EXPLORING AVENUES FOR ALZHEIMER'S DRUGS: CURRENT STATUS AND FUTURE OUTLOOK

Rathi K.[1], Wavhale R.[1], Undale V.[1], Bhole R.[1,2], Dherange S.[1]

[1]Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, India
[2]Dr. D.Y. Patil Dental College and Hospital, Dr. D.Y. Patil Vidyapeeth, Pimpri, Pune, India

Abstract
Alzheimer's disease (AD) is a progressive neurological disease that causes cognitive impairment in old aged persons. It is the cause of a wide spectrum of neurodegenerative disturbances including tauopathies, which are responsible for progressive neuronal degeneration and impaired cognitive functions. Although drug discovery researchers and pharmaceutical companies are meticulously working to develop novel drugs for AD, establishing their safety and efficacy proofs are major challenges for them. In this review, we have discussed about AD and its causes mainly focusing on molecular targets with their physiological and pathophysiological roles, therapeutic approaches, and their future perspectives. We have compiled the information about novel and promising drug targets and lead data bases that will help to select appropriate target and design novel drug molecules for the treatment of Alzheimer.

K e y w o r d s : Alzheimer's disease; neurodegenerative disorder; anti-Alzheimer drug targets; anti-Alzheimer drugs.

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Address for correspondence: Dr. Karishma M. Rathi, e-mail: karishma.rathi@dypvp.edu.in
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Information about authors
Rathi K., https://orcid.org/0000-0002-6407-6739; e-mail: karishma.rathi@dypvp.edu.in
Wavhale R., https://orcid.org/0000-0003-1614-9742; e-mail: ravindra.wavhale@dypvp.edu.in
Undale V., https://orcid.org/0000-0003-3837-7471; e-mail: vaishali.undale@dypvp.edu.in
Bhole R., https://orcid.org/0000-0002-6407-6739; e-mail: ritesh.bhole@dypvp.edu.in
Dherange S., https://orcid.org/0000-0003-3280-4508; e-mail: snehaldherange2018@gmail.com

ИЗУЧЕНИЕ ВОЗМОЖНОСТЕЙ ЛЕЧЕНИЯ БОЛЕЗНИ АЛЬЦГЕЙМЕРА: ТЕКУЩИЙ СТАТУС И ПЕРСПЕКТИВЫ НА БУДУЩЕЕ

Ратхи К.[1], Вавхале Р.[1], Ундале В.[1], Бхоле Р.[1,2], Деранге С.[1]

[1]Институт фармацевтических наук и исследований Д.Ю. Патила, Пимпри, Пуна, Индия
[2]Стоматологический колледж и больница Д.Ю. Патила, доктор Д.Ю. Патил Видьяпит, Пимпри, Пуна, Индия

Резюме
Болезнь Альцгеймера (БА) — это прогрессирующее неврологическое заболевание, которое вызывает нарушения памяти и другие когнитивные расстройства у пожилых людей. Существует широкий спектр нарушений, включая таупатии, которые отвечают за прогрессирующий нейрональный дегенеративный процесс. При том что исследователи, занимающиеся поиском лекарств, и фармацевтические компании активно работают над разработкой новых препаратов для лечения БА, установление доказательств их безопасности и эффективности вызывает значительные сложности. В обзоре обсуждается патогенез БА с фокусом внимания на молекулярных мишенях, их физиологическом и патофизиологическом значении, терапевтических подходах и их перспективах. Представлена информация о новых многообещающих мишенях для лекарственного воздействия и ведущих базах данных, которые могут помочь выбрать подходящие мишени и разработать новые молекулы для лечения БА.

К л ю ч е в ы е с л о в а : болезнь Альцгеймера; нейродегенеративное заболевание; антиальцгеймеровские мишени; антиальцгеймеровские препараты.

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Для корреспонденции: Ратхи К., e-mail: karishma.rathi@dypvp.edu.in
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
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Информация об авторах
Ратхи К., https://orcid.org/0000-0002-6407-6739; e-mail: karishma.rathi@dypvp.edu.in
Вавхале Р., https://orcid.org/0000-0003-1614-9742; e-mail: ravindra.wavhale@dypvp.edu.in
Ундале В., https://orcid.org/0000-0003-3837-7471; e-mail: vaishali.undale@dypvp.edu.in
Бхоле Р., https://orcid.org/0000-0002-6407-6739; e-mail: ritesh.bhole@dypvp.edu.in
Деранге С., https://orcid.org/0000-0003-3280-4508; e-mail: snehaldherange2018@gmail.com

