarkers could be identified in the study of molecular mechanisms of neurotoxicity of organophosphate compounds through parallel studies in humans and animals which could help to develop a protective and effective cure.

At the same time these biomarkers may also provide strategies to identify the risk in exposed individuals. In recent years natural and pharmacological agents have been found to combat the
neurotoxic effects of organophosphate compounds. Further, to assess the neurotoxic impact of specific pesticides in human populations, there is a need to perform well designed epidemiological studies which could provide useful information to research scientist working in the area of occupational, environmental and human health. Also, animal and alternate animal model research must be going on to find out the mechanisms of neurotoxicity of these pesticides at low dose levels comparable with real world exposure. Invasive research on molecular basis may improve the understanding of mechanism of neurotoxicity from organophosphate exposure and hence will be useful to develop protective measures.
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NEUROTRANSMITTERS AND NEUROCHEMISTRY IN DLB

The neurochemical profile of the brain in DLB in comparison to AD and PD has been studied from three perspectives: i) correlation with the clinical features; ii) correlation with the severity and distribution of pathological lesions; iii) the identification of rational therapeutic targets. Drugs currently used to treat psychotic features, depression, anxiety and cognitive impairment act on specific neurotransmitter systems (dopamine, 5-HT, GABA and acetylcholine).

In degenerative conditions such as AD such therapies are considered to be symptomatic or palliative at best but evidence of neurotrophic consequences of neurotransmitter signalling, mediated at the level of alterations in gene transcription, indicate that chronic manipulation of neurotransmitter function can have either neurotoxic or neuroprotective effects. In DLB the major clinical features, particularly psychotic, can occur in the absence of cortical Alzheimer type pathology or synaptic loss and may be at least partly functional. The fluctuating course of the disease also supports this idea. Such observations raise the possibility that
Neurotransmitter targeted therapies may be of particular benefit in DLB compared with AD.

Neuronal loss occurs in specific subcortical nuclei in DLB as it does in AD and PD. The systems which have received the most neurochemical attention in DLB, because of consistently observed abnormalities and likely clinical correlates, are the cholinergic (relating to cognitive and psychotic symptoms) and the dopaminergic (relating to parkinsonism). The role of noradrenergic or 5-HT systems in depression or delusions, as has been suggested in AD, has not yet been explored in DLB, nor the significance of neuropeptide changes eg somatostatin or CRF which are evident in DLB.

**Cholinergic Systems**

Cortical cholinergic abnormalities and degeneration of basal forebrain nuclei are considered to contribute to cognitive impairments including memory loss in AD. In PD, cortical cholinergic activities and nucleus basalis neuron counts, are lower in demented compared with nondemented individuals. In DLB neocortical choline acetyltransferase (ChAT) is lower than in AD and similar to that in demented PD. Cognitive impairment can be less severe in DLB than AD, and the clinical correlate of this neocortical cholinergic deficit may not be cognitive but neuropsychiatric, specifically visual hallucinations. Cholinergic activity is lower in hallucinating compared with non-hallucinating DLB cases while 5-HT activity is relatively preserved. This observation may be linked to the tendency of antimuscarinic agents such as atropine and scopolamine to induce visual hallucinations of a type similar to those experienced by patients with DLB. Such drugs interact with muscarinic M1, M3 and M4 receptor subtypes which predominate in the cortex, thalamus and striatum.

Loss of striatal ChAT in DLB, which reflects pathology of intrinsic local circuit neurons, may account for the reduced severity of extrapyramidal clinical symptoms in some DLB patients who have equivalent loss of dopaminergic substantia nigra neurons as PD patients. Loss of ChAT activity in the thalamic reticular nuclei has also been reported in DLB. The reticular nucleus receives joint
innervation from basal forebrain and brainstem pedunculopontine cholinergic nuclei. Disturbances in its function may lead to disruption of sensory processing and affect attentional or perceptive processes, possibly contributing to visual hallucinations.

In DLB the muscarinic M1 subtype is elevated in the cortex, as it is in PD, reflecting upregulation of postsynaptic receptors in response to cholinergic denervation. Together with a normal extent of receptor coupling via G proteins this suggests that cholinceptive neurons are intact in DLB. In contrast there is no up-regulation if the M1 subtype in AD, at least in advanced cases, and receptor uncoupling is widely reported. These differences reflect the more ‘destructive’ cortical pathology, including neurofibrillary tangle formation, in AD. Other muscarinic receptor subtypes remains to be examined in DLB.

The nicotinic receptor which binds nicotine with high affinity (considered to consist primarily of a4b2 subunits) is equally reduced in the cortex in DLB compared to AD and PD. In the substantia nigra, where nicotine binding is concentrated in the pars compacta in association with the pigmented dopaminergic neurons, receptor binding is as depleted in DLB as it is in PD, despite the greater loss of neurons in PD. This suggests that loss or down-regulation of the receptor may precede neurodegeneration. Nicotinic agonists upregulate the receptor and possible protective effects of nicotine may involve reversal of age or disease-related loss of the receptor. Another nicotinic receptor subtype, comprising a7 subunits, binds a-bungarotoxin and is not affected in the cortex in DLB or AD. In the thalamus this receptor is concentrated in the reticular nucleus and is reduced in both disorders although a clinical correlate of this additional thalamic cholinergic abnormality is not established.

The therapeutic implications of the cholinergic neurochemical pathology so far identified in DLB can be summarised as follows:

i) since cortical cholinergic abnormalities exist in most cases in the absence of typical Alzheimer pathology (especially tangles), and muscarinic receptors are functionally intact, cholinergic replacement therapy (anticholinesterases, muscarinic or nicotinic agonists) is likely to be more effective than in AD;
ii) since the cortical cholinergic deficits in DLB relate more to psychiatric than cognitive symptoms, therapy may be more effective in alleviating the former.

There is already some support for the second of these propositions. In AD patients the anticholinesterase tacrine has been reported to be more effective in alleviating psychotic features such as hallucinations, delusions and than in improving cognition. In a small series of patients with PD and dementia, hallucinations have been reported to be reduced or abolished in all cases treated with tacrine. Paradoxically, given that extrapyramidal movement disorder is relieved by muscarinic antagonists, parkinsonian features were not exacerbated but actually alleviated. One explanation of this effect of tacrine may be that elevating acetylcholine in the striatum leads to nicotinic as well as muscarinic stimulation resulting in greater release of nigral dopamine. Stimulation of nicotinic receptors as a therapeutic strategy in DLB may be of particular relevance because both mental and motor symptoms should be relieved. The possibility that nicotinic stimulation may also be neuroprotective has been raised by epidemiological studies of smoking in PD and AD.

**Dopaminergic systems**

The loss of pigmented substantia nigra neurons and clinical evidence of parkinsonian symptoms in DLB indicate disruption of the dopaminergic input to the striatum. Reduced dopamine or the metabolite (homovanillic acid):dopamine ratio have been reported in autopsy tissue in DLB. While a correlation between nigral neuron loss and striatal dopamine loss has been reported, interpretation is complicated by selection of patients (e.g. via neurology or psychogeriatric clinics, with less emphasis on extrapyramidal symptoms in the latter), and by treatment with neuroleptic drugs (which block D2 receptors and also reduce dopamine metabolism).

The dopamine transporter molecule is affected in both PD and DLB. SPET imaging shows that the striatal/cerebellar ratio is significantly lower in DLB compared to AD (2.1 versus 5.5). Loss of mazindol binding, which also marks the transporter,
distinguishes DLB from AD. Compared with the striatum, there is much less dopamine in the cortex and in autopsy tissue no marked changes have been observed in those cortical areas that have been examined. Although L-dopa may induce hallucinations in PD no dopaminergic parameters distinguish between patients with and without hallucinations.

The status of dopaminergic receptors in DLB is less clear. Autopsy findings suggest no alteration in D1, D2 or D3 subtypes in un-medicated patients. The absence of any D2 up-regulation, such as occurs in the course of PD in response to diminishing dopaminergic input, is surprising and suggests that basal ganglia pathology may be distinct between the two diseases. There is also clinical evidence to support this possibility. In a retrospective survey of cases, rest tremor and response to L-dopa were significantly less prevalent and myoclonus significantly more prevalent in DLB compared to PD and DLB patients are unusually sensitive to typical neuroleptic D2 antagonists. This neuroleptic sensitivity may be related to a dysregulation in D2 receptors: receptor numbers were up-regulated in patients tolerant of the drugs but not in the drug-sensitive group. In vivo SPET imaging shows a reduced caudate:putamen ratio in DLB compared to AD and may have diagnostic value.

The limited neurochemical studies so far conducted in DLB show some features similar to PD (cortical cholinergic and striatal dopaminergic deficits), and others to similar AD (striatal cholinergic deficits). D2-receptor dysregulation and changes in cortical 5-HT and turnover levels may differ in DLB compared to both AD or PD. The Consensus Guidelines for clinical diagnosis of DLB raise the possibility that DLB patients will be distinguished by their therapeutic response to cholinergic, and dopaminergic therapies.

**Pathogenesis of DLB**

*Molecular pathology of LB*

The biogenesis of LB remains incompletely understood and has previously been reviewed. In terms of disease processes it is clear that there is a group of disorders in which the formation of LB is a characteristic and invariable component of the pathogenetic
cascade. This is clearly of no help in understanding the pathogenesis of LB since these disorders are defined by the presence of LB and not the underlying disease process. In addition there is a large group of conditions in which LB, as defined by modern immunocytochemical concepts, are sometimes associated. At present there are no animal or cell models of neuronal Lewy body formation, and the mechanisms of LB formation are not yet amenable to direct experimentation. As a consequence current concepts of Lewy body pathogenesis are predominantly based on immunocytochemical observations at light microscopic and EM levels.

**Neurofilaments**

By analogy with other conditions (e.g. hepatic Mallory body formation) the LB has come to be regarded as an intermediate filament inclusion, a view which is supported by immunoelectron microscopic studies which indicate that the core filamentous component is derived from neurofilaments. Since the formation of another intermediate filament inclusion, the Mallory body, can be studied in murine models of hepatocellular toxicity this approach is now being used to gain insight into LB formation. There is no evidence for an underlying alteration in neurofilament expression in LB formation although the mechanism of their formation may involve primary damage to neurofilaments. However, the possibility remains that the primary pathogenetic insult may be directed at other intracellular targets which are crucial to the regulation and maintenance of neurofilament assembly, transport or disassembly. In this alternative model the subsequent phosphorylation and truncation of aggregated neurofilaments occurs as a secondary process.

Candidate enzymes involved in the phosphorylation of neurofilaments incorporated into LB have been sought. Cyclin-dependent kinase 5 has been proposed as a likely candidate on the basis of immunolocalisation, in both cortical and subcortical LB, together with its regulatory subunit p35nck5a. Such studies do not overcome the problem of whether phosphorylation of neurofilaments preceeds or follows LB formation.
Ubiquitin

Much interest has focused on the role of the ubiquitin pathway in LB formation and the concept has developed of LB as a cellular protective mechanism. Cortical LB purified from DLB brains reacted predominantly to an antibody recognising polyubiquitin chains rather than free ubiquitin or monoubiquitinated forms. The possibility was raised that incomplete activation of ubiquitin-mediated proteolytic pathways may contribute to the pathogenesis of LB degeneration. The dynamic nature of LB formation in comparison to some other inclusion bodies in neurodegeneration has been suggested. Recent findings of differences in the expression of both ubiquitin and the 26S proteasome in LB compared to neurofibrillary tangles have been described which support this concept.

A large diversity of other peptide constituents have been detected in LB by immunocytochemical methods but the significance of many of these should be interpreted with caution because of their normal widespread cytosolic distribution.

Clinical Genetics of AD, DLB and PD

There are marked similarities between the clinical and pathological manifestations of DLB and both AD and PD. It is likely that genes which appear to confer risk of AD and PD will also be of relevance to DLB. Studies of the genetics of neurodegeneration have drawn attention to many such risk factors, predominantly in relation to AD. This approach therefore has major potential in illuminating the basis for the overlapping clinical and pathological features of AD, DLB and PD. The following account must necessarily be preliminary since relatively few of the recently described risk factors have been studied in DLB cohorts of adequate size. This field is likely to be an area of continuing rapid advance in the next few years as many more genetic risk factors are discovered.

Alzheimer’s disease genes and DLB

There is evidence to suggest both genetic and non-genetic influences on the development of AD, the major influence being
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genetic. Twin studies have shown that there is double the risk of developing AD in monozygotic compared to dizygotic twins, suggesting that genetic factors account for up to 80% of the variance of AD. Although similar studies have not been applied in DLB it is conceivable that there is also a strong genetic influence underlying the aetiology of DLB. Pathologically confirmed DLB in monozygotic twins, and families with more than one DLB case in a generation, have been identified (I.G. McKeith and R.H. Perry; personal communication). This contrasts with PD where concordance rates for PD and familial aggregation are lower than in AD.

The role of genes in the development of AD includes both mutations associated with early onset autosomal dominant AD and genetic polymorphisms which constitute risk factors in the ‘sporadic’ population of AD cases. Mutations in the APP gene have been shown to cause familial AD in which the pathology includes LB degeneration. LB may also complicate the AD pathology found in most elderly cases of Down’s syndrome. Such findings clearly indicate that LB degeneration can occur via genetically driven pathways leading to Alzheimer’s disease.

One of the major genetic influences on AD is the e4 allele of the Apolipoprotein E (APO E) gene located on chromosome 19. APO E e4 has been shown to reduce the age at onset of developing AD. e4 homozygotes develop AD at approximately 70 years, e4 heterozygotes at 75 years, and individuals lacking the e4 allele at 80 years. Because of the association of the e4 allele with AD, and the presence of b-amyloid in DLB, several groups have reported genotyping studies in DLB. The e4 allele frequency is elevated in a manner analogous to that found in AD. In Parkinson’s disease no association is observed with APO E e4 so that DLB is more similar to AD than PD in terms of this genetic risk factor. There are however subtle differences in the APO E allele frequencies between AD and DLB in that the latter shows a higher e2 allele frequency and a reduced incidence of the e4/4 genotype.

Differences in the APO E frequencies may account for some clinicopathological differences between DLB and AD but they are unlikely to be the sole genetic determinant accounting for these differences. Several groups have investigated the possibility that
the influence of the APOE e4 allele in AD is reflected in an increased burden of the conventional neuropathological markers of the disease, bA4 amyloidosis and neurofibrillary tangles. These investigations are largely driven by the desire of proponents of the amyloid cascade hypothesis to show data relating increased risk to increased amyloidosis. Apo E interacts with the bA4 component of senile plaques and induces the formation of monofibrils, and Apo E4 shows the highest affinity for bA4. It has been hypothesised that Apo E4 acts as the most efficient pathological chaperone and induces the formation of senile plaques by promoting the accumulation of bA4. Evidence of a dose dependent increase in bA4 deposition associated with this allele has been reported which may support this model of amyloidogenesis. The results of studies using quantitation of senile plaque density in AD cortex have been controversial and unresolved. Some groups report an e4 allele dose-related increase in senile plaque density with no effect on frequency of neurofibrillary tangles. Others report that both plaques and tangles are increased with increasing APO e4 allele dose. Yet other groups report no effect of allele dose on either plaques or tangles. Similar confusion is reported for lesion density in DLB. Some groups report no relationship between plaques or tangles and allele dose. Other groups have reported that there is a relationship between allele dose and senile plaque density in ‘common’ DLB (i.e. cases with significant Alzheimer-type pathology) but not in ‘pure’ DLB. Thus it appears that the role of Apo E4 in DLB relates to the extent of associated Alzheimer-type pathology and not the LB degeneration.

Unlike dominantly inherited forms of AD the APO E e4 allele only specifies a risk for AD. Thus interactions with other genes and environmental factors must affect the disease. Some individuals who are homozygous for e4 survive beyond the ninth decade without showing symptoms of AD, and there are numerous individuals who develop AD but do not carry the e4 allele. Estimates suggest that the APO E locus accounts for 50% of AD cases at most and there are a potential four other major loci for AD alone, including regions on chromosomes 4, 6 (40), 12 and 20.
The HLA-DR locus on chromosome 6 was recently shown to be significantly associated with the risk of developing AD in those cases lacking the APO E e4 allele. HLA-DR 3 appears to specify risk for developing AD and HLA-DR 6 appears to protect against AD. This study suggests that up to 40% of AD cases can be attributable to the HLA-DR locus. Work is currently under way to determine the influence of the HLA-DR locus in DLB.

