Alzheimer's Dementia - A Narrative Review

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Abstract

Alzheimer's Disease (AD) was identified almost a century back and is slowly progressing as a global pandemic. This disease is one of the most common causes of Dementia. In this condition, an affected individual loses their recent memories and almost all cognitive functions, and eventually, the person becomes incapable of performing even the simplest of tasks. This paper aims to review the epidemiology, clinical features, diagnostic criteria, pathophysiology, and various treatment strategies of AD dementia.

Key words: Alzheimer's disease, Amyloids, Cognitive functions, Dementia

Introduction

Due to excessive and critical advances in medicine, life expectancy has drastically increased over the past two centuries (1). Mixed with decreased fertility rate in many developed and developing nations; this increased life expectancy led to an increase in the ageing population (2). Therefore, the geriatric population around the globe amplified, and so did the diseases affecting them. One such disease that primarily affects the elderly population is Alzheimer's disease (AD). It is a neurological disorder that causes irreversible degeneration of the brain cells. Most importantly, the frontal and temporal lobes, which are responsible for learning, communication, language, memory, etc., are abridged due to degenerative changes in the synapses and death of neurons.

AD stages itself as a progressive disease with a decline in cognitive functioning, mood, and behaviour (3). Clinically, Dementia presents an array of symptoms that are concomitant with a decline in mental function that is serious enough to diminish an individual's ability to carry out day-to-day activities (4). Though Dementia is considered an inexorable aftermath of ageing; it is not a part of healthy ageing. It occurs due to various reasons; with AD being the most common cause, followed by vascular Dementia (5).

In due course, the disease progresses to a state where emotional control, social behaviour, and motivation also dwindles. Furthermore, the need for assistance and constant supervision exponentially increases gradually, causing more stress to patients, caregivers, and the community.

Epidemiology, Prevalence and Incidence

The World Health Organization (WHO) listed AD as the seventh commonest cause of death globally and the third common cause in developed/higher-income countries (6). Furthermore, the organization has reported that over 55 million people are currently suffering from the disease, and the number is expected to increase up to 139 million in 2050 (6).

Clinical features:
AD classically exhibits diminished memory tailed by impairment in cognitive and executive functions. The classical triad of AD is impaired learning, aphasia, visuo-perceptive deficits. The disease onset is insidious and gradually progresses from mild to severe stages as years advance. The Diagnostic and Statistical Manual of Mental Disorders (DSM–5) describes and categorizes the mental disorders (MDs) to facilitate accurate diagnoses, management, and future research perspectives.
To meet the DSM-5 criteria for AD, a patient must satisfy the major or mild neurocognitive disorder criteria. The disease must be progressive with surreptitious onset resulting in impairment of one or more cognitive domains. The major neurocognitive disorder necessitates diminished cognitive function that is serious enough to impede the patient's day-to-day functioning that is not influenced by any other neurologic condition. The criteria for mild neurocognitive impairment, previously known as MCI, includes milder cognitive decline while retaining functionality (7).

Major domains of cognitive functions that are impaired in AD are as follows:

i. Amnesia:
This is short-term memory impairment, with long-term memory being spared initially. For instance, the affected individual will fail to pay bills or forget medical appointments. This might be followed by difficulty in retaining any new information.

ii. Aphasia
Aphasia is difficulty in finding/forming words and ultimately speaking them incoherently (8). As the condition progresses, the words simply become meaningless utterances, or the patients become mute.

iii. Apraxia
Apraxia denotes difficulty and complexity to carry out day-to-day activities such as dressing oneself, combing hair, and eating. It is essential to keep in mind that this condition is due to impairment of cognitive function and not because of any weakness.

iv. Agnosia
This word is used when the patient finds it difficult to recognize other known persons or objects. This difficulty is not due to visual disturbance but due to neurological instabilities. Agnosia can be exhibited as the inability to use the phone or TV remote, trouble in planning and executing activities.

BPSD (Behavioural and Psychological Symptoms of Dementia):
This may include restlessness, agitation, irritability, anxiety, depression, aggressive behaviour, and hallucination. The intensity of BPSD is expected to worsen as the stage of the disease advances. Nonetheless, it would decline in severity when apathy and global breakdown of functions sets in . It is imperative to tell apart BPSD from delirium and recognize the exact aetiology and treat them accordingly. The probable aetiologies for BPSD are hunger/thirst, pain, anxiety, depression, lack of sleep, adverse effects of certain medications, drug interactions, and infections (9).

Pathophysiology:
AD is characterized by progressive thinning out of the cerebral cortex. Significantly, the frontal and temporal lobes see extensive obliteration. This thinning is due to neuronal destruction of the medium-sized and large pyramidal neurons and the resultant loss of synaptic connections. Autopsy studies revealed multiple senile neuritic plaques and tangles and atherosclerotic changes all through the cortex(10). The aftermath of neuronal loss saw generalized ventricular and sulcal enlargement and cortical atrophy (11). Furthermore, the functions of the neurotransmitter pathway consisting of noradrenergic, dopaminergic, and serotonergic systems are profoundly marred. This resulted in the characteristic behavioural changes in the affected individuals. However, the factor that instigates the disease remains imprecise. Diagram 1 shows the pathophysiology of AD (12).

