Introduction to Quality By Design:

Quality by Design (QbD) is gradually evolving as a improvement of the quality of the product through its life succession. QbD is a considerable change compared to the traditional approach where formulation design and development typically consisted of univariate experiments which clues to incessant upgrading and revolution in products and processes and also offers increased regulatory flexibility within the design space.\(^1\)

History of QbD The idea of QbD had initially charted in the 1960s by management counsellor Joseph Juran, who contended that quality should be intentional relatively than just attained in a chaotic way.\(^2\) Previously, Quality was achieved final product testing and not by process design (QbD) with knowledge of process and formulation variables. The regulatory practice imposed pharmaceutical processes to be operated under pre-defined and fixed operating conditions irrespective of any sources of variability coming from raw materials or processing conditions.\(^2\)

The FDA’s document titled Pharmaceutical cGMPs defined Quality by Design as:

1. Formulating and developing drug product to meet predicted final product quality.
2. Scheming manufacturing developments.

QbD Approach towards Development According to ICH Q8 (R2), the first step in QbD is to aim the product profile. The TPP is distinct as a “forthcoming and vigorous as results of quality features of final drug product that relatively maybe proficient to confirm that the anticipated good quality, safety and effectiveness for the drug product. It forms the basis of design for the development of the product. Separately labelling thought is based on Quality Target Product Profile (QTPP) which is the quality appearances that drug should preferably own in edict to reproducibly provide the therapeutic assistance assured in the label. Examples are purity, assay. QTPP is thus an extension of TPP, purity, strength and Ex. Identity. The next step after this is identifying the Critical Quality Attributes (CQA). A CQA can be well-defined as “specificity of drug product that should be surrounded by proper boundary, range or dispersal to guarantee the preferred product quality”. A risk assessment study is done to estimate these attributes. These studies help to design a safe and efficacious product with the desired CQAs.\(^2\)

A design space is interplanetary design to produce quality product. It can be
created for separate unit operation or process as whole. Therefore, a design space is a convenient means of facilitating regulatory flexibility by allowing the manufacturers to work within an established range of inputs. A design space allows for easier post-approval marketing changes reducing the regulatory hassles and planned by the aspirant which is subjected to regulatory assessment and consent.\(^3\),\(^4\)

Quality is the suitability of a product to its purpose. A drug product that is free from contamination and defects which delivers the labeled therapeutic, pharmacokinetic benefits reproducibly has high quality.\(^5\),\(^6\) Performance, reliability, and durability are the dimensions of quality.\(^7\) Planned quality incorporated into the product is quality by design (QbD).

QbD pharmaceutical science was proposed by the Food and Drug Administration (FDA) and the International Conference on Harmonisation (ICH) in 2005.\(^8\),\(^9\) It is defined as “a systematic approach for formulation development that starts with predefined objectives and contains the product and process knowledge for process control based on sound science and quality risk management”.\(^10\) This approach demands a fully knowledge of how a product’s formulation development and process will impact on the quality of the product.\(^11\),\(^12\) This understanding is implemented through the design of the experiment (DoE).\(^13\),\(^14\) A structured and organized method includes determining and understanding the changing critical quality attributes (CQAs) of the product (including both active ingredients and excipients), for example, physiochemical bioavailability and dissolution release profile.\(^15\) CQAs are properties that impact consumer safety and product efficacy.\(^16\),\(^17\),\(^18\),\(^19\)

These factors are studied by first varying them, identifying variability and evaluating risk, and then determining which factors have a critical influence on product performance. A detailed description of all steps in the process and the expected outcome are required. QbD cannot completely prevent variability because variability can be due to instructions, environment, raw materials, devices, methods, manufacturing system, or personal factors.\(^20\) QbD implies understanding sources of variability and their impact on the final product and then controlling this variability.\(^21\) In the QbD approach objectives are defined, CQAs are identified, manufacturing is designed and developed, and sources of variation are controlled. The quality of the product is then
determined by its performance. If QbD is followed carefully, the need for final product
testing is reduced, or even eliminated.\textsuperscript{22,23}

**Quality by testing versus quality by design**

The QbD approach is different from the traditional quality by testing approach (QbT). The QbT approach is based on testing the quality of the final product to identify any batch that varies from particular manufacturing specifications using pharmacopeia methods. In the QbT approach, a poor quality batch will be detected only after the batch was manufactured. In other words, this approach might lead to a loss of materials, time and money. Furthermore, this approach cannot identify the root cause of variation nor can it suggest any way to prevent such events from happening again even though the sample batch undergoes extensive testing.\textsuperscript{7}

Recalling multiple products after distribution is evidence that inspection using QbT does not guarantee that batches which pass such tests are free from defects.\textsuperscript{7} Furthermore, applying a QbT approach does not allow any flexibility in a manufacturing process.\textsuperscript{24} Adoption of a QbD approach will overcome such problems.\textsuperscript{20} Also, when using the QbD approach operating adjustments are not considered a change if the operating design space was approved.\textsuperscript{20} Therefore, quality by design is useful throughout the product lifecycle.\textsuperscript{25} Drug discovery and development is very time consuming; QbD can reduce the time required in this stage by at least one to three years and save a minimum of $102–290 million.\textsuperscript{26} Snee et al. stated that ignoring the QbD approach is just like the tale about blind people who want to see what the elephant look like, so each one touches a different part and describes it; the blind people all came to different conclusions about the elephant’s shape.\textsuperscript{25} Process understanding gives a full image of product quality.\textsuperscript{27,28}

Design of Experiment (DoE) Nowadays, there is a growing demand from regulatory authorities to gain comprehensive understanding of pharmaceutical development of formulation and manufacturing processes to be improve for the product quality. Authorities such as the International Conference on Harmonization (ICH) have published guidelines on recommended methodology to achieve these objectives. The concept of “Quality by Design” (QbD) was introduced by ICH Q8 guideline on pharmaceutical development which states that quality should not be tested into products, but should be
QbD is a broad term that encompasses predefined target quality, physicochemical, physiological, therapeutic and clinical consideration to found desired quality products that are safe and effective.\(^5\) The design space concept is also introduced in ICH, which is “the multiple dimensions combination and interaction effect of input variables and process parameters that has been studied to give assurance of quality”.\(^5\) Pharmaceutical development is the process of design of quality product and understanding the process that consistently deliver the product for intended performance. The experience gained during pharmaceutical formulation development will help to express the design space for a formulation and process parameters. It is expected that critical quality attributes (CQA) of a product are maintained as long as changes made in process parameters, and formulation attributes are within the defined design space.\(^30\) Therefore, a really helpful element of QBD to define area is that the understanding of actors and their interaction effects by a desired set of experiments. To know the variables and their interactions, several applied mathematics experimental expriments are recognized as good techniques. DoE is a transparent and scientific approach to study the relationship and interaction between independent and dependent variables affecting the formulation and/or process and output of that formulation and/or process. It is the statistical way of testing large number of formulations and process variables in a minimum number of experimental runs.\(^30\) DoE provides not only efficient use of resources, but also provides a method of obtaining a mathematical model which can used to characterize, optimize for formulation or process.\(^31\) Full factorial and response surface designs are most popular designs in DoE. Full factorial designs consists of 2 or additional factors, every with distinct attainable values or "levels", and whose experimental units withstand all potential mixtures of those levels across all such factors. A full factorial design can also be referred to as a completely crossed design. Such AN experiment permits the investigator to study the effect of each and every factor on the response variable and the effects of interactions between multiple factors on response variable. A full factorial design contains all potential mixtures of a group of factors. This can be the foremost fool proof design Approach, however it's additionally the foremost expensive in experimental resources. The complete factorial designer supports each continuous factors and categorical factors.
with up to 9 levels. For the overwhelming majority of factorial experiments, every factor has at only 2 levels; as an example, with 2 factors each taking 2 levels, a factorial experiment would have four treatment mixtures in total, and is sometimes referred to as a 2×2 factorial the quantity. If the quantity of mixtures in an exceedingly full factorial design is just too high to be logistically possible, a fractional factorial design could also be done, within which set of the potential mixtures (usually a minimum of half) are removed. Response surface methodology (RSM) is one of the techniques used to estimate the main effects, their interaction, quadratic effects and shape of response surface. RSM is used when only a few significant factors are involved in optimization. The central composite design (CCD) and Box-Behnken design (BBD) are the most commonly used design for RSM. The BBD has advantage over CCD in that it requires fewer run when the numbers of factors investigated are three. It loses this advantage when number of factor investigated goes to four. It is an independent quadratic design in that it does not contain embedded factorial or fractional factorial design. In this design factor, variable combinations are at the midpoint of edges of the variable space and at the centre. These designs are rotatable and require 3 levels of each factor.\textsuperscript{30} In CCD, the rotatable characteristic enables to identify the optimum responses around its center point without changing the predicting variance.\textsuperscript{31} On the other hand, traditional pharmaceutical development of any dosage form involving trial and error methodology is quite time consuming, expensive and laborious. It involves the concept of “changing one variable at a time, while keeping others as constant”. This methodology is unpredictable and at times unsuccessful.\textsuperscript{32} The limitations of traditional formulation and development have paved a way for application of DoE approach in the pharmaceutical industries.

