Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Kanwal et al - 2026

DOI: http://doi.org/10.5281/zenodo.21215669

SYNAPTIC DYSFUNCTION AND NEUROPLASTICITY IN ALZHEIMER'S DISEASES: PHYSIOLOGICAL MECHANISM, PHARMACOLOGICAL INTERVENTIONS, PHYSICAL ACTIVITY, AND NURSING PROPERTIES

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Vol. 5 No. 2 (2026)

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Kanwal et al - 2026

DOI: http://doi.org/10.5281/zenodo.21215669

Author Details

Keywords:

Alzheimer's disease; synaptic dysfunction; neuroplasticity; pharmacological interventions; physical activity; nursing care; cognitive decline

Received on 24 Apr 2026

Accepted on 06 Jun 2026

Published on 21 Jun 2026

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by synaptic dysfunction and impaired neuroplasticity, which underlie cognitive decline. This review summarizes the physiological mechanisms of synaptic function, the changes in neuroplasticity associated with AD, and the pharmacological and non-pharmacological interventions aimed at preserving synaptic health. Approved and emerging drug therapies, including cholinesterase inhibitors, NMDA receptor antagonists, and disease-modifying agents targeting amyloid and tau, are discussed in terms of their effects on synaptic signaling. The role of physical activity in enhancing neuroplasticity, along with structured nursing interventions that support cognition, daily functioning, and caregiver education, is also highlighted. Integrating pharmacological, lifestyle, and nursing strategies provides a multidimensional approach to maintaining synaptic integrity, delaying cognitive decline, and improving quality of life. Early intervention and a focus on preserving neuroplasticity are essential for effective management of AD.

INTRODUCTION

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder and is the most common cause of dementia worldwide. It primarily affects older adults, leading to a gradual deterioration of memory, reasoning, and daily functional abilities. With increasing global life expectancy, the prevalence of AD is rising rapidly, creating a major public health challenge. This growing burden affects not only patients but also caregivers, healthcare systems, and national economies (1).

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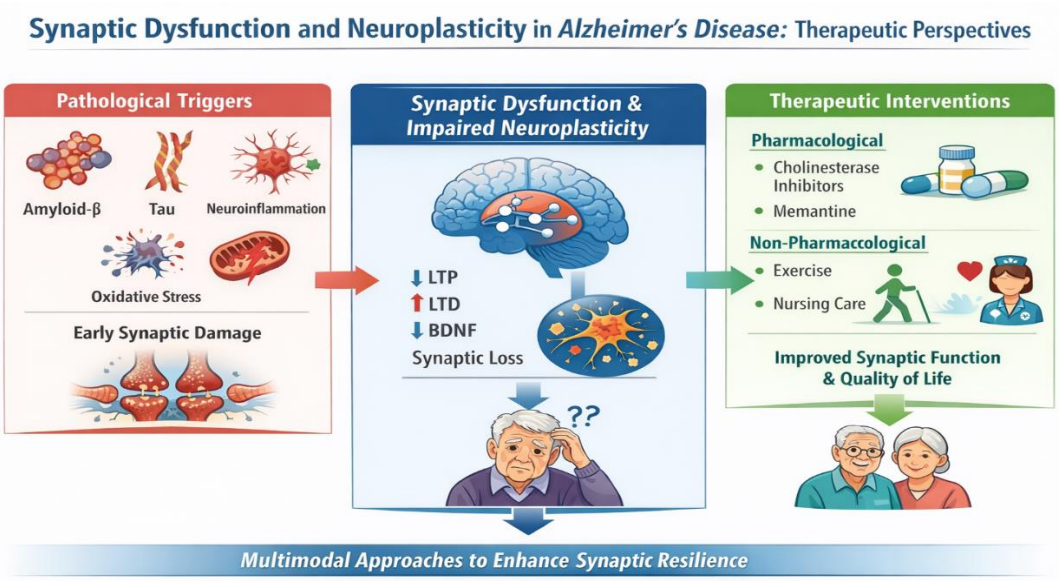

Figure 1: This figure illustrates the key pathological mechanisms leading to synaptic dysfunction and impaired neuroplasticity in Alzheimer's disease, highlighting the roles of pharmacological treatment, physical activity, and nursing care in supporting synaptic function and cognitive performance.

At the molecular level, AD is characterized by the abnormal accumulation of amyloid-β peptides outside neurons and hyperphosphorylated tau protein inside neurons. These pathological changes interfere with normal cellular processes, including synaptic signaling and neuronal survival. Importantly, such molecular disturbances begin many years before the appearance of clinical symptoms, suggesting that early functional impairment is a key driver of disease progression (2).