Various hypotheses associated with AD

I. Cholinergic hypothesis:
Studies on individuals of advanced age and AD have steadily suggested aberrations in the basal forebrain and rostral forebrain cholinergic pathways (13). These pathways seemed to be linked to the level of deterioration of cognitive function. As a consequence, the concept of the "cholinergic hypothesis" stemmed (14). This hypothesis states that "a loss of cholinergic function in the central nervous system contributes significantly to the cognitive decline associated with advanced age and AD" (15). Various types of research advocate that cholinergic oddities; such as variations in choline transport, the release of acetylcholine, expression of nicotinic as well as the muscarinic receptor, etc., can negatively influence the cognitive function. These abnormalities can impact the non-cognitive behavioural deviations and the accretion of lethal neuritic plaques in AD (16,17). Hence, this hypothesis is expected to continue as one of the valid approaches to develop drugs for the management of AD and other forms of Dementia.

II. Amyloid hypothesis:
In consonance with the amyloid hypothesis, Aβ amassing the forebrain is the critical factor for the pathogenesis of AD. Other contributing factors contributing to the pathophysiology, such as the accumulation of phosphorylated tau proteins, are propositioned to be a consequence of discrepancy concerning the production

and clearance of Aβ (18). the Gene for APP is positioned on chromosome 21. Practically every person with Trisomy 21 exhibits the primary signs of AD within 40 years of age. In vitro studies on mice models have shown diminished cognitive functions due to amyloid build-up in the brain cortex (16). Nonetheless, the amyloid hypothesis continues to be a contentious topic due to the lack of In vivo evidence to support the concept that particular neurotoxic genera of Aβ have toxic effects on brain function (19). Therefore, this theory has been reformed of late and given an ancillary role rather than considering it as the aetiology.

III. Tau hypothesis:
The tau hypothesis highlights that unwarranted or unusual phosphorylation of tau protein causes the alteration of normal adult tau into a paired helical filament (PHF) and results in the formation of neurofibrillary tangles (NFTs). These NFTs escort the breakdown of microtubules, and the destruction of the neuron's cytoskeleton and transport system, in turn instigating glitches in intercellular communication, ultimately piloting cell death (20). It was also proposed that serotonergic systems may play a crucial role in the molecular mechanisms of amyloid deposition and hyperphosphorylation of microtubules that result in tau neurofibrillary tangles (21).

ApoE hypothesis:
One common finding seen in both neurofibrillary plaques and tangles was the presence of apolipoprotein E (ApoE). The primary function of this protein is to prevent oxidative damage of neuronal-glial cells, preserve the integrity of the synaptic junctions, and bind to β-amyloids and APP. Amongst the four allelic forms of ApoE, E3 form has been found to have a maximum affinity towards the tau cells and thus prevents β-amyloids and APP-induced toxicity. However, in AD, the E4 form seems to increase in number; therefore, it might be incapable of counteracting the abnormal phosphorylation of tau (22). Besides, E4 fails to prevent the toxicity produced by excessive accumulation of β-amyloids and APP. Subsequently, the failed ApoE mechanism leads to atherosclerotic and ischaemic changes, as well as neurofibrillary tangle formation (23).
Nor-adrenergic receptor hypothesis:

The α2A receptor subtype is the key regulator of noradrenergic activity. This receptor subtype is the crucial regulator for the noradrenergic activity that constrains the inputs of the noradrenergic system into the cerebral cortex. This results in inhibition of response from this region of the brain. Though there is a lack of solid evidence suggesting the role of the noradrenergic components in the pathophysiology of AD, recent research opines that the α2A receptors of the noradrenergic system are an unusual but novel target in AD pathogenesis (24).

Diagnostic criteria:
NINCDS-ADRDA Work Group in the year 2011 updated the previous criteria and proposed the following terminologies for classifying individuals with Dementia caused by AD (25):

1. Probable AD dementia
2. Possible AD dementia
3. Probable or possible AD dementia with evidence of the AD pathophysiological process

The first two terminologies are meant for clinical use, while the third was proposed for research purposes.

I. The core clinical criteria proposed for describing Probable AD dementia must have the previously mentioned findings. Additionally, the patient must show the insidious onset of disease and progressive deterioration of cognitive function. The cognitive deficits should be evident either with a clear-cut amnestic presentation or non-amnestic presentation in the form of altered language perception, visuospatial and executive presentation.

II. A diagnosis of Possible AD dementia involves two other sub-classifications, i.e., AD dementia with atypical course or with an etiologically mixed presentation.
- In the atypical course, the cognitive deficits for AD dementia are the same as defined in the core clinical criteria. Still, there might be a sudden onset of cognitive impairment or non-contributory medical history, or the documentation reveals a progressive decline in cognitive function.
- The etiologically mixed presentation has evidence of (a) simultaneous cerebrovascular disease such as stroke, (b) features of Dementia with Lewy bodies, but it is not Dementia, (c) evidence for any other disease or medication that can substantially affect the cognition.