It is suggested that the butyrylcholinesterase gene K variant (BCHE K) is also a risk factor for AD development in conjunction with APO E e4 and increases the risk of AD 18-fold compared to the APO E e4 allele alone. This locus is being studied in both DLB and in AD and some interesting preliminary findings are apparent (Singleton et al, in preparation). Approximately 10% of the DLB population appear to be homozygous at the BCHE K locus compared to only 1 or 2% in the AD group, so that this genetic risk factor seems to distinguish the two diseases. This finding may be relevant to the hypothesis that DLB cases are more likely to respond to cholinergic therapy than AD. If DLB cases have reduced cholinesterase activity due to the BCHE K variant (BCHE K has only 30% of the activity of the normal enzyme), then application of cholinesterase inhibitors would be expected to have more effect in BCHE K homozygotes than in heterozygotes or normal individuals. Screening at the BCHE locus for mutations with reduced activity could therefore be used to identify individuals who are likely to have a good response.

Other genetic associations with AD have been reported including polymorphisms in the genes for Presenilin 1, Presenilin 2, and alpha-1 anti-chymotrypsin. Other attempts to verify these findings in AD showed no associations, nor with DLB, and it is likely that these genes do not have a major effect on disease development for either AD or DLB.

There is also a body of evidence that suggests that non-genetic factors influence the development of AD. Twin studies show that there is discordance in monozygotic twins for AD, with co-twins remaining unaffected for over a decade. Prior history of major head trauma, and of cigarette smoking have been shown to modify the risk of developing AD. Prior non-steroidal anti-
inflammatory use has been shown to protect against the development of AD. This effect may be related to the finding that the risk of AD is altered by the major histocompatibility locus class II antigen HLA-DR on chromosome 6, which is commonly associated with rheumatoid arthritis. The influence of all these factors in DLB remains to be investigated.

Parkinson’s disease

The influence of genetics on the development of PD does not appear to be as strong as that found in AD. On the basis of some twin studies it was suggested that the concordance rates for PD in twins was low, but this interpretation is now thought to be overly cautious. Several studies have shown that PD cases may show familial aggregation patterns indicating a strong genetic influence on the disease. More recently the identification of several pedigrees with pathologically confirmed autosomal dominant PD suggest that genetics may be a key component of the pathogenesis of PD.

Because of the assumption that the majority of PD is sporadic most genetic studies of PD have focused on a candidate gene approach in disease association studies. Mutations in the cytochrome P450 gene CYP2D6 (debrisoquine 4-hydroxylase) and related enzymes have been extensively studied following the hypothesis that the disease may be due to an environmental toxin interacting with a specific gene. Elevated frequencies of the common CYP2D6 mutant allele, CYP2D6B, have been found among PD patients compared to controls, with an approximate doubling of risk for subjects homozygous or heterozygous for this allele. Whilst some studies have substantiated these early findings other studies have not. Studies of the CYP2D6 gene in DLB has been equally inconclusive; one report suggesting an increased frequency of the B allele findings similar to PD, and one study showing no association. Our own studies do not support a role for the CYP2D6 B locus in DLB in that similar frequencies were found in controls, DLB and Alzheimer’s populations, though an increased frequency of the B allele was seen in PD (Atkinson et al, unpublished). The results of CYP2D6 genotyping from our studies tend to place DLB with AD rather than PD in relation to the contribution of this
genetic influence. Candidate gene approach to genetic influences in PD have also centred upon the dopaminergic system. Several genetic markers have been variably associated with PD such as monoamine oxidase A monoamine oxidase B, dopamine receptors and transporters, and catechol-O-methyl transferase. It would be of interest to ascertain the status of these genes in DLB given that dopaminergic dysfunction and pathology are also a central part of the disorder. An association of the N-acetyl transferase 2 gene locus has been reported in familial PD. This gene is involved in xenobiotic metabolism and suggests a role for these enzymes in detoxifying dopamine metabolites.

A similar approach has been applied following the finding of defects in oxidative phosphorylation in PD. Several point mutations in the mitochondrial genome have been reported in PD together with evidence of heteroplasmy (variable copy numbers of mutant mitochondrial DNA) in the PD brain. Similar associations with mitochondrial mutations are also reported in AD suggesting that they are not disease specific. Mitochondrial mutations are found in DLB at similar levels to those found in AD and PD (Neil et al, in preparation) and the possibility remains that they are may be an acquired function of neurodegeneration, although they may still be capable of accelerating the disease process.

Whilst families with autosomal dominant PD are rare, the identification of such families has recently provided a possible genetic link between PD, DLB and AD. Polymeropoulos and colleagues have reported the identification of a large PD kindred showing linkage to, and the presence of a missense mutation in, the a-synuclein gene on chromosome 4. Non-amyloid component precursor NACP, now identified as a-synuclein, has been described as a major component of neuritic plaques in AD but to date no mutations or associated polymorphisms have been linked to AD. The identification of mutations in the a-synuclein gene, and the presence of the protein in LB will no doubt provide an impetus to search both for other mutations in PD and also for associations with DLB in which LB are similarly immunoreactive for a-synuclein, and in which familial disease is recognised. In the first report of PD associated with the a-synuclein gene there was a point mutation
giving rise to an ala53thr substitution. Very recently another study has reported a family with PD in whom the gene shows an ala30pro substitution. The mechanism of neurodegeneration in these PD cases associated with a-synuclein gene mutations is not clear. Studies of the function of synucleins, which are synaptic proteins, are still awaited that will provide a link between the normal role of a-synuclein, neurofilaments and LB pathology.

EPIDEMIOLOGY OF PERIODONTITIS AND SYSTEMIC DISEASE ASSOCIATION

The prevalence of a disease is defined as the proportion of cases in a specific population at a given point. The prevalence of severe, generalized periodontitis ranges from 5-15%. Estimates are higher for mild periodontitis (21.8%) in the US. Estimating periodontal disease trends is challenging and not without controversy. Borrell and colleagues have reported decreases in periodontitis prevalence from NHANES III to NHANES 1999-2000. Others estimate that the number of adults over age 25 with some form of periodontitis will increase through 2010.

Periodontal infections are the direct result of an interaction between a tooth-associated microbial biofilm and host defenses. A mature biofilm is comprised of large numbers of gram-negative anaerobes that stimulate a host response. Neutrophils and other cells are recruited resulting from a host response and produce a variety of inflammatory mediators, including cytokines and prostaglandins. The chronicity of the local lesion is important, as it is the continued generation of inflammatory mediators and subsequent interactions derived from the host response that leads to destruction of alveolar bone and connective tissue. Research efforts have focused on this chronic inflammatory process and have defined mechanisms enabling specific bacterial cell invasion and the role of pathogens in the local destruction of oral tissues. The impact of this process extends beyond the oral cavity, as is illustrated by examples of periodontopathogenic processes believed to initiate or exacerbate systemic disease.

Genco and colleagues reviewed the epidemiology and possible mechanisms involved in periodontal and cardiovascular disease...
(CVD). They reported that some investigators find a direct effect of oral bacteria such as Porphyromonas gingivalis and Streptococcus sanguis on induction of platelet activation and aggregation, which may contribute to atheroma formation and thrombosis.

In their review they describe human studies identifying oral periodontopathogens in atherosclerotic plaque, along with animal studies implicating P. gingivalis in activating the acute-phase response. It is believed that acute-phase activation promotes lipemia and formation of atheromas.

Mechanistic models for P. gingivalis-accelerated atherosclerosis, including microbial invasion, immunological sounding, pathogen trafficking and autoimmunity, have been proposed by Gibson and colleagues. Genco and colleagues also reported several case-control and cross-sectional studies evaluating coronary heart disease and poor oral health. One study evaluated NHANES III data and found that the odds of having a heart attack increased with the severity of periodontitis, while another supported the association of specific periodontal pathogens and myocardial infarction. Most longitudinal studies reporting such an association found that the level or burden of periodontal disease was important.

Investigations of linkages of preterm birth and diabetes to periodontal disease have increased because of the enormous economical and social burden caused by these health problems. Offenbacher and colleagues report that mothers with significant periodontal disease had a 7.5 fold increase in the risk of having a preterm, low birth weight baby. A recent study by Pitiphat and colleagues report 65% higher levels of C-reactive protein (CRP) among pregnant women with periodontitis compared with periodontally healthy women. Clinical intervention trials are being conducted to investigate if non-surgical periodontal intervention therapy reduces the incidence of preterm birth and low birth weight babies. In addition, there appears to be a bi-directional relationship between periodontal disease and diabetes, with improved metabolic control seen in poorly controlled diabetics following periodontal therapy.
P. gingivalis has also been linked pathogenetically to rheumatoid arthritis (RA) through the enzyme peptidylarginine deiminase (PAD). Rosenstein and colleagues hypothesize that individuals predisposed to periodontal disease exhibit autoimmune responses, such as production of rheumatoid factor.

PAD enzyme breaks down fibrin in the periodontal pocket and parallels intra-articular breakdown of fibrin and other proteins. The authors note that several RA treatments, such as treatment with nonsteroidal anti-inflammatory drugs, ameliorate periodontal disease.

Golub and colleagues propose a “two-hit” model of chronic destructive periodontitis. They cite several animal and human studies supporting their model that a subgingival biofilm (the first hit) is followed by a disease (the second hit, such as rheumatoid arthritis), which in turn increases levels of circulating inflammatory biomarkers. The second hit also results in increased alveolar bone loss. Therefore, defining mechanisms mediating systemic induction of periodontal disease may provide improved treatment strategies for chronic local and systemic diseases.

When evaluating epidemiological studies of periodontal disease it is important to consider differences in the definition of case severity, populations sampled, sites selected and sampling procedures used in a particular study. Dietrich and Garcia note that randomized control trials are needed to assess periodontal treatment efficacy in reducing CVD and stroke, but that such an approach may not be sufficient to determine the etiology of periodontal disease in these conditions. Therefore they stress the need for further well-designed observational studies to facilitate understanding of disease relationships.

**Plausible Links Between Periodontal Disease and AD**

It is clear that periodontal disease is associated with numerous systemic diseases, although it is too soon to tell if we can add AD to the list. Investigators are currently asking whether poor oral health promotes development of AD and dementia. Thus we outline below plausible biological mechanisms linking periodontitis and AD.
Metastatic Spread of Gram-negative Bacteria from the Oral Cavity to the Brain via Transient Bacteremia or Neuronal Pathways

For years it has been known that oral bacteria can disseminate to distant sites within the body. Elderly and immunocompromised patients, such as those suffering from cancer, diabetes, or rheumatoid arthritis, may be especially vulnerable to systemic oral pathogens. Any dental procedure that causes bleeding can produce transient bacteremia. It is well documented that certain dental procedures, such as extractions, periodontal surgery, periodontal scaling and root planing, induce hematogenous seeding. The American Heart Association provides guidelines to prevent infections of the joints, cardiac valves, and endocardium caused by oral bacteria. Could oral pathogens also infect the brain with subsequent neuropathological consequences? Additionally, could the bacteremia responsible for this neuropathy be the result of chronic periodontal disease?

In individuals with good oral hygiene the number of oral pathogenic bacteria reaching the systemic circulation is small. However, this number increases twofold to tenfold in persons with periodontal disease. High levels of pathogenic bacteria, coupled with the edematous state of the infected periodontal pocket, leads to ongoing, chronic dissemination of periodontal bacteria into the bloodstream. One study demonstrated positive cultures of oral bacteria in arterial blood in 55% of patients with severe periodontal disease.

As early as 1891, it was suggested that oral bacteria could "lodge in some weak point in the brain" and result in brain infection and abscess. Indeed, there are numerous reports of brain infection testing positive for oral bacteria, with most cases specifically linked to periodontal pathogens. Brain infection by one such bacteria, Actinobacillus actinomycetemcomitans, is associated with coagulative necrosis of cortical cells and white matter.

The flora of periodontal disease consists largely of gram-negative bacteria. Current research has identified brain receptors specific for gram-negative bacteria. Brain infections by gram-negative bacteria have been linked to Alzheimer's etiology,
specifically late-onset sporadic AD. A recent histologic study demonstrated the presence of gram-negative Chlamydia pneumonia in cells of affected brain regions in 17 of 19 post mortem Alzheimer’s brains, while brains of controls were not infected. In another post mortem study, oral Treponema was found in the cortex of 14 of 16 Alzheimer’s brains compared with only 4 of 18 control brains. Treponema was detected in cells of the trigeminal ganglion, suggesting that bacteria may reach the brain through branches of the trigeminal nerve.

Overall these studies indicate that it is biologically feasible for pathogenic oral bacteria to disseminate through the bloodstream, reach the brain and either initiate or exacerbate existing lesions.

**Injury to Brain Tissue from Systemic Inflammatory Mediators Produced in Response to Periodontal Pathogens**

It is also possible that pathogenic periodontal bacteria do not “infect” the brain but rather induce a systemic inflammatory response leading to injury of brain tissue. Since host responses to periodontal disease, such as upregulation of proinflammatory mediators, show significant positive correlation with coronary artery disease and premature birth, neuropathological responses may also be induced.

Inflammation is a recurrent theme among investigations of oral and systemic diseases. The cascade of inflammatory events associated with periodontal disease begins with endotoxin, a high molecular weight lipopolysaccharide found in the cell wall of gram-negative periodontal bacteria. Endotoxin initiates inflammation locally in the periodontal pocket by stimulating inflammatory cells such as monocytes, macrophages, fibroblasts and T cells to produce cytokines and prostaglandins (PGE2). Cytokines transmit information from cell to cell at very low levels, in the nanomolar to picomolar range. Some of the most important inflammatory cytokines associated with periodontal disease are interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tissue necrotizing factor-alpha (TNF-α). IL-1 and TNF-α signal hepatic cells to produce several Type 1 acute phase proteins, among them CRP.
Studies have shown increased levels of proinflammatory cytokines in inflamed gingival tissues compared with healthy tissue and in the gingival crevicular fluid in patients with active periodontal disease. Elevated levels of acute phase proteins, including CRP, have also been demonstrated in the gingival crevicular fluid. It is suggested that inflammatory mediators produced locally may “spill over” into the systemic circulation, producing increased serum levels of cytokines and acute phase reactants. In addition, daily bacteremias, or chronic “trickling” of pathogenic periodontal bacteria into the circulation, could initiate a systemic cascade of inflammatory events resulting in a sustained elevation of inflammatory products.

Indeed investigators have found markers of systemic inflammation when analyzing the serum of individuals with periodontal infections. A study by Ebersole and colleagues showed that levels of endotoxin detectable in the blood increase with the level of oral disease. Periodontal pathogens have been shown to elicit a circulating antibody response. Abnormally elevated serum levels of PGE2 and CRP have been found in people with periodontitis. In one study of an elderly population, Bretz and colleagues found significantly higher levels of IL-6 in the blood of those with extensive periodontal disease compared with controls. This finding is noteworthy because IL-6 is associated with local production of amyloid proteins, and in the Alzheimer’s brain it may regulate production of amyloid proteins found in neuritic plaques.

Cytokines have been implicated in the pathophysiology of several psychiatric disorders, including AD, because of their ability to stimulate neurochemical, neuroendocrine, and neuroimmune changes in the brain. As noted, inflammatory mediators can damage synapses and neurons and activate microglia and the inflammatory cascade. IL-1 is particularly relevant to the pathogenesis of AD since it is overexpressed in neuritic plaques. In addition, IL-1 increases synthesis of beta-amyloid precursor protein and activates astrocytes.

Given the evidence for the role of chronic inflammation in AD, it is reasonable to suggest that long-term systemic exposure to
periodontal pathogens and their subsequent chronic production of inflammatory mediators may precipitate neuropathological changes.

NEUROLOGICAL MANIFESTATIONS OF VASCULAR DEMENTIA

Vascular dementia is a heterogeneous entity with a large clinicopathological spectrum that has been classically linked to cortical and subcortical ischemic changes resulting from systemic, cardiac, or local large- or small-vessel disease occlusion.

Symptoms of vascular dementia include the following:
• Memory impairment
• Impairment in at least 1 other cognitive domain (eg, orientation, language, praxis, executive functions, visuospatial abilities)
• Worsening of cognitive abnormalities
• Impact on activities of daily living

In a clinical setting, differences between the cognitive disturbances in vascular dementia and Alzheimer disease are of limited value in distinguishing the 2 conditions. Patients with dementia and vascular disease frequently have mixed pathology (ie, both Alzheimer disease and vascular dementia; “mixed dementia”).

