Current Neuropharmacology, 2023, *21*, 309-339

REVIEW ARTICLE

Strategies for Treatment of Disease-Associated Dementia Beyond Alzheimer's Disease: An Update

Sabiya Samim Khan[1], Gopal L. Khatik[2] and Ashok K. Datusalia[1,3,*]

[1]*Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER) Raebareli, Lucknow (UP) India;* [2]*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER) Raebareli, Lucknow (UP) India;* [3]*Department of Regulatory Toxicology, National Institute of Pharmaceutical Education and Research (NIPER) Raebareli, Lucknow (UP) India*

ARTICLE HISTORY

Received: October 26, 2021
Revised: February 27, 2022
Accepted: April 03, 2022

DOI:
10.2174/1570159X20666220411083922

Abstract: Memory, cognition, dementia, and neurodegeneration are complexly interlinked processes with various mechanistic pathways, leading to a range of clinical outcomes. They are strongly associated with pathological conditions like Alzheimer's disease, Parkinson's disease, schizophrenia, and stroke and are a growing concern for their timely diagnosis and management. Several cognition-enhancing interventions for management include non-pharmacological interventions like diet, exercise, and physical activity, while pharmacological interventions include medicinal agents, herbal agents, and nutritional supplements. This review critically analyzed and discussed the currently available agents under different drug development phases designed to target the molecular targets, including cholinergic receptor, glutamatergic system, GABAergic targets, glycine site, serotonergic targets, histamine receptors, *etc*. Understanding memory formation and pathways involved therein aids in opening the new gateways to treating cognitive disorders. However, clinical studies suggest that there is still a dearth of knowledge about the pathological mechanism involved in neurological conditions, making the dropouts of agents from the initial phases of the clinical trial. Hence, a better understanding of the disease biology, mode of drug action, and interlinked mechanistic pathways at a molecular level is required.

Keywords: Dementia, cognitive disorders, neurodegeneration, Alzheimer's disease, Parkinson's disease, schizophrenia.

1. INTRODUCTION

Memory is a cognitive process of remembering or recalling the learned or experienced scenarios [1]. Dementia and cognitive impairment cases are increasing worldwide, generating an alarming situation with an estimated to affect around 150 million humans by 2050 [2]. The reasons behind such a drastic increase may include a sedentary lifestyle, stress, and an increase in the elderly population. Cognition is the mental potential of learning processes that contribute to an individual's mental performance, including awareness, planning, perception, reasoning, and judgment. It mainly includes memory, intelligence, execution, decision making, creativity, and attention which are interconnected. Various physiological and pathological conditions, such as stress, ageing, Parkinson's disease (PD), Alzheimer's disease (AD), Schizophrenia, and HIV (human immunodeficiency virus), may result from cognitive impairment, developing a research thrust for understanding dementia and associated biology [3-6]. In the last few decades, the early-stage biomarkers and symptoms of dementia have become the center of research for ageing and cognitive diseases to identify reliable markers for neurodegenerative disease development [7]. Alongside, alternative treatment options in the form of cognitive enhancers are being explored. They are the drugs, nutraceuticals, and food supplements, which amplify or extend the core capacities of the brain and memory by improving the internal and external information processing systems. In the current scenario, most of the marketed cognition enhancers have a modest effect with no crisp understanding of their mode of action. In the current review, the updates regarding the pharmacological agents used for cognitive impairment, which may or may not be associated with other neurological conditions, are being focused on emphasizing the various pathways and mediators mainly involved in the memory formation process.

2. NEUROBIOLOGY AND MANAGEMENT OF DISEASE-ASSOCIATED COGNITIVE DYSFUNCTION AND DEMENTIA

Many diseases are associated with dementia and cognitive deficits. Cognitive dysfunctions occur *via* several pathological changes occurring in neurons due to underlying pathological conditions like Alzheimer's disease (AD), Parkinson's disease (PD), attention-deficit hyperactivity disorder (ADHD), and neurobiological conditions like stress, anx-

*Address correspondence to this author at the Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER) Raebareli, Lucknow (UP) India;
E-mail: ashokdatusalia@gmail.com

1875-6190/23 $65.00+.00

iety, depression, schizophrenia, *etc.* and atypical dementia, where pathological differentiation to a particular disease is difficult [8]. The management remains interlinked because of the coinciding clinical presentations for a major group of diseases, including several pharmacological agents and non-pharmacological approaches. Several strategies can affect cognition positively. Most interventions target disease pathology, and some affect the level of the neurotransmitter. Several pharmacological and non-pharmacological interventions like herbal medicines, pharmaceutical drugs, physical exercise, vitamins, and nutritional supplements extensively treat cognitive impairment associated with various neurological diseases. Regular exercise reduces the risk of dementia and cognitive impairment by upregulating the brain-derived neurotrophic factor (BDNF) in the hippocampus [9]. Herbal medicines, such as *Ginkgo biloba*, Shankhpushpi, *Bacopa monniera* (Bramhi), *etc.*, have been found to enhance cognitive abilities [10]. Pharmaceutical drugs improve memory by affecting pharmacological targets like neurotransmitter levels, including monoamines, acetylcholine, gamma-aminobutyric acid (GABA), *etc.*, or by enhancing cerebral blood flow and brain metabolism. Recent advances in understanding the pathological alterations occurring in diseased conditions and therapeutic interventions are discussed in detail.

2.1. Stroke Associated Dementia

It is estimated that approximately one-third of stroke victims will develop memory problems and serious difficulties in other aspects of performing daily activities. The memory problems scientifically called dementia can be so severe that they interfere with normal functioning; this is more common in aged or elderly patients. When dementia occurs after a stroke and no other cause can be found, it is called vascular dementia. Large strokes strategically located in certain brain areas or multiple small strokes in various brain regions can result in vascular dementia. Certain contributing factors like old age, prior cognitive complaints, a history of several strokes, or a stroke located on the left side of the brain all seem to increase the likelihood of dementia in the first year after a stroke. Vascular dementia can be caused by cerebrovascular disease or any other condition that prevents normal blood flow to the brain. Without a normal supply of blood, brain cells become deprived of the oxygen and nutrients required to function normally, and they often become so deprived that they die. The symptoms of vascular dementia and memory loss include an altered motor function like hindered gait and an inability to perform daily chores.

In contrast, cognitive alteration includes bradyphrenia and attention deficit. These symptoms may sometimes become difficult to be differentiated from those produced by AD, where age-related dementia remains a common factor [11]. Symptoms of dementia after stroke can also be masked by other more obvious stroke manifestations like paralysis, blindness, or lack of awareness. Another hurdle in identifying the symptoms of dementia after a stroke includes symptomatic similarity with depression, which is quite common after a stroke. To date, there is no specific pharmacological intervention available to reverse the memory loss that occurs after a stroke. Neurologists sometimes prescribe medications approved for AD to patients with vascular dementia, but still, we do not have studies addressing the applicability of these medications in patients with vascular dementia.

Cognitive impairments, including spatial memory and learning deficits, are common after ischemic stroke. Several pharmacological interventions have shown beneficial effects in memory impairment after cerebral ischemia. 17-beta-estradiol treatment combined with an enriched environment improved recovery of cognitive function after experimental brain ischemia, putatively through the upregulation of NGFI-A (Nerve Growth Factor Induced gene) in hippocampal subregions [12]. Minocycline treatment also had beneficial effects on memory impairment caused by cerebral focal ischemia. The improved function is associated with enhanced neurogenesis, reduced microglia activation in the dentate gyrus, and possibly an improved neural environment after chronic treatment with minocycline [13]. Treatment with D-JNKi, a peptide inhibitor of c-Jun N-terminal kinase (JNK), has also improved cognitive function in the object recognition test after transient focal cerebral ischemia in rats [14]. *Coeloglossumviride* (L.) *Hartm. var. bracteatum* (Wild.) extract (CE) treatment also attenuated learning and memory deficits, motor functional disability, and neuronal cell loss induced by global or focal cerebral ischemia. The results suggested that CE may be a potential candidate for the treatment of vascular dementia [15].

Some studies have shown that bryostatin-1, a highly potent protein kinase C (PKC) activator, interrupts pathophysiological molecular cascades and apoptosis triggered by cerebral ischemia/hypoxia, enhances neurotrophic activity, induces synaptogenesis, and preserves learning and memory capacity even four months later as well as long-term memory induced before the ischemic event [16]. Inhibiting poly (ADP-ribose) polymerase also benefits memory impairment after cerebral ischemia. Poly(ADP-ribose) polymerase-1 (PARP-1) is a coactivator of the transcription factor NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and is required for NF-κB mediated inflammatory responses. The brain inflammatory response induced by stroke contributes to cell death and impairs neurogenesis. Treatment with *N*-(6-oxo-5,6-dihydrophenanthridin-2-yl)-*N,N*-dimethylacetamide (PJ34), a PARP inhibitor, improved outcomes after stroke by suppressing post-stroke inflammation [17]. A study has demonstrated that activation of the Rho/Rho-kinase pathway is related to neuronal damage and the pathogenesis of spatial learning and memory impairment in stroke. The study result further demonstrated that relative long-term hydroxyfasudil treatment improved the rats' spatial learning and memory performance [18].

2.2. Parkinson's Disease-associated Dementia

PD is the second most common neurodegenerative disorder after AD, affecting 1% of the population by 65 years and 4–5% of the population by 85 years. PD is pathologically characterized by the degeneration of dopaminergic neurons in substantia nigra and the presence of intracytoplasmic inclusions (Lewy bodies) in the residual dopaminergic neurons. PD is predominantly a motor disorder clinically characterized by resting tremor, rigidity, hypokinesia, and postural instability. Still, dementia is the most debilitating symptom associated with disease progression and is a major concern for patients and caregivers. Dementia affects almost 31-80%

of patients with PD [19, 20]. A study has reported that the cumulative incidence of dementia steadily increases with the age of PD patients and may increase to 80%-90% by the age of 90 if the patient survives. At the age of 70 years, a man with PD without dementia has a life expectancy of eight years, out of which five years would be expected to be dementia-free, and subsequent three years would be expected to be with dementia [21]. Parkinson's disease dementia (PDD) includes visual and auditory hallucinations, sensitivity to neuroleptic medications, cognitive fluctuations, and sleep disturbances. Visual hallucinations are the strongest prediction of PDD and increase the risk of dementia by 20 folds over PD without hallucination. PD's cognitive symptoms include loss of decision-making ability, inflexibility to adapting changes, disorientation in familiar surroundings, problems learning new skills, difficulty concentrating, loss of short- and long-term memory, insufficient working of sequential memory, and problems using and comprehending complex language [22, 23]. Neuropsychiatric symptoms, including depression (58%), apathy (54%), anxiety (49%), and hallucinations (44%), occur even more commonly in PDD than in PD. Sleep disorders (43%), such as rapid eye movement, sleep behavior disorder, daytime sleepiness, and sleep attacks, occur frequently. Advancing age, depression, smoking, gender, family history, and genetic alterations in α-synuclein have been reported as risk factors for PDD with clinical presentations like the onset of motor symptoms, visual hallucinations, confusion, severe hypokinesia, and speech problems [24].

Dopaminergic neurons in different brain areas play a critical role in modulating different processes related to learning and memory. Dopaminergic cells in the striatal region are involved in habitual and working memory; the dorsal and ventral hippocampus is involved in spatial memory; whereas the prefrontal cortex is involved in working memory and is found to be impaired in both extreme and deficit conditions of dopamine. Dopaminergic systems in basal ganglia [SNc (Substantia nigra pars compacta), striatum, globus pallidus, and ventral tegmental area (VTA)] are also involved in reward-seeking behavior [25, 26]. Degeneration of dopaminergic neurons in basal ganglia is mainly responsible for cognitive and visual impairment in PD. Basal ganglia act as a relay center in the brain. It receives signals from various cortex regions and relays output signals to cortex regions involved in cognitive function [27]. The visual area (area TE) in the temporal lobe receives the signal from basal ganglia and lesions in basal ganglia, thus leading to visual hallucinations. Working memory is controlled by Brodmann area 46 of the prefrontal cortex, which also receives signals from basal ganglia. A lesion in basal ganglia may lead to working memory impairment [26-28]. In addition to the dopaminergic deficit, cholinergic, noradrenergic, and serotonergic dysfunctions also occur in PDD. Dopaminergic neuronal loss in the frontal cortex leads to reduced verbal fluency, working memory, and executive function. Noradrenergic neuronal loss in locus coeruleus, cerebral cortex, and hippocampus is related to attention deficit. Serotonergic neuronal loss in cortical and subcortical areas leads to depression. Reduced levels of acetylcholine due to the destruction of the cortex causes poor performance in attention and executive function tests [29].