Diagnosis of Probable or possible AD dementia with evidence of the AD pathophysiological process is made after examining for biomarkers in the brain tissue in biopsy or autopsy samples. These biomarkers are categorized into two classes:
- The first class of the biomarkers includes biomarkers of brain β-amyloids such as low CSF Aβ (42) and positive PET amyloid imaging (26,27).
- The second class of biomarkers highlights neuronal degeneration or injury. The three main bio-markers included in this class are elevated CSF tau (both total and phosphorylated tau), reduced 18fluorodeoxyglucose (FDG) uptake on PET in the temporoparietal region, and disproportionate atrophy of the parietal and temporal lobe when viewed on structural Magnetic Resonance Imaging (MRI).

Assessment

i. History:
A thorough history is the backbone for a proper diagnosis. Obtaining detailed patient history allows the clinician to arrive at a clinical diagnosis; however, the definitive diagnosis can be attained only after post-mortem examination. If the patient has Dementia due to AD, then the history might reveal the insidious onset and gradual progression of the clinical signs and symptoms. It typically shows after 2-3 years of early symptoms that are identifiable in hindsight. It will also disclose the magnitude to which the patient is suffering from functional impairment.

Questions focusing on the difficulty in carrying out daily activities will abet the clinicians to comprehend the level of functional impairment.

The facets of history taking should comprise detailed past medical and psychiatric illnesses, substance abuse, present social and financial situation. This will aid in detecting the actual root cause, thus allowing tailoring the plan according to the patient's needs.

ii. Mental State Examination (MSE):
MSE is done to illustrate the signs and symptoms of AD & Dementia. Performing this examination will apprise the diagnosis and hence the management. MSE collects data regarding the details of mood, thought process, perception, and changes in behaviour. Examining the degree of insight and capacity is vital for making future decisions, be it medical management or social and financial plans.

iii. Cognitive testing:
This will aid in comprehending the extent of cognitive impairment and thereby quantifying it. Also, the areas affected are spotted and monitored. However, it is essential to account for the patient's premorbid functioning, educational level, language barrier, and acute conditions at the time of the test. Nonetheless, this testing alone is not adequate to arrive at a diagnosis.

Montreal Cognitive Assessment (MoCA) and Modified Mini-Mental state examination (MMSE) are the most commonly used cognitive tests. Hoops et al. in 2009 compared these two tests and suggested that MoCA and not MMSE has satisfactory properties to perform psychometric tests to detect mild cognitive impairment (MCI) (28).28

If time is scarce, the cognitive function can be tested by employing a memory impairment scale and a clock drawing test. More assenting test results are obtained by performing the Mini-Cog test, AD8 screening test, the four-item version of the MoCA, and the General Practitioner Assessment of Cognition (GPCOG).

iv. Physical examination:
This is done to assess the overall health of the patient. Blood pressure, pulse rate, and body temperature are monitored, followed by a thorough neurological examination. The neurological examination includes assessment of focal signs, abnormal reflexes, nerve lesions, gait disturbances. Performing this examination helps in differentiating AD dementia from Vascular Dementia and Dementia associated with Parkinson's disease.

Investigations

Complete blood picture analysis comprising total blood count, blood glucose, HbA1c, ESR, lipid profile, urea, electrolytes, vitamin B12, folic acid, and tests to assess the liver function and thyroid function should be carried out. Tests for Syphilis, HIV, Wilson's disease (Ceruloplasmin level), UTI, ECG, and EEG may be helpful (29).

Brain Imaging:
Brain imaging plays an important role in the study of AD and associated Dementia. More recently, contrast CT, structural and functional MRI, particularly 3T MRI, and positron emission tomography (PET) analysis have taken over the radio-diagnosis specialization to identify complex neurological diseases. The studies of cerebral metabolism with fluoro-deoxy-D-glucose (FDG) and amyloid tracers such as Pittsburgh Compound-B (PiB) have revealed the typical amendments that occur even at the prodromal and pre-symptomatic stages of the brains of the individuals affected with AD dementia (30). The indications for imaging are enumerated in Table 2.

Fluorodeoxyglucose- Positron Emission Tomography (FGD-PET) aids in measuring cerebral metabolic rates of glucose as a proxy for neuronal activity in AD (31). Many studies show a reduction in CMRglc early in AD (32). Amyloid PET analysis of the atypical presentation of AD dementia assists in arriving at a diagnosis and deciding the treatment plan. The following changes are seen in imaging studies of a patient with AD:
1. Atrophy of cerebral hemispheres with the corresponding ventricles showing considerable enlargement.
2. The earliest signs are noted in the medial temporal lobe and limbic lobe, such as the posterior cingulate (33). Atrophic changes are, however, noted predominantly in the entorhinal cortex, followed by the hippocampus, amygdala, and parahippocampus (34).
3. Alterations in the brain are noted in the neocortical and all the concomitant regions in a symmetrical manner. This change of the cortices is said to be associated with the spread of neurofibrillary tangles (35).
4. Hypoactivity of the hippocampal region can be noted during functional imaging.

It has to be kept in mind that not all patients will exhibit all the findings mentioned above. These changes must be clinically correlated with the history, neurological examination, laboratory investigations, and disease diagnostic criteria.

Differential diagnosis

The differential diagnosis of AD Dementia includes Huntington's disease and Parkinson's disease, Normal Pressure Hydrocephalus, pseudodementia, hypothyroidism, Vitamin B12 or folic acid deficiency, hypercalcemia, substance abuse, delirium, etc. AD dementia can be clearly distinguished from the conditions mentioned above if the diagnostic criteria and proper investigations and examinations are carried out chronologically.