Vascular dementia may have less significant memory dysfunction than Alzheimer disease. It is also thought that frontal dysfunction due to widespread involvement of subcortical structures in vascular dementia may lead to a dysexecutive syndrome with abulia and apathy. In contrast, a cognitively impaired patient with vascular risks factors but no history of cerebrovascular disease is most likely to have Alzheimer disease. One study highlighted the interaction of environmental and genetic factors contributing to the predisposition to vascular dementia.

Diagnosis

The diagnosis of vascular dementia is usually made on the basis of clinical, neuroimaging, or neuropathologic evidence of cerebral ischemia in the presence of progressive cognitive decline.
Examination for vascular dementia includes the following:

- Evaluation of the temporal arteries: Decreased pulsatility, local tenderness, and thickening associated with giant cell arteritis may be noted
- Funduscopic evaluation: End-organ effects of hypertension and diabetes mellitus may provide important information
- Cardiac auscultation: Cardiac rhythmic and valvular abnormalities may be detected
- Neurologic assessment: Spasticity, hemiparesis, visual field defects, pseudobulbar palsy, and extrapyramidal signs confirm focal pathology
- Cognitive assessment with a standardized tool (eg, Mini Mental Status Examination, Short Blessed questionnaire): Low scores may provide corroborative evidence of a cognitive disturbance

**Testing**

All patients with dementia should have laboratory testing to rule out reversible causes of dementia. The following studies may be useful for identifying or excluding other disorders:

- Complete blood count (CBC)
- Electrolyte levels
- Thyroid-stimulating hormone (TSH) levels
- Folate and vitamin B-12 levels

The American Academy of Neurology no longer recommends syphilis screening in the routine evaluation of dementia if patients come from geographic regions with a very low base rate of syphilis. In specific cases, screening for syphilis is indicated. If the clinician has reason to suspect an angiitis affecting cerebral vessels, then an erythrocyte sedimentation rate (ESR) and specific panels may be ordered.

**Imaging studies**

In patients with newly diagnosed dementia, obtain neuroimaging studies (ie, CT scanning or MRI of the head) to rule out treatable causes of dementia and to aid in the differential diagnosis. The following findings may be observed:
Vascular dementia: Multiple cortical, and more commonly subcortical, infarcts or single strokes affecting the thalamus, angular gyrus, and the territory supplied by the anterior cerebral arteries.

Dementia: Decreased white-matter density on CT scanning or decreased T1 or increased T2 signal intensities on MRI; multiple pathologies, including small vessel disease and decreased integrity of the blood-brain barrier, have been associated with these findings.

Management

Nonpharmacologic strategies may help with behavior problems in patients with vascular dementia. No approved pharmacologic treatment exists for vascular dementia, so pharmacologic therapy is directed toward risk factors or symptoms. Treat patients with risk factors for cerebrovascular disease. The individual approach combines a vascular risk factor modification and various therapies addressing the specific subtypes of stroke (eg, antiplatelet drugs to prevent cerebral infarction in large and small artery diseases of the brain, carotid endarterectomy or stenting for tight carotid artery stenosis, and oral anticoagulants to prevent cardiac emboli).

Administer antiplatelet agents when indicated, depending on the nature of the patient’s underlying vascular pathology. Management of vascular disease and dementia in a young patient with suspected uncommon causes of stroke (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL] or angiitis) involves ruling out these conditions with the appropriate testing procedures (ie, skin biopsy, cerebral angiography). The decision to use anticoagulation therapy in these patients may be challenging due to the increased risk of falls and potential noncompliance in this group.

Manage behavioral and psychiatric disturbances such as depression and psychosis with serotonin reuptake inhibitors. In patients with agitation, environmental modification and/or pharmacologic intervention with sedation can be useful. There is limited evidence that cholinesterase inhibitors (eg, donepezil,
rivastigmine, galantamine) may have a role in the treatment of vascular dementia. These agents have proven symptomatic efficacy in Alzheimer disease, and their use in vascular dementia may have some justification given the prevalence of dementia with mixed pathology.

Although lipid-lowering agents given in late life have not demonstrated a reduction in the risk of cognitive decline and dementia, women who are treatment-resistant for high levels of low-density lipoprotein (LDL) cholesterol may be at increased risk of decline in visual memory.

NEUROPATHOLOGIC EVALUATION

A standard protocol was used for brain removal, sectioning and preserving of tissue, and quantifying AD pathology and cerebral infarctions, as described in detail elsewhere. To briefly describe here, brains were removed in a standard fashion and cut coronally into 1-cm slabs that were visually inspected and photographed. After slabs were fixed in 4% paraformaldehyde for 3–21 days, they were dissected into blocks that were embedded in paraffin and cut into 6-µm sections. Bielschowsky silver stain was used to visualize neuritic plaques, diffuse plaques, and neurofibrillary tangles in five brain regions: midfrontal gyrus, superior temporal gyrus, inferior parietal gyrus, entorhinal cortex, and the CA1 sector of the hippocampus. A measure we labeled “global AD pathology” was based on counts of neuritic plaques, diffuse plaques, and neurofibrillary tangles identified by a modified Bielschowsky silver stain in 5 brain regions, with standard scores averaged across pathology types and regions. Composite summary measures of the percent area occupied by amyloid- and the density of neurofibrillary tangles were developed by averaging the values for each lesion for all regions assessed.

Neuropathologic diagnoses were established by a board-certified neuropathologist blinded to age and all clinical data. NIA-Reagan, Braak, and CERAD classifications were scored. Infarctions were documented along with their age, volume (in mm3), side, and location. Lewy bodies were identified with antibodies to α-synuclein, as described elsewhere.
Assessment of Covariates

Demographic Variables

These included age at death, gender, years of education, and race. Early life Socioeconomic status was based on four indicators - parental education (mean years of schooling completed by the participant’s mother and father), paternal occupation (the father’s principal occupation coded according to perceived prestige), total number of children in the family, and community-level socioeconomic status. These indicators were converted to z scores and averaged to yield a composite index, with higher z-scores indicating higher socioeconomic status.

Medical comorbidities

Participants in the ROS and MAP studies undergo a comprehensive medical history interview at baseline evaluation, which includes numerous self-report questions pertaining to various diseases. Medical conditions such as head trauma, hypertension, heart condition, hypothyroidism, and cancer were rated as absent or present (0 or 1) as determined by self-report; stroke was diagnosed based on self-report plus clinical examination, as previously described. Participants were asked to bring all prescription and over-the-counter medications to the visit; these medications were inspected, identified, and coded using the Medi-Span ® system (Medi-Span, Inc., Indianapolis, IN).

Reading level

This was assessed at baseline using a modified form of the National Adult Reading Test. Participants were asked to read aloud a series of words with atypical spelling-sound correspondences (e.g., epitome, impugn).

Past Cognitive activity

We used previously established composite measure of past cognitive activity. At baseline, persons were asked about time typically spent in 7 common activities that involve information processing as a central component: viewing television; listening to radio; reading newspapers; reading magazines; reading books;
playing games such as cards, checkers, crosswords, or other puzzles; and going to museums. Frequency of participation in each activity was rated on a 5-point scale: every day or about every day (5 points); several times a week (4 points); several times a month (3 points); several times a year (2 points); and once a year or less (1 point). The questionnaire included 30 items, with 11 items about childhood (3 items for age 6 and 8 items for age 12), 10 items about young adulthood (age 18), and 9 items about middle age (age 40). Responses to each item were averaged to yield the composite measure.

**APOE genotyping**

Blood was collected with acid citrate dextrose anticoagulant and stored at room temperature. Lymphocyte separation was performed within 24 hours of collection. DNA was extracted from approximately 2-3 million cells, and genotyping was performed by an investigator blinded to all clinical and postmortem data as previously described.

**Statistical Analyses**

Descriptive statistics were used to show the demographic characteristics of participants. As described in greater detail below, studentized residuals were generated from a linear regression model of global cognition variable on global pathology. This residual served as an outcome variable. Analyses involved two steps. We first conducted four separate multiple linear regression, in which the residual was separately regressed against each of the four predictor variables of interest (early life socioeconomic status, reading level, presence of APOEe4 alleles, and post cognitive, with additional terms to control for age, gender, race and years of education. To determine the relative contribution of each predictor variable, we then performed stepwise regression with the 4 demographic variables forced in first, and then entering the variables using a selection criterion of $p < 0.05$. Statistical significance was determined by an alpha level of $p < 0.01$. All statistical tests were two-sided. Statistical analyses were performed using SAS (SAS Institute, Cary, NC).
Differential Diagnosis of Dementia

DIFFERENTIAL DIAGNOSIS

Alzheimer’s disease accounts for between 50 and 70 percent of all cases of dementia. Many researchers believe Alzheimer’s is caused by the accumulation of protein plaques in the brain. The plaques interfere with communication between brain cells and cause the cells to die, leading to memory loss, changes in judgment and other behavioral changes characteristic of Alzheimer’s.

Physical changes in the brain can cause other forms of dementia as well. Diagnosis may be complicated by coexisting conditions or when symptoms and pathologies of various dementias overlap.

Making an accurate diagnosis helps patients receive the treatment and support services appropriate for their condition and maintain the highest possible quality of life.

Mixed Dementia

Key features
- The term “mixed dementia” is most commonly applied when hallmark pathologies of Alzheimer’s disease and vascular dementia coexist but can also describe Alzheimer’s and coexisting pathology of other forms of dementia.
- These pathologies may interact in important ways to increase likelihood of clinically significant cognitive decline.
Recent studies suggest that the prevalence of mixed dementia is greater than previously appreciated. Mixed dementia prevalence may also become more common with increasing age.

**Treatment**
- As with vascular dementia, lifelong attention to cardiovascular risk factors and overall health of the heart and blood vessels could play a key role in preventing mixed dementia. These measures might also help delay or prevent progression of symptoms in older adults.
- Since most of the drugs approved to treat Alzheimer’s disease have shown a similar benefit in treating vascular dementia, there is reason to believe they may also be of help in mixed dementia. Two of the drugs – galantamine (Razadyne) and rivastigmine (Exelon) – have been shown to offer modest benefit in mixed dementia.
- No drugs are currently approved by the FDA to treat mixed dementia.

**Pathological substrate**
A combination of Alzheimer’s neuropathologies – including amyloid plaques and neurofibrillary tangles – and neuropathologies of another form of dementia are likely present.

**DIFFERENTIAL DIAGNOSIS OF VASCULAR DEMENTIA**

**Key features**
- Historically considered the second most common cause of dementia, accounting for about 20 to 30 percent of cases.
- Traditionally, uniform diagnostic criteria for vascular dementia have been lacking. The clearest clinical picture may be impairment in one or more cognitive domains within a few months after a stroke, sometimes termed post-stroke dementia.
  - Specific cognitive domains affected depend on stroke location.
Deficits in attention and executive function are common.

Memory loss may or may not be prominent, depending on whether the stroke affected memory areas.

Specific cognitive domains affected depend on stroke location.

Decline may appear relatively suddenly and may or may not progress. Progression may be stepwise, occurring in discreet, sudden changes rather than gradually.

Daily activities may be impaired.

Focal neurological signs consistent with stroke may be present.

The patient may have a history of high blood pressure, elevated lipids, vascular disease, diabetes or past heart attacks or strokes.

Vascular damage in the mid-brain regions may cause a gradual, progressive cognitive impairment that looks much like Alzheimer’s disease.

“Pure” vascular dementia may be relatively unusual; vascular changes may more commonly coexist with Alzheimer’s plaques or other neuropathologies.

The Hachinski Ischemic Scale is a tool widely used to identify a likely vascular component once a dementia diagnosis has been established. A shortened 7-item version of the HIS has been validated. A score of 2 suggests vascular involvement.

Treatment

Because vascular dementia is closely tied to diseases of the heart and blood vessels, many experts consider it the most potentially treatable form. Monitoring of blood pressure, weight, blood sugar and cholesterol should begin early in life. Active management of these risk factors, avoidance of smoking and excess alcohol and treatment of underlying heart and blood vessel diseases could play major roles in preventing later cognitive decline for many individuals.
For certain older adults who develop vascular dementia, active management of these factors could help avoid symptom progression.

- Once vascular dementia develops, no drugs are approved by the FDA to treat it.
- Most of the drugs used to treat cognitive symptoms of Alzheimer’s disease have also been shown to help individuals with vascular dementia to about the same modest extent they help those with Alzheimer’s. However, one clinical trial of donepezil (Aricept) for vascular dementia reported that a significantly greater number of deaths occurred in study participants receiving donepezil than in those taking a placebo.

**Pathology**

Vascular dementia occurs when impaired blood flow to parts of the brain deprives cells of food and oxygen. This impairment typically follows stroke-induced blockage of one or more blood vessels. Vascular damage often coexists with amyloid plaques and other neuropathologies associated with Alzheimer’s disease.

**DEMENTIA, PSEUDODEMENTIA AND DELIRIUM: DIFFERENTIAL DIAGNOSIS**

Delirium—The physician must distinguish between delirium and dementia. Delirium is a transient, acute mental disturbance that manifests as disorganized thinking and a decreased ability to pay attention to the external world.

Delirium is often caused by infectious disease, brain tumor, poisoning, drug or alcohol intoxication or withdrawal, seizures, head trauma, and metabolic disorders. It is important to treat underlying conditions promptly, as they may be life-threatening or progressive if left untreated.

Symptoms of delirium include the following:

- Disorientation as to person, place, and time
- Memory impairment
- Rambling, irrelevant, incoherent speech
• Reduced level of consciousness

Pseudodementia—Many elderly people fear that their memory and other mental abilities are diminishing as they grow older, even if this is not the case. Some may be anxious, depressed, or suffering from pseudodementia, a type of severe depression that occurs mostly in elderly people.

The cognitive changes that resemble dementia include slow motor movements and thinking and short-term memory loss. Patients who are depressed may be apathetic and answer questions without attempting to provide the correct response. They may exhibit poor eye contact and little spontaneous movement.

Laboratory Tests

Depending on the patient's medical history and neurological examination, one or more diagnostic tests may be performed to identify the underlying cause of dementia.

Neuropsychological tests are administered to assess difficulties in attention span, perception, memory, problem solving, and social and language skills. Responses to these tests may provide diagnostic clues.

For example, a patient with Alzheimer’s disease is usually cooperative, attentive, and gives appropriate responses, but will display memory loss. A patient with hydrocephalus is usually distracted and less cooperative.

Blood tests may be ordered if the history and physical examination indicates an infectious, metabolic, or toxic condition. The results help the physician rule out Alzheimer’s and help determine an effective treatment plan.

• B12, folate, thiamine levels (vitamin deficiency)
• Blood glucose (hypoglycemia)
• Complete blood count (anemia)
• Drug screen (drug toxicity)
• Electrolytes (hypercalcemia, hypermagnesemia, hypernatremia)
• Liver function (liver disease)
• Lumbar puncture (normal-pressure hydrocephalus, encephalitis, meningitis)
Differential Diagnosis of Dementia

- Thyroid function (hypothyroidism)
- VDRLT (syphilis and HIV infection)

Huntington’s disease is diagnosed by analyzing DNA in the blood sample and counting the number of times the genetic code for the mutated HD gene is repeated. Individuals diagnosed with HD usually have 40 or more such “repeats”; those without it, 28 or fewer. Similarly, an analysis of DNA in the blood sample may reveal the ApoE4 gene, which is found in about one-third of Alzheimer’s disease patients.

Electroencephalography (EEG) traces brain wave activity. Some central nervous system disorders cause distinct changes in brain wave activity. Alzheimer’s disease generally reveals “slow” waves. An EEG can help distinguish a severely depressed or delirious patient whose brain waves are normal from a patient with a degenerative neurological disease.

Imaging tests (CT scan, MRI scan, PET scan) can detect structural, or physical, changes in the brain caused by stroke, blood clots, tumors, head injury, or hydrocephalus. A CT scan can show the characteristic structural changes that occur with Huntington’s disease.