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Abbrevations: 5-HT — 5-Hydroxytryptamine; Aβ — Amyloid-beta; Ach — Acetylcholine; AChE — Acetylcholinesterase; AChEIs — Acetylcholinesterase Inhibitors; AMPA — Alpha-Amino-3-Hydroxy-5-Methyl-4 Isoxazole Propionic Acid; APP — Amyloid Precursor Protein; ATP — Adenosine Triphosphate; BBB — Blood-Brain Barrier; BACE1 — Beta-secretase 1; BuChE — Butyrylcholinesterase; CADD — Computer-Aided Drug Design; Cdk5 — Cyclin-dependent kinase 5; ChE — Cholinesterase; ChEIs — Cholinesterase Inhibitors; DAD — Dementia in Alzheimer's Disease; GDP — Gross Domestic Product; GSK-3 — Glycogen Synthase Kinase-3 beta; HTS — High-Throughput Screening; MAO-B — Monoamine oxidase B; MAOI — Monoamine Oxidase Inhibitors; MAP — Microtubule-Associated Protein; MTs — Microtubules; NFTs — Neurofibrillary Tangles; NMDA — N-Methyl-D-Aspartate; NMDAR — N-Methyl-D-Aspartate Receptors; NPS — Neuropsychiatric Symptoms; PHFs — Paired Helical Filaments; SAR — Structural Activity Relationship.

Introduction. Alzheimer's disease (AD) is a progressive, multifaceted, and irreversible neurological disease that causes cognitive and memory impairment in old aged persons [1, 2]. Alzheimer's disease is expected to increase in global prevalence from 26.6 million cases in 2006 to 106.8 million cases by 2050 [3–5]. World dementia expenditures were estimated to be US$ 604 billion in 2010, accounting for 1% of global GDP. Alzheimer's disease is characterized by a gradual loss of episodic memory, behavior, speech, and cognitive function, followed by language and visuospatial deficits [6, 7]. A wide range of neuropsychiatric symptoms such as depression, anxiety, delusions, apathy and hallucinations are regularly observed [8–11]. The clinical characteristics of AD are extracellular deposits of insoluble beta-amyloid (Aβ) protein, perivascular deposits of Aβ, and intracellular development of tau protein-based neurofibrillary tangles. The loss of cholinergic neurons in regions of the brain linked with better mental performance, such as the neocortex and hippocampus, is a prominent characteristic [10, 11]. Even though several markers including low acetylcholine, Aβ deposits, tau-protein aggregation, neurofibrillary tangles (NFTs), oxidative stress, and bio-metal dyshomeostasis are associated with it, its aetiology is not yet clear [12, 13]. AD is associated with tau hyperphosphorylation, inflammation, oxidative stress, aberrant neurotransmission involving acetylcholine, glutamate, norepinephrine, serotonin, and dopamine, as well as changes in second messengers, protein kinases, and a number of other pathways. N-methyl-Daspartate (NMDA), Monoamine oxidase B (MAO-B), Cyclin dependent kinase 5 (Cdk5), Acetylcholinesterase (AChE), Betasecretase 1 (BACE1), Glycogen synthase kinase-3 beta (GSK-3), and Butyrylcholinesterase (BuChE) were all used to do the association study [14–16]. Many small compounds and bioproducts have been explored for the treatment of AD in recent decades, yet there are still no medications that have effective disease-modifying effects. Being, a major and growing public health concern, more effective medicines to treat and delay illness development are urgently needed. Although drug discovery researchers and pharmaceutical companies are meticulously working to develop novel drugs for AD, establishing their safety and efficacy proofs are major challenges for them. As many effective medications modulate numerous sites, drug repositioning is an alternate paradigm for fastest and cost-effective drug discovery. This "polypharmacology" can be a therapeutic prerequisite for complex disorders [11, 12, 17]. In this review, we have discussed about AD and its causes mainly focusing on molecular targets with their physiological and pathophysiolgical roles, therapeutic approaches, inhibitors and their future perspective.

Potential Alzheimer's drug target

In AD the eight different targets like N-methyl-Daspartate, Cyclin dependent kinase 5, Monoamine oxidase B, Acetylcholinesterase, Betasecretase 1, Glycogen synthase kinase-3 beta, and Butyrylcholinesterase play an important role in complete pathophysiology of disease.