Risk factors

The risk factors for AD dementia can be broadly divided into modifiable and non-modifiable factors (Diagram 2) (11):

I. Modifiable risk factors:
Head injury, type 2 diabetes mellitus, cardiovascular factors (stroke, heart disease, and hypertension), high cholesterol, obesity in midlife, depression in later life, smoking and alcohol abuse, reactive oxygen species (ROS), estrogen deficit, etc., are considered as modifiable risk factors.

II. Non- modifiable :
Family history, genetic factors, increasing age, Latino and African ethnicities, female gender, trisomy 21 are non-modifiable risk factors. The familial form (1% of AD) is due to variations in genes coding for the proteins such as presinilin1, presenilin 2, APP. Inheritance of the APOE4 gene is a risk factor for acquiring the disease.

Biomarkers

:
Inspecting reliable biomarkers may benefit physicians in detecting the precise pathophysiology of AD during the pre-symptomatic stage. Biomarkers with high sensitivity and specificity enable diagnosis of the disease at the early stages. The following are the most commonly examined and predictable biomarkers for AD dementia:

APP: It has been well established that the presence of senile plaques and neurofibrillary tangles, when closely examined, revealed that they are composed of Aβ and APP. Therefore, if altered proteolytic processing of APP can be detected in AD patients, then measuring APP or its derivatives will aid as a diagnostic marker.

Aβ: APP is present in all tissues, especially present in excess in AD cases. This compound is cleaved by β-secretase to produce ectodomain (sAPP-β). The ensuing cleavage by γ-secretase further releases 38–43 Aβ peptides (36). Since it is already a fact that Aβ42 is the predominant component of the senile plaques, various researchers have suggested Aβ42, as well as other Aβ species, as an investigative tool (37).

Tau and p-tau: Neurofibrillary tangles seen in the brains of individuals affected by AD are chiefly composed of tau, a microtubule-associated protein. Since increased levels of CSF tau is present in other neurodegenerative disorders such as stroke and cortico-basal degeneration, researchers have instigated to specifically probe the phosphorylated forms of tau and consider it as diagnostic biomarkers for AD (38).

Amyloid: Five amyloid PET ligands that are verified in AD patients have yielded assuring results (39).

The ATN Biomarker Classification by the NIA-AA in 2018 is given in Table 1(40)

Isoprostanes: Emerging research and its evidence advocates that oxidative damage could be a significant component in the pathophysiology of AD. The isoprostanes, especially the F2-isoprostanes, are the end-products of the lipid peroxidation process; therefore, these by-products are profoundly inspected (41). It has been learned that these substances are increased in the frontal and temporal cortex of AD. Hence, it is thoughtful to consider this product as a biomarker.

Imaging biomarkers:
Functional MRI (fMRI) studies have disclosed aberration in brain activity of AD patients, such as decreased activation of the entorhinal cortex, supramarginal gyrus, prefrontal regions, anterior inferior temporal lobe, medial temporal lobe, hippocampal regions, and increased activation of medial parietal cortex and posterior cingulate (42).

PET enables in examining the regional cerebral metabolism by employing CMRglc using FDG-PET. Perceived alteration in the brains of the patients with AD involves decreased metabolism in temporoparietal, posterior cingulate, hippocampal complex, medial thalamic regions, and mamillary bodies (38).

Prevention

The aim of prevention should be to prevent or arrest the primary neuropathology, reduce risk factors, and enhance protective factors. Consuming nutrition-rich foods such as the Mediterranean diet, unsaturated fatty acids, lots of fruit and vegetable intake is essential. Physical activity is advised, at least at a moderate intensity. Music therapy, and audiological rehabilitation for patients with hearing loss, is suggested for those suffering from AD. Prevention of sleep deprivation and treating sleep apnea, if present, is recommended. Medication and treatment to reduce the severity of modifiable risk factors are mandated. Depression, particularly late-onset, is linked to acquiring AD within the next five years when contrasted with people with similar risk factors (42). Hence, monitoring and treating Depression in the elderly is essential.

Recent research suggests that anxiety is perhaps leveraging the amyloid in driving the expression of cognitive disorder. Hence, monitoring and treating anxiety may be beneficial.

Screening

Cognitive testing in asymptomatic people with a family history of AD or vascular risk factors is not recommended for screening purposes. However, monitoring for symptoms of cognitive impairment in older adults and those who are at risk for developing AD is advisable. If a cognitive concern arises, a validated cognitive assessment should be carried out as a part of the complete examination/workup.

Managaement

Management of AD incorporates both psychosocial and psycho-educational interventions. Patients with mild or moderate AD would benefit from exercise and group cognitive stimulation. Psychosocial and psycho-educational interventions are also crucial for caregivers. They should include problem-focused and emotion-focused coping

strategies, education, counselling, information regarding services, enhancing carer skills, problem-solving, and strategy development.

Medications

Medications such as Acetylcholinesterase inhibitors, Donepezil, rivastigmine, galantamine, N-methyl-D-aspartate (NMDA) receptor antagonist, memantine and memantine XR formulation, and a combination of Donepezil and memantine are currently available for the medical management of AD dementia (Table 3).