**MODELLING APPROACHES FOR DEVELOPING QbD:** \textsuperscript{33}

A number of modelling approaches can be proposed for initializing design spaces for pharmaceutical manufacturing mainly divided into three classes:

1. D.O.E.
2. Semi-empirical methods to advance operating regime plans and scaling guidelines.
3. First-principle models in which restricted number of experiments requisite to validate the model.
DESIGN SPACE METHOD USING DOE METHOD:

DoE can be used to know factors influencing end products according to the standards using design space methods. DoE is conducted to evaluate whether the variables in a process are feasible or not. The variables ranked as high risk are evaluated by conducting DoE studies to gain process understanding. DoE can competently screen and optimize formulation variables and recognize the desired combination of excipients within the design space. DoE study can be performed to optimize the critical process parameters and their ranges in a design space. These methods are incorporated in DoE includes:

1. Experimental design
2. Randomized trials
3. Statistical analysis
4. Multi-dimensional models for optimization or control

Three different levels:

1. A laboratory scale screening to identify process parameters on the drug release and CPPs.
2. A laboratory scale optimization to optimize CPP ranges.
3. A pilot scale robustness to confirm the knowledge gained from lab scale.

ANOVA results should attend all DoE data analysis, particularly when the consequence of the model terms is concerned. After DoE studies and establishment of a design space, the next fundamental step towards QbD is to design a control strategy. Control strategy is defined as “a strategic customary of controls, resulting from present product and process attentive that promises process concert and quality of product”. It may include the following: Rheostat of input substantial attributes Product Provisions Controls for unit operations

Monitoring program: There is a significant that the policy to validate control of excipients properties created on the understanding of their effects and not relying solely on compendia standards. A control strategy can include different elements.

Process Analytical Technology (PAT) PAT is a part of control strategy which ensure that process ruins within an established design space. PAT consents incessantly screen, check, investigate, tendency and adjust manufacturing processes. PAT is
defined as a scheme for design, scrutiny and resistor on appropriate extents of quality constraints and recital characteristics of materials and inprocess constituents in mandate to confirm end product quality.\textsuperscript{36}

Real Time Release Testing (RTRT): It is modification of analytical control from an off line, post manufacturing approach to an approach where data is generated during manufacturing, i.e. The process of quality control is shifted upstream into the production process. RTR does not mean less testing, in fact, it often means more analytical data is generated. It provides for control closer to the source of variability in the process and allows for Real Time Release of the batch. RTRT allows leveraging of enhanced process understanding i.e. It facilitates the implementation of corrective actions in real time.\textsuperscript{37}

**FACTORIAL DESIGN – AN OPTIMIZATION TECHNIQUE:** \textsuperscript{38}

It is used to formulate an satisfactory pharmaceutical formulation in the straight conceivable time in pharmaceutical Formulation & Development (F & D) center. The formula developed by the F & D center is then tried at the pilot plant scale and manufacturing scale. Ideally, minor changes are to be made during the scale-up. It is, therefore, very essential to study the formulation from all perspectives. In addition to the art of formulation, statistical analysis is helpful to pharmaceutical formulation to produce better quality product. The levels of factors can be varied independently at two or more levels. A factor is an consigned variable like concentration, temperature, pH etc. Predictions based on the results of an undersigned experiment will be more variable than those which would be obtained in a designed experiment, in particular, factorial design.

**Mechanistic understanding and manufacturing control: Performance tests**

Immediate release (IR) dosage forms are the most commonly used oral formulation because they have many advantages for industries and consumers. Oral preparations are convenient to administer and mostly easy to manufacture.\textsuperscript{39} IR dosage forms first disintegrate, dissolve, and then get absorbed by the body. The first two processes can be evaluated using standardized tests. Mechanistic understanding through in vitro experiments allows the formulator to adapt drug release pattern for optimized absorption. These tests are also used to confirm product performance from the early development stage to the final manufacturing stage before the batch is released.\textsuperscript{40} Disintegration tests and dissolution tests are important performance tests used for oral
preparations.

Alzheimer’s disease (AD), characterised by Alois Alzheimer in 1907, could be a progressive neurodegenerative disorder of the brain and is that the commonest different kind dementia among the senior. It affects over twenty million people worldwide and this range can considerably increase within the future at the side of the rise of the number of senior within the population. Its prevalence will increase with age, from 100 percent at sixty five years to almost five hundredth at eighty five years. In keeping with the “cholinergic hypothesis”, impairment within the cholinergic perform is of important importance in AD particularly the brain areas coping with learning, memory, behavior and emotional responses that embrace the cerebral mantle and also the hippocampus. Brain atrophy is that the most blatant clinical finding in AD during which the amount of neurotransmitter (ACh) are decreased because of its fast chemical reaction by acetylcholinesterase (AChE) accelerator. Moreover, a broad vary of evidences have shown that accelerator AChE produces secondary non-cholinergic functions that embrace promotion in beta-amyloid (Aβ) deposition within the kind dodderly plaques/neurofibrillary tangles within the brain of afflicted people. Thus, AChE inhibition has been documented as a important target for the effective management of AD by a rise within the availableness of neurotransmitter within the brain regions and reduce within the Aβ deposition in all the major causes for cognitive state within the world is Alzheimer’s disease (AD). The predominance of AD doubles each 5 years on the far side sixty five. Scientists created considerable research on AD within the previous couple of years; but, a lot of continues to be unknown. AD largely affects maturity maturity on top of seventy five years. Alzheimer’s disease is encephalopathy leading to the death of brain cells. A lot of or less dementedness is comparable to AD, which ends in loss of intellectual activities. Dementedness isn't a disease dementia encephalopathy that accompany the symptoms of diseases that embody changes in temperament and behavior. A substantial variety of individuals are suffering with AD. It ends up in poignant the work and life long hobbies. Alzheimer’s dementia 1st recognized as sickness in European nation and recently in Europe and America. The psychotic symptoms, like delusions and hallucinations square measure according in most of the AD patients and there symptoms cause early institutionalization. The brain consists of
billions of neuro cells and every neuron transfer the knowledge to different neurons to make a network. The neurons will perform specific functions. In AD patients, the training skills and memory power will decrease increasingly. The analysis on AD reveals that the associated anatomical and chemical changes occur. These changes include nerve cell degeneration and levels of dementia within the brain of AD patients\textsuperscript{51}.