TREATABLE DEMENTIAS

- Reactions to medications. Some medications have side effects that mimic the symptoms of dementia. Even a single dose of a medicine may trigger such a reaction in an older person or in someone whose liver fails to eliminate the drug normally. Interactions among two or more drugs may lead to reversible symptoms of dementia as well.
- Metabolic abnormalities. Decreased thyroid function (hypothyroidism) can result in apathy or depression that mimics dementia. Hypoglycemia, a condition in which there isn’t enough sugar in the bloodstream, can cause confusion or personality changes. Pernicious anemia caused by an inability to absorb vitamin B-12 also can cause cognitive changes. Similarly, changes in blood sodium, calcium, heavy metals, or other compounds can cause a reversible dementia.
• Nutritional deficiencies. Chronic alcoholism can be associated with deficiencies of thiamin (vitamin B-1), which can seriously impair mental abilities. Severe deficiency of niacin (vitamin B-3) may cause pellagra, a neurological illness with features of dementia. Dehydration also can cause confusion that may resemble dementia.

• Emotional problems. The confusion, apathy and forgetfulness associated with depression are sometimes mistaken for dementia, particularly in older individuals. Similarly, bipolar disease, schizophrenia, and obsessive-compulsive disorder can be misdiagnosed as FTD.

• Infections. Meningitis and encephalitis, which are infections of the brain or the membrane that covers it, can cause confusion, memory loss or sudden dementia. Untreated syphilis or Lyme disease can damage the brain and cause dementia.

• Normal-pressure hydrocephalus. If cerebrospinal fluid builds up in the ventricles of the brain, the brain tissue is compressed even though the fluid pressure remains normal. This may cause dementia. If this condition is identified in time, it may be treated by draining the excess fluid via a tube (shunt).

Alzheimer’s disease

There can be significant overlap between Alzheimer’s disease and frontotemporal dementia. In Alzheimer’s disease disinhibition, overeating, loss of sympathy for others, and apathy are not usually prominent presenting features. More typical of Alzheimer’s disease than FTD are the following:

• sparing of socially appropriate behavior,
• severe memory problems,
• difficulty with visuospatial tasks like navigation and
• a relatively normal neurological examination.

In FTD on neuropsychological testing, look for low performance on letter and category fluency tests, but better performance on the verbal memory subscales, block design test and drawing tests. Use imaging to confirm orbitobasal (ventromedial) frontoinsular and/
or anterior temporal atrophy versus parietal atrophy or more generalized atrophy.

**Psychiatric problems**

Many FTD patients show symptoms of obsessive-compulsive disorder and in particular, repetitive compulsive behaviors are a core feature of FTD. Delusions and are euphoria are also common with FTD, sometimes leading to the misdiagnosis of either schizophrenia or bipolar illness. Depression is not common in FTD, but apathy and emotional withdrawal are and this can lead to the misdiagnosis of depression. Even though FTD patients often appear to be depressed, when you ask them about their mood, they often offer that they feel happy.
Basic Clinical and Diagnostic Characteristics of Senile Dementia

THE STAGES OF DEMENTIA

Dementia refers to a category of diseases that cause loss of memory and deterioration in other mental functions. Dementia occurs due to physical changes in the brain and is a progressive disease, meaning it gets worse over time. For some people, dementia progresses rapidly, while it takes years to reach an advanced stage for others. The progression of dementia depends greatly on the underlying cause of the dementia. While people will experience the stages of dementia differently, most people with dementia share some of the symptoms.

Types of dementia

The symptoms and progression of the disease depend on the type of dementia a person has. Some of the most commonly diagnosed forms of dementia are:

*Alzheimer’s disease*

Alzheimer’s disease is the most common form of dementia. It accounts for 60 to 80 percent of cases. It’s usually a slowly progressing disease. The average person lives four to eight years after receiving the diagnosis. Some people may live as many as
20 years after their diagnosis. Alzheimer's occurs due to physical changes in the brain, including a buildup of certain proteins and nerve damage.

**Dementia with Lewy bodies**

Dementia with Lewy bodies is a form of dementia that occurs due to clumps of a protein in the cortex. In addition to memory loss and confusion, dementia with Lewy bodies can also cause:

- sleep disturbances
- hallucination
- imbalance
- other movement difficulties.

**Vascular dementia**

Vascular dementia, also known as post-stroke or multi-infarct dementia, accounts for about 10 percent of all cases of dementia. It's caused by blocked blood vessels. These occur in strokes and other brain injuries.

**Parkinson’s disease**

Parkinson’s disease is a neurodegenerative condition that can produce dementia similar to Alzheimer’s in its later stages.

The disease more commonly leads to problems with movement and motor control, but it also can cause dementia in some people.

**Frontotemporal dementia**

Frontotemporal dementia refers to a group of dementias that often cause changes in personality and behavior. It can also cause language difficulty. Frontotemporal dementia can occur due to a range of conditions, including Pick’s disease and progressive supranuclear palsy.

**Mixed dementia**

Mixed dementia is dementia in which multiple types of dementia-causing brain abnormalities are present. This is most commonly Alzheimer’s and vascular dementia, but it can include other forms of dementia as well.
How is dementia diagnosed?

No single test can determine whether you have dementia. Diagnosis is based on a range of medical tests and your medical history. If you exhibit symptoms of dementia your doctor will perform:

- a physical exam
- a neurological exam
- a mental status tests
- other laboratory tests to rule out other causes of your symptoms

Not all confusion and memory loss indicate dementia, so it’s important to rule out other conditions, such as drug interactions and thyroid problems. Some common tests used to diagnose dementia include:

**Mini-mental state examination (MMSE)**

The MMSE is a questionnaire for measuring cognitive impairment. The MMSE uses a 30-point scale and includes questions that test memory, language use and comprehension, and motor skills, among other things. A score of 24 or higher indicates normal cognitive function. While scores 23 and below indicate that you have some degree of cognitive impairment.

**Mini-Cog test**

This is a short test for helping your doctor diagnose dementia. It involves these three steps:

1. They’ll name three words and ask you to repeat them back.
2. They’ll ask you to draw a clock.
3. They’ll ask you to repeat back the words from the first step.

**Clinical dementia rating (CDR)**

If your doctor diagnoses you with dementia, they’ll also likely assign a CDR score. This score is based on your performance in these and other tests, as well as your medical history. The scores are as follows:

- A score of 0 is normal.
Basic Clinical and Diagnostic Characteristics of Senile Dementia  

- A score of 0.5 is very mild dementia.
- A score of 1 is mild dementia.
- A score of 2 is moderate dementia.
- A score of 3 is severe dementia.

What are the stages of dementia?

Dementia progresses differently in everyone. Many people will experience the symptoms associated with the following stages of Alzheimer’s disease:

**Mild cognitive impairment (MCI)**

MCI is a condition that can affect older people. Some of these people will go on to develop Alzheimer’s disease. MCI is characterized by losing things often, forgetfulness, and having trouble coming up with words.

**Mild dementia**

People may still be able to function independently in mild dementia. However, they’ll experience memory lapses that affect daily life, such as forgetting words or where things are. Common symptoms of mild dementia include:

- memory loss of recent events
- personality changes, such as becoming more subdued or withdrawn
- getting lost or misplacing objects
- difficulty with problem-solving and complex tasks, such as managing finances
- trouble organizing or expressing thoughts

**Moderate dementia**

People experiencing moderate dementia will likely need more assistance in their daily lives. It becomes harder to perform regular daily activities and self-care as dementia progresses. Common symptoms during this stage include:

- increasing confusion or poor judgment
- greater memory loss, including a loss of events in the more distant past
• needing assistance with tasks, such as getting dressed, bathing, and grooming
• significant personality and behavior changes, often caused by agitation and unfounded suspicion
• changes in sleep patterns, such as sleeping during the day and feeling restless at night

Severe dementia

People will experience further mental decline as well as worsening physical capabilities once the disease progresses to the point of severe dementia. Severe dementia often can cause:
• a loss of the ability to communicate
• a need for full-time daily assistance with tasks, such as eating and dressing
• a loss of physical capabilities, such as walking, sitting, and holding one’s head up and, eventually, the ability to swallow, to control the bladder, and bowel function
• an increased susceptibility to infections, such as pneumonia

What is the outlook for people with dementia?

People with dementia will progress through these stages at different speeds and with differing symptoms. If you suspect you may be experiencing early symptoms of dementia, talk to your doctor. While no cure is available for Alzheimer’s and other common dementias, early diagnosis can help people and their families make plans for the future. Early diagnosis also allows people to participate in clinical trials. This helps researchers develop new treatments and eventually find a cure.

THE BASICS OF DEMENTIA

Dementia is the loss of cognitive functioning, which means the loss of the ability to think, remember, or reason, as well as behavioral abilities, to such an extent that it interferes with a person’s daily life and activities. Signs and symptoms of dementia result when once-healthy neurons (nerve cells) in the brain stop working, lose connections with other brain cells, and die. While everyone loses some neurons as they age, people with dementia experience far
Basic Clinical and Diagnostic Characteristics of Senile Dementia

Researchers are still trying to understand the underlying disease processes involved in the disorders. Scientists have some theories about mechanisms that may lead to different forms of dementias, but more research is needed to better understand if and how these mechanisms contribute to the development of dementia.

While dementia is more common with advanced age (as many as half of all people age 85 or older may have some form of dementia), it is not a normal part of aging. Many people live into their 90s and beyond without any signs of dementia.

Memory loss, though common, is not the only sign of dementia. For a person to be considered to have dementia, he or she must meet the following criteria:

Two or more core mental functions must be impaired. These functions include memory, language skills, visual perception, and the ability to focus and pay attention. These also include cognitive skills such as the ability to reason and solve problems.

The loss of brain function is severe enough that a person cannot do normal, everyday tasks. In addition, some people with dementia cannot control their emotions. Their personalities may change. They can have delusions, which are strong beliefs without proof, such as the idea that someone is stealing from them. They also may hallucinate, seeing or otherwise experiencing things that are not real.

Types of Dementia

Various disorders and factors contribute to the development of dementia. Neurodegenerative disorders such as AD, frontotemporal disorders, and Lewy body dementia result in a progressive and irreversible loss of neurons and brain functions. Currently, there are no cures for these progressive neurodegenerative disorders.

However, other types of dementia can be halted or even reversed with treatment. Normal pressure hydrocephalus, for example, often resolves when excess cerebrospinal fluid in the brain is drained via a shunt and rerouted elsewhere in the body. Cerebral vasculitis responds to aggressive treatment with
immunosuppressive drugs. In rare cases, treatable infectious disorders can cause dementia. Some drugs, vitamin deficiencies, alcohol abuse, depression, and brain tumors can cause neurological deficits that resemble dementia. Most of these causes respond to treatment. Some types of dementia disorders are described below.

**Tauopathies**

In some dementias, a protein called tau clumps together inside nerve cells in the brain, causing the cells to stop functioning properly and die. Disorders that are associated with an accumulation of tau are called tauopathies.

In AD, the tau protein becomes twisted and aggregates to form bundles, called neurofibrillary tangles, inside the neurons. Abnormal clumps (plaques) of another protein, called amyloid, are prominent in spaces between brain cells and are a hallmark of the disease. Both plaques and tangles are thought to contribute to reduced function and nerve-cell death in AD, but scientists do not fully understand this relationship. It is not clear, for example, if the plaques and tangles cause the disorder, or if their presence flags some other process that leads to neuronal death in AD.

Other types of tauopathies include the following disorders:

Corticobasal degeneration (CBD) is a progressive neurological disorder characterized by nerve-cell loss and atrophy (shrinkage) of specific areas of the brain, including the cerebral cortex and the basal ganglia. The disorder tends to progress gradually, with the onset of early symptoms around age 60. At first, one side of the body is affected more than the other side, but as the disease progresses both sides become impaired. An individual may have difficulty using one hand, or one’s hand may develop an abnormal position.

Other signs and symptoms may include memory loss; trouble making familiar, focused movements (apraxia) such as brushing one’s teeth; involuntary muscular jerks (myoclonus) and involuntary muscle contractions (dystonia); alien limb, in which the person feels as though a limb is being controlled by a force other than oneself; muscle rigidity (resistance to imposed movement); postural instability; and difficulty swallowing.
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(dysphagia). People with CBD also may have visual-spatial problems that make it difficult to interpret visual information, such as the distance between objects. There is no cure for CBD. Supportive therapies are available to reduce the burden of certain symptoms. For example, botulinum toxin can help control muscle contractions. Speech therapy and physical therapy may help one learn how to cope with daily activities.

Frontotemporal disorders (FTD) are caused by a family of brain diseases that primarily affect the frontal and temporal lobes of the brain; they account for up to 10 percent of all dementia cases. Some, but not all, forms of FTD are considered tauopathies. In some cases, FTD is associated with mutations in the gene for tau (MAPT), and tau aggregates are present. However, other forms of FTD are associated with aggregates of the protein TDP-43, a mutated protein found among people with a type of ALS that is inherited. Mutations in a protein called progranulin may also play a role in some TDP43-opathies.

In FTD, changes to nerve cells in the brain’s frontal lobes affect the ability to reason and make decisions, prioritize and multitask, act appropriately, and control movement. Some people decline rapidly over 2 to 3 years, while others show only minimal changes for many years. People can live with frontotemporal disorders for 2 to 10 years, sometimes longer, but it is difficult to predict the time course for an affected individual. In some cases, FTD is associated with progressive neuromuscular weakness otherwise known as amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease). The signs and symptoms may vary greatly among individuals as different parts of the brain are affected. No treatment that can cure or reverse FTD is currently available.

Clinically, FTD is classified into two main types of syndromes:

- **Behavioral variant frontotemporal dementia** causes a person to undergo behavior and personality changes. People with this disorder may do impulsive things that are out of character, such as steal or be rude to others. They may engage in repetitive behavior (such as singing, clapping, or echoing another person’s speech). They may overeat compulsively; lose inhibitions, causing them to say or do
inappropriate things (sometimes sexual in nature); or become apathetic and experience excessive sleepiness. While they may be cognitively impaired, their memory may stay relatively intact.

- **Primary progressive aphasia (PPA)** causes a person to have trouble with expressive and receptive speaking—finding and/or expressing thoughts and/or words. Sometimes a person with PPA cannot name common objects. Problems with memory, reasoning, and judgment are not apparent at first but can develop and progress over time. PPA is a language disorder not to be confused with the aphasia that can result from a stroke. Many people with PPA, though not all, develop symptoms of dementia. In one form of PPA, called semantic PPA or semantic dementia, a person slowly loses the ability to understand single words and sometimes to recognize the faces of familiar people and common objects.

Other types of FTDs include:

- **Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17)**, a rare form of dementia that is believed to be inherited from one parent and is linked to a defect in the gene that makes the tau protein. The three core features are behavioral and personality changes, cognitive impairment, and motor symptoms. People with this type of FTD often have delusions, hallucinations, and slowness of movement and tremor as seen in Parkinson's disease. Typical behavioral/personality characteristics include apathy, defective judgment, and compulsive and abusive behavior. Diagnosis of the disorder requires the confirmed presence of clinical features and genetic analysis. Palliative and symptomatic treatments such as physical therapy are the mainstays of management.

- **Pick's disease**, a tauopathy subtype of FTD characterized by hallmark Pick bodies—masses comprised of tau protein that accumulate inside nerve cells, causing them to appear enlarged or balloon-like. Some of the symptoms of this rare neurodegenerative disorder are similar to those of
AD, including loss of speech, inappropriate behavior, and trouble with thinking. However, while inappropriate behavior characterizes the early stages of Pick’s disease, memory loss is often the first symptom of AD. Antidepressants and antipsychotics can control some of the behavioral symptoms of Pick’s disease, but no treatment is available to stop the disease from progressing.

Progressive supranuclear palsy (PSP) is a rare brain disorder that damages the upper brain stem, including the substantia nigra (a movement control center in the midbrain). This region also is affected in Parkinson’s disease, which may explain an overlap in motor symptoms shared by these disorders. Eye movements are especially affected, causing slow and then limited mobility of the eye. The most common early signs and symptoms include loss of balance, unexplained falls, general body stiffness, apathy, and depression. A person with this type of dementia may suddenly laugh or cry very easily (known as pseudobulbar affect). As the disorder progresses, people develop blurred vision and a characteristic vacant stare that involves loss of facial expression. Speech usually becomes slurred, and swallowing solid foods or liquids becomes difficult. PSP gets progressively worse, but people can live a decade or more after the onset of symptoms. Dextromethorphan, a common ingredient in cough medicine, has been approved for the treatment of pseudobulbar affect.

Argyrophilic grain disease is a common, late-onset degenerative disease characterized by tau deposits called argyrophilic grains in brain regions involved in memory and emotion. The disease’s signs and symptoms are indistinguishable from late-onset AD. Confirmation of the diagnosis can be made only at autopsy.