Though numerous medications are available to treat motor features of PD, none of them are effective in improving cognitive symptoms. These may even worsen the psychiatric symptoms of PDD. The strongest evidence for pharmacologic treatment of PDD is with cholinesterase inhibitors. The FDA has approved rivastigmine for PDD treatment. It is a centrally acting inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). The most common adverse effects include nausea, vomiting, tremor, diarrhea, anorexia, and dizziness [30, 31]. Tacrine, donepezil, and galantamine have also been beneficial for PDD [32, 33]. However, tacrine's use is limited by poor oral bioavailability, the necessity for four-times daily dosing, and many adverse drug reactions (including nausea, diarrhea, urinary incontinence, and hepatotoxicity). The worsening of motor symptoms was observed with donepezil, and it was reported to be well tolerated with mild adverse effects like nausea and arrhythmia [34].

Anti-Parkinson agents have also shown some beneficial effects on PDD. Levodopa may benefit working memory and causes visual hallucinations, psychosis, confusion, and increased cognitive fluctuations in advanced PD. Anticholinergic agents have been shown to induce β-amyloidosis and senile plaque formation and may even worsen the condition. Dopamine receptor agonists, pramipexole and pergolide, reduce depression but have not yet proved effective for reducing cognitive symptoms in advanced PD [35]. Surgical interventions, such as thalamotomy, thalamic stimulation (used to treat tremors), pallidotomy, and deep brain stimulation (used to treat dyskinesia), may further worsen the cognitive complications in PD. Surgery's adverse side effects include brain hemorrhage, infarction, seizures, and even death. Developments in nanotechnology (implantable carbon nanotubes and nanochips) assure greater safety and precision for delivering impulses in the substantia-nigra, reducing the side effects of surgery [36].

2.3. Brain Injury

Brain injury is considered the major cause of death and disability worldwide. Memory dysfunction is a major anomaly post-injury episode among various neurological manifestations. Human and animal studies suggested that critical brain regions (cortex and hippocampus) for memory function have been found disrupted in traumatic brain injury (TBI). Studies have reported that a two-fold increase may be observed in the occurrence of dementia or AD in the case of moderately severe TBI, while a four-fold rise in risk may be observed in severe TBI cases. It tends to alter the manifestations presented clinically in dementia cases and lowers the age of dementia onset. It has been found that the TBI (moderate-to-severe cases) has led to the development of proteinopathies where an excessive accumulation of amyloid protein was observed along with the tau hyperphosphorylation localized in glial cells in sulci and perivascular neurons. The brain injury may also lead to neuroinflammation due to microglia activation and disruption of the BBB. The principally injured brain regions include the orbitofrontal and anterior temporal cortex in the case of TBI.

In contrast, in other brain injuries, the frontal neocortex is involved in focal neuropathology instead of the mesolimbic or parietal region alterations observed in AD. The diffuse axonal injury leads to altered axonal transport of proteins

like Aβ (Amyloid beta) and hyperphosphorylated-tau and their aggregation. The integrity of white matter is being altered, where anisotropy can be observed in the case of fibre bundles like corpus callosum and cingulum in the condition of acute brain injury. In contrast, in the case of AD and mild cognitive impairment, the whole brain white matter connectivity is disrupted, causing disturbances in the long-range tracts like uncinate fasciculus, superior longitudinal fasciculus, cingulum, inferior frontal-occipital fasciculus, and corpus callosum [37].

TBI causes a deficit in episodic memory due to physiological disruption of circuitry involving the hippocampus. Therefore, the connection between dentate gyrus, CA3, and CA1 regions can be disrupted. In the DG region, the principal cell type, *i.e.*, granule cell, acts as a filtering media, which regulates the incoming excitability of the signals to the hippocampus. In normal conditions, the granule cells have low propensities to generate a high action potential due to strong inter-neuronal connections having GABAergic neurons. Still, in the brain injury situation, hyperexcitability is observed in the DG region, causing its hindered filtering potential; this may be due to the diminished GABAergic transmission on the granule cells [38]. Studies have also shown that the glutamatergic inputs to the somatostatin-positive interneurons increase, leading to more action potential generation [39]. The episodic memory formation and retrieval are dependent on the CA1 and CA3 areas of the hippocampus, which is also affected by brain injury. The neurons of the CA3 area are prone to death upon TBI, while the neurons in the CA1 region become hypoexcitable where the Schaeffer collaterals fibre volley amplitude is reduced with recoverable glutamatergic events from both NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors. It indicates that the glutamatergic innervation increases though the post-synaptic machinery might be disrupted [40, 41]. However, several studies reported an increase in excitability of CA1 neurons, marking a lacuna in examination studies related to experimental variability factors like time point of evaluation, injury severity, injury model, *etc.* The effect on working memory due to TBI can be studied by evaluating the brain's prefrontal cortex region, which is strongly connected to the hippocampus. The function of the prefrontal cortex (PFC) is affected such that an increase in the Ca^{+2}-permeable AMPA receptors is found to be upregulated with diminished brain activity and impairment in working memory. Several potential strategies for memory dysfunction have improved post-TBI dementia, such as neural stem cell transplantation, dietary therapy with branched amino acids (glutamate precursor derivatives), and enrichment in environmental settings. These strategies have been tested in animal models; however, their clinical applicability is yet to be established [42].

2.4. Mixed Dementia

AD is the most common form of dementia in old age patients. However, it has been found that dementia in elderly patients cannot be explained by the clinical presentation of dementia found in patients with AD or even vascular dementia (VD). Such a clinical condition with overlapping symptoms and AD and VD pathologies is called mixed dementia (MD) [43]. MD has a prevalence rate of 22-24% among all the reported dementia cases [44].

The MD diagnosis has no agreement among various international referents like NINDS-AIREN (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseigementen Neurosciences) and ADDTC (Alzheimer's Disease Diagnostic and Treatment Centres) and also, DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) and ICD-10 (International Classification of Diseases, 10^{th} Revision), each differing in their specific diagnostic criteria [44]. The ADDTC has used the term 'AD with cerebrovascular disease' instead of MD due to the second occurrence of ischemic brain disease associated with a primary systemic or brain disorder, playing a role as a causal factor for dementia. The symptoms may differ at each stage based on the severity of vascular damage and senile plaque deposition in the patient's brain, ranging from decreased performance in cognitive activities, attention, and vasoconstriction response to spatial memory function impairment. We can also observe abnormal episodic memory and impaired thoughts, which overlap with AD clinical presentations, and impairment of executive functions and processing rate, generally observed in VD. As per ICD-10, MD diagnostic attribution depends upon the conjoining criteria for AD and VD. Even the DSM-V has mentioned MD under the umbrella 'Major Neurocognitive Disorder with Multiple Etiologies' term meaning that the diagnostic confirmation may depend upon the medical history, physical investigation, or laboratory evaluation stating that multiple etiological factors led to the disorder [45]. The risk factors include atherosclerosis, obesity, dyslipidemia, hypertension, diabetes, tobacco smoking, and vascular brain injury.

Dementia associated with AD and VD includes the involvement of two main theories: amyloid theory and vascular theory. Dementia, disregarding its subtype, begins to develop pathological modification several years before the first observation of clinical symptoms. The pathological changes in the vascular system begin with collagen deposition in endothelial membrane and thickening of the basal membrane of capillary beds, occurring due to a sedentary lifestyle and other conditions like hypertension, hypercholesteremia, diabetes mellitus, and cardiac disease, leading to a decreased number of terminal capillaries and blood vessels in the body and the brain as well. Several factors leading to cerebrovascular damage include macrovascular arteriosclerosis, microvascular atherosclerosis, brain infarcts, minor hemorrhage, amyloid angiopathy, and white matter lesions, all leading to the cerebrovascular disease that leads to the manifestation of cognitive decline exceeding the normal ageing, called a vascular cognitive impairment, which progresses further and impairs daily life activities. While considering the protein deposition in AD conditions, it can be majorly observed in the neocortex and hippocampus regions, including both diffuse and neuritic plaques. Also, the tau tangles are observed in a semi-quantitative amount in the hippocampus and neocortex regions [44].

The treatment includes several non-pharmacological and pharmacological interventions targeting symptomatic and preventive measures. Early-stage non-pharmacological inter-

ventions like adequate control of blood pressure, blood glucose, cholesterol, and triglyceride, along with maintaining a healthy diet and regular exercise (≥ 3 times a week for ≥ 30 minutes), would help to delay the progression of cognitive decline associated with AD and VD, aiding to maintain normalcy in daily life activities. Psychological and social assistance and support are also critical for the working group of patients [44]. However, there are no specific drugs for MD treatment, but the drugs used for AD and VD management have proven useful for MD management.

2.5. Frontotemporal Dementia

The group of conditions wherein the degeneration is noted markedly in neurons of the frontal lobe, or anterior temporal lobe of the brain or both regions is termed frontotemporal dementia (FTD), leading to behavioral abnormalities and/or language impairment [42, 46]. The debilitating cognitive dysfunction is generally preceded by certain behavioral changes like decreased interpersonal conduct as irritability, impulsiveness, or lack of empathy, personal hygiene habits and language controls are affected, which then progresses to a decline in intelligence quotient (IQ), disorientation, and lately to profound dementia but the case of AD is quite different where the amnesia precedes a decline in social behavior [46]. There is no specific treatment for FTD, but symptomatic treatments are targeted. Several anti-depressants, anti-psychotic, neuropeptides, and anti-epileptic agents have been studied to manage the behavioral symptoms. Antidepressants like paroxetine, sertraline, and citalopram trazodone have shown an improvement in repetitive behavior as well as the neuropsychiatric index (NPI). Atypical antipsychotics like quetiapine, risperidone, and aripiprazole have been shown to improve agitation behavior with no effect on NPI, whereas olanzapine has improved NPI scores. Antiepileptic agents like valproic acid, topiramate, and carbamazepine, which have a mood-stabilizing effect, have limited evidence in clinical studies. Still, case reports prove their effectiveness for behavioral symptom management in FTD. Neuropeptide oxytocin, upon intranasal administration, showed possible trends in improvement of apathy and empathy. While discussing the management of the cognitive symptoms, AChE inhibitors are the first class of drugs due to their effective ability to treat AD-related memory impairment. Still, the use is limited as donepezil and rivastigmine have shown worsening and only a slight improvement in the NPI score, respectively. When tested for effectiveness in FTD, NMDA antagonist memantine has shown beneficial effects on daily activities and cognition. Motor symptoms management becomes important when FTD is associated with parkinsonism. The dopamine replacement therapy with levodopa/carbidopa has limited effect in this case, restricting its use only for symptomatic management [47]. Behavioral therapy is an acceptable strategy for FTD management [48].

2.6. Other Neurologically Linked Dementia/ Cognitive Dysfunction

Dementia is a complex disorder linked with several other pathological conditions like depression, schizophrenia, diabetes, *etc.* The characteristic pathological overlaps between the two or more conditions, leading to an insignificant diagnostic characterization of the underlying cognitive dysfunction.

Schizophrenia's (SCZ) relationship to FTD has been studied for several decades. The phenotypic similarities in the two cases have led to being diagnosed as either Schizophrenia or FTD at the first instance but not as a co-existing disease initially. SCZ cases have altered cingulate, prefrontal, and temporal cortex regions, leading to auditory hallucinations and thought disorientation symptoms. At the same time, the FTD shows hypometabolism in frontal and temporal lobe areas, cingulate gyrus, and medial thalamus of the brain. Though Hughlings Jackson's hypothesis for the negative and positive symptoms related to SCZ has been postulated, the exact pathophysiology is still a big mystery to the researchers [49, 50]. The common pathway involved in both conditions includes the impaired GABA excitatory and inhibitory activity balance, impairing the working memory. The alteration of the dopaminergic neuron functioning in the limbic region of the brain has led the researcher to use first-generation antipsychotics to treat the cognitive dysfunction and negative symptoms in SCZ, though with a limited application due to lack of efficacy and high incidences of side effects, including dyskinesia, weight gain, extrapyramidal motor symptoms, and sedation. Second-generation antipsychotics have a higher affinity for the serotonergic ($5HT_{2A}$) receptor than the dopaminergic (D_2) receptor. Several other novel approaches are being studied, including NMDA-glycine site agonist, dopaminergic D_1 agonist, mGluR type 2/3, or 5 and 5-HT_{1A} receptor agonist [51, 52]. Human Immunodeficiency Virus (HIV) associated neurocognitive disorder (HAND) is a group of neurological impairments observed along with AIDS due to manifestation by HIV. HIV-associated dementia (HAD) shows manifestation in subcortical regions like deep white matter, hippocampus, basal ganglia, and hippocampus, leading to psychomotor delays, alteration in mood, anxiety levels, memory, abstraction, information processing, attention, and decisive powers [53, 54]. Based on the complexity of the viral manifestation in the brain and its effect, several targets have been focused upon for the trial of drugs and their actions. Minocycline (anti-inflammatory, tetracycline antibiotic) suppresses the JNK pathway activation, lowering the nitric oxide (NO) levels and mitogen activated protein kinase (MAPK) activation. Memantine (anti-excitotoxicity, NMDA receptor blocker) shows its effectiveness in excitotoxicity induced cognitive dysfunction. Selegiline (antioxidant and a monoamine oxidase-B inhibitor) can attenuate the oxygenated free radicals, but the effectiveness is yet to be proven clinically. The biological peptides like insulin, insulin-like growth factor - 1 (IGF-1), and fibroblast growth factor - 2 (FGF-2) are also being evaluated for their action on cognitive impairment associated with various pathological conditions, through intranasal and other routes [55, 56].