Synaptic dysfunction is now considered a central feature of Alzheimer's disease and a major contributor to cognitive decline. Synapses play a vital role in communication between neurons, and their loss disrupts learning and memory processes. Studies have shown that synaptic density correlates more strongly with cognitive impairment than classical pathological hallmarks such as amyloid plaques, emphasizing the importance of synaptic health in AD (3).

Neuroplasticity refers to the brain's capacity to adapt structurally and functionally through changes in synaptic strength and connectivity. This process underlies learning, memory formation, and recovery from injury. In

Alzheimer's disease, neuroplastic mechanisms are disrupted, resulting in impaired synaptic remodeling and reduced adaptability of neural networks. These alterations limit the brain's ability to compensate for ongoing neurodegeneration (4,5).

Current pharmacological treatments for Alzheimer's disease are primarily aimed at symptom relief rather than disease modification. Approved medications, such as acetylcholinesterase inhibitors and

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glutamate receptor antagonists, provide modest improvements in cognition and daily functioning. At the same time, experimental therapies targeting amyloid, tau, and synaptic preservation are under active investigation, though their long-term clinical benefits remain uncertain (6,7).

In addition to pharmacological approaches, non-drug strategies play an important role in managing Alzheimer's disease. Regular physical activity has been associated with improved cognitive performance and enhanced synaptic function in older adults. Furthermore, nursing care significantly contributes to patient well-being by supporting daily activities, promoting cognitive engagement, and enhancing overall quality of life through structured and individualized interventions (8,9).

This review examines the physiological mechanisms of synaptic dysfunction and neuroplasticity in AD, current pharmacological and experimental treatments, the role of physical activity in enhancing brain function, and the contribution of nursing practice toward holistic care.

2. Physiology of Synaptic Function and Neuroplasticity

Synaptic function is the fundamental process by which neurons communicate with one another in the brain. A synapse consists of a presynaptic terminal, a synaptic cleft, and a postsynaptic membrane (10). When an electrical impulse reaches the presynaptic terminal, neurotransmitters are released into the synaptic cleft and bind to receptors on the postsynaptic neuron. This interaction allows signals to be transmitted efficiently across neural networks and is essential for cognition, memory formation, and behavior (11).

Neurotransmitters play a central role in synaptic signaling and determine whether synaptic communication is excitatory or inhibitory. Glutamate is the primary excitatory neurotransmitter in the brain and is critical for learning and memory, while gamma-aminobutyric acid (GABA) serves as the main inhibitory neurotransmitter, maintaining balance within neural circuits (12). Proper regulation of these neurotransmitters ensures stable synaptic transmission and prevents excessive neuronal excitation or suppression (13).

Neuroplasticity refers to the ability of synapses to change their strength in response to neuronal activity. One of the most studied forms of synaptic plasticity is long-term potentiation (LTP), which enhances synaptic strength following repeated stimulation. In contrast, long-term depression (LTD) weakens synaptic connections. Together, these mechanisms allow the brain to encode new information, adapt to environmental changes, and refine neural circuits throughout life (14).

Structural plasticity is another important aspect of neuroplasticity and involves physical changes in synaptic architecture. This includes the formation, elimination, or reshaping of dendritic spines, which are small protrusions on neurons that receive synaptic input. Structural remodeling of synapses supports long-term learning and memory by stabilizing functional changes at the cellular level (15,16).

Neurotrophic factors are essential regulators of synaptic function and plasticity. Brain-derived neurotrophic factor (BDNF), in particular, supports neuronal survival, promotes synapse formation, and enhances synaptic strength. Adequate levels of neurotrophic signaling are necessary for

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maintaining synaptic integrity and enabling adaptive plastic responses during learning and memory processes (17, 18).

Overall, normal synaptic physiology and neuroplasticity depend on precise coordination between neurotransmission, receptor activity, intracellular signaling, and structural adaptation. These processes allow the brain to remain flexible and responsive across the lifespan. Disruption of any of these mechanisms can compromise neural communication and cognitive performance, laying the foundation for neurodegenerative conditions such as Alzheimer's disease (19,20).

3. Synaptic Dysfunction in Alzheimer's Disease

Synaptic dysfunction is one of the earliest pathological changes observed in Alzheimer's disease and occurs before widespread neuronal loss (21). Research indicates that synapses are highly vulnerable to disease-related stressors, leading to impaired communication between neurons. This early synaptic failure disrupts neural networks responsible for memory and cognition, explaining why cognitive symptoms may appear even when brain atrophy is still limited (22).