**Synucleinopathies**

In these brain disorders, a protein called alpha-synuclein accumulates inside neurons. Although it is not fully understood what role this protein plays, changes in the protein and/or its function have been linked to Parkinson’s disease and other disorders.
One type of synucleinopathy, Lewy body dementia, involves protein aggregates called Lewy bodies, balloon-like structures that form inside of nerve cells. The initial symptoms may vary, but over time, people with these disorders develop very similar cognitive, behavioral, physical, and sleep-related symptoms. Lewy body dementia is one of the most common causes of dementia, after Alzheimer’s disease and vascular disease. Types of Lewy body dementia include:

- **Dementia with Lewy bodies (DLB),** one of the more common forms of progressive dementia. Symptoms such as difficulty sleeping, loss of smell, and visual hallucinations often precede movement and other problems by as long as 10 years, which consequently results in DLB going unrecognized or misdiagnosed as a psychiatric disorder until its later stages. Neurons in the substantia nigra that produce dopamine die or become impaired, and the brain’s outer layer (cortex) degenerates. Many neurons that remain contain Lewy bodies.

- Later in the course of DLB, some signs and symptoms are similar to AD and may include memory loss, poor judgment, and confusion. Other signs and symptoms of DLB are similar to those of Parkinson’s disease, including difficulty with movement and posture, a shuffling walk, and changes in alertness and attention. Given these similarities, DLB can be very difficult to diagnose. There is no cure for DLB, but there are drugs that control some symptoms. The medications used to control DLB symptoms can make motor function worse or exacerbate hallucinations.

- **Parkinson’s disease dementia (PDD),** a clinical diagnosis related to DLB that can occur in people with Parkinson’s disease. PDD may affect memory, social judgment, language, or reasoning. Autopsy studies show that people with PDD often have amyloid plaques and tau tangles similar to those found in people with AD, though it is not understood what these similarities mean. A majority of people with Parkinson’s disease develop dementia, but the
time from the onset of movement symptoms to the onset of dementia symptoms varies greatly from person to person. Risk factors for developing PDD include the onset of Parkinson’s-related movement symptoms followed by mild cognitive impairment and REM sleep behavior disorder, which involves having frequent nightmares and visual hallucinations.

Vascular Dementia and Vascular Cognitive Impairment

Vascular dementia and vascular cognitive impairment (VCI) are caused by injuries to the vessels supplying blood to the brain. These disorders can be caused by brain damage from multiple strokes or any injury to the small vessels carrying blood to the brain.

Dementia risk can be significant even when individuals have suffered only small strokes. Vascular dementia and VCI arise as a result of risk factors that similarly increase the risk for cerebrovascular disease (stroke), including atrial fibrillation, hypertension, diabetes, and high cholesterol.

Vascular dementia also has been associated with a condition called amyloid angiopathy, in which amyloid plaques accumulate in the blood-vessel walls, causing them to break down and rupture. Symptoms of vascular dementia and VCI can begin suddenly and progress or subside during one’s lifetime.

Some types of vascular dementia include: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). This inherited form of cardiovascular disease results in a thickening of the walls of small- and medium-sized blood vessels, eventually stemming the flow of blood to the brain. It is associated with mutations of a specific gene called Notch3, which gives instructions to a protein on the surface of the smooth muscle cells that surround blood vessels. CADASIL is associated with multi-infarct dementia, stroke, migraine with aura (migraine preceded by visual symptoms), and mood disorders. The first symptoms can appear in people between ages 20 and 40. Many people with CADASIL are undiagnosed. People with first-degree relatives who have CADASIL can be
tested for genetic mutations to the Notch3 gene to determine their own risk of developing CADASIL.

Multi-infarct dementia. This type of dementia occurs when a person has had many small strokes that damage brain cells. One side of the body may be disproportionately affected, and multi-infarct dementia may impair language or other functions, depending on the region of the brain that is affected. Doctors call these “local” or “focal” symptoms, as opposed to the “global” symptoms seen in AD that tend to affect several functions and both sides of the body. When the strokes occur on both sides of the brain, however, dementia is more likely than when stroke occurs on one side of the brain. In some cases, a single stroke can damage the brain enough to cause dementia. This so-called single-infarct dementia is more common when stroke affects the left side of the brain—where speech centers are located—and/or when it involves the hippocampus, the part of the brain that is vital for memory.

Subcortical vascular dementia, also called Binswanger’s disease. This is a rare form of dementia that involves extensive microscopic damage to the small blood vessels and nerve fibers that make up white matter, the “network” part of the brain believed to be critical for relaying messages between regions. The symptoms of Binswanger’s are related to the disruption of subcortical neural circuits involving short-term memory, organization, mood, attention, decisionmaking, and appropriate behavior. A characteristic feature of this disease is psychomotor slowness, such as an increase in the time it takes for a person to think of a letter and then write it on a piece of paper.

Other symptoms include urinary incontinence that is unrelated to a urinary tract condition, trouble walking, clumsiness, slowness, lack of facial expression, and speech difficulties. Symptoms tend to begin after age 60, and they progress in a stepwise manner. People with subcortical vascular disease often have high blood pressure, a history of stroke, or evidence of disease of the large blood vessels in the neck or heart valves. Treatment is aimed at preventing additional strokes and may include drugs to control blood pressure.
Mixed Dementia

Autopsy studies looking at the brains of people who had dementia suggest that a majority of those age 80 and older probably had “mixed dementia,” caused by both AD-related neurodegenerative processes and vascular disease-related processes. In fact, some studies indicate that mixed vascular-degenerative dementia is the most common cause of dementia in the elderly. In a person with mixed dementia, it may not be clear exactly how many of a person’s symptoms are due to AD or another type of dementia. In one study, approximately 40 percent of people who were thought to have AD were found after autopsy to also have some form of cerebrovascular disease. Several studies have found that many of the major risk factors for vascular disease also may be risk factors for AD.

Researchers are still working to understand how underlying disease processes in mixed dementia influence each other. It is not clear, for example, if symptoms are likely to be worse when a person has brain changes reflecting multiple types of dementia. Nor do we know if a person with multiple dementias can benefit from treating one type, for example, when a person with AD controls high blood pressure and other vascular disease risk factors.

Other Conditions That Cause Dementia

Doctors have identified many other conditions that can cause dementia or dementia-like symptoms.

Other Brain Diseases

Creutzfeldt-Jakob disease (CJD). A rare brain disorder that affects about one in every million people worldwide each year, CJD belongs to a family of diseases known as the transmissible spongiform encephalopathies, or TSEs. Spongiform refers to the fact that the brain becomes filled with microscopic swellings that give the appearance of holes, like a sponge. CJD and other TSEs are believed to be caused by infectious proteins called prions that become misfolded. Scientists believe that the presence of misfolded prions can trigger normal proteins to misfold as well, causing a chain reaction. These abnormal prion proteins tend to clump together, which is believed to be related to the brain damage.
Symptoms usually begin after age 60, and most people die within a year of onset. In most cases, CJD occurs in people who have no known risk factors for the disease; however, an estimated 5 to 10 percent of cases in the U.S. are associated with genetic mutations. In addition, a type of CJD, called variant CJD (vCJD), has been found in Great Britain and several other European countries. vCJD has been observed to affect people who are younger than those with other forms of CJD and is believed to be caused by eating beef from cattle infected with a TSE called bovine spongiform encephalopathy, more commonly known as “mad cow disease.” Inherited forms of CJD include:

- Fatal familial insomnia. This prion disease causes a part of the brain involved in sleep to slowly degenerate. People with the disease have trouble sleeping and may show signs of poor reflexes and hallucinations.

- Gerstmann-Straussler-Scheinker disease. Symptoms include a loss of coordination (ataxia) and dementia that begin when people are 50 to 60 years old.

Huntington’s disease. This hereditary disorder is caused by a faulty gene for a protein called huntingtin. Symptoms begin around age 30 or 40 years and include abnormal and uncontrollable movements called chorea, as well as gait changes and lack of coordination.

Huntington’s disease may affect a person’s judgment, memory, and other cognitive functions. As the disease progresses, these cognitive problems worsen, and motor difficulties lead to complete loss of ability for self-care. Children of people with Huntington’s have a 50 percent chance of having the disorder.

Secondary dementias. These dementias occur in people with disorders that damage brain tissue. Such disorders may include multiple sclerosis; meningitis; encephalitis; and Wilson’s disease, in which excessive amounts of copper build up to cause brain damage. In rare cases, people with brain tumors may develop dementia because of damage to their brain circuits or a buildup of pressure inside the skull. Symptoms may include changes in personality, psychotic episodes, or problems with speech, language, thinking, and memory.
Head Injury

Chronic traumatic encephalopathy, initially known as dementia pugilistica, is caused by repeated traumatic brain injury (TBI), such as in boxers or in people who suffered multiple concussions while playing a contact sport. People with this condition often develop poor coordination, slurred speech, and other symptoms similar to those seen in Parkinson’s disease, along with dementia, 20 years or more after the TBI events. This form of dementia also is characterized by brain atrophy and widespread deposits of tau aggregates. In some individuals, even just 5 to 10 years beyond the TBI events, behavioral and mood changes may occur. Dementia may not yet be present and the brain may not have atrophied, but small focal deposits of tau are seen in the brain at autopsy.

Subdural hematoma, or bleeding between the brain’s surface and its outer covering (the dura), is common in the elderly after a fall. Subdural hematomas can cause dementia-like symptoms and changes in mental function. With treatment, some symptoms can be reversed.

Reversible Dementias

Many conditions that cause dementia can be reversed with the appropriate treatment.

- Cerebral vasculitis, an inflammation and necrosis (tissue death) of blood vessel walls, can cause a form of dementia that may resolve when the person is treated with immune suppressants.
- Some studies have shown that people with depression are at increased risk of developing dementia. Severe depression can cause dementia and can be treated.
- Infections can cause confusion or delirium due to related fever or other side effects associated with the body’s response to a foreign entity.
- Metabolic disorders of the nervous system, such as mitochondrial disorders, leukodystrophies, and lysosomal storage diseases, can lead to dementia.
- Metabolic problems and endocrine abnormalities such as thyroid problems, low blood sugar levels (called
hypoglycemia), and low or high levels of sodium or calcium also may also cause dementia.

- Normal pressure hydrocephalus is an abnormal buildup of cerebrospinal fluid in the brain. Elderly individuals with the condition usually have trouble with walking and bladder control before onset of dementia. Normal pressure hydrocephalus can be treated or even reversed by implanting a shunt system to divert fluid from the brain.

- Nutritional deficiencies of vitamin B<sub>1</sub> (thiamine), caused by chronic alcoholism, and vitamin B<sub>12</sub> deficiencies can be reversed with treatment.

- Paraneoplastic syndromes (a group of symptoms that may develop when substances released by some cancer cells disrupt the normal function of surrounding cells and tissue) can cause symptoms that resemble dementia. Such symptoms generally occur in people with cancer when the body's immune response to the cancer also ends up targeting proteins in the central nervous system. In many cases, the neurologic condition occurs before the cancer is detected. Circulating antibodies against brain proteins are common in both neurologic and cancer conditions.

- Side effects of medications or drug combinations may cause dementias that arise quickly or develop slowly over time.

**Environmental Factors**

Environmental factors may play a role in the development of certain types of dementia. This relationship is complex, however, since a person may carry genetic mutations that influence his or her response to environmental factors. Examples of environmental factors include:

  Anoxia. Anoxia and a related condition, hypoxia, are terms often used to describe a state in which there is a curtailed supply of oxygen to an organ’s tissues. Anoxia and hypoxia can lead to the loss of neurons and diffuse brain injury. Characteristics of the resulting dementia include confusion, personality changes, hallucinations, or memory loss. This type of dementia commonly
occurs in people who survive cardiac arrest. Poisoning. Exposure to lead, mercury, other heavy metals, or poisonous substances can lead to symptoms of dementia. These symptoms may or may not resolve after treatment, depending on how severely the brain is damaged. Substance abuse. People who have abused substances such as alcohol and recreational drugs sometimes display signs of dementia even after the substance abuse has stopped. This condition is known as substance-induced persisting dementia.

**Infectious Disease**

HIV-associated dementia (HAD) can occur in people who are positive for the human immunodeficiency virus, the virus that causes AIDS. HAD damages the brain’s white matter and leads to a type of dementia associated with memory problems, social withdrawal, and trouble concentrating. People with HAD may develop movement problems as well. The incidence of HAD has dropped dramatically with the availability of effective antiviral therapies for managing the underlying HIV infection.

**RISK FACTORS FOR DEMENTIA**

The following risk factors can increase a person’s chance of developing one or more kinds of dementia. Some of these factors can be modified, while others cannot.

- **Age.** The risk goes up with advanced age.
- **Alcohol use.** Most studies suggest that drinking large amounts of alcohol increases the risk of dementia, while drinking a moderate amount may be protective.
- **Atherosclerosis.** The accumulation of fats and cholesterol in the lining of arteries, coupled with an inflammatory process that leads to a thickening of the vessel walls (known as atherosclerosis), can hinder blood from getting to the brain, which can lead to stroke or another brain injury. For example, high levels of low-density lipoprotein (LDL, or “bad” cholesterol) can raise the risk for vascular dementia. High LDL levels also have been linked to AD.
- **Diabetes.** People with diabetes appear to have a higher risk for dementia, although the evidence for this association is
modest. Poorly controlled diabetes, however, is a well-proven risk factor for stroke and cardiovascular disease-related events, which in turn increase the risk for vascular dementia.

- Down syndrome. Many people with Down syndrome develop early-onset AD, with signs of dementia by the time they reach middle age.

- Genetics. One’s likelihood of developing a genetically linked form of dementia increases when more than one family member has the disorder. But in some cases, such as with CADASIL, having just one parent who carries a mutation increases the risk of inheriting the condition. In other instances, genetic mutations may underlie dementias in specific populations. For example, a mutation of the gene TREM2 has been found to be common among people with a form of very early onset frontotemporal dementia that runs in Turkish families.

- Hypertension. High blood pressure has been linked to cognitive decline, stroke, and types of dementia that affect the white matter regions of the brain.

- Mental illness. Depression has been associated with mild mental impairment and cognitive function decline.

- Smoking. Smokers are prone to diseases that slow or stop blood from getting to the brain.

Diagnosis

Doctors first assess whether the individual has an underlying treatable condition such as depression, abnormal thyroid function, drug-induced encephalopathy, normal pressure hydrocephalus, or vitamin B$_{12}$ deficiency. Early diagnosis is important, as some causes for symptoms can be treated. In many cases, the specific type of dementia that a person has may not be confirmed until after the person has died and the brain is examined.

An assessment generally includes:

- Patient history. Typical questions about a person’s medical and family history might include asking about whether dementia runs in the family, how and when symptoms
began, and if the person is taking certain medications that might cause or exacerbate symptoms.

- Physical exam. Measuring blood pressure and other vital signs may help physicians detect conditions that might cause or occur with dementia. Such conditions may be treatable.

- Neurological evaluations. Assessing balance, sensory function, reflexes, vision, eye movements, and other functions helps identify signs of conditions that may affect the diagnosis or are treatable with drugs. Doctors also might use an electroencephalogram, a test that records patterns of electrical activity in the brain, to check for abnormal electrical brain activity.

The following procedures also may be used when diagnosing dementia:

- Brain scans. These tests can identify strokes, tumors, and other problems that can cause dementia. Scans also identify changes in the brain’s structure and function. The most common scans are computed tomographic (CT) scans and magnetic resonance imaging (MRI). CT scans use X-rays to produce images of the brain and other organs. MRI scans use a computer, magnetic fields, and radio waves to produce detailed images of body structures, including tissues, organs, bones, and nerves.

- Other types of scans let doctors watch the brain as it functions. Two of these tests are single photon-emission computed tomography, which can be used to measure blood flow to the brain, and positron emission tomography (PET), which uses radioactive isotopes to provide pictures of brain activity. These scans are used to look for patterns of altered brain activity that are common in dementia. Researchers also use PET imaging with compounds that bind to beta-amyloid to detect levels of the protein, a hallmark of AD, in the living brain.

- Cognitive and neuropsychological tests. These tests measure memory, language skills, math skills, and other abilities related to mental functioning. For example, people
with AD often show impairment in problem-solving, memory, and the ability to perform once-automatic tasks.

- **Laboratory tests.** Many tests help rule out other conditions. They include measuring levels of sodium and other electrolytes in the blood, a complete blood count, a blood sugar test, urine analysis, a check of vitamin B12 levels, cerebrospinal fluid analysis, drug and alcohol tests, and an analysis of thyroid function.