Depression is another neurological condition often linked to dementia, but the distinction is still unclear whether depression is a causative factor or a consequence of dementia [57]. The comorbidity of depression with diabetes also leads to higher cognitive deficit reports than patients with either of these conditions. Cognition decline generally starts before diabetes is diagnosed (prediabetes stage), affecting the frontal and prefrontal cortex regions and impacting working memory and executive function [58]. The pathophysiological pathway between depression, cognitive dysfunction, and

Table 1. Various interventions are used to improve disease-associated dementia or cognitive dysfunction.

Class of Agent	Agent	Action
Nutrients	Acetyl-L-Carnitine Phosphatidylserine	It provides acetyl equivalents for the production of acetylcholine [60]. Increases the production of nerve growth factor (NGF) by cultured nerve cells and helps them respond better to NGF [61].
	CoenzymeQ10/ Ubiquinone	*In vitro* research demonstrates its role in acetylcholine release and provides neuroprotection by inhibiting β amyloid and inflammation [62, 63].
	α-Lipoic acid	Anti-inflammatory, antioxidant, carbonyl scavenging, and metal-chelating increase cerebral blood flow and neuroprotective properties and stimulate the ACh synthesis pathway [64].
	CoenzymeQ10/ Ubiquinone	Neuroprotective action reduces brain atrophy and oxidative stress and promotes energy production [65].
	Docosahexaenoic acid, ω-3 fatty acids	Increased cortico-hippocampal reduced glutathione levels and glutathione reductase activity and suppressed the increase in lipid peroxide and reactive oxygen species levels in the cerebral cortex and hippocampus of the AD model rats [66].
	Vitamin B_6, B_{12}, and Folic acid	A lower level of these vitamins leads associated with cognitive decline [67].
	Vitamin E	Potent reactive oxygen species scavenger affects SOD and Sir2 (silent information regulator 2), which play an important role in resistance to oxidative stress [68].
Pharmaceutical Drugs	Aducanumab	Monoclonal antibodies directed to aggregated forms of Amyloid β and reduce its buildup [69, 70].
	Melatonin	Improves some aspects of sleep, memory, and mood in elderly patients [71].
	Nicotine	Stimulates nicotinic cholinergic receptors and has been proposed to act through modulation of signaling pathways, *i.e.*, increased extracellular-signal-regulated kinase 1/2 (ERK1/2) and cAMP response element-binding protein (CREB) phosphorylation [72].
	Caffeine	Restores brain adenosine levels, reduces the expression of both Presenilin 1 and β-secretase and reduces the Aβ production [73].
	Methylphenidate, Modafinil	Affects the catecholamines, serotonin, glutamate, gamma amino-butyric acid, orexin, and histamine systems [74].
	Rivastigmine	Acetylcholinesterase inhibitor and butyrylcholinesterase inhibitor [75].
	Galantamine Donepezil	Acetylcholinesterase inhibitors potentiate the α4β 2-like nAChR (nicotinic acetylcholine receptor) current at doses of 100 nM—1μM and reversibly potentiate the NMDA-induced currents mediated by c-AMP in cortical neurons [76]. Still, recent data suggested that AChE-Is can have negative cognitive effects in a healthy population [77].
	Ispronicline (TC-1734)	Partial agonist of brain-selective α4β2 nicotine acetylcholine receptor [78].
	Memantine, neramexane	Reversible glutamate NMDA receptor antagonist [79].
	Atomoxetine	Increased acetylcholine efflux and increased cholinergic neurotransmission in cortical regions and the medial prefrontal cortex mediated through α1 and D1 receptor activation [80].
	Piracetam	Enhancement of brain metabolism, modulating cholinergic and glutamatergic systems neurotransmission, improving neuroplasticity, and reducing lipofuscin (age pigment) buildup in the brain [81].
	Nefiracetam	Potentiates AMPA receptor-mediated fast excitatory post-synaptic potential (fEPSP) through CaMKII (Calcium-calmodulin dependent protein kinase 2) activation and enhances NMDA receptor-dependent LTP (long-term potentiation) by enhancing post-synaptic CaMKII and protein kinase C (PKC) activities [82].
	Rolipram	Phosphodiesterase type-4 inhibitor enhances LTP formation by increasing the level of c-AMP and enhancing the cAMP/PKA/CREB pathway [83].

(Table 1) contd….

Class of Agent	Agent	Action
Pharmaceutical Drugs	D-cycloserine	Facilitates declarative learning and hippocampal activity in humans; acts as a co-agonist on *N*-Methyl-D-Aspartate receptor [84].
	Antidepressant drugs	Increase synaptic plasticity in brain regions associated with mood disorders and memory, such as the hippocampus, amygdala, and prefrontal cortex [85].
	Guanfacine	α-2A adrenergic agonist; increases regional cerebral blood flow in the dorsolateral prefrontal cortex of monkeys performing a spatial working memory task [86].
	Tolcapone	Catechol-O-methyl transferase (COMT) inhibitor; enhances executive memory processes by increasing the amount of dopamine in the prefrontal cortex [87].
	Hydergine	Increases blood supply to the brain [88] and normalizes the brain levels of serotonin [89].
	Neuropeptides	vasopressin, corticotrophin-releasing hormone (CRH), somatostatin, substance P, neuropeptide Y, and thyrotrophin-releasing hormone (TRH) show improvement in cognitive performance [90].
	Pyritinol	Enhances neuronal metabolism [91].
	ondansetron	Role in the enhancement of memory function in schizophrenia [92].
	Nicergoline	Increases cerebral blood flow, antioxidant, and neuroprotectant properties [93].
	Centrophenoxine	Increasing acetylcholinesterase activity, decreasing the deposition of the age pigment, lipofuscin; increasing the content of serotonin (5-HT) and the fluidity of brain membranes [94].
	Dopaminergic agonist	Dihydrexidine shows D1/D5 receptor agonist activity, releases acetylcholine, and improves cognition in rats [95]. A-412997 shows D4 receptor agonist activity and improves cognitive performance [96].
	Glucocorticoid receptor agonist	Dexamethasone and glucocorticoid receptor type II agonist RU 28362 show their memory-enhancing property by affecting the noradrenergic signaling and the cAMP/PKA pathway within the basolateral nucleus of the amygdala and increasing the histone protein acetylation [97].
	Cytidine-5-diphosphocholine	Improves memory in cerebral stroke, AD, and other neurovascular diseases by preventing hippocampal neuronal cell death [98].
	Cotinine	Reduces Aβ aggregation in the brain, prevents memory loss, and stimulates the Akt/GSK3 pathway *in vivo* [99].
Other Methods	Transcranial Magnetic Stimulation	Noninvasive, nonpainful, and safe method. Improve memory by activating the hypothalamic neurons [100].

type 2 diabetes is not completely understood. The involvement of microvasculature dysfunction in T2DM-linked dementia and depression is hypothesized based on available literature and studies [59].

2.7. Current Status of Drug Development for Disease-Associated Cognitive Dysfunction and Dementia

Different methods and approaches are explored to manage disease-associated cognitive dysfunction and dementia, as presented in Table **1**.

2.8. Drugs Acting on Cholinergic Targets

Acetylcholine has long been known for its involvement in cognitive function, particularly attention, learning, and memory. Degeneration of the cholinergic system is one of the aspects of the pathophysiology of AD. It has also been postulated to contribute to the cognitive deficits of various neuropsychiatric disorders, including schizophrenia [101]. There is ample evidence that decreased nicotinic and muscarinic acetylcholine receptors and functions in the cortex and hippocampus are associated with altered learning, memory, and cognitive functions [102]. Both ionotropic nicotinic receptors (nAChR) and metabotropic muscarinic acetylcholine receptor (mAChR) agonists have been implicated in cognitive enhancement. Besides, decreased activity of choline acetyltransferase, a biosynthetic enzyme for acetylcholine production, has been widely correlated with poor cognitive function [103].

Various drugs targeting cholinergic receptors are given in Fig. (**1**). Varenicline was the first nAChR agonist approved by the USFDA. It has been found to have complete agonist properties at the α_7nAChR and partial agonist at $\alpha_4\beta_2$ nAChR. Preclinical evidence showed that varenicline improves recognition memory in rats [104]. Activation of α_7nAChR

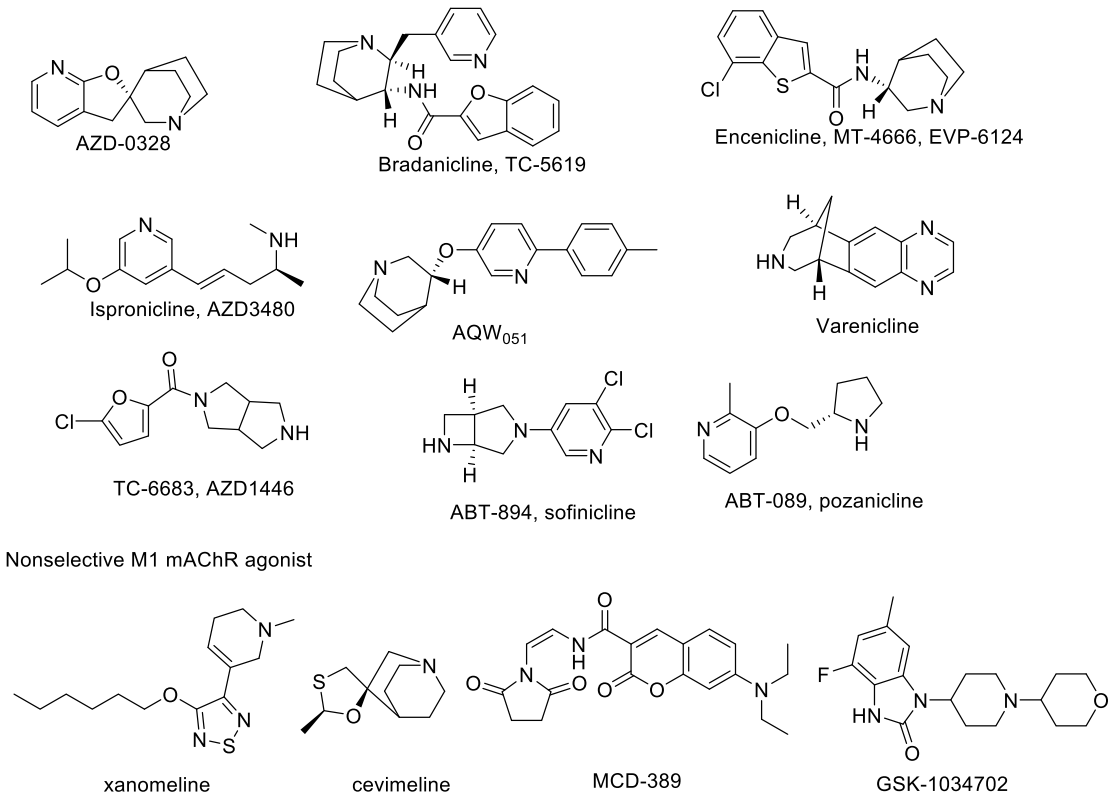

Fig. (1). Drugs acting on cholinergic target.

produces a procognitive and neuroprotective effect, but it has not shown significant efficacy for memory impairment associated with schizophrenia in the clinical trial phase II [105, 106]. TC-6683, AZD-1446, ABT-894/sofinicline, A-87089; ABT-089/pozanicline are $\alpha_4\beta_2$ agonists which have completed phase II clinical trials for the treatment of AD, mild cognitive impairment, and attention deficit hyperactivity disorder. Dexmedetomidine is an α_2-receptors agonist with sedative, anxiolytic, analgesic, and anesthetic effects. The drug currently exists in phase II clinical trial and exerts a protective effect against cognitive impairments in rats with post-traumatic stress disorder (PTSD) and in phase IV for the postoperative cognitive disorder.