Amyloid-β oligomers play a critical role in synaptic damage in Alzheimer's disease. Unlike amyloid plaques, soluble oligomeric forms of amyloid-β directly interfere with synaptic signaling by altering receptor function and calcium homeostasis (23). These toxic effects impair synaptic plasticity and weaken synaptic connections, ultimately leading to memory deficits and cognitive decline (24).

Tau pathology also contributes significantly to synaptic dysfunction in Alzheimer's disease (25). Abnormal phosphorylation of the tau protein leads to its mislocalization from axons to synaptic compartments. This disrupts cytoskeletal stability and interferes with synaptic vesicle transport, reducing synaptic efficiency and weakening neuronal communication (26).

Synaptic dysfunction in Alzheimer's disease is further amplified by neuroinflammatory processes. Activated microglia and astrocytes release inflammatory mediators that alter synaptic structure and function (27). Chronic inflammation promotes excessive synaptic pruning and disrupts synaptic homeostasis, accelerating cognitive impairment as the disease progresses (28).

Mitochondrial dysfunction and oxidative stress also contribute to synaptic impairment in Alzheimer's disease. Synapses require high levels of energy to maintain neurotransmission and plasticity. Damage to mitochondrial function reduces ATP availability and increases oxidative damage, making synapses particularly susceptible to degeneration under pathological conditions (29).

Overall, synaptic dysfunction in Alzheimer's disease results from the combined effects of amyloid toxicity, tau pathology, neuroinflammation, and metabolic stress. These interconnected mechanisms disrupt synaptic signaling and plasticity, leading to progressive cognitive decline. Understanding these processes is essential for developing interventions that protect synapses and slow disease progression (30, 31).

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4. Neuroplasticity Changes in Alzheimer's Disease

Neuroplasticity is essential for maintaining cognitive function, but in Alzheimer's disease, this adaptive capacity becomes progressively impaired (32). One of the earliest changes observed is a reduction in activity-dependent synaptic remodeling, which limits the brain's ability to strengthen or weaken synapses in response to experience. This loss of flexibility contributes to deficits in learning and memory seen in individuals with AD (33).

Long-term potentiation (LTP), a key cellular mechanism underlying memory formation, is markedly reduced in Alzheimer's disease. Studies have shown that amyloid-β interferes with NMDA receptor signaling, which is crucial for inducing and maintaining LTP. As a result, synaptic strengthening is compromised, leading to poor memory encoding and retrieval (34).

In contrast to reduced LTP, long-term depression (LTD) is often enhanced in Alzheimer's disease (35). Excessive LTD weakens synaptic connections and accelerates synapse loss. This imbalance between LTP and LTD shifts neural networks toward reduced connectivity, contributing to cognitive deterioration and impaired information processing (36).

Neuroplasticity in Alzheimer's disease is also affected by impaired neurotrophic support. Reduced levels of brain-derived neurotrophic factor (BDNF) have been reported in patients with AD, limiting synaptic growth and maintenance. Decreased BDNF signaling further weakens synaptic resilience and accelerates neurodegenerative processes (37).

Age-related neuroinflammation further disrupts neuroplastic processes in Alzheimer's disease. Chronic activation of microglia and astrocytes alters synaptic signaling and inhibits plastic remodeling. Persistent inflammatory signaling interferes with learning-related synaptic changes, worsening cognitive impairment over time (38).

Despite these impairments, some degree of compensatory neuroplasticity may persist in the early stages of Alzheimer's disease. Functional imaging studies in humans suggest that alternative neural networks may temporarily support cognitive function. However, as pathology advances, these compensatory mechanisms become overwhelmed, leading to progressive cognitive decline (39).

5. Pharmacological Interventions Targeting Synaptic Function

Current approved pharmacological treatments for Alzheimer's disease primarily aim to improve synaptic transmission by enhancing neurotransmitter availability. Acetylcholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, work by increasing acetylcholine levels at synapses (40). Acetylcholine plays a key role in learning and memory, and its deficiency is closely linked to synaptic dysfunction in AD. These drugs provide modest cognitive benefits, particularly in the early and moderate stages of the disease (41).

Memantine is another approved medication that targets synaptic dysfunction through modulation of glutamatergic signaling. It acts as a non-competitive antagonist of NMDA receptors, reducing excessive calcium influx that can damage synapses while preserving normal neurotransmission. By protecting synapses from excitotoxicity, memantine helps stabilize cognitive function in patients with moderate to severe Alzheimer's disease (42).