- **Presymptomatic tests.** Some dementias are associated with a known gene defect. In these cases, a genetic test could help people know if they are at risk for dementia. People should talk with family members, their primary health care professional, and a genetic counselor before getting tested.

- **Psychiatric evaluation.** This will help determine if depression or another mental health condition is causing or contributing to a person's symptoms.

**Treatment**

Some dementias are treatable. However, therapies to stop or slow common neurodegenerative diseases such as AD have largely been unsuccessful, though some drugs are available to manage certain symptoms.

Most drugs for dementia are used to treat symptoms in AD. One class of drugs, called cholinesterase inhibitors, includes donepezil, rivastigmine, and galantamine. These drugs can temporarily improve or stabilize memory and thinking skills in some people by increasing the activity of the cholinergic brain network.

The drug memantine is in another class of medications called NMDA receptor agonists, which prevents declines in learning and memory. NMDA receptor agonists work by regulating the activity of the neurotransmitter glutamate. When glutamate activity levels are excessive, neurons may die. Memantine may be combined with a cholinesterase inhibitor for added benefits. These drugs are sometimes used to treat other dementias as well. None of these drugs can stop or reverse the course of the disease.
• Creutzfeldt-Jakob disease. There are no treatments to cure or control CJD. Management focuses on reducing symptoms and making people comfortable.

• Dementia with Lewy bodies. Drugs available for managing DLB are aimed at relieving symptoms such as stiffness, hallucinations, and delusions. However, many of the agents for treating the physical symptoms, particularly antipsychotics, can make the mental health symptoms worse. Conversely, drugs used to treat mental health symptoms can exacerbate physical symptoms. Studies suggest that AD drugs may benefit people with DLB.

• Frontotemporal disorders. There are no medications approved to treat or prevent FTD and most other types of progressive dementia. Sedatives, antidepressants, and other drugs used to treat Parkinson’s and Alzheimer’s symptoms may help manage certain symptoms and behavioral problems associated with the disorders.

• Parkinson’s disease dementia. Some studies suggest that the cholinesterase inhibitors used in people with AD might improve cognitive, behavioral, and psychotic symptoms in people with Parkinson’s disease dementia. The U.S. Food and Drug Administration has approved one Alzheimer’s drug, rivastigmine, to treat cognitive symptoms in PDD.

• Vascular dementia. This type of dementia is often managed with drugs to prevent strokes. The aim is to reduce the risk of additional brain damage. Some studies suggest that drugs that improve memory in AD might benefit people with early vascular dementia. Most of the modifiable risk factors that influence development of vascular dementia and VCI are the same risk factors for cerebrovascular disease, such as hypertension, atrial fibrillation, diabetes, and high cholesterol. Interventions that address these risk factors may be incorporated into the management of vascular dementia.
Current Research

In 2012, the President announced the National Plan to Address Alzheimer’s Disease, a national effort to expand research in Alzheimer’s and related dementias prevention and treatment and to move the most promising drugs from discovery into clinical trials. The Plan aims to prevent and effectively treat Alzheimer’s and related dementias by 2025. Its foundation is the 2011 National Alzheimer’s Project Act (NAPA), which was developed to create and maintain a national strategy to overcome the disease. The National Plan calls for increased federal funding for AD research, support for those affected by AD and their families, increased public awareness about AD, and improved data collection and analysis to better understand the impact of AD on people with the disease, families, and the health and long-term care systems. These goals also apply to AD-related dementias, including dementia with Lewy bodies as well as frontotemporal, mixed (characteristics of more than one type of dementia occur simultaneously), and vascular dementias.

The National Institute of Neurological Disorders and Stroke (NINDS), a component of NIH, is the leading federal funder of research on nervous system disorders. Another NIH Institute, the National Institute on Aging (NIA), is the leading federal funder of research on AD. Together, these Institutes are world leaders in supporting research on the dementias, including Lewy body dementia, frontotemporal disorders, and vascular dementia.

Although scientists have some understanding of these dementias and the mechanisms involved, ongoing research may lead to new ways to diagnose, treat, or perhaps prevent or block disease development. Current areas of research include:

Drugs. A number of agents that might slow the progression of AD and other dementias are in various stages of testing.

The NIA-supported Alzheimer’s Disease Cooperative Study (ADCS) is a consortium of academic medical centers and clinics set up by NIH in 1991 to collaborate on the development of promising Alzheimer’s treatments and diagnostic tools.

In the latest round of studies, the ADCS will test drug and exercise interventions in people in the early stages of the disease,
examine a medication to reduce agitation in people with Alzheimer’s dementia, and test a cutting-edge approach to speed testing of drugs in clinical trials. Because Alzheimer’s-related brain changes begin years before symptoms appear, the A4 (Anti-amyloid Treatment in Asymptomatic Alzheimer’s Disease) trial is testing a promising therapy in the early stages of the disorder. This secondary prevention trial will test an amyloid-clearing drug in the symptom-free stage of the disease in 1,000 cognitively healthy older volunteers whose brain scans show abnormal levels of amyloid accumulation. Another of the newly funded ADCS drug trials is the Prazosin for Treating Agitation trial, which will test the use of the generic drug prazosin as a treatment for agitation that may also be well-tolerated in frail and elderly people.

Exercise. Researchers are assessing the effectiveness of a supervised aerobic exercise program to enhance general cognition in adults with age-related cognitive decline. They predict that greater cognitive gains will be made by individuals with more fitness gains. Another study will determine if exercise prevents memory loss from getting worse, and if it improves daily functioning and attitudes of those with probable AD. Researchers also hope to gain a better understanding of the effects of exercise and cognitive training on improving brain function in healthy older adults who may be at risk for developing AD.

Genetics. Several genes—most notably ApoE and the gene for tau (MAPT)—have been implicated in AD and other forms of dementia. Many dementia-related disorders share genetic and other characteristics of AD. Some families share a particular genetic mutation that causes dementia. Researchers are using samples of a person’s genetic material, or genome, to identify genes that may be responsible for the development of dementia and AD. For example, NIH-funded researchers recently examined ApoE’s role in the development of late-onset AD and found that one of the three forms of the ApoE gene triggers an inflammatory reaction and damages the blood vessels that feed the brain. Other researchers have identified a gene variant of TREM2 that is involved with a form of frontotemporal dementia that runs in families. Additional research may identify novel genes involved with FTD and other
neurodegenerative diseases, perhaps leading to therapeutic approaches where delivery of normal genes would improve or restore normal brain function.

Imaging. Clinical imaging may help researchers better understand changes in the brains of people with dementia, as well as help diagnose these disorders. Magnetic resonance imaging may reveal structural and functional differences in the brains of individuals with Parkinson’s disease dementia and AD and identify small vessel disease. PET scanning uses ligands—radioactive molecules that bind to proteins to show chemical functions of tissues and organs in the body—to help produce images of brain activity. Scientists funded by NIA are testing new PET ligands that bind to beta-amyloid for early detection of Alzheimer’s-type pathology and cognitive decline. Studies of PET ligands that bind to aggregates of tau are ongoing in people with very early-stage AD.

International efforts. The International Alzheimer’s Disease Research Portfolio (IADRP) helps individuals learn about AD research at public and private organizations in the U.S. and abroad. It also helps organizations leverage resources and avoid duplication of effort. The Common Alzheimer’s Disease Research Ontology—a classification system that allows organizations to integrate and compare research portfolios—was developed by NIA, NIH, and the Alzheimer’s Association.

Proteins. One feature that several major dementias have in common is an excess in the brain of certain proteins or protein fragments that have taken abnormal forms thought to be toxic to brain cells. NIH-funded research projects are aimed at better understanding the toxic effects of protein buildup and how it is related to the development of AD and related dementias. Some of these protein abnormalities can be detected in cerebrospinal fluid.

For example, an abnormally high accumulation of beta-amyloid protein in the brain is a hallmark of AD. NINDS-funded researchers are determining which neural pathways are affected by beta-amyloid and contribute to the development of Alzheimer’s pathology and symptoms. NINDS funding also led to a genetically
engineered rat model of AD that has the full array of brain changes associated with the human disease and may be used to better define causes and effects of AD related to beta-amyloid accumulation. Funding also was provided by NIA, the National Institute of Mental Health (also part of NIH), and other organizations.

In FTD, AD, and other neurodegenerative diseases, the protein tau collects in abnormal tangled masses of filaments that disrupt nerve signaling, cause cell death, and impair cognition. NINDS-funded researchers are determining whether specific forms of tau interfere with nerve cell signaling and decrease memory function. Others are studying how tau pathology spreads from cell to cell. Tau-related investigations are aimed at identifying common mechanisms of FTD, as well as biomarkers (signs that may indicate disease risk and progression, and improve diagnosis) that will speed the development of novel therapeutics for PDD and other forms of dementia.

Similarly, the abnormal accumulation of the protein alpha-synuclein is a hallmark of Parkinson’s disease and Lewy body dementia. Scientists hope to identify what causes alpha-synuclein to form abnormal aggregates and become toxic to nerve cells, and to understand why the aggregation is an age-related phenomenon in Parkinson’s disease and other synuclein-related disorders.

Sleep. The sleep and wakefulness cycle plays an integral, but not well understood, role in many dementias, including dementia with Lewy bodies, AD, prion dementias, and PDD. Sleep studies in individuals during periods of excessive daytime sleepiness and nocturnal sleep can help determine if fluctuations in mental status among people with DLB are related to excessive daytime sleepiness. Sleep studies also can assess whether declining cognition is predicted by sleep-related and neurobehavioral markers in parkinsonism.

Stem cells. Scientists are exploring various types of cells, including stem cells, to discover nerve cell mechanisms that lead to the initiation and progression of AD and other forms of dementia. Significant research efforts have focused on induced pluripotent stem cells (iPSC), which can be “reprogrammed” from skin cells
into any cell type in the body, including nerve cells. NINDS funds three research consortia to develop well-characterized iPSC for amyotrophic lateral sclerosis (ALS), Huntington’s disease, and Parkinson’s disease. These cells can then be used by the research community to study the effects of mutant genes and misfolded proteins on nerve cell function and health, as well as to test potential drugs and therapies for AD and related dementias.

**ALZHEIMER’S DISEASE**

Most common type of dementia; accounts for an estimated 60 to 80 percent of cases.

Symptoms: Difficulty remembering recent conversations, names or events is often an early clinical symptom; apathy and depression are also often early symptoms. Later symptoms include impaired communication, poor judgment, disorientation, confusion, behavior changes and difficulty speaking, swallowing and walking.

Revised criteria and guidelines for diagnosing Alzheimer’s were published in 2011 recommending that Alzheimer’s be considered a slowly progressive brain disease that begins well before symptoms emerge.

Brain changes: Hallmark abnormalities are deposits of the protein fragment beta-amyloid (plaques) and twisted strands of the protein tau (tangles) as well as evidence of nerve cell damage and death in the brain.

**Vascular dementia**

Previously known as multi-infarct or post-stroke dementia, vascular dementia is less common as a sole cause of dementia than Alzheimer’s, accounting for about 10 percent of dementia cases.

Symptoms: Impaired judgment or ability to make decisions, plan or organize is more likely to be the initial symptom, as opposed to the memory loss often associated with the initial symptoms of Alzheimer’s. Occurs from blood vessel blockage or damage leading to infarcts (strokes) or bleeding in the brain. The location, number and size of the brain injury determines how the individual’s thinking and physical functioning are affected.
Brain changes: Brain imaging can often detect blood vessel problems implicated in vascular dementia. In the past, evidence for vascular dementia was used to exclude a diagnosis of Alzheimer’s disease (and vice versa). That practice is no longer considered consistent with pathologic evidence, which shows that the brain changes of several types of dementia can be present simultaneously. When any two or more types of dementia are present at the same time, the individual is considered to have “mixed dementia”.

**Dementia with Lewy bodies (DLB)**

Symptoms: People with dementia with Lewy bodies often have memory loss and thinking problems common in Alzheimer’s, but are more likely than people with Alzheimer’s to have initial or early symptoms such as sleep disturbances, well-formed visual hallucinations, and slowness, gait imbalance or other parkinsonian movement features.

Brain changes: Lewy bodies are abnormal aggregations (or clumps) of the protein alpha-synuclein. When they develop in a part of the brain called the cortex, dementia can result. Alpha-synuclein also aggregates in the brains of people with Parkinson’s disease, but the aggregates may appear in a pattern that is different from dementia with Lewy bodies.

The brain changes of dementia with Lewy bodies alone can cause dementia, or they can be present at the same time as the brain changes of Alzheimer’s disease and/or vascular dementia, with each abnormality contributing to the development of dementia. When this happens, the individual is said to have “mixed dementia.”

**Mixed dementia**

In mixed dementia abnormalities linked to more than one cause of dementia occur simultaneously in the brain. Recent studies suggest that mixed dementia is more common than previously thought.

Brain changes: Characterized by the hallmark abnormalities of more than one cause of dementia — most commonly, Alzheimer’s
and vascular dementia, but also other types, such as dementia with Lewy bodies.

**Parkinson’s disease**

As Parkinson’s disease progresses, it often results in a progressive dementia similar to dementia with Lewy bodies or Alzheimer’s.

Symptoms: Problems with movement are common symptoms of the disease. If dementia develops, symptoms are often similar to dementia with Lewy bodies.

Brain changes: Alpha-synuclein clumps are likely to begin in an area deep in the brain called the substantia nigra. These clumps are thought to cause degeneration of the nerve cells that produce dopamine.

**Frontotemporal dementia**

Includes dementias such as behavioral variant FTD (bvFTD), primary progressive aphasia, Pick’s disease, corticobasal degeneration and progressive supranuclear palsy.

Symptoms: Typical symptoms include changes in personality and behavior and difficulty with language. Nerve cells in the front and side regions of the brain are especially affected.

Brain changes: No distinguishing microscopic abnormality is linked to all cases. People with FTD generally develop symptoms at a younger age (at about age 60) and survive for fewer years than those with Alzheimer’s.

**Creutzfeldt-Jakob disease**

CJD is the most common human form of a group of rare, fatal brain disorders affecting people and certain other mammals. Variant CJD (“mad cow disease”) occurs in cattle, and has been transmitted to people under certain circumstances.

Symptoms: Rapidly fatal disorder that impairs memory and coordination and causes behavior changes.

Brain changes: Results from misfolded prion protein that causes a “domino effect” in which prion protein throughout the brain misfolds and thus malfunctions.
Normal pressure hydrocephalus

Symptoms: Symptoms include difficulty walking, memory loss and inability to control urination.

Brain changes: Caused by the buildup of fluid in the brain. Can sometimes be corrected with surgical installation of a shunt in the brain to drain excess fluid.

Huntington’s Disease

Huntington’s disease is a progressive brain disorder caused by a single defective gene on chromosome 4.

Symptoms: Include abnormal involuntary movements, a severe decline in thinking and reasoning skills, and irritability, depression and other mood changes.

Brain changes: The gene defect causes abnormalities in a brain protein that, over time, lead to worsening symptoms.

Wernicke-Korsakoff Syndrome

Korsakoff syndrome is a chronic memory disorder caused by severe deficiency of thiamine (vitamin B-1). The most common cause is alcohol misuse.

Symptoms: Memory problems may be strikingly severe while other thinking and social skills seem relatively unaffected.

Brain changes: Thiamine helps brain cells produce energy from sugar. When thiamine levels fall too low, brain cells cannot generate enough energy to function properly.

THE MAJOR CAUSES OF DEMENTIA

Alzheimer’s disease, vascular disease, FTLD, and dementia with Lewy bodies are the most common diseases that cause dementia both in the elderly and in younger patients, although not in those who are younger than 35 years. However, the clinical features of these diseases in younger patients can differ from those seen at a later age.

Alzheimer’s disease

Alzheimer’s first patient was only 51 years at the time of presentation and, for the next 50 years, Alzheimer’s disease was
referred to as a presenile dementia. It was the work of Blessed and colleagues that led to the recognition of the importance of the disease in the elderly: these authors showed that the brains of patients who had so-called senile dementia when they died had senile plaques and neurofibrillary tangles that were qualitatively the same as those seen in presenile Alzheimer’s disease. This finding led to the view that the disease was the same regardless of age and the term Alzheimer’s disease has since been used to include all ages. This has been a valuable advance but has masked important differences. One obvious difference is that, compared with elderly individuals, younger patients have fewer comorbidities such as renal disease and heart disease, and lower medication use, which can exacerbate cognitive impairment. Co-existent cerebrovascular disease is also less common in younger patients, whereas there is frequent co-existence of Alzheimer’s disease with vascular disease in the older population.