M_1 mAChR is the major brain postsynaptic cholinergic receptor and is localized in the cortex, hippocampus, striatum, and thalamus, regulating acetylcholine's effects. Xanomeline, a mAChR agonist (M1/M4), has been studied for clinical trial phase I and phase II for AD and schizophrenia conditions. It has shown significant improvisation of cognitive function but has several unwanted effects due to peripheral M5 antagonistic action, leading to limited patient compliance (ncats.gov.in; clinicaltrials.gov accessed on 07-May.2020). SK-1034702, an M1 receptor agonist, has completed a phase I clinical trial. Furthermore, α_7 nicotinic receptor agonists play an important role in treating cognitive and perceptual disturbances in schizophrenia [107]. The investigational drug AZD-0328/ AR-R23465XX has completed phase I clinical trial in AD patients and participated in phase II trial for schizophrenia patients. However, the study has been terminated due to the inability of the drug to meet the target product profile. TC-5619/Bradanicline has completed phase II clinical trial with the result showing no benefit of the drug, whereas MT-4666/ EVP-6124/Encenicline had entered phase III clinical trial, but this study has been terminated due to gastrointestinal side effects for the treatment of AD and cognitive impairment associated with schizophrenia [108, 109]. Ispronicline (AZD3480), a selective partial agonist at the $\alpha_4\beta_2$ nAChR, has completed a phase II clinical trial and shows a promising role in elderly subjects with age-associated memory impairment (AAMI). The novel α_7-nACh receptor agonist, *i.e.*, AQW051, a cognition-enhancing agent, was also found to have a beneficial effect in AD. AQW051 entered in phase II clinical trial, but later, the study was terminated. The same drug has shown positive effects in schizophrenic patients in phase II trials. Ladostigil is a reversible AChE and BuChE inhibitor with neuroprotective activity against neurodegenerative disorder. It also increases the activity of catalase and glutathione reductase while decreasing the intracellular production of ROS in a cytotoxic model of human SH-SY5Y neuroblastoma cells [110]. Ladostigil shows a potentially beneficial effect in treating AD by decreasing apoptosis *via* inhibition of the cleavage and prevention of caspase-3 activation. With these data, the drug made its place in phase II clinical trial and was promising in treating dementia in elderly patients. Similarly, certain other drugs like DMXAB/GTS-21 (α_7nAChR agonist), ANAVEX2-73/Blarcamesine (selective sigma-1 receptor: SIGMAR1 agonist), SSR180711, and AVL-3288/CCMI (positive allosteric modulator of α7 nAChR) have shown promising activity in the animal models for cognitive diseases [111-113], and have entered into clinical trials at different phases for AD, ADHD, and schizophrenia. Other agents like selective α_7 nAChR agonist A-582941 and PHA-543613 have positively affected cognitive dysfunctions related to AD [114, 115].

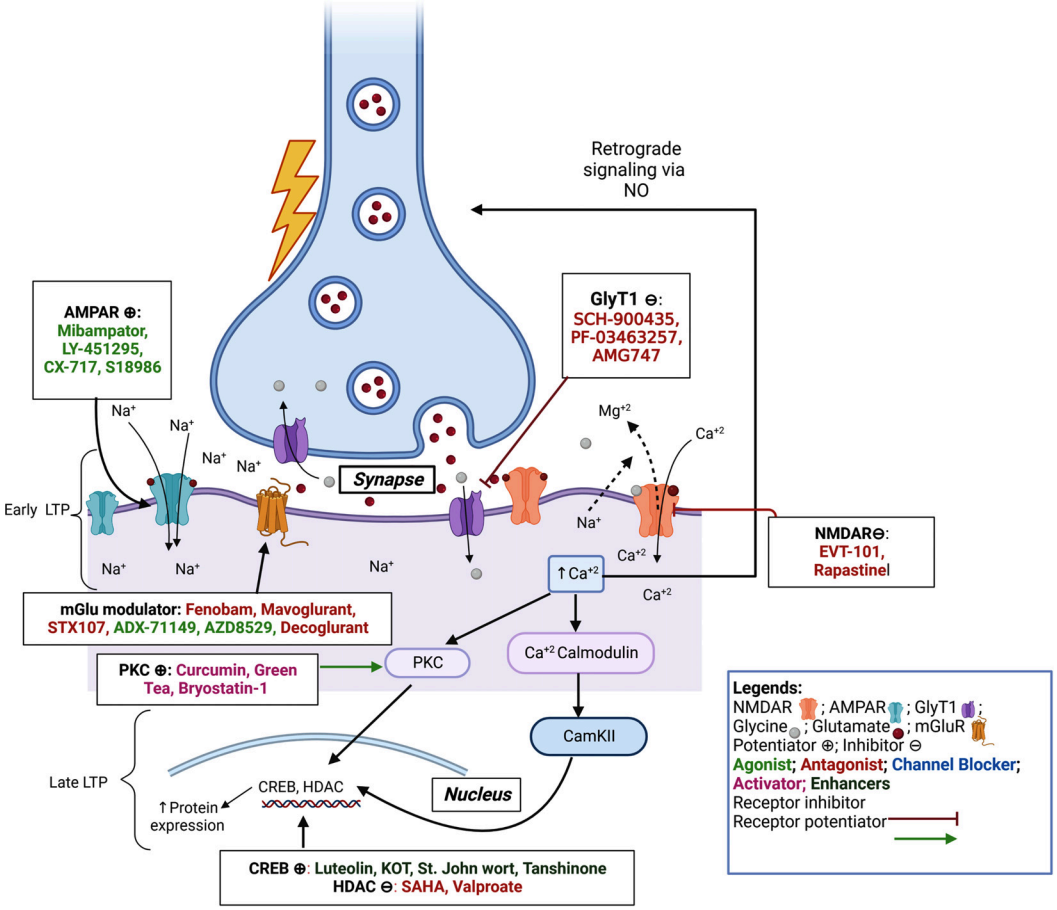

Fig. (2). Excitotoxic pathway and drugs acting on it: NMDA, AMPA, and mGlu receptors are involved in the excitotoxicity process in cells. The early phase LTP is modulated by AMPAR (blue) action activated by Glut released from presynaptic vesicles, causing its activation and import of sodium ions, leading to depolarization. The depolarized membrane potential and Glut (red) and Gly (grey) together allow activation of NMDAR (pink) by binding to their respective binding sites on NMDAR, allowing Ca^{2+} ions influx. The mGluR (yellow) allows the influx of Ca^{2+} ions in a cell at the late phases of LTP, leading to stronger signaling in the cell. The Ca^{2+} ions activate Ca^{2+}/Calmodulin protein activating protein kinase (PKC, CaKII), leading to increased mRNA and protein expression like CREB, HDAC, *etc.* The Ca^{2+} ions also activate the NOS leading to NO production and retrograde signaling and releasing Glut from presynaptic sites. The entire cycle helps in the formation of neuroprotective protein expression. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

ABT-560 has shown promising effects in the preclinical model of cognitive deficit; anyhow, it failed to produce similar results in the clinical trial. Posiphen is currently under clinical trial phase I/II for patients with early AD (Medicines in Development for Older Americans Report 2013), which acts by blocking the translation of the SNCA gene at 5'UTR and inhibits the expression of α-synuclein protein and APP (amyloid precursor protein) gene. Finally, BMS-933043 is a novel partial agonist of α_7 nACh receptor that has shown its efficacy in the cognitive impairment preclinical model and is under clinical trial phase I to treat cognitive deficits associated with schizophrenia [116].

2.9. Drugs Acting on Glutamatergic Targets

Glutamate is the major excitatory neurotransmitter in the mammalian CNS and has been recognized to play a major role in learning and memory processes. Many companies have developed agents that act on glutamate *via* NMDA and AMPA receptors (Fig. **2**).

These agents increase synaptic plasticity, compensate for the loss of glutamate signaling in disease and normal ageing, and increase the production of neurotrophic factors, such as BDNF. Ampakines (*e.g.*, LY-451395) and related agents potentiate the action of AMPA receptors to increase LTP (Fig. **3**). CX516 represents a novel pharmacological intervention, showing a positive AMPA-type glutamate receptor modulatory activity, which facilitates learning and memory in animal models, and has completed the Phase II/III clinical trial showing a positive effect on the cognitive capabilities in patients with stable schizophrenia in combination with other drugs like olanzapine, clozapine or risperidone [117, 118].

LY-451395 has completed a phase II clinical trial for AD, showing no significant differences between the treatment groups [119]. Other AMPA-targeted agents in different stages of the drug development process are CX-1739 and CX-717. S-18986, a novel compound that promotes long-term potentiation, facilitates post-synaptic responses by positively modulating the AMPA receptor and potentiates

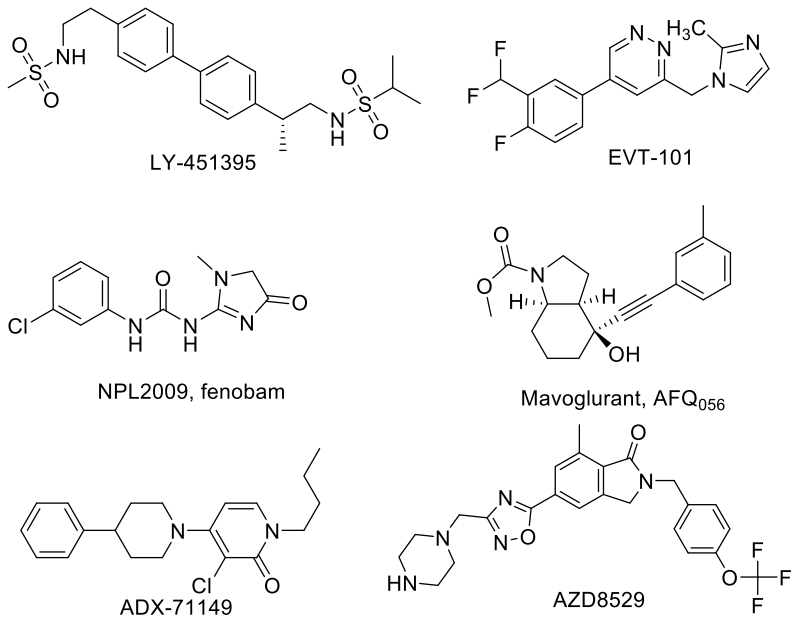

Fig. (3). Drugs acting on Glutamatergic targets.

AMPA-induced release of noradrenaline in rat brain slices, thus slowing the progression of mild cognitive impairment [120]. It was also found to improve the oxidative stress status in the hippocampus and prelimbic cortex. Allosteric modulators of AMPA receptors can enhance the expression of BDNF mRNA in cultured primary neurons. Consequently, the long-term elevation of endogenous BDNF expression represents a potentially promising therapeutic approach for behavioral disorders with this novel drug S18986, which was under phase II clinical trial (NCT00202540), but the trial was prematurely terminated due to safety concerns regarding reporting of adverse events, including flu-like syndrome without fever, increase in a liver enzyme, and decrease in platelets (from a clinical study report) [121].

Several NMDA antagonists like memantine have been developed. EVT-101 is a potent and selective NR2B subtype-specific antagonist originating from Roche and has an improved side effect profile compared to nonselective NMDA receptor antagonists. It was in a phase II clinical trial for treatment-resistant depression, but the study was terminated due to difficulty in recruiting patients [122]. GLYX-13/ Rapastinel is a tetrapeptide (Thr-Pro-Pro-Thr) novel NMDA receptor glycine-site functional partial agonist tested in the rat. It was found to have therapeutic potential as a learning and memory enhancer due to enhancing LTP and suppressing LTD (Long term depression). Thus, extrapolated use of this agent as a nootropic and neuroprotective entity was hypothesized *in-vivo*. It was used for major depressive disorder and showed a positive effect in phase II clinical trial, showing amelioration of depressive symptoms. Positive allosteric modulation of mGlu5 receptors enhances synaptic plasticity and cognition [123]. NPL2009/fenobam has entered phase II of the clinical trial, showing no adverse event reported and a significant clinical effect on the Fragile X syndrome condition in its phase I result [122].

ADX-71149, a mGlu2 positive allosteric modulator (PAM), has completed a phase II clinical trial for major depressive disorder with no additional efficacy of the drug [108]. AZD8529, a novel selective PAM of mGluR2, entered in phase II clinical trial for schizophrenia and has shown no efficacy on the disease condition. Decoglurant, a negative allosteric modulator (NAM) of the mGlu2/3 receptor, has completed a phase II clinical trial with registry no. NCT01457677 and did not show any pro-cognitive or antidepressant effect on patients with major depressive disorder [124]. AFQ056, a NAM of mGlu5 receptor, has shown its efficacy in the animal model for Fragile X Syndrome but has failed to show similar action in humans in both adolescents as well as adult patients, leading to a termination of phase II clinical trial of the drug and its repurposing for cocaine use disorder. A similar agent, STX107, entered in phase II clinical trial to treat fragile X syndrome, but the study was suspended for further evaluation. Considerable pharmacological evidence suggests that activation of group II mGlu receptors can distinctly inhibit synaptic transmission and modulate presynaptic glutamate release [125, 126]. ADX-47273, a positive allosteric modulator of the mGlu5 receptor, has shown antipsychotic and improved cognitive activity in animal studies. In addition, it increased long-term potentiation and adaptive learning, which was impaired by ethanol exposure [127].