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Beyond symptomatic treatments, disease-modifying therapies targeting amyloid pathology have gained significant attention. Monoclonal antibodies such as aducanumab and lecanemab are designed to reduce amyloid-β accumulation in the brain. By lowering amyloid burden, these therapies aim to preserve synaptic integrity and slow cognitive decline, although their clinical benefits and safety profiles continue to be debated (43).

Tau-targeted therapies are also under investigation as potential strategies to protect synaptic function. These approaches include tau aggregation inhibitors, kinase inhibitors, and anti-tau antibodies (44). By preventing tau misfolding and spread, such treatments aim to reduce synaptic disruption and neuronal toxicity associated with tau pathology. However, most tau-based therapies are still in clinical trial phases (45).

Several experimental drugs aim to enhance synaptic resilience by targeting neuroplastic mechanisms directly. These include agents that modulate synaptic receptors, intracellular signaling pathways, or neurotrophic factor activity. Although still under development, such approaches reflect a shift toward preserving synaptic health rather than focusing solely on protein aggregation (46).

Despite advances in drug development, pharmacological interventions alone have limited effectiveness in addressing the complexity of synaptic dysfunction in Alzheimer's disease. Combination strategies that integrate drug therapy with lifestyle interventions and supportive care may offer greater benefits (47). Continued research into synapse-focused treatments remains essential for improving long-term outcomes in individuals with AD (48).

Table 1: Synaptic Dysfunction, Neuroplasticity, and Multimodal Management in Alzheimer's Disease.

Domain	Explanation	Citations
Alzheimer's disease burden	Alzheimer's disease is the most common cause of dementia worldwide, with increasing prevalence due to aging populations and a significant socioeconomic impact	(1)
Core neuropathology	Accumulation of amyloid-β plaques and hyperphosphorylated tau disrupts neuronal communication and synaptic integrity	(2)
Synaptic loss and cognition	Synaptic loss correlates more strongly with cognitive decline than amyloid plaques or neurofibrillary tangles	(3)
Neuroplasticity in health	Neuroplasticity enables learning and memory through synaptic remodeling and activity-dependent signaling	(4,5)
Early synaptic dysfunction in AD	Synaptic dysfunction occurs early in Alzheimer's disease, preceding extensive neuronal loss	(21,22)
Amyloid-β synaptic toxicity	Soluble amyloid-β oligomers impair calcium homeostasis and glutamatergic synaptic transmission	(23,24)

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Tau-mediated synaptic damage	Hyperphosphorylated tau disrupts cytoskeletal stability and synaptic vesicle transport	(25,26)
Neuroinflammation	Activated microglia and astrocytes promote synaptic pruning and functional decline	(27,28)
Impaired synaptic plasticity	Amyloid-β reduces long-term potentiation and enhances long-term depression, weakening memory circuits	(34-36)
Reduced neurotrophic support	Decreased levels of brain-derived neurotrophic factor limit synaptic growth and resilience	(37)
Compensatory neuroplasticity	Early disease stages show temporary compensatory neural network reorganization	(39)
Cholinesterase inhibitors	Drugs such as donepezil and rivastigmine enhance cholinergic synaptic transmission with modest symptomatic benefits	(40,41)
NMDA receptor antagonists	Memantine reduces excitotoxicity while preserving physiological synaptic signaling	(42)
Limitations of pharmacotherapy	Current pharmacological treatments do not prevent progressive synaptic degeneration	(68,69)
Role of physical activity	Regular physical activity improves cognition and supports synaptic efficiency in Alzheimer's disease	(49,50)
Exercise-induced neuroplasticity	Exercise enhances hippocampal connectivity and synaptic function	(51,52)
Exercise and BDNF	Physical activity increases BDNF expression, promoting synaptic maintenance	(53)
Nursing care interventions	Nursing care supports cognitive engagement, mobility, emotional stability, and daily functioning	(57-61)
Cognitive stimulation	Nursing-led cognitive activities promote synaptic activation and mental performance	(59)
Holistic management approach	Combined pharmacological, physical, and nursing interventions provide optimal synaptic support	(70,71)

6. Physical Activity and Synaptic Plasticity in Alzheimer's Disease

Regular physical activity has been consistently associated with better cognitive health in older adults, including those at risk for or living with Alzheimer's disease (49). Human observational studies indicate that individuals who engage in regular exercise show slower cognitive decline and better

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memory performance compared to sedentary individuals. These benefits are thought to be linked to exercise-induced support of synaptic function and maintenance of neural connectivity (50).