A study by Xu H et al. in 2021 suggested that the global improvement of AD based on CIBIC score was 27% when ACE inhibitors were prescribed. In contrast, the score was 16% in placebo (44). 1 in 4 patients who receive medications for AD dementia get a clinically notable benefit. However, the value of cognitive and functional improvement varies considerably among individuals with AD, but nearly all trials for ACE inhibitors in MCI did not show statistically significant benefit.

The follow-up of the patients must include a multidimensional approach; wherein all domains must be evaluated at least annually. The visits can be scheduled every six months at most, except if new concerns arise or if there is a plan of starting new medications. Patients with BPSD require more frequent monitoring. Since this disease puts a lot of pressure and stress on the caregivers, they should be evaluated regularly for burnout. Zarit Burden Interview scale may be beneficial for that purpose.

De-prescribing Anti Dementia Drugs:
Firstly, it is crucial to consider the patient's wish (if the patient is currently able to make decisions) and any advanced directives and Substitute Decision Making (SDM). De-prescribing should be gradual, and medications should be reinstated if the patient shows any clinical signs of decline in cognitive function or if the neuropsychiatric symptoms improved while cognition and functionality declined. The circumstances that require de-prescribing the medications are explained in Table 4.

BPSD

In clinical settings, neuropsychiatric symptoms can present often and might be difficult to understand initially. It is vital to understand the causes of BPSD and try to reverse them before deciding to medicate. Management of BPSD largely depends on the cause, patient profile, and the presenting symptom. Management options include non-pharmacological methods, ECT, and medications like SSRIs, Trazodone, Gabapentin, and Antipsychotics. Agitation is usually noted quickly as it poses risk to patients and staff, but other symptoms can go unnoticed for a while. When managing BPSD, it is important to start by non-pharmacological measures as it has shown better outcomes in research (Table 5). After we have tried to reverse possible causes and if non-pharmacological measures bear no fruit, we might consider medications as we aim to increase the quality of life. Antipsychotics should be avoided initially, due to the black box warning by the FDA and because it can lead to a series of side effects (45).

Antipsychotics may be used in selected cases where the fast intervention is required due to inefficacy of alternative therapies, and there is risk of deterioration in a patient having severe symptoms. Monitoring closely for the side effects is vital in practice, especially because the geriatric population is more vulnerable to medication side effects in general, and the brains affected by dementia can be extra sensitive to antipsychotics. Davies et al in 2018 developed a sequential algorithm for managing agitation and aggression associated with AD and mixed type of dementia (Diagram 3) (45). It is important to keep in mind that some symptoms are less likely to respond to medications like wandering, hoarding, repetitive activity, vocalizations, undressing, inappropriate voiding, eating inedible objects. Hence, the use of medications might not change the outcome and only add the burden of side effects and drug interaction (46). Deprescribing antipsychotics is vital and has shown promising results in recent studies. It is recommended to de-prescribe after no more than eight to 12 weeks. The suggested tapering strategy in case of BPSD is elaborated in table 6 (47).

Future treatment

The forthcoming and prospective remedial measures for AD should be directed at the etiologic pathologies, mainly the neurofibrillary tangles (composed of p-tau) and senile plaques (Aβ). Research focusing on anti-amyloid, anti-tau, and attempts to alter the neural circuit are underway. The EU/US/Clinical Trials in AD Task Force in 2016 evaluated many clinical trials that focused on remedies for AD dementia to detect which drug or treatment modality is effective (41). The task force could not give any definite solution and treatment options that could completely cure the disease or remove the risk factors (48). However, the meeting in 2020 concluded that it is premature to use remote estimations for clinical trials for novel experimental medications. Nonetheless, non-invasive and multi-domain remote study approaches could be made feasible during the times of the ongoing COVID-19 pandemic (49).

Conclusion

The prevalence of AD has its graph in an increasing trend. Although AD was discovered almost a century ago, there is no permanent remedy to cease, hold back or even decelerate the advancement of this neurodegenerative disease. Although various diagnostic methods such as advanced imaging modalities and biomarker evaluation have come into play, the medical fraternity is still lacking complete knowledge about the aetiology and pathogenesis of the disease. While there is more emphasis on the treatment options that provide symptomatic relief and reduce disease progression, further research is required to detect the disease at the initial stage and provide a definite cure for the disease.

Table 1: ATN Biomarker Classification proposed by the NIA-AA in 2018

Amyloid (A) aggregates	CSF Aβ42, or Aβ42/ Aβ40 ratio Amyloid PET
Tau (T) aggregates	CSF phosphorylated tau Tau PET
Neurodegeneration (N)	CSF total tau Anatomic MRI FDG PET

Table 2: Enumerating the indications for imaging

Indications for imaging:

a. The onset of cognitive impairment signs/symptoms must be within the past 2 years.
b. There must be an unexpected and unexplained decline in cognition and/or functional status in a patient already known to have Dementia.
c. Recent history of significant trauma to the head.
d. Unexplained neurological manifestations such as headache, seizures, Babinski sign, altered gait, etc
e. Patient with a history of cancer.
f. Factors that can increase the risk of intracranial bleeding are present
g. Symptoms suggestive of Normal-pressure hydrocephalus (NPH) are present
h. There is a significant presence of vascular risk factors.