2.10. Drugs Acting on Glycine Targets

Glycine enhances excitatory neurotransmission by binding to the NMDA complex in cortical and hippocampal structures, suggesting cognition. Local glycine concentrations in the forebrain are controlled by the action of the high-affinity glycine transporter type-1 (GlyT1) (Fig. **4**). Therefore, NMDA receptor function can be enhanced by increasing glycine in the synaptic space of NMDA receptors by inhibiting GlyT1. D-cycloserine, a glycine site partial agonist of NMDA receptor, has shown its efficacious action for reversing the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced memory impairment and neurodegeneration in the PD rat model [128]. Several GlyT1 inhibitors,

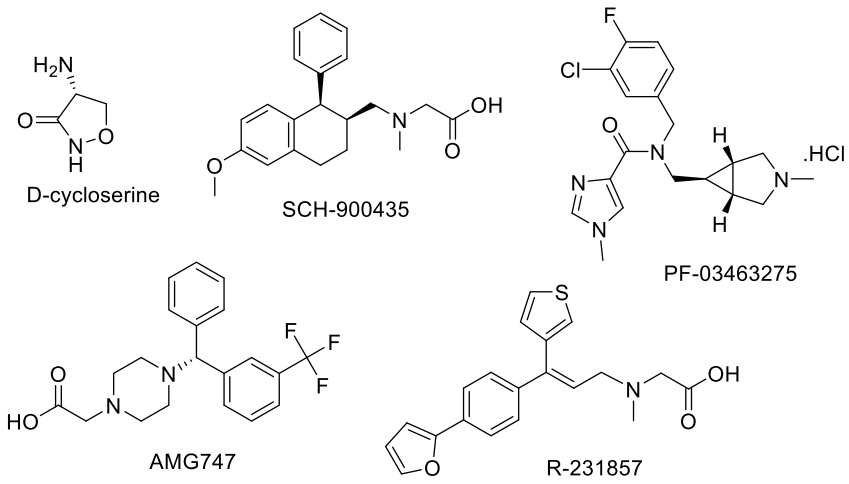

Fig. (4). Drugs acting on Glycine target

SCH-900435, PF-03463275, JNJ17305600, AMG747, and R-231857, have been developed in different phases of the clinical trial for schizophrenia and cognitive impairment associated with schizophrenia [108]. SCH-900435/ Org 25935/ MK-8435, a glycine transporter GlyT-1 inhibitor developed by Organon International, has completed a phase II clinical trial as an adjunct therapy with the antipsychotic drug for the management of negative symptoms in schizophrenia patients but did not show any significant advantageous effect in attenuating negative symptoms or improving cognition [129]. PF-03463275 has entered a phase II clinical trial for observing the effect of GlyT1 inhibitor on patients with schizophrenia or schizoaffective disorder with a trial registry NCT01911676 [130]. AMG747 has entered the phase II clinical trial, but the study has been terminated due to toxic epidermal necrolysis observed in schizophrenia patients with negative symptoms [131].

2.11. Drugs Acting on the GABAergic System

GABA (γ-aminobutyric acid) is the principal inhibitory neurotransmitter in the mammalian CNS. It has been proposed that full-positive allosteric modulators of α2, α3, or α5 may have therapeutic potential for treating cognitive dysfunction associated with schizophrenia [123]. GABA-$A_{\alpha 2/3}$ agonist MK-O777 reverses the ketamine-induced working memory impairment, but a recent study suggested that MK-0777 has little benefit for cognitive impairment in people with schizophrenia [108]. L-830982, α 2/3 agonist, is in phase II clinical trial for cognitive impairment associated with schizophrenia. The α5 subunits of the GABA receptor are localized in the hippocampus. It has been reported that an inverse agonist selective for α5 subunit-containing $GABA_A$ receptors improves memory encoding and recall but not consolidation in the Morris water maze [125]. RG1662 (α5 inverse agonist) is currently in phase I clinical trial for cognitive disorders [108]. AC-3933/radequinil, a partial inverse agonist for the benzodiazepine receptor developed by Dainippon Pharmaceutical Co. Ltd., was found to reverse the GABAergic inhibitory effect on cholinergic neurons and thus facilitate acetylcholine release in rat hippocampal slices, resulting in improved cognition. This has completed phase II clinical trial for the treatment of AD but failed to show promising efficacy. GABA-B antagonist SGS742/CGP-36742 is under a phase II clinical trial, to be used in AD, has shown promising results in a study as a therapy for cognitive impairment by reducing CREB2 (cAMP-response element binding protein 2) activity as seen in rat and improving the working memory, attention, and psychomotor speed (Fig. **5**) [132].

2.12. Drugs Acting on PDE Targets

PDE (phosphodiesterase) inhibitors act as cognition enhancers by blocking the metabolism of cAMP and/or cGMP that enhances neuronal function in the striatum, amygdala, cortex, and hippocampus. Pfizer discovered PF-04447943 (PDE9 inhibitor) and PF-02545920 MP-10 (PDE10 inhibitor). PF-04447943 has completed a phase II clinical trial for AD, showing no improvisation of behavior and cognitive symptoms and causing gastrointestinal adverse events [133]. PF-02545920/mardepodect has completed a phase II clinical trial for schizophrenia [108]. The drug HT-0712, a PDE4 inhibitor, is currently under a phase II clinical trial and was effective in improving age-associated memory impairment and CREB-regulated genes in aged mice. Cilostazol, a potent inhibitor of PDE3, leads to phosphorylation-dependent activation of transcription factor cAMP-responsive element-binding protein (CREB), thus upregulation of Bcl-2 (B-cell lymphoma 2) and COX-2 (Cyclooxygenase-2) expressions, thereby improving cognitive impairment in post-stroke patients. The drug is under a phase IV clinical trial. It shows a positive effect on AD therapy by reducing Aβ accumulation and tau phosphorylation *via* a significant decrease in ApoE-mediated Aβ aggregation in a mouse model (Fig. **6**) [134, 135].

2.13. Drugs Acting on Serotonergic Targets

Activation of the 5-HT4 (serotonin type 4) receptor leads to the secretion of a soluble non-amyloidogenic form of the amyloid precursor protein (sAPP-alpha), which has neuroprotective, neurotrophic, and cognition-enhancing effects, and it also decreases the extracellular accumulation of amyloid-beta [126]. PRX-03140, a highly selective 5-HT_4 partial agonist, has been evaluated in a phase II clinical trial to treat AD at Epix Pharmaceuticals, showing a significant improvisation [136]. Dimebolin, SB-742457/ GSK-742457, SAM-531/ PF-5212365/ WAY-262531, Lu-AE-58054, and

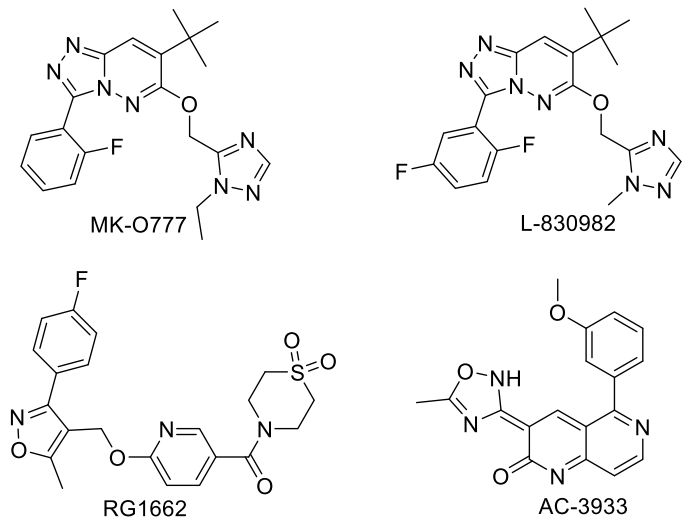

Fig. (5). Drugs acting on GABAergic target.

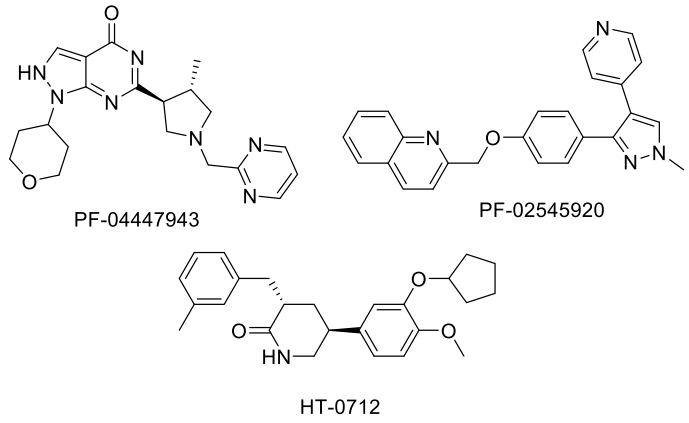

Fig. (6). Drugs acting on PDE target.

SGS-518 are developed as 5-HT6 receptor antagonists with improved affinity and better CNS penetration properties (Fig. **7**). These compounds are under different clinical trial phases to treat AD and cognitive impairment associated with schizophrenia (CIAS) [108, 137]. Fluoxetine, an SSRI (Selective serotonin reuptake inhibitor), increased hippocampal population spike amplitudes and excitatory postsynaptic potential slopes in rats. Also, a few studies have been conducted where the potential for the drug to promote recovery of function is shown after DG damage [138]. Another SSRI drug, escitalopram, even after a relatively short treatment period, was effective in treating depression in the elderly and may help improve cognitive performance for social stimuli. Avagacestat (BMS-708163), a selective γ-secretase inhibitor, decreases CSF (Cerebrospinal fluid) Aβ concentrations and has completed phase II clinical trial, where it was found to be well tolerated at low doses, but statistically, insignificant improvement was observed for the treatment of patients with mild to moderate AD [139].

Aripiprazole is a partial agonist at D_2 dopamine receptors, serotonin 5 HT1A, and 5-HT7 receptors, whereas an antagonist at serotonin 5-HT2A and 5-HT6 receptors. Administration of aripiprazole leads to an improvement in PCP (Phencyclidine or phenylcyclohexyl piperidine)-induced cognitive impairment in mice. A clinical trial of this drug reached phase IV for co-therapy with quetiapine or risperidone in schizophrenia with no significant effect on cognitive or psychiatric symptoms, but it has been well-tolerated and safe with a significant effect on prolactin levels [140]. Brexpiprazole is a novel dual serotonin-dopamine activity modulator with partial agonist activity at 5-HT1A and D2/3 receptors and possesses potent antagonist effects on 5-HT2A, α1B-, and α2C-adrenergic receptors. Brexpiprazole reverses the PCP-induced cognitive impairment in the animal model [141, 142]. Quetiapine (D2 and 5-HT2 antagonist), a new antipsychotic drug, prevents memory impairment by protecting the cultured cells against oxidative stress and decreases Aβ plaques in the brains of APP/presenilin-1 (PS-1) double-mutant mice. It also decreases the β-secretase activity and expression and the level of C99 (an APP C-terminal fragment following cleavage by β-secretase) [144]. Chronic administration of quetiapine prevents PCP-induced memory impairment. It decreases the Bcl-XL/Bax ratio in the posterior cingulate cortex, ameliorating cognitive impairment and brain apoptotic processes. The drug has reached phase IV clinical trial [143]. Lecozotan, a selective 5HT1A receptor antagonist, shows increased learning and memory in rats by

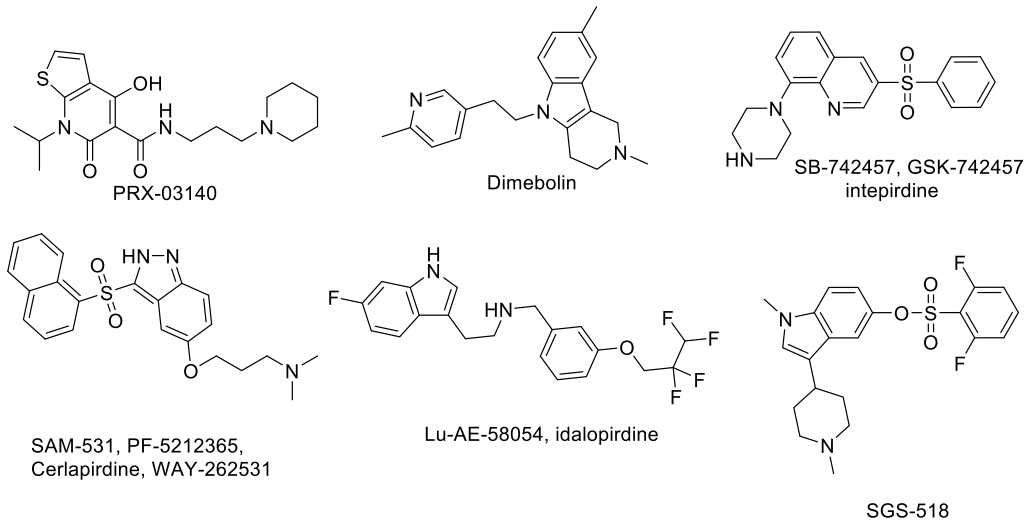

Fig. (7). Drugs acting on Serotonergic target.