Clinical studies in humans suggest that aerobic exercise can enhance neuroplasticity by improving synaptic efficiency and brain network function (51). Exercise interventions have been associated with increased hippocampal volume and improved memory in older adults, indicating preserved synaptic adaptability. These findings highlight physical activity as a non-pharmacological strategy capable of influencing brain structure and function (52).

Physical activity has also been shown to influence synaptic plasticity through modulation of neurotrophic factors in humans. Exercise interventions increase circulating levels of brain-derived neurotrophic factor (BDNF), which supports synaptic growth and maintenance. Elevated BDNF levels have been associated with improved learning and memory, suggesting a biological pathway through which physical activity promotes synaptic resilience (53).

In individuals with mild cognitive impairment or early Alzheimer's disease, structured exercise programs have demonstrated positive effects on cognitive performance and daily functioning. Randomized controlled trials indicate that moderate-intensity physical activity can improve executive function and slow cognitive decline, potentially by preserving synaptic plasticity and neural efficiency (54).

Neuroimaging studies in physically active older adults reveal improved functional connectivity within memory-related brain networks. Increased connectivity reflects healthier synaptic communication and more efficient neural signaling. These changes may help compensate for early pathological changes in Alzheimer's disease and support cognitive reserve (55).

Despite strong evidence supporting the benefits of physical activity, variability in exercise type, duration, and intensity influences outcomes. Individualized exercise programs that consider physical ability, disease stage, and patient preference may provide the greatest benefit. Integrating physical activity into comprehensive Alzheimer's care plans represents a practical and low-risk approach to supporting synaptic health and neuroplasticity (56).

7. Nursing Perspectives and Practices in Supporting Synaptic Health in Alzheimer's Disease

Nursing care plays a central role in the long-term management of Alzheimer's disease by addressing both cognitive decline and functional dependence. Nurses are often responsible for implementing daily care strategies that promote safety, independence, and cognitive engagement (57). Through continuous patient interaction, nurses can identify early changes in behavior and cognition, allowing timely adjustments to care plans that support brain function and overall well-being (58).

Cognitive stimulation is a key nursing intervention aimed at preserving synaptic activity and mental function in individuals with Alzheimer's disease. Structured activities such as memory exercises, conversation therapy, and orientation techniques encourage neural engagement and may help slow cognitive decline. Nurses play a crucial role in delivering these interventions consistently and adapting them to individual cognitive abilities (59).

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DOI: http://doi.org/10.5281/zenodo.21215669

Physical activity and mobility support are also essential components of nursing care in Alzheimer's disease. Nurses encourage safe movement and daily physical activities that enhance circulation, reduce inflammation, and support brain health. By promoting regular physical engagement, nursing interventions may indirectly contribute to the maintenance of synaptic plasticity and cognitive performance (60).

Emotional support and stress reduction are critical aspects of nursing care that influence cognitive and synaptic health. Psychological stress can worsen cognitive symptoms and negatively affect neural function. Nurses provide emotional reassurance, establish routines, and create calming environments that reduce anxiety and behavioral disturbances in patients with Alzheimer's disease (61).

Education and support for caregivers are another vital nursing responsibility. Nurses train caregivers in effective communication strategies, behavioral management, and daily care techniques. Educated caregivers are better equipped to provide cognitively supportive environments that encourage patient engagement and preserve remaining cognitive abilities (62).

Finally, holistic nursing care integrates medical treatment, lifestyle modification, and psychosocial support to optimize outcomes in Alzheimer's disease (63). By coordinating multidisciplinary care and advocating for patient-centered approaches, nurses contribute significantly to preserving function and quality of life. Such comprehensive care models emphasize the importance of synaptic health within broader dementia management strategies (64).

8. Discussion

This review highlights synaptic dysfunction as a central pathological process in Alzheimer's disease that links molecular abnormalities to cognitive decline. Evidence across human studies shows that synaptic loss and impaired synaptic signaling occur early in the disease and are more closely associated with cognitive symptoms than classical neuropathological markers alone. These findings reinforce the concept that Alzheimer's disease is fundamentally a disorder of synaptic failure rather than simply neuronal death (65).

Alterations in neuroplasticity further contribute to disease progression by limiting the brain's ability to adapt to ongoing synaptic injury. Disruption of long-term potentiation, enhancement of long-term depression, and reduced neurotrophic support collectively impair learning-related synaptic remodeling (66). Human neuroimaging and biomarker studies suggest that compensatory plasticity may temporarily preserve cognitive function, but this capacity diminishes as pathological burden increases (67).