The AD is related to advancing age and a lot of current among octogenarians. The poor and uneducated are a lot of liable to this disease than made and educated. It's expected that the AD patients increase considerably because the population ages. The scientists try to develop the ways of diagnosing the disease within the initial stages and ways that to assist the AD victims. The scientists and health care personnel are looking out higher ways that to assist the AD patients. It's projected that the number of american citizens with AD might increase thrice within the next fifty years that's from four millions to fourteen millions. \textsuperscript{52}

The Alzheimer’s disease is classed as below:

a. Forgetfulness  
b. Confusion  
c. Dementia  

a. Forgetfulness this is often diagnosed as temporary cognitive state. The victims usually forget names of kin and social group and misplace things frequently. This stage might include activity changes additionally to loss of naturalness and social withdrawal.  
b. Confusion during this stage, the psychological feature deterioration is prominent and there's pronounced cognitive state. The victims frequently forget places and vital dates. The noticeable attribute of this stage is poor judgment and alter of individual’s personality. Dementia during this part, there's a serious loss of AD victims struggle to spot kin and social group finally they're going to become infirm\textsuperscript{53}.

Identification it's vital to grasp to identify of dementedness connected health problem and straightforward to diagnose a patient with these forms of symptoms. The dementedness is classified as: one. Primary undifferentiated dementedness. Primary differentiated dementia and three. Secondary dementia. The primary cluster produces the dementia by poignant the brain directly, as those seen in Alzheimer’s. Each have similar symptoms and may not be differentiated by easy ways. The first differentiated dementia includes loss of muscular management. The secondary dementia is owing to temporary disfunction of the brain and is curable, however correct identification is
crucial. Therefore, these 3 varieties of diseases cause identification issues for the medical
personal\textsuperscript{54}. The patients utterly rely upon the care takers during the last stage of AD. AD occurring in time of life or above, within the form of dementia which ends in cognitive state, confusion and emotional. Half the affected people suffer from dementia and it's predominant within the aged people on top of eighty five and fewer than five hundredth of the victims square measure established with Alzheimer's disease\textsuperscript{55}.

The word “dementia” is derived from Latin the word which means without mind. Dementia is a disease, associated with an assembly of symptoms which includes deterioration of intellectual function and other cognitive skills leading to gradual decline in daily activities.\textsuperscript{56} The most commonly used terms of dementia is given in the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM – IV, 1994) and World Health Organization’s (WHO) International Classification of Diseases (ICD – 10, 1992). The term dementia includes a number of different subtypes of which the most common form is AD. At the first visit he found memory impairment, as well as reading and writing difficulties. When she died in 1906 a post mortem examination was performed on her brain. Alzheimer found gross cortical atrophy, nerve cell loss, neuro fibrillary and senile plaques tangles Until 1950, arteriosclerosis was generally considered to be the major cause of dementia in the elderly. In 1951, Today we realize that the case identified by Alzheimer was merely the tip of the iceberg and that dementia is one of the major health problems of old age. Moreover, even after 100 years we still do not understand the etiological, clinical and pathological mechanism of the disease except the rare cases of genetic mutations associated with the familial disease. This thesis reveals the detection of the factors, biochemical markers of the disease in common clinical practice. Majority of AD patients have no obvious family history of disease and is therefore classified as so-called sporadic AD cases. There are however rare known genetic forms of AD\textsuperscript{57}. These genetic forms of AD, collectively referred to as Familial Alzheimer’s Disease (FAD), are associated with specific mutations that are inherited in an autosomal dominant manner. The discovery of these mutations has been instrumental in supplying tools for studying the molecular pathology of AD. Epidemiology Currently over 24 million people worldwide are estimated to be demented\textsuperscript{58}. Almost half of the demented people, 46% live in Asia, 30%
in Europe and 12% in North America. Most of the AD cases are sporadic cases with millions affected worldwide. The familial or inherited form of AD represents only 1-10% of cases. The prevalence and incidence of dementia in various studies.

**ALZHEIMER'S DISEASE A HIGH LIGHT:**

In the year 1907 a German psychiatrist Alois Alzheimer was the very first person who was working on the aged person dementia problem which were not known properly during that time studied on dementia occurring in the aged suffers coined the term Alzheimer disease. On investigation on the patient he noticed senile plaque and neurofibrillary tangles (cerebral cortex) while doing autopsy in a memory lost 50 year female patient named Auguste D. It is recognized by cognitive impairment and psychiatric complications. The possible treatment were available in the treatment of this disease includes in the current and past history includes Pharmacodynamics, Possible mode of action of drugs, which are claimed to treat dementia can be enlisted as follows. The drug can follow any one of the below enlisted mechanism to elicit their response.

1. Increasing global / regional cerebral blood flow (CBF)
2. Direct support of neuronal metabolism.
3. Improving the level of neurotransmission.
4. Improvement of discrete cerebral functions, e.g. memory

All cerebroactive drugs, basic assumption has been that improvement in cerebral circulation is possible, real and therapeutically useful.

**DRUGS ACTIVE IN CEREBRAL**

a. **Cholinergic activators:**
   - Tacrine,
   - Rivastigmine,
   - Donepezil,
   - Galantamine.

b. **Glutamate (NMDA) antagonist:**
   - Memantine

c. **Miscellaneous cerebroactive drugs:**
   - Piracetam,
   - Pyritinol,
Dihydroergotoxine,
Piribedil,
Ginkgo biloba.

Tacrine is the first centrally acting anti-cholinesterase to be introduced for AD can work to compensate the level of acetyl choline in the nerve terminals of brain by preventing it degradation by blocking the hydrolyzing enzyme but due to presence of muscuranic blocking side effects had made it limited use many other natural and semisynthetic cholinesterase inhibitors are widely used in the management of the disease symptoms in the treatment. It has mild side effects.

New drugs under research which are hoped for the treatments:

- Cholesterol-lowering drugs.
  - Atorvastatin
  - Simavastatin.

- ANTI-OXIDANTS.
  - Vitamin E,
  - Ginkgobilba,
  - Melatonin,
  - Idebenone and
  - folic acid

- ANTI-INFLAMMATORY DRUGS.
  - Aspirin,
  - Ibuprofen,
  - Indomethacin
Chapter I

Introduction

INHIBITORS OF BETA-AMYLOID PLAQUES.

- Metal chelator (Desferrioxamine, Clioquinol),
- Vaccines (AB-42 can-1792),
- Monoclonal antibody (m266)

NERVE GROWTH FACTOR TO KEEP NEURONS HEALTHY

Also there is a predominant role of cholinergic muscarinic receptor system in learning and memory deficits but also speculated multiple neurotransmitter receptor interplay. These nerve growth factor are having direct role in the stimulation of the growth of nerve which are having specific role. The possible mode in the treatment of the AD is to improve the cholinergic transmission across the brain. These growth stimulating factors are having a key role in promoting the growth of the nerve when the new nerve get generated or damaged nerve got repaired they can release the synthesized neurotransmitter both synthesis and release become active and also it can be treated by pharmacological intervention to increase cholinergic transmission.

NOOTROPIC AGENTS:

Nootropics (psychotherapeutic agents/ “smart drugs”), act as a booster in brain which facilitate the acquisition of memory and enhance memory retention (LaddeShivakumar). They can overcome or retard cognitive decline occurring in old age and in some diseased condition. These drugs should possess the following properties:

- Facilitate learning acquisition and memory consolidation, and prevent or mitigate impairment of memory induced by aging, amnesic agents and other adverse factors.
- Facilitate interhemispheric transfer of information.
- Improve tonic cortical control over subcortical centres.
- Not to induce any overt behavioral or autonomic effects even on long term administration.