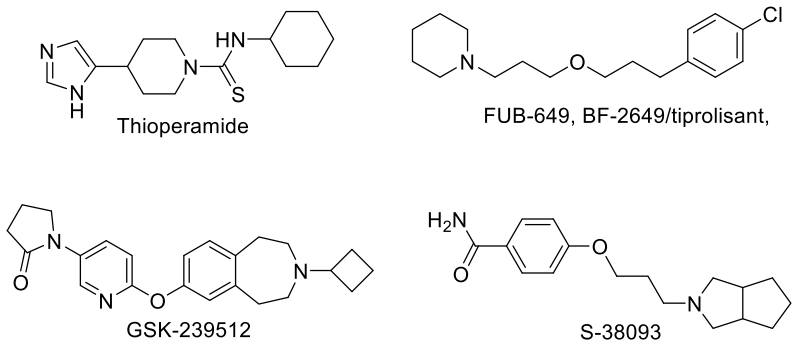

Fig. (8). Drugs acting on Histaminergic target.

stimulating the release of glutamate and acetylcholine in the hippocampus [145, 146].

2.14. Drugs Acting on Histaminergic Targets

Animal studies show that histamine has been implicated in cognitive functions. Histamine H_3 receptors inhibit the release of several neurotransmitters involved in cognition. H3 receptor antagonists are currently under evaluation in a clinical trial for cognitive disorders in dementia, CIAS, narcolepsy, and excessive daytime sleepiness. H3 antagonist, thioperamide, reverses the scopolamine-induced spatial orientation, working memory, and passive avoidance impairments in animals [147]. Several H_3 receptor antagonists like FUB-649, BF-2649/tiprolisant, GSK-239512, S-38093, and SAR-110894 are in phase II clinical development for the treatment of AD and CIAS (Fig. **8**) [108]. H_3 inverse agonist MK-0249 has completed the phase II clinical trial (NCT00420420), showing no effective improvement in cognitive deficits associated with AD [148].

2.15. Miscellaneous Agents

APH-0703/APH-1104, a bryostatin I analogue, is a PKC modulator that activates the alpha-secretase pathway, stimulating the generation of sAPP and thus decreasing the plaque deposition and cognitive deficits in AD. This drug was approved for phase II clinical trial in 2012, but no further updates have been posted. AVN101 is a serotonin 5-HT6 receptor antagonist currently under phase II clinical trial for AD [149]. Levetiracetam is currently in phase II clinical trial (NCT01044758) as a potential drug for treating cognitive impairment in older patients, where the study proved to effectively reverse the synaptic dysfunction and deficits in learning and memory in hAPP mice. It acts by binding on SVA2, synaptic vesicle protein in the brain, and modulates neurotransmitter release [150]. Finally, an irreversible selective monoamine oxidase-B (MAO-B) inhibitor rasagiline has completed a phase II clinical trial in the treatment of dementia for elderly patients with AD, and the study showed its potential therapeutic effect on the symptomatic treatment of the cognitive disorder in patients with neurodegenerative disorders (NCT02359552) (Fig. **9**) [151, 152].

In bilateral common carotid artery occlusion (BCCAO), celecoxib (NSAID: non-steroidal anti-inflammatory drug) improves behavioral alterations, glutathione defense, and attenuates acetylcholinesterase activity and TNF-α levels to be neuroprotective against ischemia-reperfusion injury-induced memory dysfunction, neuroinflammation, and oxidative damage. The drug is under phase III clinical trial to treat age-associated memory impairment (NCT00009230). Another nonsteroidal anti-inflammatory derivative, CHF5074/ itanapraced, has been reported as a γ -secretase modulator *in vitro* and inhibits plaque deposition, reversing memory deficit *in vivo* in transgenic mouse models of AD. It has completed a phase II clinical trial (NCT01303744) to

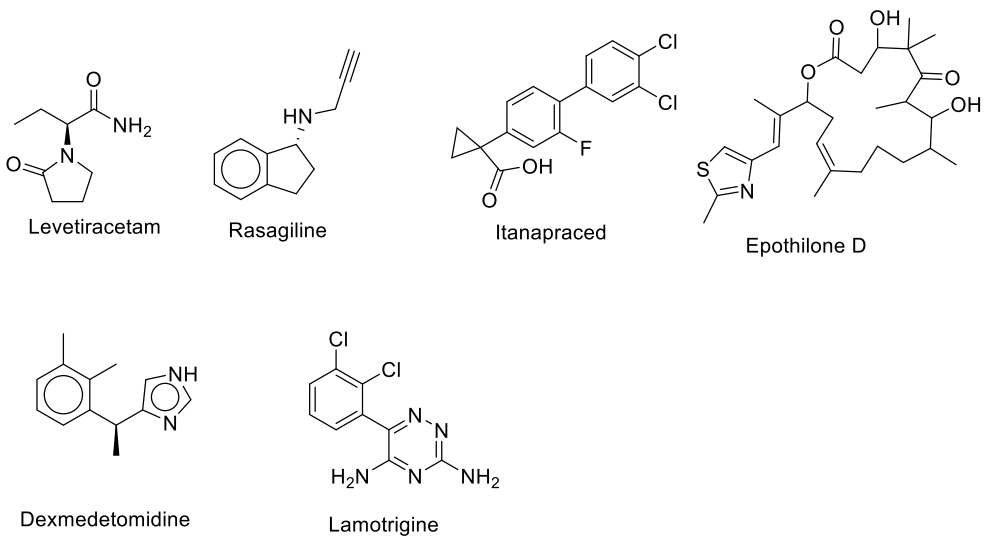

Fig. (9). Miscellaneous agents.

treat AD in young to elderly patients. It has selectively reduced the pro-inflammatory activities of microglial cells and increased their ability to eliminate neurotoxic Aβ aggregates in the brain by phagocytosis [153-155]. Isoflavones (Novasoy, SIF) have completed a phase II clinical trial (NCT00205179) and have shown to have a good effect on the improvement of memory in older patients with memory dysfunction, mainly by showing inhibitory action on protein tyrosine kinases (EGFR/VEGFR/Her2) and modulating ERα/β, with a result of no major improvement in cognition. SIF pretreatment was found to protect the synaptic plasticity, alleviating learning and memory impairment in rats induced by $A\beta_{1-42}$. These results suggested that SIF can improve long memory performance in mice. The studies showed that chronic isoflavone supplementation in males activates ERβ, thus improving cognition deficit disorder. In postmenopausal women, SIF supplementation had a positive effect on improving cognitive function and visual memory [156, 157]. The drug BMS-241027/Epothilone D/ KOS-862 has completed a phase I clinical trial (NCT01492374), and it was found that very low doses of it may be useful in the treatment of AD by increasing the stability of microtubules in older patients with taxol like mechanism (Fig. **9**). The neuroprotective action of carvedilol (alpha-1 blocker) in aluminum chloride and colchicine-induced cognitive impairment and associated oxidative damage in rats has promoted its use for the treatment of AD and has completed phase IV clinical trial (NCT01354444).

Dihydrexidine (DAR-0100), the first complete D1 agonist that has completed a phase II clinical trial (NCT02507206), showed improvement in cognitive activity in young and elderly individuals. TNF-alpha acts as a mediator for the disruption of synaptic memory mechanism caused by Aβ. The drug etanercept, the antagonist of TNF-alpha, which is currently under a phase II clinical trial, shows potential as an intervention for treating AD (NCT01068353). Lamotrigine (Na^+ channel blocker) is used as a treatment for young to older patients suffering from memory impairment and has completed a phase IV clinical trial (NCT01142310) since a study showed that it causes the reduction of the Aβ and upregulation of BDNF and NGF in APP and PS1 mice. A novel pharmacological intervention, ST101, is under a phase II clinical trial (NCT00842673). It was found to activate T-type voltage-gated calcium channels (VGCCs), causing acetylcholine (ACh) release in the hippocampus region in mice. Currently, MEM 1003/ BAY-Z-4406, a dihydropyridine compound, has completed a phase II clinical trial for AD (NCT00257673), possibly reducing the slow afterhyperpolarization (sAHP) period and increasing cell excitability, thus improving spatial memory and attention dependent performance in aged rats. In a study, the effect of a novel L-type Ca^{2+} channel antagonist, MEM 1003, was evaluated on delay and trace eye blink conditioning (a simple form of associative learning) in older female New Zealand white rabbits, showing enhanced learning. In a study on rats, a bilateral injection of insulin was administered into the dorsal hippocampus, transiently enhancing the hippocampal-dependent memory. Metformin has completed a phase II clinical trial to observe the drug's effect on biomarkers of AD in older patients (NCT01965756). It is currently under phase II/III clinical trial to treat mild cognitive impairment (NCT04098666). It was found that L-methionine induces memory impairment, and metformin shows a beneficial effect in preventing this impairment by normalizing oxidative stress in the hippocampus. Metformin also prevents brain mitochondrial dysfunction, thus restoring learning behavior, which is impaired by long-term HFD consumption. The db/db mice have increased Aβ levels, so metformin attenuated the increase of total tau, phospho-tau, and activated JNK. It also attenuated the reduction of synaptophysin in the hippocampus [158, 159]. Pioglitazone is under a clinical trial for the treatment of cognitive impairment. Various studies reported that it offered protection against scopolamine-induced memory dysfunctions by affecting the cholinergic system, possibly due to its antioxidant action and a significant neuroprotective effect, thus having therapeutic potential against AD. It also improves the morphine-induced impairment of memory acquisition through the NO pathway. In STZ rats, pioglitazone was found to have a positive effect on improving cognitive performance by lowering oxidative stress and improving cerebral glucose utilization, thereby suppressing the expression of APP, BACE1 (beta-secretase1), RAGE

(Receptor for advanced glycation end-products), NF-κB-p65, and activated PPARγ (Peroxisome proliferator-activated receptor-γ) in the hippocampus and cortex. Hence, it can be exploited for dementia associated with diabetes and age-related neurodegenerative disorder. Pioglitazone treatment also reduced oxidative stress by reducing malondialdehyde (MDA) and increasing glutathione levels; these results showed its beneficial effects on cognitive impairment in MPTP-induced PD in rats [160]. Pioglitazone also reduces NMDA-mediated calcium current and transient current, thus improving cognition through the glutaminergic pathway's involvement [161, 162]. Another antidiabetic drug, rosiglitazone, counteracts the increase in IL-1β (interleukin-1β) and IFN-γ (interferon-γ) levels induced by Aβ42 oligomers in hippocampal slices on LTP, which could be the mechanisms of action of rosiglitazone on improvement in memory deficits. The chronic treatment with rosiglitazone, a high-affinity agonist at PPARγ, facilitates Aβ clearance. The study showed that an improvement in insulin resistance might justify improving cognitive performance in older individuals with mild cognitive impairment (MCI) and type 2 diabetes. The drug has completed a phase III clinical trial, and there was no statistically significant improvement in cognition or global function of patients, but the drug was found to be safe and tolerable, showing no safety concerns (NCT00348140) [163]. Exenatide (GLP-1 agonist) was found to improve the cognitive effect in PS1-KI mice by increasing the brain anaerobic glycolysis rate and improving the impaired long-term potentiation in diet-induced obesity in mice. This study can be employed on an older patient suffering from impaired cognition. It is currently in phase III clinical trial (NCT02847403) [164, 165]. The drug liraglutide is a GLP-1 agonist and is under a phase II clinical trial to be employed as a treatment for older patients who have dementia (NCT01843075) since a study has shown its effects on alleviating the hyperphosphorylation of tau and neurofilament proteins by enhancing O-glycosylation of neuronal cytoskeleton protein, improving the JNK and ERK (Extracellular-signal regulated kinases) signaling pathway, and decreasing the neural degeneration, thereby exerting the protective effects on memory impairment induced by i.c.v. injection of STZ (Streptozotocin) in mice [166-169].

EGb 761/ Tanakan® (*Ginkgo biloba* extract) improves cognitive abilities by increasing SOD and GSH-Px, decreasing the level of MDA, upregulating the ratio of Bcl-2/Bax, and downregulating the level of cleaved Caspase3. The antioxidant properties of EGb 761 aid in neuroprotective and neurotrophic actions on the hippocampus and explain the improvement in memory in both humans and experimental animals [170, 171]. EGb 761 inhibits Aβ oligomerization and its deposits in transgenic *Caenorhabditis elegans;* thus, it has a therapeutic activity for preventing and treating AD in older patients, and it is currently under phase II clinical trial (NCT03090516)**.** However, long-term treatment with *Ginkgo biloba* extract in phase IV clinical trial did not reduce the risk of AD progression in patients (NCT00276510) [172]. Souvenaid, a nutritional supplement, aids in the formation of synapses, and its function is currently assessed in a phase II clinical trial. It has shown improved memory performance and brain activity in an earlier randomized clinical trial [173]. Cinacalcet is in a phase II clinical trial. Moreover, it was found to show a good effect in enhancing the memory in young individuals by allosteric activation of the calcium-sensing receptor [174].