Autosomal dominant familial Alzheimer’s disease is also more common in individuals with younger onset; sporadic Alzheimer’s disease in individuals younger than 50 years is rare. Although mutations in the amyloid precursor protein (APP) and presenilin-1 and presenilin-2 (PSEN1 and PSEN2) genes, which are associated with familial Alzheimer’s disease, are seen in older patients with Alzheimer’s disease, most patients present below the age of 65 years. In general, individuals with familial Alzheimer’s disease present with features similar to individuals with later-onset sporadic Alzheimer’s disease with prominent episodic memory impairment. This similarity has meant that the insights gained from the studies of pre-manifest and early familial Alzheimer’s disease can be generalised to the more common older-onset sporadic disease. However, unlike patients with sporadic disease, patients with familial Alzheimer’s disease generally have myoclonus, relative preservation of naming, and, in some cases, prominent speech production deficits. Rarely, some patients have features that are not seen in late-onset sporadic disease. In patients with PSEN1 deletions and some point mutations, spastic paraparesis can be a prominent and even a presenting feature years before the onset of cognitive impairment; rarely, a cerebellar ataxia is seen. Mutations in the prion protein (PRNP) gene might cause a clinical
syndrome that closely resembles familial Alzheimer’s disease. There are also important phenotypic variants within the group of patients with younger-onset sporadic Alzheimer’s disease: patients who have non-amnestic deficits collectively comprise about a third of cases who present with young onset compared with about 5% of later-onset presentations. Within the range of non-amnestic disorders, presentations with executive behavioural or language dysfunction are well documented; however, the most frequent phenotype is a biparietal or more posterior biparieto-occipital presentation, so-called posterior cortical atrophy, particularly in those with onset between 50 years and 65 years. The cortical nature of the visual impairment might not be identified, and these patients often have many appointments with opticians and ophthalmologists because of the difficulty they have with locating and perceiving objects. Such patients might not fulfill criteria for Alzheimer’s disease, having relatively preserved episodic memory. The association with the ApoE\(^{4}\) genotype seen with amnestic Alzheimer’s disease might not be observed in patients with posterior cortical atrophy, hinting at neurobiological differences between these groups of patients.

The ApoE\(^{4}\) genotype might contribute to a more aggressive clinical disease course in younger patients. A language variant of Alzheimer’s disease, so-called logopenic progressive aphasia, characterised by prolonged word-finding pauses, anomia, and impaired sentence processing, is also more common in younger patients. The extensive anatomical overlap between the logopenic and posterior cortical atrophy syndromes underlines the posterior emphasis of cortical involvement in the younger-onset Alzheimer’s disease variants.

There is an important association between early-onset Alzheimer’s disease and Down’s syndrome. From a neurobiological perspective, recognition of the role of APP over-production due to increased gene dosage with trisomy 21 was an important clue to the identification of the \(\text{APP}\) gene and the amyloid hypothesis of Alzheimer’s disease pathogenesis. Clinically, people with Down’s syndrome have a substantially increased risk of developing younger-onset dementia after the age of 35 years. Alzheimer’s
Disease changes at post mortem are essentially universal, while the prevalence of clinical dementia in individuals with Down’s syndrome has been estimated as 15–25% overall and increases steeply with increasing age. Clinical assessment is particularly challenging in this population, particularly as indices of executive and social and emotional functioning might be more important than tests of memory in indicating the onset of clinical dementia.

**Vascular dementia and vascular cognitive impairment**

The term vascular dementia has been problematic for the same reasons as the term dementia, and the term vascular cognitive impairment is preferable. Impairment of episodic memory is less prominent in vascular dementia than in Alzheimer’s disease, particularly in patients with small vessel disease in whom impairment of executive function and cognitive slowing (subcortical dementia) are more common. White matter changes indicative of small vessel disease and lacunar infarcts are commonly seen on MRI scans in elderly individuals and are particularly common in association with Alzheimer’s disease, often indicating “mixed dementia”. In younger patients there is usually, but not invariably, an association with vascular risk factors but intensive investigation might identify rarer causes, including mitochondrial disease or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Amyloid angiopathy is important to recognise as some patients might have an inflammatory component that could be responsive to steroids; lobar microhaemorrhages seen on T2*-weighted MRI might help detection. APP duplications are commonly associated with a prominent amyloid angiopathy with cerebral haemorrhages and seizures. Treatable causes such as cerebral vasculitis are also more commonly found in younger patients than in the elderly.

**Frontotemporal lobar degeneration**

The broad descriptive term frontotemporal lobar degeneration (FTLD) refers to the regional atrophy of a group of non-Alzheimer’s disease degenerative dementias. These dementias are associated with three classic clinical syndromes: behavioural variant FTLD, semantic dementia (a fluent aphasia with loss of word meaning),
Basic Clinical and Diagnostic Characteristics of Senile Dementia

and progressive non-fluent aphasia (a disorder typified by effortful, non-fluent speech). FTLD accounts for a greater proportion of dementias in younger patients than in elderly patients, although this might be partly attributable to ascertainment bias: patients with young-onset dementia are more likely to be studied post mortem and elderly patients with FTLD might be misdiagnosed. This bias might also be associated with the high heritability of FTLD: about 20–40% of FTLD cases are familial in series from specialist referral centres. Among the FTLD syndromes, the behavioural variant is the most heritable and semantic dementia the least heritable, perhaps accounting for recent evidence suggesting that a high proportion of patients with semantic dementia present over the age of 65 years. In cases of autosomally dominant inherited FTLD in which a mutation has been determined, microtubule-associated protein tau (MAPT) and progranulin (GRN) gene mutations are approximately equally represented. Age at onset tends to be younger in patients with MAPT-associated FTLD than in patients with GRN-associated FTLD, but onset age can be highly variable even within a family. Other rare gene mutations have recently been described (table 2).

The extent to which age at onset affects FTLD phenotype is unclear: for the behavioural variant, early-onset and later-onset forms all show a similar range of phenotypes.

FTLD is pathologically heterogeneous and prediction of the underlying pathological process on the basis of the clinical phenotype is generally difficult. Two broad histopathological groupings collectively account for most cases (whether sporadic or inherited): diseases with tau-positive cellular inclusions and diseases with tau-negative, ubiquitin-positive cellular inclusions containing TAR-DNA binding protein (TARDBP; also known as TDP-43). Morphological features of deposition of TARDBP have recently been linked to particular clinical syndromes, suggesting a possible pathogenetic framework that might help resolve the current nosological confusion surrounding FTLD. Among the major FTLD subtypes, the characteristic clinico-anatomical syndrome of semantic dementia has the closest pathological correspondence with tau-negative TARDBP pathology seen in more than 75% of cases; behavioural variant FTLD has wide anatomical and
pathological heterogeneity. Non-fluent speech breakdown, particularly in the context of parkinsonism, is more frequently associated with tau pathology, including progressive supranuclear palsy, corticobasal degeneration and Pick’s disease; however, these associations are of limited predictive value in individual patients. The presence of lower motor neuron signs are associated with ubiquitin pathology.

A recently identified small subgroup of patients with fused-in-sarcoma (FUS)-positive, TARDBP-negative ubiquitinated inclusions commonly presents with a behavioural syndrome before the age of 40 years; substantial caudate atrophy can be a consistent feature in this group.

**Dementia with Lewy bodies and Parkinson’s disease dementia**

Dementia with Lewy bodies, the second most common cause of dementia in the elderly, is typically associated with the development of a cognitive syndrome with frontal/parietal involvement, well formed visual hallucinations, and fluctuations, followed by the development of parkinsonism. Dementia with Lewy bodies is characterised pathologically by Lewy bodies, senile plaques, and variable tangle formation. A rare pure form comprises only Lewy bodies with a much younger onset; in a series of nine cases from Japan, eight had an onset before 40 years of age. In other patients, dementia is increasingly recognised as a common feature of advancing Parkinson’s disease, but develops less frequently and with a longer latency in patients with young-onset disease. Patients with early-onset parkinsonism are more likely to have an underlying genetic cause. Of these, mutations in the parkin (PARK2) gene are not typically associated with dementia, but α-synuclein triplications and mutations in the glucocerebrosidase gene can be associated with prominent cognitive impairment, in some cases resembling classic dementia with Lewy bodies.

**Dementia plus syndromes**

There are many causes of young-onset dementia, and detailed coverage of them all is beyond the scope of this Review. However,
the clinical concept of dementia plus syndromes (ie, the dementia syndromes in which cognitive impairment is accompanied by additional neurological or systemic features) can be useful to guide a structured approach to clinical diagnosis and investigations. The pattern of cognitive domains that are impaired can be relatively specific in terms of the underlying molecular pathology; for example, posterior cortical atrophy is most frequently associated with Alzheimer’s disease pathology and a verbal semantic memory impairment with ubiquitin-positive, tau-negative inclusions.

However, many diseases present with a non-specific memory or frontosubcortical impairment. In these cases, the additional neurological features or systemic features (dementia plus) can be very informative.

Careful examination is mandatory as presence of one of these additional features narrows the differential diagnosis. For example, the presence of a gaze palsy restricts the differential diagnosis and the additional presence of splenomegaly makes a diagnosis of Niemann-Pick disease type C very likely. These dementia plus syndromes are summarised in panels 1 and 2.

**Ataxia**

Spinocerebellar ataxia (particularly types 2, 12, and 17), paraneoplastic diseases, prion diseases (particularly familial forms and variant CJD), DRPLA (common in Japan), fragile x-associated tremor ataxia syndrome, familial British and Danish dementias, mitochondrial disorders, superficial siderosis, neuronal ceroid lipofuscinosis (Kuf’s disease), Niemann-Pick disease type C, multiple system atrophy (dementia usually mild, if present), Alexander’s disease, and multiple sclerosis

**Pyramidal signs**

Multiple sclerosis, frontotemporal lobar degeneration with motor neuron disease, Alzheimer’s disease (some presenilin mutations), spinocerebellar ataxias, phenylketonuria, familial British and Danish dementias, hereditary spastic paraparesis (SPG4), adrenoleukodystrophy, vanishing white matter disease, polyglucosan body disease, polycystic lipomembranous sclerosing leukoencephalopathy
**Dystonia/chorea**

Huntington’s disease (and Huntington’s disease-like syndromes 1-3), Kuf’s disease (characteristic facial dyskinesia), Wilson’s disease, neuroacanthocytosis, pantothenate kinase-associated neurodegeneration (neurodegeneration with brain iron accumulation), Lesch-Nyhan syndrome, DRPLA, corticobasal degeneration, neuroferritinopathy, anti-NMDA receptor-mediated limbic encephalitis, variant CJD

**Bucco-lingual mutilation**

Neuroacanthocytosis, Lesch-Nyhan syndrome

**Akinetic-rigid syndrome**

Lewy body disease (dementia with Lewy bodies and Parkinson’s disease dementia), progressive supranuclear palsy, multiple system atrophy (dementia usually mild, if present), Huntington’s disease (particularly juvenile onset), corticobasal degeneration, dementia pugilistica, Wilson’s disease, pantothenate kinase-associated neurodegeneration (neurodegeneration with brain iron accumulation), frontotemporal lobar degeneration with parkinsonism-17, Alzheimer’s disease (usually advanced)

**Peripheral neuropathy**

Neuroacanthocytosis, cerebrotendinous xanthomatosis, HIV infection, giant axonal neuropathy, alcohol-related diseases, metachromatic leukodystrophy, porphyria, adrenoleukodystrophy, GM2 gangliosidosis, polyglucosan body disease, Krabbe’s disease, sialidosis, Fabry’s disease, mitochondrial disorders, spinocerebellar ataxias

**Myoclonus or early seizures**

Prion disease, Alzheimer’s disease, Lewy body disease, DRPLA, mitochondrial disorders, Gaucher’s disease, GM2 gangliosidosis, neuroserpinopathy, polycystic lipomembranous sclerosing leukoencephalopathy, subacute sclerosing panencephalitis, progressive myoclonic epilepsy syndromes, Kuf’s disease, Lafora body disease, sialidosis
**Gaze palsy**

Niemann Pick disease type C (vertical supranuclear; early downgaze loss), Gaucher’s disease (horizontal supranuclear), progressive supranuclear palsy (vertical supranuclear), mitochondrial disorders, spinocerebellar ataxias, paraneoplastic disorders, Whipple’s disease

**Deafness**

Superficial siderosis, mitochondrial disorders, familial Danish dementia, alpha mannosidosis, sialidosis

**Dysautonomia**

Lewy body disease, multiple system atrophy, prion disease (fatal familial insomnia), porphyria, adrenoleukodystrophy, anti-NMDA receptor-mediated limbic encephalitis

The dementia plus syndromes describe patterns of cognitive impairment (dementia) plus additional neurological or systemic features that aid investigation and diagnosis of the underlying disease process. This list cannot be comprehensive. Note that vascular disease, structural disorders, and (para) neoplastic disease can be associated with a wide range of presentations. DRPLA=dentatorubral-pallidoluysian atrophy. CJD=Creutzfeldt-Jakob disease.

**Diagnoses not to be missed**

A diagnosis of dementia tends to attract therapeutic nihilism and, although treatment is only symptomatic for many patients with degenerative dementias, many other non-degenerative diseases that can present with cognitive impairment or in which dementia is the major or only feature can be successfully treated. The following are examples of diseases that can mimic Alzheimer’s disease and often present in young-onset dementia clinics.

**Sleep apnoea**

Patients with sleep apnoea can present with memory complaints and, depending on when they are examined, can show cognitive deficits. This presentation is not uncommon: sleep apnoea was reported in 8% of patients presenting to a young-onset
dementia clinic. In addition to the typical constellation of snoring, morning headache, and daytime somnolence, more subtle clues can include refractory nocturnal seizures or cerebrovascular disease.

The mechanism of cognitive dysfunction might be intermittent hypoxaemia or sleep deprivation. Cognitive improvement, particularly in executive functioning, can be achieved by treating patients with obstructive sleep apnoea, although the effects might not always be substantial.

**Transient epileptic amnesia**

The syndrome of transient epileptic amnesia is characterised by fluctuations in cognitive function associated with episodes of anterograde amnesia or retrograde amnesia for discrete time periods (eg, vacations or other salient events for which the patient has essentially no recollection).

Exacerbation of deficits after sleep is a characteristic feature. Other clinical features of temporal lobe seizures often coexist but these are variable and pure amnestic seizures can occur.

Temporal lobe spikes can be evident on a standard electroencephalogram (EEG), but prolonged recording might be needed. There might be evidence of hippocampal damage (altered signal or subtle volume loss) on MRI. Although treatment with anticonvulsants might prevent seizures, and some patients have improvements in cognition, complete resolution of cognitive complaints is unusual.

**Limbic encephalitis**

The past few years have seen substantial advances in our understanding of limbic encephalitis, a rare syndrome associated with subacute onset of cognitive impairment attributable to medial temporal lobe, amygdala, insula, and orbitofrontal cortical involvement, often accompanied by seizures, psychiatric features, and temporal lobe signal change on MRI.

Once infectious causes, including herpes viruses, have been excluded, an immune-mediated process is most likely. In addition to well established paraneoplastic antibodies (including Hu, Ma2,
CV2/CRMP5) targeted against intraneuronal antibodies, a range of antibodies directed against cell-surface antigens (including voltage-gated potassium channels, the NMDA receptor, the GABA<sub>B</sub> receptor, and the AMPA glutamate receptor) are now associated with a limbic encephalitis phenotype.

Certain clinical features can give clues to the causative antibody (eg, older onset with hyponatraemia with voltage-gated potassium channels antibodies; younger female adult/child with dyskinesias in anti-NMDA receptor-mediated limbic encephalitis).

In cases of immune-mediated limbic encephalitis, an underlying tumour should be sought and treated if identified; best available evidence suggests that tumour-negative cases should be treated promptly with immunosuppression.

Several antibody-negative patients might also respond to immune modulation and it is likely that further causative antibodies are yet to be determined; Hashimoto’s encephalopathy might fall into this category, with the involvement of thyroid antibodies as an epiphenomenon.