CLASSIFICATION OF NOOTROPIC AGENTS WITH MECHANISM OF ACTION:

A number of drugs, belonging to different chemical families or groups are claimed to show nootropic activity. These are
Nootropic (Cognition Enhancers):

Piracetam and its congeners aniracetam and oxiracetam. (effective in energy metabolism). This category of drug are widely used in almost all part of the world not only with the aged population but also with the young and children those who are having difficulty in remembering or poor memory or children with attention deficient disorder. They are widely used in different formulation. Especially with children it is used in the form of syrups. Even it is well documented and used widely due to having a promising role in the improvement of memory with poor learners and widely marketed in India under different names also the global market of the drug was found to be high it covers a major instrest in the economical sector of the countries, but the exact mechanism behind this is not clear but it is thought to be due to increase in the release of the ATPs in the nerve terminals which can boost up the neuro humerol transmission across the synapse region.

Metabolic Enhancers:

Dihydroergotoxin (Codergocrine), Nicergoline, Piribedil, Pentoxyfylline. The main action of this metabolic improving drug is that it can increase the activity of the cardiovascular system by their direct role on the blood circulation by having a influence on blood vessels in the cranial system. These act by increasing global or regional cerebral blood flow (CBF)/ it can also due to the stimulating property in the central nervous system is considered as a psycho stimulations in the regions of higher centers in the brain.

Cholinergic activators or Cholinesterase inhibitors:

Tacrine, Rivastigmine, Donepezil, Gelantamine, Alicept, Exelon. AChE prevent the break down of the neurotransmitter ACh (label B). Thus ACh is given extra time to transmit messages. Acetyl choline is the major neurotransmitter in the transmission of the nerve impulses in the formation of the memory in the nervous system and it was thought that the reduction in the level of acetyl choline is the major reason behind the pathogenesis of the alzheimers diases and a hypothesis is also put forward which explains the role of acetyl choline the formation of the memory and it is called as cholinergic hypotheis. The current allopathic treatment of alzheimers disease uses
anticholine esterase inhibitors which can block the enzyme reversibly there by it can prevent neuronal degradation of acetyl choline.

**Vasoactive cerebral protectors:**

Pyritinol (Pyrithioxine). They protects the brain and other nevers by its property of nourishment it can increase the nourishment in the tissue this can be achieved by constant supply of brain the regions like brain which depens on high amount of oxygen and glucose and also causes vasodilation which can increase the cerebral blood circulation and provide a constant supply of nutrients which are required for the synthesis of the essential substances which can nourish the brain or they can also have an influence on the sympathetic overflow by having a modulatory role on the synthesis of sympathetic nervous system neurotransmitter like nor adrenaline which can show its effects on monoamine receptors. Vasodilation is considered to be an important phenomenon in the regulation of the circulation which required since increase in blood supply in the brain regions can keep it highly active and can supply rich nutrients and also help in the activation of some nerve which are engaged in the regulation of the normal physiological functions in the body.

**Anti-inflammatory drugs:**

Steroids and NSAIDs. They can reduce various secondary mediators of inflammation which can be seen the vesicles or on the packet where get filled with the fluids, which can elevate the signs of inflammation their by leading to stress on the cell some times leading to permanent loss of cellular structure and also normal function leading to necrosis. But neurons once destructed cannot be regenerated. Neuro inflammation is considered as one of the major risk factors in occurence of many nervous diseases. The released secondary mediators for the inflammatory packet plays a crucial role in the progression of the disease, even they are also prone to number of infection caused by bacteria. Nerve cells with inflammation causes degeneration of the original structure of the nerve cells such that it makes it function less. The only possible way to combat this is by using NSAIDs which can prevent the formation and release of the secondary mediators of the inflammation. Mono therapy with non steroidal anti inflammatory agents shown a promising role in the improvement of the disease system by unknown mechanism, still it is
unclear. Many drugs under this category are available in the market which possess strong anti-inflammatory action. Prevention of neuro inflammation by using these category of drugs some time can improve cognition by its neuro protective function but individually drug cannot be used in treatment of alzheimers disease but in combination it can be used but how drugs engaged in workd is still remains unclear.

**Antioxidants:**

Many naturally available sources are rich in vitamins which includes fruits and vegetables which possess a strong free radical scavenging action in the their by it can prevent neuronal degeneration and also effective as neuropro-tective agents Vit E & C, Ginkgo biloba, Flavanoid. Lycopin which is obtained from the tomato is also claimed for the anti-oxidant activity. Even lycopining is used in the topical applications to prevent the age induced wrinkiling of the skin which causes due to the death of the cells due to generated free radicals which shows promising role in the management of the alzheimers disease.

**MISCELLANEOUS DRUGS:**

The below mention categories of drugs do not influence the major pathway concerned with the alzheimers disease but it can show betterment or improvement in the alzheimers disease by acting on some of the compensory pathway. That is the reason s they are not mention under the category of nootropic agents. Different categories of drug can be used in treatment of alzhimers disease available in combination with the nootropics in market they includes :

**ANGIOTENSIN CONVERTING ENZYME INHIBITOR:**

It belongs to a class of antihypertensive and also very widely drugs under this category used in the management of various cardiac complications medicate their action by preventing the formatin of active angiotensin II. ACE inhibitors like captopril, enalapril a trandilapril has comparable effects of nootropic drug oxiracetam. Further ramipril and losartan have shown significant improvement in basal as well as scopolamine-impaired performance in experimental animals.
5HT₃ ANTAGONIST:
Serotonin is a amine neurotransmitter which elicts its action by binding on its specific receptor they are many in number they can show site dependent actions. many of antagonist of serotonin receptors are widely used for their different pharmacological actions. Among that one drug is Ondansetron, a selective 5HT₃ antagonist which is widely used as an anti-emetic agent some experimental studies on animals shown that ondesetron shown significantly improvement in the learning and memory.

ESTROGEN:
Estrogen is a sex hormone of females which regulate the puberty and adulthood in the women. studies suggests that improvement in memory was observed in some postmenopausal women. Estrogen is having a negative impact in the memory due its rapid feedback mechanism by auto regulating mechanism.

L-ARGININE:
Arginine is a aminoacid they are categorized under excitatory neurotransmitter they mediate their action via binding with N-methyl D aspartate receptors which are found on the terminals. It is also suggests to posses antioxidant activity. This property of the drug made it usage in the combination of the anti-oxidant prepration and generally it is used in the aged population as a preventive drug in the management of the alzheimers disease also it can be used.

Animal studies suggest that Nitric oxide (NO) enhance memory, also NO precursor, L-arginine administration increases the NO concentration in brain. nitric oxide can increase in the cerebral blood flow by dilating the arteries. This property of gases can helps in the supply of proper glucose

SSRIS:
Serotonin is also called as five hydroxyl tryptamine or 5-HT is a amine neurotransmitter plays a pivotal role in the transmission of sensory nerve impulses. It is synthesized and secreted from serotogenic nerves terminals its secretion is auto regulated by reuptake mechanism which hinders its concentration in the nerve terminals as memory is a complex process which involves a multi neurotransmitter enganged with it
many studies suggests that decrease in amine transmitter can also cause
dementia in persons, now already in the market these reuptake inhibits are widely used
Selective serotonergic antidepressant drugs fluoxetine, sertraline and tianeptine have
influence on cognitive behavior in both depressive and non-depressive animals. The
drugs attenuated the cognitive deficits observed in depressive rats and produced
retention deficits in non-depressive rats.

CRITICALITY:
India stands for world’s second largest populated country, and major portion of
the elder population and a very less percentage of young population and very small
portion of children (attention deficient syndrome) also affected by very miserable
and highly care dependence nerve degenerative disease of Alzheimer’s affects anyone at
anytime of their whole life concerned without having any warning indicators or any
type of early symptoms due to confusion in the diagnosis of particular type of dementia
and it may be linger in many cases until it takes the final stage due to disease
progression. Alzheimer’s in India also quickly becoming often more and more common
due to the globalization, as the society is also trying in expanding into one of the
world’s largest and fastest running industrial giants among the entire world. The
severity of occurrence of the disease in the aged people are increasing very fast rate
the research work are not meeting the demand in the field because for many years
the disease was considered as one of the very common neglected disease due to the lack
of information of the disease about its pathogenesis and also with the possible
common reasons for the occurrence of the disease. Research and epidemiological studies
suggests that not only the aged peoples are affected by the disease but also the young
and adults are also suffering with the disease the reason is very quiet commonly the
anxiety and stress very commonly seen in the present generation which is making the
population to face many dangerous disease among them dementia is one of the serious
and stands for the second position in the death and reduced life of the person the first
cardio vascular disease stands which causing majority of the death incidences in the
adult and young population.