Pharmacological therapies currently approved for Alzheimer's disease offer limited protection against synaptic deterioration. While cholinergic and glutamatergic agents improve synaptic signaling temporarily, they do not address the underlying mechanisms driving synaptic loss (68). Disease-modifying therapies targeting amyloid and tau represent a shift toward mechanism-based treatment, yet their modest clinical effects highlight the complexity of synaptic pathology and the need for multi-target strategies (69).

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https://pakjmcr.com/index.php/1/about
Online ISSN 3007-2387
Print ISSN 3007-2379

DOI: http://doi.org/10.5281/zenodo.21215669

Growing evidence from human studies shows that physical activity enhances synaptic plasticity and cognitive reserve, improving brain connectivity, neurotrophic signaling, and vascular health, which may slow cognitive decline (70). Integrating lifestyle interventions with pharmacological treatment and nursing care through cognitive stimulation, emotional support, physical activity promotion, and caregiver education helps maintain synaptic function and daily independence (71). A multidimensional approach targeting synaptic health offers the greatest potential to delay decline, highlighting the need for early, integrated interventions.

9. Conclusion

Alzheimer's disease is fundamentally a disorder of synaptic dysfunction and impaired neuroplasticity. Pharmacological treatments provide modest symptomatic relief, while physical activity and nursing interventions support synaptic health and cognitive function. Combining these strategies in a multidimensional, patient-centered approach offers the best potential to slow cognitive decline, maintain independence, and improve quality of life. Early, integrated interventions targeting synapses and neuroplasticity are essential for optimal management.

References

Better MA. Alzheimer's disease facts and figures. Alzheimer's Dement. 2023 Apr;19(4):1598-695.

Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO molecular medicine. 2016 Jun;8(6):595-608.

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1991 Oct;30(4):572-80.

Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology. 2008 Jan;33(1):18-41.

Palop JJ, Mucke L. Network abnormalities and interneuron dysfunction in Alzheimer's disease. Nature Reviews Neuroscience. 2016 Dec;17(12):777-92.

Anand P, Singh B. A review of cholinesterase inhibitors for Alzheimer's disease. Archives of pharmacal research. 2013 Apr;36(4):375-99.

Deters KD, Mormino EC, Yu L, Lutz MW, Bennett DA, Barnes LL. TOMM40-APOE haplotypes are associated with cognitive decline in non-demented Blacks. Alzheimer's & Dementia. 2021 Aug;17(8):1287-96.

Zheng Y, Xu X, Zheng B. [Retracted] Clinical Observation on the Effect of Systematic Nursing Intervention on Cognitive Function, Life Activity Ability, and Quality of Life of Senile Dementia Patients. Evidence-Based Complementary and Alternative Medicine. 2021;2021(1):2839142.

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN 3007-2387
Print ISSN 3007-2379

DOI: http://doi.org/10.5281/zenodo.21215669

Erickson KI, Hillman C, Stillman CM, Ballard RM, Bloodgood B, Conroy DE, Macko R, Marquez DX, Petruzzello SJ, Powell KE. Physical activity, cognition, and brain outcomes: a review of the 2018 physical activity guidelines. Medicine and science in sports and exercise. 2019 Jun;51(6):1242.

Koshimizu H, Leiter LM, Miyakawa T. M4 muscarinic receptor knockout mice display abnormal social behavior and decreased prepulse inhibition. Molecular brain. 2012 Apr 2;5(1):10.

Südhof TC. The synaptic vesicle cycle. Annu. Rev. Neurosci. 2004 Jul 21;27(1):509-47.

Meldrum BS. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. The Journal of Nutrition. 2000 Apr 1;130(4):1007S-15S.

Bourke-Waite A. Innovations in scholarly peer review at Nature Publishing Group and Palgrave Macmillan. Insights. 2015 Jul 7;28(2):93-9.

Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993 Jan 7;361(6407):31-9.

Yuste R, Bonhoeffer T. Morphological changes in dendritic spines associated with long-term synaptic plasticity. Annual review of neuroscience. 2001 Mar;24(1):1071-89.

Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. Nature Reviews Neuroscience. 2009 Sep;10(9):647-58.

Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. Nature Reviews Neuroscience. 2013 Jan;14(1):7-23.

Paoletti P, Bellone C, Zhou Q. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. Nature Reviews Neuroscience. 2013 Jun;14(6):383-400.

Yates D. Unravelling the genetics of autism. Nature Reviews Neuroscience. 2012 Jun 1;13(6).

Friston K. The free-energy principle: a unified brain theory? Nature Reviews Neuroscience. 2010 Feb;11(2):127-38.

Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. 2002 Oct 25;298(5594):789-91.