3. NEWER TARGETS TO TREAT COGNITIVE DISORDERS AND DEMENTIA

3.1. HDAC (Histone deacetylase) Inhibitors

Epigenetic mechanisms, such as histone acetylation and DNA methylation, are important for memory processes in the adult brain. Chromatic plasticity and histone acetylation are altered in cognitive ageing, neurodegeneration, and neuropsychiatric diseases. Inhibitors of histone deacetylase (HDAC) exhibit neuroprotective potential in animal models of various brain diseases like PD, AD, stroke, schizophrenia, and Rubinstein Taybi Syndrome. HDAC inhibitors like SB (Sodium butyrate), 4-PB(4-phenylbutyrate), valproate, and SAHA are in different phases of clinical trials for the treatment of neurodegenerative diseases (Fig. **10**) [175]. Valproic acid (VPA) could ameliorate spatial memory impairment and Aβ deposition *via* the inhibition of inflammation by reducing the increased expression in IL-1β and tumor necrosis factor-α (TNF-α) in the hippocampus and cortex of APP/ PS1 transgenic mice [176]. VPA inhibits histone deacetylase 1 (HDAC1) enzyme activation, thus attenuating the prenatal hypoxia-induced Aβ-induced memory deficits [177]. Furthermore, the significant induction of melatonin MT2 receptor expression by VPA affects the hippocampal regions involved in memory. In autism, the administration of VPA enhances the paired-pulse facilitation (PPF) and long-term potentiation (LTP), representing short- and long-term synaptic plasticity [178]. VPA was under phase IV clinical trial (NCT00375557) used in elderly patients but was withdrawn.

3.2. cAMP-Responsive Element-Binding Protein (CREB) Enhancers

CREB/CRE mediated transcription plays a key role in nervous system development, cell survival, synaptic plasticity, and long-term memory formation [179]. Dysregulation of the CREB/CRE transcriptional cascade leads to a deleterious effect on cell survival and synaptic plasticity. Both CREB inhibition and chronic CREB activation trigger cell death *via* the pro-apoptotic and excitotoxic mechanisms, respectively [180, 181]. Augmentation of CREB-mediated transcription provides beneficial effects on synaptic plasticity and neuronal survival. A traditional Chinese medicinal plant, Kami-ondam-tang (KOT), significantly increased step-through latency in the passive avoidance task by increasing the expressions of phosphorylated Akt, phosphorylated CREB, and BDNF in the hippocampal CA1 and dentate gyrus [182]. Luteolin, a flavonoid, enhances long-term potentiation and memory formation by potentiating CREB signaling (Fig. **11**) [183]. 73,000 compounds were screened in a quantitative high-throughput screening format by assaying CREB-mediated β-lactamase reporter gene expression, out of which 1800 compounds were found effective, enhancing the CREB-mediated gene expression phosphodiesterase-4 or protein phosphatase activity by inducing cAMP production or protein kinase A activity [184]. Tanshinone I enhances learning and memory by increasing the ERK/CREB signaling in the hippocampus [185]. N-butanolic extract of

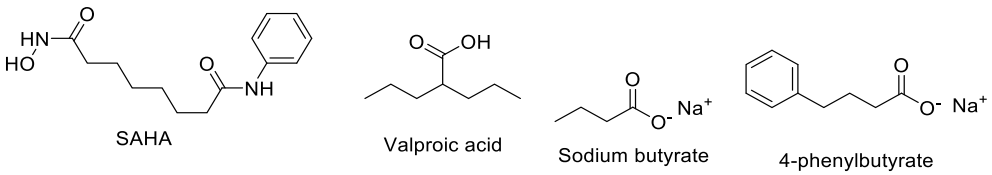

Fig. (10). HDAC inhibitor.

Opuntiaficus-indica var. saboten enhances long-term memory in the passive avoidance task in mice by mediating the ERK-CREB-BDNF signaling pathway and increasing immature neuronal survival [186]. In 18-month-old rats, St. John's wort (*Hypericumperforatum*) reduces the aging-induced decline of spatial memory, possibly by the activation of CREB regulated genes associated with memory formation [187]. Considering evidence, CREB mediated transcription is an excellent target for the development of cognitive enhancers.

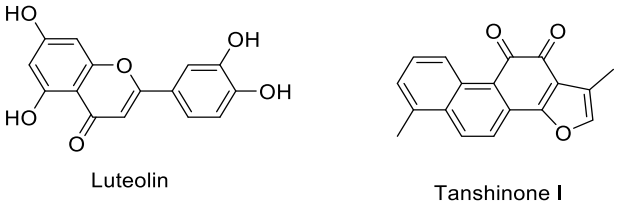

Fig. (11). CREB enhancers.

3.3. Glycogen Synthase Kinase-3 Inhibitors

Glycogen synthase kinase-3 (GSK-3) is a multifunctional cellular serine/threonine-protein kinase that inhibits glycogen synthase and is involved in several diverse human diseases, including AD, PD, bipolar disorder (BPD), type-2 diabetes, and cancer [188-190]. GSK-3β is an important regulator of the balance between LTD and LTP, which plays an important role in learning and memory formation [191]. Lithium, a GSK-3β inhibitor, facilitates neurogenesis and reduces Aβ-induced cognitive impairment and hippocampal CA3 neuron loss [192-194]. GSK-3β-selective inhibitor SB-216763 provides only modest improvement in memory retention [194]. The phase II clinical trial of tideglusib showed the cognition-enhancing property in mild to moderate AD patients treated for 24 weeks [195]. Recently, it has been reported that curcumin improves memory and provides neuroprotection in AD by activating the Wnt/β-catenin signaling pathway by inhibiting the activity of GSK-3β (Fig. **12**) [196].

3.4. Protein Kinase C Activators

Protein kinase C (PKC) isoforms are ubiquitously expressed and activated in the central nervous system by Ca^{2+}, phospholipids and diacylglycerol, phorbol esters, or other PKC activators (Fig. **13**) [197]. PKC isoforms play an essential role in many types of learning and memory. Activation of PKC enhances synaptogenesis in the hippocampus, but overactivation of PKC leads to memory impairment [198, 199]. Intracerebroventricular (ICV) injection of PKC inhibitors causes marked memory impairment in passive avoidance and Morris water maze tasks. At the same time, curcumin-induced PKCδ degradation leads to improved spatial learning in adult and aged Wistar rats [200]. It is evident that PKCδ inhibition leads to the enhancement of polysialyltransferases (PST) activity; as a result, polysialylation of the neural cell adhesion molecule increases, which is necessary for the consolidation processes of hippocampus-based learning [201]. Activation of PKC by (–)-epigallocatechin gallate, the most active polyphenolic constituent of green tea, enhances learning and memory by facilitating presynaptic glutamate release [202]. Another natural marine product, bryostatin-1, also activates PKC, enhancing learning and memory by stimulating protein synthesis and synaptogenesis [203]. Activation of the PKC isozymes is an attractive therapeutic strategy for improving memory for future research.

Exebryl-1 reduces Aβ, plaque, and tangle load in AD patients and shows marked improvement in hippocampus-dependent memory, Morris water maze learning, and probe trials [204]. Moreover, testosterone supplementation enhances cognitive function [205]. Its formulation (Androgel 1%) is in phase III clinical trial. Estradiol has also completed a phase II/III clinical trial to treat dementia in young to older patients with AD (NCT00066157). The findings showed that older men with MCI improved memory on E_2 treatment. In the medial prefrontal cortex, norepinephrine, dopamine, and serotonin levels were found to decrease on chronic estrogen treatment, thus contributing to the improvement in memory. Raloxifene, a selective estrogen receptor modulator, treatment increases brain activation, thus suggesting cortical arousal where cognition domains exist.

The drug has completed a phase II clinical trial to treat AD and was found to show a positive effect on memory. Furthermore, raloxifene treatment improves cognition in young individuals with schizophrenia (NCT00368459). The cysteine protease inhibitor, E64d, improves memory impairment and reduces brain Aβ by inhibiting cathepsin B [206]. Several antibody-based products have currently reached clinical trials, such as PLY2062430 (solanezumab), AAB-001 (Bapineuzumab), GSK933776A, PF-04360365, and MABT5102A. Long-term systemic administration of antibodies against the APP beta-secretase cleavage site to transgenic mice improves cognitive functions by reducing brain inflammation and incidence of microhemorrhage [207]. Solanezumab has completed a phase III clinical trial in patients with AD. However, the drug failed to improve cognitive function significantly in mild AD [208]. Bapineuzumab underwent a phase II clinical trial showing no significant efficacy in mild to moderate AD patients [209]. An anti-Aβ antibody, GSK933776A, has also completed a phase I clinical trial in patients with AD and evidenced its target in plasma and CSF without causing brain ARIA-E/H (amyloid-related imaging abnormalities-edema or hemorrhage) [210]. PF-04360365 (Ponezumab) was found to be safe and

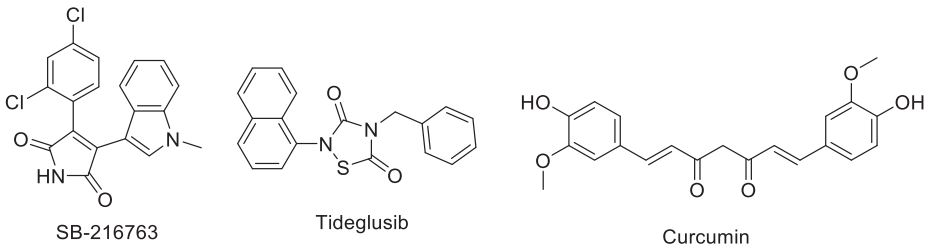

Fig. (12). GSK3β inhibitors.

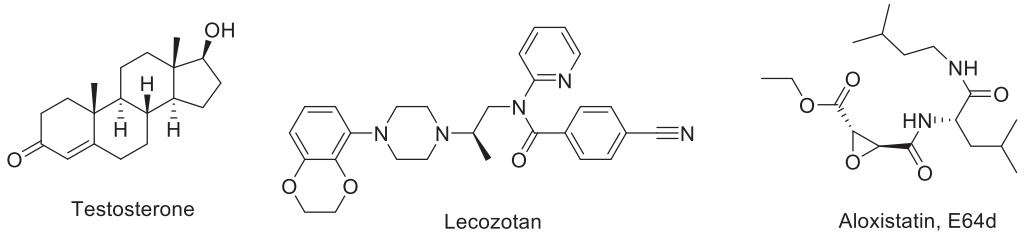

Fig. (13). Protein kinase C activators.

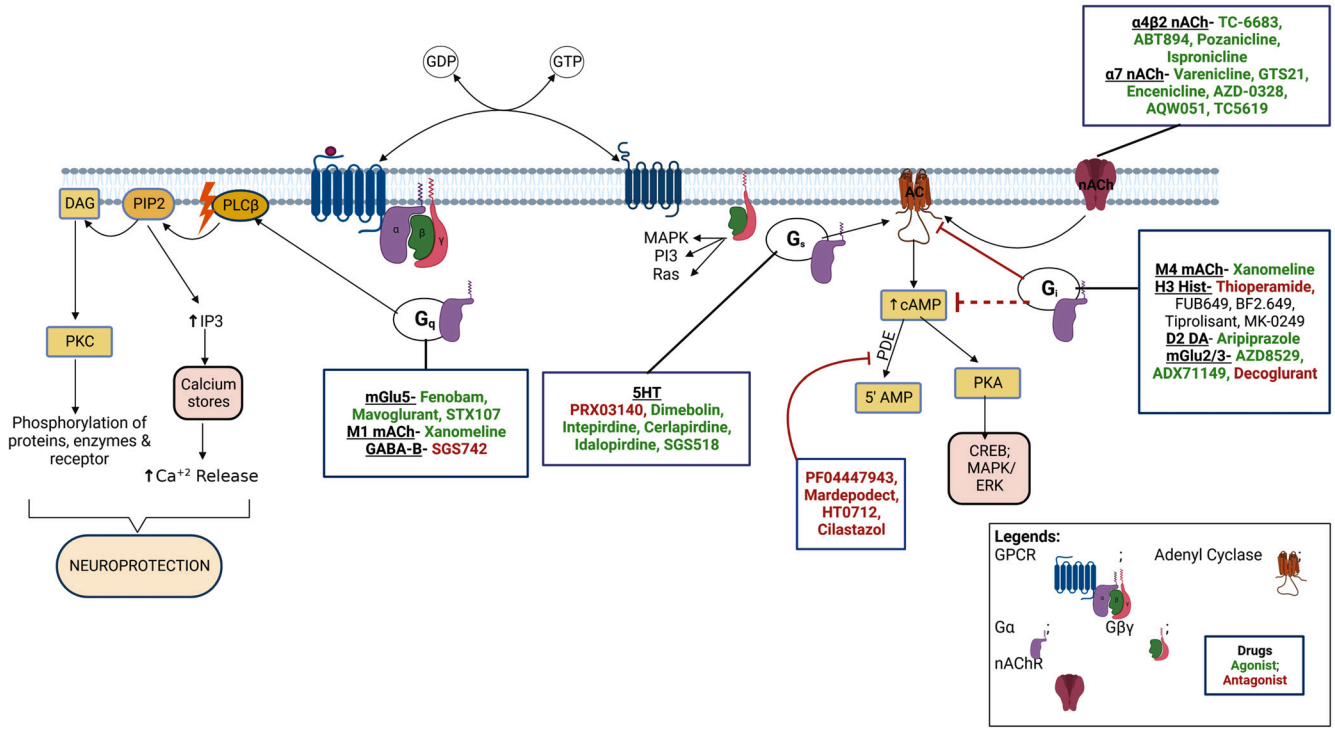

Fig. (14). Drugs acting on ionic and metabotropic targets. The metabotropic targets include GPCRs (Blue) with Gs, Gi, and Gq subtypes. When stimulated by ligand, the receptor activates the G-protein, dissociating the Gα (Purple) subunit and activating the secondary messenger. The Gq protein activates PLC in the membrane, which causes the conversion of phospho-inositol biphosphate (PIP2) to diacylglycerol (DAG). The PIP2 is converted to Inositol triphosphate (IP_3), which stimulates the release of Ca^{+2} from the calcium stores like the endoplasmic reticulum. At the same time, the DAG activates PKC, leading to phosphorylation of proteins helping in neuroprotection. The G-βγ (Green, Pink) can also activate pathways like MAPK, PI3, Ras, *etc.* The Gq protein includes receptors like mGlu5, M_1mACh, and GABA-B. The Gs type of GPCR activates the adenyl cyclase (AC, Brown) in the membrane, increasing the cAMP levels, activating protein kinase (PKA), and increasing protein expression by activating CREB MAPK, ERK, *etc.* This includes receptors like 5HT4 and 5HT6 involved in cognitive processes in CNS. The cAMP is converted to 5' AMP by phosphodiesterase enzyme, leading to its inactivation. The Gi subtype of GPCR tends to block the AC receptor inhibiting the cAMP cycle. It includes receptors like M_4mACh, Histamine H3, Dopamine D_2, and mGlu2/3 involved in the memory and cognition processes of the brain. The ionic nACh receptor acts by the movement of sodium and potassium ions through the channels, leading to modulation of cellular processes by acting upon AC. The nACh receptor includes α_7 and $\alpha_4\beta_2$ receptors. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

Table 2. Drugs under clinical trial.