Nerve is of the two type’s afferent nerves and the efferent nerves. These afferent
nerves carry information from sensory organs to the brain any type of stimulation that can stimulate the afferent nerve fibres in the terminals of the nerve which can be connected with the organs, it immediately sends the impulses to the brain. As a respond to this stimulus brain sends impulses through efferent nerves, this type of communication is only possible through the involvement of secretion of some chemical substances they are called as the neurotransmitters. It is the answer given by the brain to the questions given the sensory afferent nerve fibres through efferent nerve. This is called as communication.

Memory is one consider as a complicated phenomenon which involves many inter-neuron secretion for the completion of these complicated phenomenon. Imbalance in the neurotransmitter can leads to neurodegenerative disorders. Some examples can be considered to explain in the neurotransmitter levlel in the brain increase in dopamine leads to schizophrenia. Dopamine is an amine neurotransmitter gets secreted from dopamergic nerves, which are secreted from five different path way which is having different physiological role.

Dopamine shows its actions by binding to dopamnergic receptors which are once again five in numbers. Dopamine is responsible for regulating the personality of the person, like behavior of the persons, posture, locomotion, eating pattern of the person. There is a direct relation ship between dopamine and memory. Many of the drugs which are claimed for Nootropic action and are already used in the current medical practice are having a property to inhibit dopamine action, which is a quiet common side effect with the treatment. Where decrease is the motor action which can be seen in the patient s who are all treated with Piracetam.

Neurotransmitters of memory includes acetyl choline, upon cholinergic nerve stimulation the nerve terminals secretes acetyl choline which can show its actions by binding to cholinergic muscuranic receptors. Many hypothesis are focused on the cholinergic transmission and their deficits and their major role in the memory. Based on this consideration cholinergic hypothesis generated suggests that acetyl choline is the major neurotransmitter of all cranial nerve which are having a direct link with the brain and having a major role in the memory. And even it have been suggested that the
patients suffering from amnesia are having common problem with the acetyl choline level. Many of the drugs in the treatment are targeted on the metabolism of acetyl choline. It is metabolized by two enzymes called as pseudo cholinesterase and butryl choline esterase, decrease in the level of acetyl choline causes deficit in the memory.

Learning and the Memory is a very complicated process which requires involvement of many neurotransmitters with the proper conduction of the nerve impulses. Many type of learning can be enlisted according to the exposure of the person to the daily events, even though for success full learning there should be proper secretion of neurotransmitters.

Histamine is an amine neurotransmitter secreted from the inflammatory packets are called as autocoids are also called as local hormones. Histamine can also show its central action by binding on the histamanergic receptors located centrally; here histamine is acting as a neurotransmitter in the communication of the nerve. Even for learning histaminergic nerve stimulation is thought to be essential. They are considered as a minor pathway but even though they are having a prominent role in the learning behavior of the persons. This action cannot be neglected as they can cause stimulation of various areas of the brain which are concend with the learning and storage of the learned phenomenon.

Other neurotransmitter having role in learning is aspartate. Aspartate is a amino acid which is categories as a excitatory neurotransmitter which mediates its action through binding to NMDA receptor (n- methy d aspartate receptor) they are considered as excitatory stimulus shown through the stimulation.

Serotonin is another neuro-transmitters which is produced and secreted upon the response to the stimulation that arised in the neverve, which can travel the entire nerve which secrete a chemical substance which is commonly called as a neurotransmitter form the serotogenic nerve fibers which upon secretion can show its physiological resone upon binding through different types of 5-HT receptors which are widely distributed in the body and even the regions of central nervous system and even they can engage with the learning and storage phenomenon in the human and in the higher vertebral animals.
Neuropeptides are also a transmitter in the nerve terminals which elicits their effect through G protein coupled receptors, which includes endorphins, dynorphins, enkaphalins, they mediate in the transmission of sensory information towards the brain. During their sensory information transmission they, relay on many neurotransmitters which get secreted in the pre synaptic nerve terminals which includes nor-adrenaline, acetyl choline, GABA, aspartate and many more. The neuro peptides are also called as happy hormones, which can mediate many response through sensory afferent and they can elicit their response through motor nerves, which are efferent in nature.

GABA is an inhibitory neuro transmitter which can elicit their response through binding receptor of GABA. GABA receptors are of two types one is G-protein linked receptors and the others is ligand gated ion Chanel receptors. Neurobehaviour processing in the brain are mediated through chlorine Chanel receptor mediated. They helps in the relay of information form the sensory nerves in the junctional areas of the brain.

Some studies also suggests that the involvement of cholinergic nicotinic receptors in the learning and its storage. Nicotine is a alkaloid which can stimulate some category of receptors depending on this the name nicotinic receptors have been given. Even for the transmission of sensory information their processing the involvement of nicotine can been observed. Acetyl cholines which are considered as a primary neurotransmitter in the processing of information through sensory nerves can also bind on the same binding site of the nicotine. This nicotine is considered as a agonist of the cholinergic nicotinic receptors. They can also potentiate the action of cognitive process by stimulation action.

1. Glutamate (NMDA, AMPA receptors)
2. Acetylcholine (Muscarinic, Nicotinic)
3. Dopamine (D₁, D₂ receptors)
4. 5-HT (serotonin) (5-HT₃, 5-HT₁A receptors)
5. Nor-adrenalin (α, β-receptors)
6. Neuropeptides (G-protein coupled peptidergic receptors)
7. GABA-β-carbolines (GABA-A / Benzodiazepine receptors)

8. Neuro steroids (NMDA / GABA-A receptors).

9. Histamine (H1)

Memory, learning and behavior also rely on neurotransmitters, Acetylcholine found to be the main neurotransmitter in learning and memory. The reduced AChE activity (hippocampus and cortex) is reported in Alzheimer’s disease which leads to the loss of memory to lead normal life tasks.

Cholinergic agonists and anti-cholinesterase inhibitors work synergistically if these combinations are used or sometimes if used alone in the management of dementia works by showing improvement in memory and related learning. It has been suggested from many research that the major receptors involved in the learning and also storage of memory are several types of nicotinic receptors and they are directly linked in the process of memory.

Alzheimer’s disease (AD) is one of the major health and socio-economical burden with the aged population of the country in many parts of the world and the documented rate 14.2% in India.

Neurodegenerative diseases are many in types among them major problems with dementia is one of the major mental health issues in both developed and industrialized countries across the world. Population census predicts many developed countries elderly (crossed sixties) are going to increase seventy percentage in the year 2020 among it India contributes 14.2 percentage.

Alzheimer disease is a type of neurodegenerative disease where a nerve death leads to an imbalance and missed communication between nerves such that sensory and motor information transmission will be get disturbed, sometimes it may be temporary but many a times it becomes permanent changes in the individual.

There are many reasons for nerve death and changes in the nerve architecture making it unable to involve in the normal physiological roles. Degeneration of cholinergic nerve holds a direct and prominent role in Alzheimer's disease.

Some studies in India reveals that persons above 40 years of age show 0.43%
prevalence where as those aged above 65 years show 2.44% prevalence. The causes for dementia may be due to AD (50 to 70%), blood vessel disease (20 to 30%) or by other nervous disorders. Approximately over 10 million people around the world are affected by Alzheimer’s disease and the severity increases with increase in age.