Arendt T. Synaptic degeneration in Alzheimer's disease. Acta neuropathologica. 2009 Jul;118(1):167-79.

Walsh DM, Selkoe DJ. Aβ oligomers–a decade of discovery. Journal of Neurochemistry. 2007 Jun;101(5):1172-84.

Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, Regan CM. Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nature medicine. 2008 Aug;14(8):837-42.

Min SW, Cho SH, Zhou Y, Schroeder S, Haroutunian V, Seeley WW, Huang EJ, Shen Y, Masliah E, Mukherjee C, Meyers D. Acetylation of tau inhibits its degradation and contributes to tauopathy. Neuron. 2010 Sep 23;67(6):953-66.

Ittner LM, Götz J. Amyloid-β and tau—a toxic pas de deux in Alzheimer's disease. Nature Reviews Neuroscience. 2011 Feb;12(2):67-72.

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN 3007-2387
Print ISSN 3007-2379

DOI: http://doi.org/10.5281/zenodo.21215669

Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K. Neuroinflammation in Alzheimer's disease. The Lancet Neurology. 2015 Apr 1;14(4):388-405.

Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, Merry KM, Shi Q, Rosenthal A, Barres BA, Lemere CA. Complement and microglia mediate early synapse loss in Alzheimer's mouse models. Science. 2016 May 6;352(6286):712-6.

Meirovithz E, Sonn J, Mayevsky A. Effect of hyperbaric oxygenation on brain hemodynamics, hemoglobin oxygenation and mitochondrial NADH. Brain research reviews. 2007 Jun 1;54(2):294-304.

Silva-Alves LM, de Barcelos Filho PC, Franci CR. Estrogen receptors ERα and ERβ participation in hypothalamus–pituitary–adrenal axis activation by hemorrhagic stress. Neuroscience. 2017 May 4; 349:239-52.

Hernandez LF, Obeso I, Costa RM, Redgrave P, Obeso JA. Dopaminergic vulnerability in Parkinson's disease: the cost of humans' habitual performance. Trends in Neurosciences. 2019 Jun 1;42(6):375-83.

Penzes P, Cahill ME, Jones KA, VanLeeuwen JE, Woolfrey KM. Dendritic spine pathology in neuropsychiatric disorders. Nature Neuroscience. 2011 Mar;14(3):285-93.

Lightman SL, Conway-Campbell BL. The crucial role of pulsatile activity of the HPA axis for continuous dynamic equilibration. Nature Reviews Neuroscience. 2010 Oct;11(10):710-8.

Keyes PC, Adams EL, Chen Z, Bi L, Nachtrab G, Wang VJ, Tessier-Lavigne M, Zhu Y, Chen X. Orchestrating opiate-associated memories in thalamic circuits. Neuron. 2020 Sep 23;107(6):1113-23.

Hsieh H, Boehm J, Sato C, Iwatsubo T, Tomita T, Sisodia S, Malinow R. AMPAR removal underlies Aβ-induced synaptic depression and dendritic spine loss. Neuron. 2006 Dec 7;52(5):831-43.

Fagiolini M, Jensen CL, Champagne FA. Epigenetic influences on brain development and plasticity. Current opinion in neurobiology. 2009 Apr 1;19(2):207-12.

Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nature Reviews Neuroscience. 2009 Jun;10(6):397-409.

Risher WC, Croom D, Kirov SA. Persistent astroglial swelling accompanies rapid, reversible dendritic injury during stroke-induced spreading depolarizations. Glia. 2012 Nov;60(11):1709-20.

Stern Y. Cognitive reserve in ageing and Alzheimer's disease. The Lancet Neurology. 2012 Nov 1;11(11):1006-12.

Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database of systematic reviews. 2018(6).

Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, Grossberg GT, Khachaturian AS, Vergallo A, Cavedo E, Snyder PJ, Khachaturian ZS. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain. 2018 Jul 1;141(7):1917-33.

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN 3007-2387
Print ISSN 3007-2379

DOI: http://doi.org/10.5281/zenodo.21215669

Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. New England Journal of Medicine. 2003 Apr 3;348(14):1333-41.

Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, O'Gorman J. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016 Sep 1;537(7618):50-6.

Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer's disease. Nature Reviews Neurology. 2018 Jul;14(7):399-415.

Jadhav S, Avila J, Schöll M, Kovacs GG, Kövari E, Skrabana R, Evans LD, Kontsekova E, Malawska B, de Silva R, Buee L. A walk through the tau therapeutic strategies. Acta neuropathologica communications. 2019 Feb 15;7(1):22.