Table 3: Common medications prescribed for the treatment of AD dementia

MEDICATION	
Acetylcholinesterase (ACE) inhibitors Side effects: nausea, vomiting, diarrhea, anorexia, syncope, bradycardia (can theoretically slow heart rate)	
Donepezil (in mild to severe cases of AD)	5 mg PO QAM x 4weeks, then 10 mg QAM. (The dosage may be increased to 23 mg daily in moderate to severe cases, but advised to increase after 3 months on 10 mg).
Rivastigmine (skin patch) (in mild to severe cases of AD)	4.6mg twice a day for 4 weeks, then 9.5 mg twice a day.
Galantamine (in mild to severe cases of AD)	8mg daily for 4weeks, then 16 mg daily. (The dosage may be increased to 24 mg daily after 4 weeks of being on 16mgs).
NMDA receptor antagonist	
Memantine (in moderate to severe cases of AD)	5 mg daily then increase by 5mg increments every week. (Maintenance dose is 10 mg BD (lower in renal impairment))
Memantine XR formulation Side effects: sedation, headache, constipation	7 mg daily for 1 week (The dosage may be increased by 7 mg every week, maximum dose 28 mg daily).
Combination Pill Donepezil/Memantine	Doses: 10mg/28mg Best after trial of the medication and stability is seen Titrate 10/7, 10/14, 10/21, 10/28 (mgs)

Table 4: Indications for de-prescribing AD medications

De-prescribing the medications can be attempted in the following circumstances:
- Clinically meaningful worsening of Dementia
- No clinically meaningful benefit was observed during treatment.
- An individual with severe or end-stage Dementia.
- Development of intolerable side effects (might respond to dose reduction if applicable.)
- Medication adherence is poor, or inability to assess the effectiveness of the medication.

Table 5: Non-pharmacological interventions and management of behavioural and psychological symptoms of dementia in residential care 46

Categories	Non-pharmacological intervention
Sensory Enhancement/ Relaxation	• massage and touch • individualized music • white noise • controlled multisensory stimulation (Snoezelen) • art therapy • aroma therapy
Social Contact: Real or Simulated	• individualized social contact • pet therapy • 1:1 social interaction • simulated interactions/family videos
Behaviour Therapy	• differential reinforcement • stimulus Control
Structured Activities	• recreational activities • outdoor walks • physical activities
Environmental Modifications	• wandering areas natural/enhanced • environments • reduced stimulation • light therapy
Training and Development	• staff education (e.g: CARE Program, P.I.E.C.E.S., proper communication) • staff support • training programs for family caregivers

Table 6: Deprescribing antipsychotic drugs in BPSD (47)

The following strategy is recommending while deprescribing drugs in cases of BPSD • Reduce to 75%, 50%, and 25% of the original dose on a biweekly basis before stopping • Alternatively, reduce the previous dose by approximately 50% every week down to 25% of the initial dose, then stop
Additionally, • For patients with severe baseline BPSD symptoms or longstanding use of antipsychotics, we recommend slower tapering, close monitoring for withdrawal symptoms, and establishing a clear intervention plan emphasizing the use of nonpharmacologic approaches first, in the event of increased severity or recurrence of neuropsychiatric symptoms • Furthermore, tapering might need to be individualized depending on the starting dose, available dosage forms, and how tapering is tolerated
For those prescribed antipsychotics for the treatment of insomnia, the following regimen is recommended: • If the patient has been taking an antipsychotic for a short period of time (eg, <6 wk), stop antipsychotic use immediately. • If the patient has been taking the antipsychotic for a longer period of time, consider tapering the dose first before stopping. If there are concerns on the part of either the patient or the prescriber about possible side effects of immediate discontinuation, tapering can also be considered • All patients should be counselled about nonpharmacologic approaches to sleep (so-called sleep hygiene)