Allopathic psychoactive drugs have been the main stay of treating mental illness in India and worldwide. Some nootropic agents (Piracetam) are widely used but the resulting chemophobia associated with them and other similar agents has made their use limited.

During last few years there has been increase in usage of alternative medicines by the patients for such ailments, many herbal medicines have been accepted in our country for treating anxiety disorders and cognitive dysfunctions’ Anticholinesterase are best used in alzheimer’s disease shown effective action in CNS but lack of information about it and predictivity of effect is a unsolved matter.

Limited information about AD is further expanding, prediction of treatment with ChEI but not having complete solvation. So we need an ideal drug in cognitive symptoms.

**DEMENTIA:**

Dementia is usually chronic and progressive in nature not a disease, but rather a group of symptoms caused by the impact of multiple diseased brain is generally defined as the “destruction of personal skills in knowing what is happening which is going to interfere with the social well being”. In dementia, performance of learned motor skills; social skills and control of emotions are primarily affected but not the events from long-term memory.

Dementia not only causes a terrible reduction in the quality of life of the sufferer but also causes difficulty to the care giver because the persons who are suffering with dementia require a complete care and it will be a burden to the care giver which makes the life struggling. The causes of dementia are many among them primary importance is given to the free radicals. Human body is exposed to different types of environmental toxins daily in one or the other forms due to his routine works. And also due to the exposure of the body to some chemical substances, which may also
introduce through food, or through inhalation due to pollution, or as a side effect of a
drug or some time due to exposure to the sunlight can generate oxygen free radicals.
Drug after administration undergoes metabolism even these metabolic products
generation due to metabolism also generates free radicals which can cause neuronal
damage along with some tissues in the body which cannot be controlled, but the
fact which is severe is once the nerve cells dies there is not regeneration of the
cell such that permanently it will be get lost which may serve as a chief cause for the
neurodegenerative diseases.

Neuronal metabolism is considered as the second most reason for the dementia
because, nerve cells need more supply of ATPs it will get supplied continuously by
its own metabolism if the metabolism occurs under anerobic conditions then there will
accumulation of lactic acid may occurs in the nerve cells which alters their PH. It may
decreased or the cells will be get exposed to the acidic envorniment in this
acidic envornment many of the enzymes will be inactive or protein degradation may
occurs, chromatin condensation may occurs and alos it will leads to the generation of
oxygen free radicals overall all defined mechanism becomes a possibilities for the
degeneration of the nerve cells which ultimately causes dementia.

Aging is consider as a major complication in the dementia because majority of
the dementia cases are seen in the elders age is consider as a risk factor in the
occurrence of the disease also in the progression of the disease too. During aging many
physiological changes which arises due to dys functions of various organ systems which
will not favour normal homeostasis in the body which can slowly precipitate dementia.
Other major problem faced during ageing is apoptosis it is nothing but programmed
cell death it is quiet common in the aged people, neuronal death occurred during aging
will become as a precipitating factor for the dementia.

The above mentioned factor can increase DNA damage it may due to the release
of oxygen free radicals, which can also causes genetic manipulation and causes
the major reason for the neuronal death. The damaged DNAs will be not in the condition
to produce the precursor for the transcriptions and there by new protein supposed to be
produced for the normal survival of the cell may be effected. Even the free
radicals causes damage to the proteins in the cell wall and the major reason for this is thought to be the ageing as it increases the physiological response in the body.

**SYMPTOMS OF DEMENTIA:**

- memory loss
- Inability to concentrate
- Reduced in personal skills
- Reduced performance in decision making
- Mental confusion
- Changes in the sense organs functions
- Cannot identify any objects or persons
- Sleeplessness
- Disorientation (place, people, time, vision)
- Absent or impaired language ability (aphasia)

**DIFFERENT STAGES IN THE DISEASE**

1. Stage of Pre-Dementia: this stage can be seen quite before the occurrence of the symptoms of the dementia very early it can been seen in this period the person may develop some symptoms or some times it may be devoid of the symptoms, if care taken during this period the disease can be postponed for some years. Stage of pre dementia is normally seen within two months of the progenessis of the disease.

2. Stage of Early-Dementia: this stage is seen very late period of life when primarily symptoms started with the begging of the dementia. It is considered to occur after a long duration of an average of twenty years. This stage is seen for a longer time or the person who started suffering form the disease stays back in this stage for the long time.

3. Stage of Moderate-Dementia: this stage is an intermediate stage and can be seen for a moderate duration of years of one to five years in the dementia stage.

4. Stage of Advanced-Dementia: in this period the severity of the disease will be more the person stays in the stage for the duration of more than ten years in average. in this stage all the symptoms, which can be enlisted in the AD can be
seen in the patient who is suffering from the disease and who had already crossed the other three stages of dementia. Treating the person who is in the last i.e. advanced stage is difficult, also the person's life becomes miserable because he has to completely depend on the care giver for his remaining lifespan.

**PATHOLOGICAL CHANGES IN THE AD**

The below explanation are about the changes in the brain during AD. Memory storage occurs basically in two regions of the brain: the hippocampus and cerebral cortex. The hippocampus stands second in the storage of information; primary preference can be given to the cerebral cortex. Even though hippocampus is having a major prominent work in the processing of sensory signals of the memory. In Alzheimer's disease, patients' brain autopsy shown that a severe shrinkage in the hippocampus region, which is the main pathological changes that occurs in the AD. Due to the shrinkage in the hippocampus region reduced in the blood circulation around the region and leads to nutrition deficiency which leads to neuro degeneration which occur in the majority of the cases due to the irreversible type of cell injury.

In the irreversible type of cell injury occurs here due to the shrinkage of the hippocampus generates an anerobic environment in the brain which causes changes in the normal physiology of the cells which causes acidic environment, the pH of the cell reaches to the acidic due to formation of lactic acid the entire internal environment turns to acidic which causes functional changes in the cell some time it can cause permanent damage to the cell become irreversible in their normal functions which can leads to slow death of the cells surrounding the hippocampus which will becomes the chief cause in the progression and occurrence of disease in the sufferers.

Cerebral ischemia is the major reasons for many type of neuronal disorders because lack of oxygen can causes immediate type of metabolic changes in the cell which can cause permanent and non repair able changes in the cell.
CAUSES OF DEMENTIA:
Dementia-like symptoms may temporary develops with under listed reasons .
1. Drugs (almost all the drug which can generate free radicals and can cause changes in the internal envernoment of the cell by change in the pH )
2. Alcohol caused Dementia in chronic and mild drunkers: chronic usage of the alcohol in the young age also in the elders can precipitate the disease and it is considered as a major risk factor.
3. Substance Abuse many centrally acting drug which are having hallucination effect which are abused by many peoples called as drug adicts for its pleasurable effect in the brain can cause a texture change in the formation and release of the neurotransmitter which may become a greater risk factor in the occurrence and also in the advancement of the disease.
4. Cigerate smoking and usage of tobacco: people those who are having a habbit of smoking more number of cigeratte in a day who are called as Chain smokers are having a high risk of occurrence of the disease and the ratio is too higher, when it is compared with smokers than that of non- smoker.
5. Vitamin Deficiency: vitamins are the micro nutrients which are essential for maintainence of normal physiology of the body and proper functioning of the nervous system. Vitamins are the major source of protection in the body they can counteract the free radicals generated in ongoing events. They act as anti oxidants. It is consider that the generation of free radicals are having a pathogentic role in the occurrence of the disease.

Vitamins in normal concentration in the blood can over come or act as a prophylactic substance either it can prevent this type of cell injury process which occurs due to the exposure of the cell to the oxygen free radicals. Vitamins are having neuro protective action due to the property of neutralization of the oxygen free radicals. So the diet should consists of vitamins supplimesnts regularly. The vitamins defecieny may occur to vitamin deficiency diet consumption or due to distrubtion in the absorption in the vitamin from the diet consumed due to failure in the transport mechanism.
6. Infectious Diseases: infection if not treated completely, or even after treating if resistance developed due to immunological deficiencies are due to development of the resistance in the host or may due to occurrence of new infectious disease when the treatment is in progress and even some time failure of the drug in the treatment of the infections it may cause permanent damage to the nerve structure which is the major reasons for the cause of dementia and some examples for the uncurable disease which occur due to infections includes Whipple's disease, Syphilis, Creutzfeldt-Jakob disease, HIV infection they can increase the risk of dementia.