Drug Name	Clinical Trial ID	Target	Indication	Trial Stage	Outcome/ Termination Reason	Refs.
Cholinergic Receptor						
TC-6683/ AZD-1446	NCT01012375	$\alpha_4\beta_2$ agonist nAChR	ADHD	Phase IIb	No significant effect	[214]
ABT-894	NCT00429091		ADHD	Phase II	Positive result	[215]
A-87089/ ABT-089 Pozanicline	NCT00555204		AD	Phase II	Futility criterion-related termination	[216]
Ispronicline/ AZD3480/ TC-1734-112	NCT00109564	$\alpha_4\beta_2$nAChR partial agonist	Age associated memory impairment	Phase IIb	Positive effect	[217]
Xanomeline	NCT03697252	M_1/M_4mAChR agonist	Schizophrenia	Phase II	Positive results	[218]
GSK-1034702	NCT01371799	M_1agonsit	Cognitive dysfunction	Phase I	Completed	[219]
Varenicline	NCT00802919	α_7nAChR agonist	Schizophrenia	Phase II	No significant effect	[220]
DMXBA/ GTS-21	NCT00100165/ NCT00419445		Schizophrenia/ ADHD	Phase II	No effect on cognition significantly but the negative symptoms were ameliorated	[221]
MT-4666/ Encenicline	NCT02327182		AD	Phase III Terminated	GI side effects	[222]
AZD-0328	NCT00669903		Schizophrenia	Phase II Terminated	Inability to meet the target product profile	[223]
AQW051	NCT00825539		Schizophrenia	Phase II	Positive effect	[224]
TC-5619	NCT01488929		Schizophrenia	Phase II	No benefit of the drug	[225]
SSR180711	NCT00602680	α_7nAChR Partial agonist	Mild AD	Phase II Terminated	Insufficient expected benefit-risk	Clinicaltrials.gov
AVL-3288/ CCMI	NCT02978599	PAM of α_7nAChR	Schizophrenia	Phase I	No efficacy of the compound	[226]
Ladostigil	NCT01429623	Reversible AchE and BuChE inhibitor	MCI	Phase II	No effect on cognition but reduced brain and hippocampal atrophy	{Schneider, 2019 #14} [227]
Posiphen	NCT02925650	APP 5'UTR region inhibitor	Early AD	Phase I/II Recruiting	NA	Clinicaltrials.gov.in
ANAVEX2-73, blarcamesine	NCT02756858	SIGMAR1 agonist	Mild to moderate AD	Phase II/ III	NA	[228]
Glutamatergic System						
CX516/ Mibampator	NCT00235352	AMPAR potentiator	Stable Schizophrenia	Phase II/III	Positive Effects on cognition	[229]
LY-451395	NCT00843518		AD	Phase II	No significant improvement	[119]
S 18986	NCT00202540		Behavioral disorder	Phase II Terminated	ADR reported	[230]

(Table 2) contd….

Drug Name	Clinical Trial ID	Target	Indication	Trial Stage	Outcome/ Termination Reason	Refs.
GLYX-13/ Rapastinel	NCT01234558	NMDA antagonist	Major depressive disorder	Phase II	Amelioration of depressive symptoms	[231]
NPL2009/fenobam	NCT00637221	NAM of mGlu5	fragile X syndrome	Phase I/ II	No ADR and clinical efficacy proved	[232]
AFQ056/ Mavoglurant	NCT01433354			Phase II Terminated	Negative outcomes	[233]
STX107	NCT01325740			Phase II Suspended	NA	Clinicaltrials.gov.in
ADX-71149/ JNJ-40411813	NCT01582815	PAM of mGlu2	Major Depressive Disorder	Phase II	No significant effect	[234]
AZD8529	NCT00921804		Schizophrenia	Phase II	No efficacy	[235]
Decoglurant	NCT01457677	NAM of mGlu2/3	Major Depressive Disorder	Phase II	No significant pro-cognitive effect for test compound	[124]
Glycine						
SCH-900435/ Org 25935/ MK-8435	NCT00725075	GlyT1 inhibitors	Negative symptoms of Schizophrenia	Phase II Completed	No significant improvement	[236]
PF-03463275	NCT01911676			Phase II Recruiting	NA	Clinicaltrials.gov.in
AMG747	NCT01568229			Phase II Terminated	Toxic Epidermal Necrolysis ADR reported for test compound	[131]
GABAnergic System						
MK-O777/ L-830982/ TPA023	NCT00129441	GABA-$A_{\alpha 2/3}$ agonist	Schizophrenia	Phase II	Little benefit for cognitive impairment	[237-239]
RG1662/ Basmisanil/ RO5186582	NCT02024789	GABA-$A_{\alpha 5}$ inverse agonist/ NAM	Cognitive impairment associated with Down's Syndrome	Phase II	No efficacy	[240]
AC-3933/ Radequinil	NCT00359944	partial inverse agonist for the BDZ receptor	AD	Phase II	Lack of efficacy	[241]
SGS742/ CGP-36742	NCT00093951	GABA-B antagonists	AD	Phase II	Improved working memory and psychomotor speed with test compound	Clinicaltrials.gov.in
Tramiprosate/ ALZ-801	NCT04770220	GABA mimetic action/ Aβ42 stabilization	AD	Phase II	Safe and well-tolerated; Reduction in CSF Aβ42 levels	[70, 242]
PDE Inhibitors						
PF-04447943	NCT00930059	PDE_9 inhibitor	AD	Phase II	No clinical improvisation	[133]
PF-02545920/ Mardepodect	NCT01175135	PDE_{10A} inhibitor	Schizophrenia	Phase II	No effect	[243, 244]
HT-0712	NCT02013310	PDE_4 inhibitor	AAMI	Phase II	Improved memory and cognition	[245]
Cilostazol	NCT01409564	PDE_3 inhibitor	AD	Phase IV	Delays the regional cerebral metabolism	[246]

(Table 2) contd….

Drug Name	Clinical Trial ID	Target	Indication	Trial Stage	Outcome/ Termination Reason	Refs.
Serotonergic System						
PRX-03140	NCT00384423	5-HT_4 partial agonist	AD	Phase II	Clinically efficacious	Clinicaltrials.gov.in
SB-742457/ Intepirdine/ RVT-101/ GSK-742457	NCT02585934	-	Mild to moderate AD	Phase III Completed	Efficacious	[247]
SAM-531/ Cerlapirdine/ PF-5212365/ WAY-262531	NCT00895895			Phase II Terminated	NA	Clinicaltrials.gov.in
Lu-AE-58054/ Idalopirdine	NCT02006654			Phase III Completed	No cognitive improvement	[248]
Avagacestat BMS-708163	NCT00810147	selective γ-secretase inhibitor	Mild to moderate AD	Phase II Completed	Well tolerated but test drug not significantly efficacious	[139]
Aripiprazole/ Abilify/ OPC 14597	NCT00325689	partial agonist at D_2 receptors	Schizophrenia	Phase IV Completed	No psychiatric advantage	[249]
Others						
Levetiracetam	NCT01044758	SVA_2 binding modulates NT release	MCI	Phase II Completed	Reverses synaptic dysfunction	[250]
Rasagiline	NCT02359552	MAO-B inhibitor	Dementia with AD	Phase II	Potential effect	[251]
Celecoxib	NCT00009230	NSAID	AAMI	Phase III	-	[252]
CHF5074/ Itanapraced	NCT01303744		AD	Phase II	-	[153]
BMS-241027/ Epothilone D	NCT01492374	Microtubule stabilization	AD	Phase I	Effective	[253]
Dihydrexidine/ DAR-0100	NCT02507206	Full D_1 agonist	Cognitive deficit	Phase II	Improved cognition	[254]
Etanercept	NCT01068353	TNF-alpha antagonist	AD	Phase II	Potential intervention	[255]
Lamotrigine	NCT01142310	Na^+ channel blocker	Memory Impairment in AD	Phase IV Completed	Improved cognitive function	[256]
ST101	NCT00842673	T-type voltage gated Ca^{+2} channel blocker	Memory deficits	Phase II	-	[257]
Metformin	NCT01965756 NCT04098666	AMPK	AD and MCI	Phase II Phase II/III	-	[258]
Exenatide	NCT02847403	GLP-1 agonist	Cognitive impairment	Phase III	-	[259]
Liraglutide	NCT01843075	GLP-1 agonist	Dementia	Phase II	-	[260]
EGb 761	NCT03090516	Antioxidant	AD	Phase II/III Recruiting	NA	[261]
Raloxifene	NCT00368459	SERM	AD	Phase II	Improved cognition	[262]
PQ912 (Varoglutamstat)	NCT03919162	Glutaminyl cyclase inhibitor	Early AD	Phase II	Safe and well-tolerated, efficacy result not published	[263]

well-tolerated but not effective in patients with mild to moderate AD in phase II clinical trial [211]. Similarly, MABT5102A (crenezumab) did not qualify the criteria to be efficacious in mild to moderate AD management in clinical trial phase II [212]. Activating the somatostatinergic nervous system in the hippocampus by FK962 ameliorates cognitive impairment in rats [213].

CONCLUSION AND FUTURE PERSPECTIVES

Cognitive impairment associated with several neurological disorders is becoming a growing concern for society as the incidences rise with time and an aging population. The molecular mechanism underlying memory formation and cognition has been extensively studied, leading to the discovery of many potential therapeutic targets to date. Still, the research continues as many stones are yet to be turned. The researchers have focused on connecting the dots between several neurological disorders and memory deficits and unveiled the neurobiological pathway of memory formation and cognition. The trends in past years have been set upon discovering pharmaceutical agents for management, and several molecules are under clinical trial for their potential use in treating neurological disorders (Table **2**). The limelight has been grabbed by agents acting on the cholinergic targets, leading to the discovery of several agents like galantamine and rivastigmine donepezil, *etc.*, widely used clinically for cognitive disorders management. Alongside, FDA approval of the newest of its class agent, aducanumab, which targets amyloid peptide aggregation, has brought hopes for more such breakthrough research and newer class agents. Researchers nowadays are also trying to target peripheral redirection and disposal of the peptide aggregated in the CNS using mAb like m266 or aggrephagy (autophagic targeting of the aggregates) or by GPCR mediated removal of aggregates. The missing bridge between efficient management of such cognitive disorder lies in the diagnosis and early-stage detection of the memory impairment due to its resemblance to general forgetfulness and amnesia, having similar clinical presentations at initial stages. When the disease leads to a progressed stage, it becomes difficult to be managed by pharmacological agents. Hence, the major focus needs to be on such early-stage biomarkers discovery. Recent studies have shown that technological advances have allowed exploring nuclear and genetic targets for developing pharmacological agents as a therapeutic alternative for disease-associated cognitive disorder and dementia management, leading to the discovery of several microRNAs and small interfering RNAs as suitable targets. As mentioned in this review, several clinical trials are going on, and efficient collaboration between the researcher, clinical researcher, and pharmaceutical industries might bring us closer to developing efficient drug targets and optimum therapy for disease-associated dementia.

LIST OF ABBREVIATIONS

PD = Parkinson's Disease

AD = Alzheimer's Disease

HIV = Human Immunodeficiency Virus

ADHD = Attention-Deficit Hyperactivity Disorder

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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