Diagram 1: Pathophysiology of AD dementia

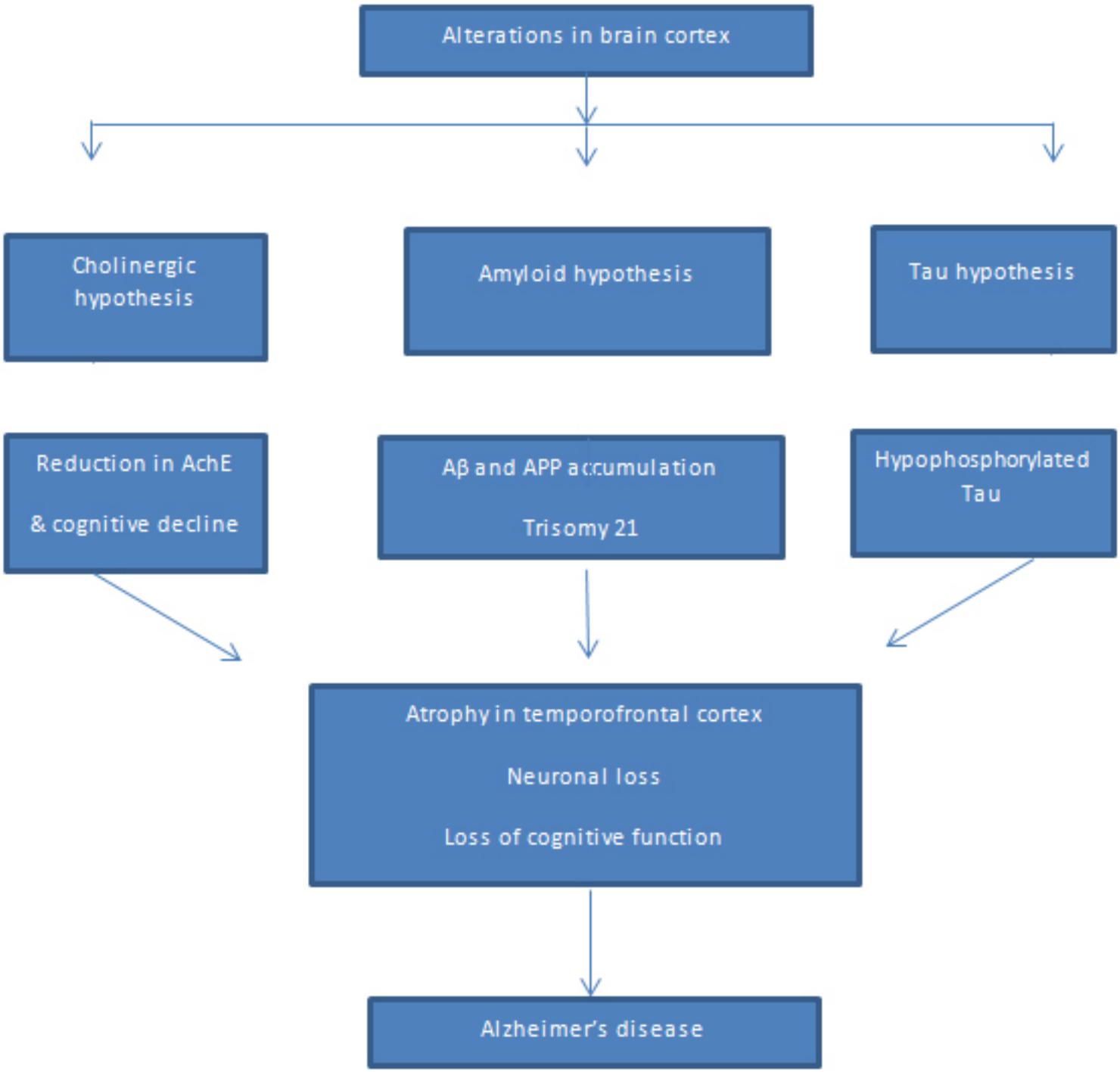


Diagram 2: Risk factors for AD dementia as proposed by Farlow MR8

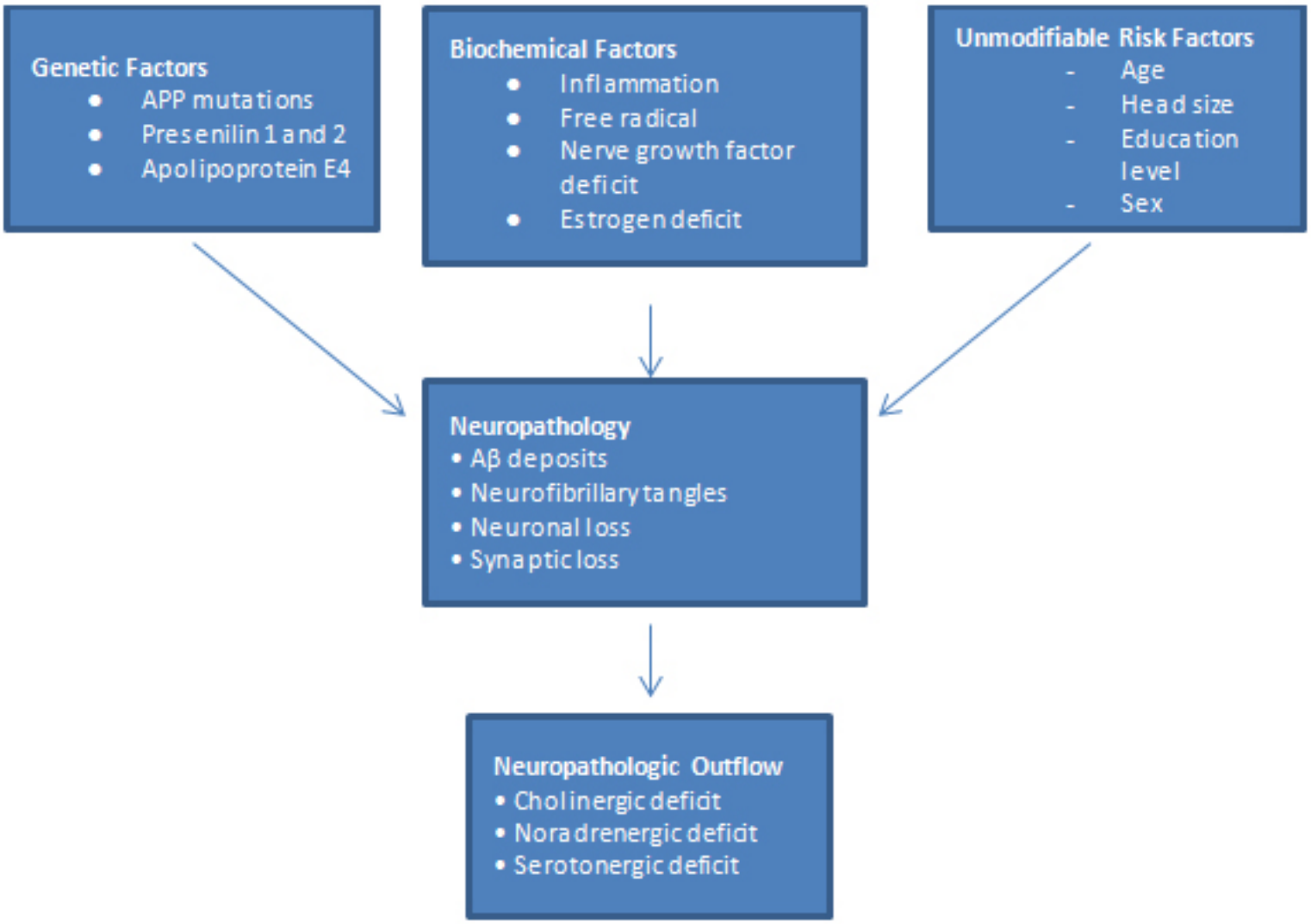