7. Metabolic Disorders like hyperglycemia include diabetes mellitus. Insulin deficiency is the major reason for diabetes mellitus but the complications are shown due to hyperglycemia which increases polyol formation in the body which changes the internal environment of the cell there by it can cause neuropathy in the sufferers. The best possible way to control dementia is only possible by maintaining normal blood glucose level this can be possible by regular medication and regular exercise and monitoring of blood glucose level.

8. Pseudodementia: a mixture of reasons may stimulate the disease pathogenesis like stress and food habit, disease triggering factor is cell damage it may be due reactive oxygen free radical or anxiety stress, this is considered as a major risk factor in occurrence of the disease. Still advance in age around in the late life of a person at age sixty the disease occurs mainly due to the inflammatory reply to many physiological and pathological reasons.

9. Brain Tumors: cancer is considered to be the major burden in the occurrence of dementia. Many of neurodegenerative diseases are due to the lack in the maintainance and nourishment in the cancerous growth due to disturb in the normal feed back mechanism it disturb the normal well being in the tissue due to imbalance in the regeneration and degeneration which may become one of the major reasons for the neurodegeneration.

10. Toxins: exogeneously administred toxins which may arise due to increase in the dosage of drug used in the treatment of the diseases. Some times due to the invasion of pathogens into the body as the metabolic waste they can release the metabolite
which are toxic in nature which can cause damage to the cellular structure in the nerve some time it turn to be irreversible in nature, which may become one of the chief reasons for the dementia and other type of neurodegenerative diseases in human. Exposure to the industrial hazards and chemicals and consuming of artificial and packed food and preservative used in the packed food are also acts as the chemical mediators in the development of dementia.

11. Normal-pressure hydrocephalus: the cerebro spinal fluid has a major role in the regulation of the pressure in the brain and its surrounding tissues by a very well known phenomenon called as bovensic action. The cerebrospinal fluid distributes the weight of the brain uniformly. The pressure which occurred in the cerebro spinal fluid can also helps in the exchange of the required nutrients form the fluid to the brain tissues and also the liberated waste products of the metabolism form the brain tissue to the cerebro spinal fluid. Any factors which can cause increase in the pressure of cerebro spinal fluid or which causes decrease in the quantity of cerebro spinal fluid causes a tension in the nerves surrounding the brain which can be damaged some time the damage become permanent can cannot be repaired and even cannot be re synthesized so permanently causes dementia.

12. Subdural hematoma: even the internal bleeding called as hamerrohage in the blood vessels like emboli can obstruct the active blood circulation which can slowly causes cellular changes in the brain. Which may be the permenant changes and which cannot be rapirable.

13. Head injuries such as trauma due to accidents

Dementia may occur in different persons due to different reasons and even there are several types dementia are seen but some dementia which occur due to sudden exposure of some stimuli are reversible (drugs, alcohol, hormone, vitamin imbalances or depression) & some dementia which occur due to sudden exposure of some stimuli can become irreversible type (disease which may occurred due to infection which causes weakening of the blood brain barrier and also can effects the nerves in the nervous system can become a major reason for the occurrence of the disease or head injury) and it become a permanent type of demntia.
Alzheimer disease is a general type of dementia, the dementia can be classified by different ways depending on their clinical presentation, major type of classification uses symptoms as the major parameter in the classification, because by observing the symptom it become easy to diagnose the disease in the primary condition. But the symptoms of all dementia is almost same only by proper diagnosis and thorough detail examination makes it easier to identify the disease. Depending on the appearance of the disease or appearance of disease symptoms alzheimers disease can be classified in two types they are

1. Early onset alzheimers disease
2. Late onset alzheimers disease.

The first type of alzheimers disease ie early onset is seen before sixty years of age and the second type i.e, late onset is seen when person crosses sixty years of age.

**SYMPTOMS OF ALZHEIMER'S DISEASE:**

The pathophysiology of AD may begin long before clinical symptoms are apparent. There is an extended time course, with risk factors from genetic predisposition and environment in the clinical expression of the disease. Symptoms like decreased concentration is the major symptom which destroy persons life style and make him to dependent to caretakers for doing their routine works due to demensia which make the condition worsen than the normal.

Some research also suggests that Atrial Fibrillation can also causes blood coagulation causing stroke leads to Alzheimer's Disease. The clotted blood inside the capillaries in the major blood vessels are called as emboli, once this emboli formation occurs it obstruct the passage of blood in the respective blood vessels, especially brain tissue which requires more blood circulation is affected a lot. It may leads to the shrinkage of the region which is supplied with affected blood vessels. The only possible ways to overcome this type of complications is to rule out the emboli and the normal circulation should be achieved in the blood vessels.

Alzheimer’s disease pathogenesis and progression of the disease can be given schematically by using the following flow chart. Which explains the overall the involvements of many mechanisms in the precipitation and elevation of alzheimers
disease in the victim

AMYLOID HYPOTHESIS

In the extra cellular space upon the stimulation of the secondary messangers in favoured environment it leads to the deposition of plaques of beta amyloid proteins. In the same way in the intra cellular space upon the stimulation of the secondary messangers in favoured environment it leads to the deposition of NFT. Due to the change in the internal environment of the cell it will leads to disturb the homeostasis mechanism of the cell. Homeostasis is the maintainence of the internal environment of the cell even there is slight fluctuation in the internal environment by utilizing body componentsary mechanism. Due to this disruption it leads to disturb calcium ion concentration in the cell.

Calcium ion act as secondary messanger in the cell communication. Alteration in the calcium ion concentration leads to interfere in cell communication so fails to exhibit homeostasis. It leads to generation of oxygen free radicals, the generated oxygen free radicals causes some irreversible changes in the cells in the nerves making it permanently damaged and function less. This may be the major pathogenesis step involved in the progression of the disease. Because the nerve tissue once get damaged and it is difficult to get repair and also the regeneration is not possible. It may leads to deficient in the number of the nerve tissue there by the release of the neurotransmitter by the nervous system will be affected a lot there by leads to the abnormality in the normal physiological function of the body. When cholinergic nerve concerned this can lead to disturb in the both learning and memory tasks in the humans. Various substances stimulates formation of plaques and tangles, inflammatory reaction includes Microglia, Astrocytes, Free radicals.

NEUROCHEMISTRY

The neurochemical imbalances occurs with AD. Researchers reported that neurotransmitter level in cerebral cortex is directly propotional to the neuronal number. Degradation of neurons causes reduced neurotransmitter level a new hypothesis called cholinergic hypothesis bases on this factor.

It not only occurs with destricution of neuron but also due to elevated levels of
two enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) which hydrolyses acetyl choline, which causes a drastic decrease in the level of acetyl choline a primary neurotransmitter of cholinergic nervous system which helps in consolidation of memory. The current available therapy also depends on targeting this enzyme by inhibiting it for protecting acetyl choline from degradation.

**SYNAPTIC AND NEURONAL DEATH (NEURODEGENERATION)**

Synapse is the effective junction in between the nerve terminals where the essential informatins are transferred between the nerve through a chemical mediators called as neurotransmitters, here we can find two nerves connected through a chemical connection rather than anatomacial connections. They are very much essential for a nerve to communicate. Depending on nerve secretion at the terminal neurotransmitter the nerves are named like acetyl choline form cholinergic nerve.