Selkoe DJ. Preventing Alzheimer's disease. science. 2012 Sep 21;337(6101):1488-92.

Snyder PJ, Alber J, Alt C, Bain LJ, Bouma BE, Bouwman FH, DeBuc DC, Campbell MC, Carrillo MC, Chew EY, Cordeiro MF. Retinal imaging in Alzheimer's and neurodegenerative diseases. Alzheimer's & Dementia. 2021 Jan;17(1):103-11.

Millan MJ, Andrieux A, Bartzokis G, Cadenhead K, Dazzan P, Fusar-Poli P, Gallinat J, Giedd J, Grayson DR, Heinrichs M, Kahn R. Altering the course of schizophrenia: progress and perspectives. Nature reviews Drug discovery. 2016 Jul;15(7):485-515.

Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Archives of Neurology. 2001 Mar 1;58(3):498-504.

Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia? A systematic review and meta-analysis of longitudinal studies. BMC Public Health. 2014 May 27;14(1):510.

Maaß A, Düzel S, Goerke M, Becke A, Sobieray U, Neumann K, Lövdén M, Lindenberger U, Bäckman L, Braun-Dullaeus R, Ahrens D. Vascular hippocampal plasticity after aerobic exercise in older adults. Molecular psychiatry. 2015 May;20(5):585-93.

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR. Exercise training increases the size of the hippocampus and improves memory. Proceedings of the national academy of sciences. 2011 Feb 15;108(7):3017-22.

Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. Journal of Psychiatric Research. 2015 Jan 1; 60:56-64.

Lautenschlager NT, Cox KL, Flicker L, Foster JK, Van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP. Effect of physical activity on cognitive function in older adults at risk for Alzheimer's disease: a randomized trial. Jama. 2008 Sep 3;300(9):1027-37.

Bherer L, Erickson KI, Liu-Ambrose T. A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. Journal of Aging Research. 2013;2013(1):657508.

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387
Print ISSN 3007-2379

Kanwal et al - 2026

DOI: http://doi.org/10.5281/zenodo.21215669

Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. The Lancet Neurology. 2014 Aug 1;13(8):788-94.

Birditt KS, Tighe LA, Nevitt MR, Zarit SH. Daily social interactions and the biological stress response: Are there age differences in links between social interactions and alpha-amylase? The Gerontologist. 2018 Nov 3;58(6):1114-25.

McCormack B, McCance TV. Development of a framework for person-centred nursing. Journal of Advanced Nursing. 2006 Dec;56(5):472-9.

Woods B, Rai HK, Elliott E, Aguirre E, Orrell M, Spector A. Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane database of systematic reviews. 2023(1).

Hustey FM, Palmer RM. Implementing an Internet-based communication network for use during skilled nursing facility to emergency department care transitions: challenges and opportunities for improvement. Journal of the American Medical Directors Association. 2012 Mar 1;13(3):249-53.

Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. Bmj. 2015 Mar 2;350.

Gitlin LN, Winter L, Dennis MP, Hodgson N, Hauck WW. A biobehavioral home-based intervention and the well-being of patients with dementia and their caregivers: the COPE randomized trial. Jama. 2010 Sep 1;304(9):983-91.

Gentleman S. [S1–02–03]: LINKING TRAUMATIC BRAIN INJURY TO NEURODEGENERATIVE DISEASE. Alzheimer's & Dementia. 2017 Jul;13(7S_Part_3): P170-.

Nannini A, Houde SC. Translating evidence from systematic reviews for policy makers. Journal of Gerontological Nursing. 2010 Jun 1;36(6):22-6.

DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1990 May;27(5):457-64.

Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. Nature Reviews Neuroscience. 2018 Nov;19(11):687-700.

Dennis NA, Cabeza R. Neuroimaging of healthy cognitive aging. In The handbook of Aging and Cognition, 2011 Mar 15 (pp. 1-54). Psychology Press.

Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimer's & Dementia. 2021 Apr;17(4):696-701.

Mehta D, Jackson R, Paul G, Shi J, Sabbagh M. Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015. Expert opinion on investigational drugs. 2017 Jun 3;26(6):735-9.

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387
Print ISSN 3007-2379

DOI: http://doi.org/10.5281/zenodo.21215669

Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Ballard C, Banerjee S, Burns A, Cohen-Mansfield J, Cooper C. Dementia prevention, intervention, and care. The Lancet. 2017 Dec 16;390(10113):2673-734.

Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. In Mayo Clinic Proceedings 2011 Sep 1 (Vol. 86, No. 9, pp. 876-884). Elsevier.