**Clinical assessment**

The clinical assessment of a patient with cognitive impairment should be the same regardless of age but the breadth of the differential diagnosis in younger patients, which includes many rare diseases, demands a structured approach. The first objective is to determine the pattern of cognitive and behavioural deficit. The second objective is to determine the involvement of the nervous system more generally.

Finally, the general physical examination should not be overlooked because clues to the cause of cognitive dysfunction might lie outside the nervous system. Clinicians should be aware that a patient might initially be referred to non-cognitive specialist clinics; thus, patients with Kuf’s disease or Wilson’s disease might present to a movement disorders specialist at a stage when the cognitive impairment is mild or even absent. However, all patients can present with cognitive impairment when other features are either less salient or absent; for example, the cognitive presentation of multiple sclerosis.
Cognitive assessment

Much information can be obtained from the bedside assessment of different domains of cognitive function, although widely used instruments such as the mini-mental state examination tend to focus on memory, language, and literacy skills, at the expense of non-dominant hemisphere skills. Testing of executive function at the bedside is often difficult to interpret, but reduced verbal fluency might be a useful non-specific indicator of cognitive dysfunction. Dyspraxia and apperceptive agnosia are suggestive of organic disease, implicating dominant and non-dominant parietal function, respectively.

A useful bedside distinction can be made between cortical dementia and subcortical dementia. Cortical dementia is characterised by clear errors in specific domains with relative preservation of cognitive speed, and is exemplified by Alzheimer’s disease and semantic dementia. By contrast, subcortical dementia is characterised by profound slowing of cognition, with a frontal dysexecutive syndrome and impairment of memory retrieval, and is exemplified by progressive supranuclear palsy. In general, the cognitive pattern of dementia plus syndromes is predominantly subcortical.

The association of cognitive slowing and behavioural changes has long been associated with disorders of the basal ganglia but similar syndromes are seen with diseases that affect subcortical white matter pathways or ascending projections linking the brainstem to the cortex.

These ascending systems are vulnerable to many metabolic disturbances and to drugs and disturbances to these systems account for the pattern of cognitive dysfunction most widely seen with systemic disease.

Although bedside cognitive examination can be informative, a formal neuropsychological assessment is necessary to characterise the patient’s cognitive syndrome in detail. The neuropsychologist uses tests of graded difficulty with well established, age-related normative data so that cognitive performance can be compared across specific domains. It is important to determine premorbid
function as far as possible, by use of details of educational attainment, employment history, and reading skills. However, serial assessment is often necessary to be confident of a decline in cognition: neuropsychometry offers the further advantage of quantification of any interval change in performance, bearing in mind that practice effects lead to an improvement in some scores in healthy individuals (eg, IQ scores).

**Dementia plus syndromes and associated diseases—systemic features**

**Cataracts**
- Myotonic dystrophy, cerebrotendinous xanthomatosis, mitochondrial disorders, familial Danish dementia

**Splenomegaly**
- Niemann-Pick disease type C, Gaucher’s disease

**Tendon xanthomas**
- Cerebrotendinous xanthomatosis

**Bone cysts**
- Polycystic lipomembranous sclerosing leucoencephalopathy

**Paget’s disease**
- Valosin-associated frontotemporal lobar degeneration

**Renal impairment**
- Fabry’s disease, Lesch-Nyhan syndrome, mitochondrial disorders

**Hepatic dysfunction**
- Wilson’s disease, Gaucher’s disease, mitochondrial disorders

**Respiratory failure**
- Frontotemporal lobar degeneration and motor neuron disease, Perry syndrome, mitochondrial disease (eg, POLG), anti-NMDA receptor-mediated limbic encephalitis

**Gastrointestinal dysfunction**
- Coeliac disease, Whipple’s disease, porphyria
Anaemia

Vitamin B12 deficiency, neuroacanthocytosis (McLeod’s syndrome), Wilson’s disease, Gaucher’s disease

Skin lesions

Behçet’s disease, systemic vasculitides and connective tissue disease, Fabry’s disease

Metabolic or infectious crises

Vanishing white matter disease, Alexander’s disease, ornithine transcarbamylase deficiency, alpha mannosidosis, porphyria

Hyponatraemia

VGKC limbic encephalitis: The dementia plus syndromes describe patterns of cognitive impairment (dementia) plus additional neurological or systemic features that aid investigation and diagnosis of the underlying disease process. This list cannot be comprehensive. Note that vascular disease, structural disorders, and (para) neoplastic disease can be associated with a wide range of presentations. POLG=polymerase (DNA directed), gamma. VGKC= voltage-gated potassium channel.

Behavioural and psychiatric assessment

The behavioural examination begins during history-taking, with an assessment of the patient’s bearing, their interactions with others, and their spontaneous conversation.

This assessment is particularly important in patients with behavioural variant FTLD, who might not have deficits on formal cognitive testing but who might make fatuous remarks, perseverate, or have environmental dependency (eg, spontaneously attempting to write with the examiner’s pen). Patients with loss of emotional reactivity might appear inexplicably aloof or hostile.

The patient’s approach to testing might also be informative (impulsive in frontal cortical syndromes, slow in subcortical syndromes). Conversely, patients with Alzheimer’s disease generally have a well preserved social appearance but might appear passive during the interview, turning often to their partner to answer questions (the “head turning” sign).
In addition to close observation of the patient, it is important to record a history of behavioural and psychiatric (including major mood or psychotic) symptoms, emphasising the need for a corroborating history from an informant who knows the patient well. Some dementias (commonly dementia with Lewy bodies and occasionally FTLD) might present with prominent delusions or other psychotic features; conversely, the profound apathy of negative symptom schizophrenia might mimic a degenerative frontal lobe syndrome.

Some patients who present with a static behavioural syndrome and normal imaging might have non-degenerative FTLD phenocopies. Features of REM sleep behaviour disorder should also be sought in the history as this favours a diagnosis of dementia with Lewy bodies.

**Neurological examination**

The additional neurological features of a dementia plus syndrome are frequently mild. Careful clinical examination is therefore essential to narrow the large range of potential underlying pathological changes (panels 1 and 2).

The range and speed of pursuit and saccadic eye movements can be useful in refining the differential diagnosis (eg, to identify the supranuclear gaze palsy of progressive supranuclear palsy, Niemann Pick type C disease, and Gaucher’s disease).

The presence of a jaw jerk or pout, brisk tendon reflexes, and gait apraxia can indicate an underlying vascular disorder. Fasciculations, which can be the clue to lower motor neuron involvement in some types of FTLD, can be restricted to the deltoids and triceps in the absence of long tract signs.

Fine myoclonus of the hands in familial Alzheimer’s disease might emerge only when the patient is relaxed or distracted.

**General examination**

Although systemic ill health (eg, renal or hepatic dysfunction) can be readily apparent from the history or on routine blood tests, a careful general examination is needed to ensure that important clues are not overlooked.
Examination of the fundi and blood pressure are mandatory for the identification of vascular disease and vascular risk factors. Inspection of the skin might reveal stigmata of a vasculitic or connective tissue disorder.

Subtle splenomegaly in the absence of hepatomegaly is found in adult-onset Niemann-Pick disease type C, and Achilles tendon xanthomata are found in cerebrotendinous xanthomatosis. Systemic findings might also point to an underlying neoplasm; in particular, the breasts and testes should be examined if a paraneoplastic syndrome is a possibility. The patient’s history could be suggestive of obstructive sleep apnoea with loud snoring or daytime sleepiness, which can be supplemented by examining for a crowded oropharynx or large collar size.

Laboratory investigations

The investigations commonly undertaken in older patients with dementia also apply to young-onset dementia but the broader differential diagnosis mandates a full investigation. The order of investigation follows the general rule of the simplest test first and the most complex and invasive last, which is the order we have detailed below.

The extent of the blood tests will, however, depend on the individual patient. For example, neurogenetics is usually confined to those with a positive family history or additional features such as Paget’s disease, which is suggestive of FTLD associated with valosin-containing protein (VCP) mutations.

All patients with young-onset dementia should have structural neuroimaging and CSF examination as recommended by the American Academy of Neurology and European Federation of Neurological Societies guidelines. Decisions about whether to undertake tissue biopies are based on the clinical phenotype and usually confined to the dementia plus syndromes. Cerebral biopsy is occasionally needed to diagnose cerebral vasculitis.

Blood tests

Routine haematological and biochemical blood tests are more useful for detecting comorbidity than for establishing the
underlying cause, although metabolic encephalopathies are more likely to occur in younger patients than in older patients.

The choice of tests depends on the background and age of the patient, and testing for syphilis or HIV is more relevant in certain settings and, although not routine, should always be considered. Auto-antibodies, antineuronal antibodies, and antibodies implicated in limbic encephalitis should be screened for in patients with rapid-onset dementias or in patients with signs of systemic disease. White cell enzyme and very long chain fatty acid assays are relevant for detection of various metabolic disorders that present in early adulthood, whereas multiple blood films might be necessary to substantiate a diagnosis of neuroacanthocytosis.

Neurogenetics

Neurogenetics has transformed our ability to make precise diagnoses and has extended our understanding of the phenotype of many diseases (eg, leading to the recognition that spastic paraparesis can be associated with some PSEN1 mutations; table 2). Genotyping is often labour-intensive and expensive, although it is anticipated to become less so with novel technologies.

Moreover, at present, screening is impractical in diseases in which many mutations, some family-specific, might be causative. Thus, for some diseases, it is still preferable to establish the diagnosis on the basis of a metabolic profile (eg, increased copper excretion and low ceruloplasmin in Wilson’s disease), and many metabolic disorders can best be determined by direct enzyme assay.

Rational use of a neurogenetics service relies on an accurate and complete family history in all patients presenting with young-onset dementia, with the caveat that a family history might not always be apparent because of censoring by premature death, non-paternity, or de-novo mutations.

Imaging

Historically, the main role of neuroimaging was to exclude a space-occupying lesion, and a CT scan is usually adequate for that purpose. However, MRI offers substantial advantages in enabling assessment of signal change and diagnostic patterns of regional brain atrophy.
Signal change, particularly in the white matter, best seen with T2 or fluid-attenuated inversion recovery (FLAIR) acquisitions, is an important clue to underlying inflammatory disorders such as multiple sclerosis, vasculitis, limbic encephalitis, or CADASIL (in which there is a characteristic anterior temporal lobe white matter change).

Specific patterns of altered signal on FLAIR or diffusion imaging can suggest a prion disease; diffusion imaging is particularly sensitive and should be included if this diagnosis is suspected.

MRI sequences sensitive to iron deposition can provide specific clues to several metabolic and genetic disorders (eg, neuroferritinopathy and pantothenate kinase-associated neurodegeneration).

Specific patterns of atrophy, best seen with a volumetric MRI acquisition, can be invaluable in differential diagnosis, reflecting the characteristic patterns of selective neuronal vulnerability (eg, bilateral hippocampal atrophy in Alzheimer’s disease; asymmetric antero-inferior temporal lobe atrophy in semantic dementia).

Longitudinal imaging enables changes over time to be visualised and quantified. Metabolic and molecular imaging have an emerging role in the assessment of patients with young-onset dementia. Although fluorodeoxyglucose PET imaging (or single photon emission computed tomography imaging) can show temporo-parietal hypometabolism in Alzheimer’s disease, this rarely adds to the visualisation of hippocampal atrophy on structural MRI.

By contrast, evidence of frontal hypometabolism can be useful to identify patients with early FTLD (particularly behavioural variant FTLD) and minimum atrophy. PET imaging with ligands such as Pittsburgh B compound (PiB) can show the presence of amyloid, and is likely to emerge as an important diagnostic adjunct in Alzheimer’s disease and amyloid angiopathy. Extensive systemic imaging including CT and whole body PET might be needed to search for primary tumours in suspected paraneoplastic syndromes.
Neurophysiology

EEG has tended to fall out of favour in the assessment of cognitive impairment, but the characteristic EEG changes of periodic complexes in some prion diseases and in subacute sclerosing panencephalitis are valuable. Early slowing or loss of alpha rhythm is a feature of Alzheimer’s disease but there is relative preservation of this alpha rhythm in the FTLDs. The EEG can also be used to detect covert epileptiform changes in amnestic syndromes due to partial seizures. Electromyography and nerve conduction studies can be used to identify neuropathies or myopathy in the dementia plus syndromes and can help to establish anterior horn cell dysfunction in patients with FTLD and motor neuron disease.
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Preface

Senile dementia is a disease caused by degeneration of the brain cells. It is different from normal senility in the elderly in that the patient’s brain function will gradually deteriorate resulting in progressive loss of memory and mental abilities, and noticeable personality changes.

Clinical investigations of Alzheimer’s disease (AD) have been limited by diagnostic inaccuracy. We employed explicit clinical inclusion and exclusion criteria to identify subjects with senile dementia of the Alzheimer type. In a consecutive series of 26 postmortem examinations from this sample, AD was histologically verified in all subjects and was the primary dementing illness. Seventeen of the 26 SDAT subjects had been diagnosed when only mildly demented. Two control subjects were examined neuropathologically; AD was absent in both. We conclude that research clinical diagnostic criteria for SDAT, even in its mild stage, are valid.

Dementia is an umbrella term for a set of symptoms including impaired thinking and memory. It is a term that is often associated with the cognitive decline of aging. However, issues other than Alzheimer’s can cause dementia. Other common causes of dementia are Huntington’s Disease, Parkinson’s Disease and Creutzfeldt-Jakob disease.

Dementia describes a clinical syndrome that encompasses difficulties in memory, language, and behaviour that leads to impairments in activities of daily living. Alzheimer’s disease is the most common subtype of dementia, followed by vascular dementia, mixed dementia, and dementia with Lewy bodies. Because the global population is rapidly ageing, dementia has become a concern worldwide; the illness places considerable burden on individuals and their families and also on health and social care provision.
Dementia is the loss of cognitive functioning, which means the loss of the ability to think, remember, or reason, as well as behavioral abilities, to such an extent that it interferes with a person's daily life and activities. Signs and symptoms of dementia result when once-healthy neurons (nerve cells) in the brain stop working, lose connections with other brain cells, and die. While everyone loses some neurons as they age, people with dementia experience far greater loss.

Various disorders and factors contribute to the development of dementia. Neurodegenerative disorders such as AD, frontotemporal disorders, and Lewy body dementia result in a progressive and irreversible loss of neurons and brain functions. Currently, there are no cures for these progressive neurodegenerative disorders.

Dementia is a common neurologic syndrome with significant impact on the mortality and morbidity of elderly persons with the most common forms being Alzheimer disease and vascular dementia. Vascular dementia is a heterogeneous entity with a large clinicopathological spectrum that has been classically linked to cortical and subcortical ischemic changes resulting from systemic, cardiac, or local large- or small-vessel disease occlusion. Thus, the diagnosis of vascular dementia is usually made on the basis of clinical, neuroimaging, or neuropathological evidence of cerebral ischemia in the presence of progressive cognitive decline. On the other hand, vascular pathology often coexists with Alzheimer disease, and this poses an additional diagnostic challenge. This has led to the existence of the diagnostic term of mixed dementia. All the matter is just compiled and edited in nature. Taken from the various sources which are in public domain.

It is hoped that the book will serve the purpose of students and scholars on the subject and can be useful to them in allied fields.

—Editor
ABOUT THE BOOK

Senile dementia is a disease caused by degeneration of the brain cells. It is different from normal senility in the elderly in that the patient’s brain function will gradually deteriorate resulting in progressive loss of memory and mental abilities, and noticeable personality changes. Dementia is often incorrectly referred to as “senility” or “senile dementia,” which reflects the formerly widespread but incorrect belief that serious mental decline is a normal part of aging. Diagnosing dementia can be difficult owing to its insidious onset, symptoms resembling “normal ageing” memory loss, and a diversity of other presenting symptoms—for example, difficulty in finding words or making decisions. An individual’s ability to accommodate, compensate, or even deny his or her symptoms in the early stages should also be considered. The individual’s family may also have noticed difficulties in communication and personality or mood changes; family concern is of particular importance. Increasing frequency of patients’ visits to their general practice, missed appointments, or confusion over drugs may also be warning signs. Dementia is a common neurologic syndrome with significant impact on the mortality and morbidity of elderly persons with the most common forms being Alzheimer disease and vascular dementia. Vascular dementia is a heterogeneous entity with a large clinicopathological spectrum that has been classically linked to cortical and subcortical ischemic changes resulting from systemic, cardiac, or local large- or small-vessel disease occlusion. It is hoped that the book will serve the purpose of students and scholars on the subject and can be useful to them in allied fields.

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