Alzheimer disease is a type of neurodegenerative disease where a nerve death leads to an imbalance and missed communication between nerves such that sensory and motor information transmission will be get disturbed, sometimes it may be temperoral but many a times it becomes permanant changes in the individual.

There are many reasons for nerve death and changes in the nerve artitecture making it unable to involve in the normal physiological roles. Degeneration of cholinergic nerve holds a direct and prominent role in alzhimer’s disease.

**Granulovacuolar degeneration** are more commonly found in Alzheimer’s disease.

Change of nerve cells during Alzheimer’s disease it can cause disintgreation of microtubules leading to the degeneration of the nerve and nerve structure get change making it functionless and also death of the group of the nerve the main reason for this the deposition of beta amyloid plaques, upon precipitation it generates an oxygen lack environment there by causes cell injury the neuronal injury once occur it become permanent and irreversibl. So the dementia once occurs in the person in any of his/her life span will be permanent and irreversbile. But if care taken in the primary stage it can be controlled and even we can prevent of occurenc e of the disease
HYPOTHESIS OF ALZHEIMER’S DISEASE:

Alzheimer disease is one of the major serious complication among the central nervous disorders caused primarily due to neuro degeneration, upto many years the pathogenesis of AD was not known and it was neglected with the confusion of age induced disease but recently a great importance have been given in this area and lot of research works are in progress in theis area. As in the world total population the major propotion of the population is form elders who is living in their fourties and above. Even some epidemiological studies also suggests that by the year 2020 the worlds elders population will be get double there the complication occurs with this disease also get double off, so this area of research is having lot of pressure in development of the new drug to manage the needy. Years together in the research on this area concludes with Various hypothesis which are put forward in order to understand the possible pathogenesis of alzheimer’s disease and very important among them are summersied here very briefly. Even many hypothesis are becoming very strong in the treatment of the disease with relevant scientific documentation of the disease throughout the world.

TAU HYPOTHESIS:

Among all hypothesis put forward to understand the possible pathogenesis of alzheimers disease tau hypothesis is having a major role in the precipitation of the disease. Tau proteins are the micro filamentary proteins upon exess gene expression the production of this tau proteins get increases which then slowly starts to deposits on the nerve surface causing it to diseased by interfere with its neuronal communication mechanisms leading to death of the nerve cells. The nerve cells once under go degeneration then they donot have the protpery to degenerate so it causes permanent damage in the suffers. This occurs mainly due to the Presence of neurofibrillary tangles which appear like a paired helical filament –PHF arises, it occurs due to accumuilation of tau proteins a microtubule-associated protein (MAP),
Dig 1: Disease progression in tau hypothesis

**STEPS INVOLVED IN THE PATHOGENESIS OF AD TAU HYPOTHESIS**

- Accumulation of phosphate in the surface of tau protein will causes it to develop a filament which is paired by its nature. The first step phosphorylation is the activation step which then stimulates the other steps in the progression of the disease.
- Now on the free surface of the neurons the paired helical structural filaments starts to deposit very slowly.
- The paired helical structure form some kind of non functional proteins which are called as non functional tau proteins which got deposited on the surface of the neurons then starts to interfere with the normal function of the neurons. Some time even it can cause irreversible nerve damage.
- The other possible mode of action of tau protein in the pathogenesis of alzheimer's disease is that it can stimulate the formation of neutric plaque. Once the formation of neutric plaque started in the nerve it is the indication of the approach of nerve towards its end. When plaques are deposited in high number slowly the nerves start dying, so it causes a permanent dementia in the person.
**Amyloid Hypothesis:**

Accumulation of beta-amyloid plaques which is made up of beta-amyloid proteins and apoE, is the main pathogenesis behind the hypothesis. APP is a amyloids precursors proteins which can be seen in between the cell membrane. Different enzymes can seen in this region which includes alpha, beta and gamma secretases, among this alpha secretase plays a major role in the precipitation of AD. These alpha secretases causes break down of APP into small fragments, they will be more soluble fragments when comparing with the source from where they got generated. The small pieces are having the property of aggregation they starts grouping together, they can also disturb in the synaptic transmission after getting precipitated on the synaptic region they can cause impairment in the memory.

The aggregated parts of amyloid proteins then strats to deposit on the nerve fibrils, but during prolong exposure it causes toxicity in the nerves. They can cause inflammation in the nerve due to this the deth of the nerve cells may occur. Even apoptosis may also be affected.

**INFLAMMATION:**

Serum amyloid P and alpha1 antichymotrypsin are inflammatory proteins causes inflammation in brain areas which has a chief major prominent in AD. In the current allopathic treatment many of the anti-inflammatory agents are used in the combination while treating alzheimers disease, as alone anti-inflammatory agents are not having any role in the treatment of the disease. But it can act synergistically by preventing neuro inflammation. Relief form inflammation by using this catogery agents hasten the drug theraphy. Even the neuro inflammation causes permentant damage to the nerve structure and even also causes necrosis in the blood vessels which can generate hypoxia conditions in the surrounding tissues which can cause a permanent non repairable damage.

**FREE RADICALS:**

Role of oxygen-free radicals in promoting amyloid aggregation, accumulation of this proteins was identified as a hallo mark in the patients of Alzheimer's disease (AD) especiaaly in lack of oxygen environment like ischemic and tissue-hypoxia.
**CHOLINERGIC HYPOTHESIS:**

The neurochemical imbalances occurs with AD. Researchers reported that neurotransmitter level in cerebral cortex is directly propotional to the neuronal number. Degradation of neurons causes reduced neurotransmitter level a new hypothesis called cholinergic hypothesis bases on this factor. It not only occurs with destricution of neuron but also due to elevated levels of two enzymes *acetylcholinesterase* (AChE) and *butyrylcholinesterase* (BuChE) which hydrolyses acetyl choline.

**ACETY CHOLINE PATHWAYS**

The acetyl choline secreted form the para-sympathetic nerves. Upon stimulation it will be get synthesized from precursors which can be seen the vesciles in the parasympathetic nerve terminals along with the enzyme synthesizing it. The areas involved in the synthesis of acetyl choline are Neocortex, Frontal,Amygdale, Hippocampus, Nucleus basalis of meynert. Acetyl choline synthesis is a simple esterification reaction ie is called acetate activating step with the help of the enzyme choline synthetase.

**CHOLINERGIC IMPARIMENT**

Turn over of acetyl choline is the natural feed back mechanism to regulate its concentration in the nerve terminals. It will be regulated by auto receptors situated in the nerve terminals and already secreted neurotransmitter it will be balanced by some metabolizing enzyme present in the nerve terminals they inclue acetyl choline esterase and butryl choline esterase. Due to over activation some time it causes complete metabolism of the released acetyl choline it leads to the deficiency of the neurotransmitter, which leads to abnormalities when disturbed to the normal physiological role. SDAT disease affects 3 major areas in the brain, Cerebral cortex, Basal forebrain, hippocampus
BRAIN AREAS IN ALZHEIMER’S DISEASE:

![Diagram of brain areas](image)

Dig 2: Alzheimer’s disease (areas in brain)

ALZHEIMER'S DISEASE OVER VIEW

A highlight on some of the pathophysiological properties which are involved in the alzheimers disease.

1. Formation and deposition of amyloid plaques in the nerve tangles
2. formation of neuro fibrilllary tangles
3. neuronal dengenaration
4. beta amyloid is a proteinous substance can precipitate in the nerve terminals leading to cause impairment in the transmission and neuronal death. These amyloid plaques upon depositon can cause neuro toxicity which becomes the chief cause for the progession of the AD.
5. APP gene gama secretase increase in A beta formation
6. Tangles haing aggregation of highly phosphorylated tau protein neuronal protein
7. Cholinergic system dysfunction or abnormalities in the formation and secretion of acetyl choline form the parasympathetic nerve terminals, making it to secrete less amount of acetyl choline which does not match the requierement or degradation of the secreted acetyl choline by choline esterase enzymes.