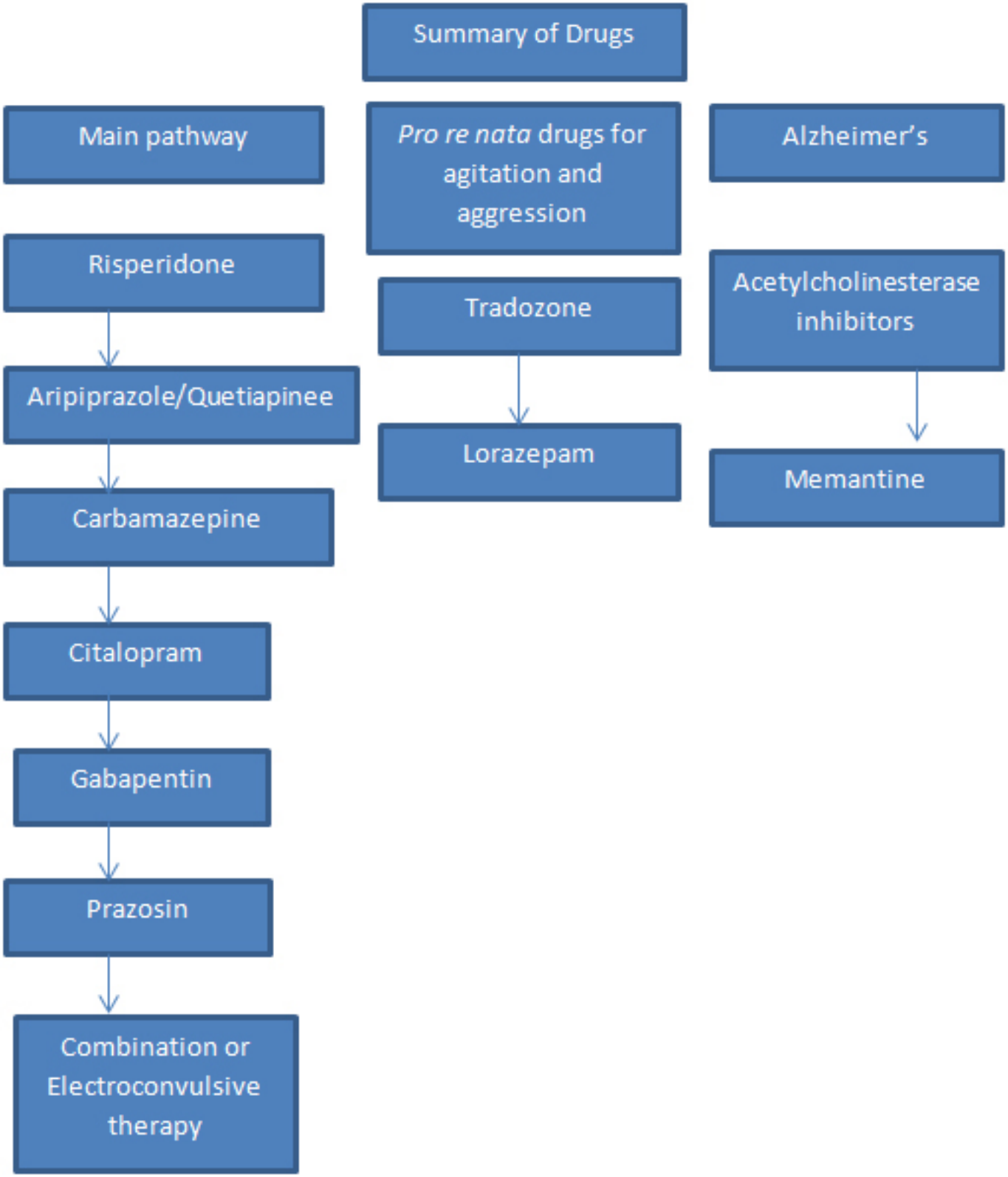


Diagram 3: Algorithm for management of agitation and aggression in AD45



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