Conventional drug target acetylcholine esterase

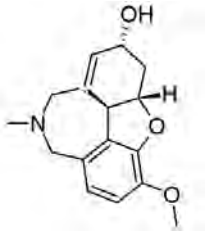
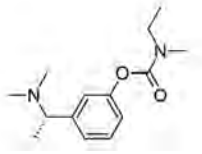
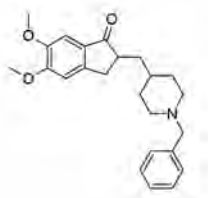
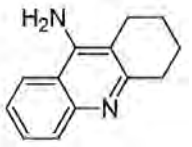
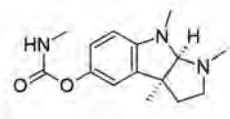
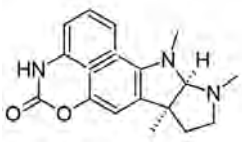
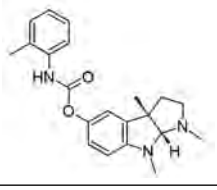
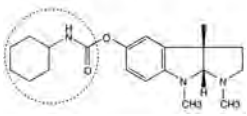
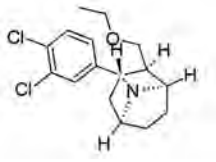
Role and pathophysiology. ACHe and BuChE are two types of cholinesterase. AChE is mostly prevalent in the blood and brain synapses. BuChE is mostly found in liver. ACh is hydrolyzed by AChE to generate choline and acetate ions. The main difference between the two enzymes is the substrate. Because cholinergic deficiency is an early and consistent finding in AD, AChE remains a prospective target for symptomatic improvement [17]. Cholinesterase enzymes hydrolyze ACh andlower its concentration, particularly AChE found in synaptic clefts of cholinergic neurons [18]. A decrease in cholinergic neurotransmission associated with ACh level has been associated with memory deficits in AD patients. AChE inhibitors enhance cholinergic neurotransmission by preventing acetylcholine's hydrolysis and, subsequently, increasing its synaptic levels. Cholinergic pathways in the cerebral cortex and basal forebrain are disrupted in AD patients, which leads to cognitive impairment [1].

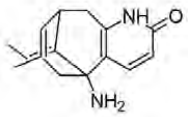
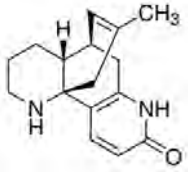
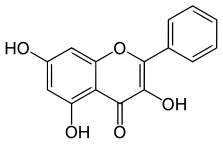
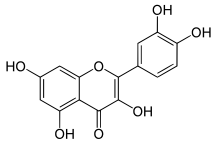
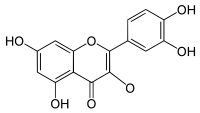
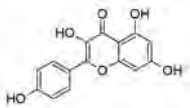
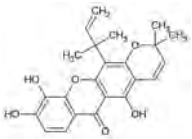
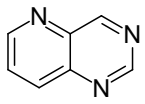
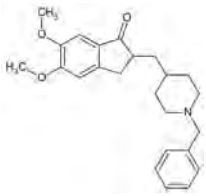
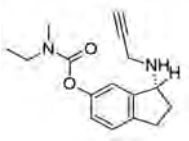
Therapeutic approach. Recent attempts to treat AD have centered on enhancing cholinergic function with cholinergic receptor agonists or AChE inhibitors (AChEIs) shown in Table 1. AChEIs should improve cholinergic neurotransmission by increasing endogenous AChE levels in the brain. AChEIs are generally effective at meliorating global cognitive dysfunction, particularly in improving attention [20]. Despite these advancements, cholinesterase (ChEIs) are still important from a heuristic standpoint: they are a tool for investigating the role of the cholinergic system in cognitive processes in healthy and pathological conditions, they may provide drug development leads, and may have new therapeutic implications [21]. Currently the only approved therapy in the United states is ChEIs [22].

Future perspectives. Traditional inhibitors are substances taken from nature. Analogs of these drugs, natural chemical derivatives, and synthetic hybrids are examples of other inhibitors. These inhibitors have fewer negative effects than typical medications and may have better features, such as increased BBB permeability and

Table 1

Acetylcholinesterase inhibitors

Marketed AchEInhibitors **[17, 18]**		
Sr. No	**Drug Name**	**Structure**
1	Galantamine (naturally occurring substances)	
2	Rivastigmine	
3	Donepezil	
4	Tacrine (withdrawn drug due to hepatotoxicity)	
5	Physostigmine (withdrawn drug due to hepatotoxicity)	
New Cholinesterase Inhibitors		
A. *Physostigmine Derivatives*		
1	*Phenserine*	
2	*Tolserine*	
3	*Esolerine*	
B. Norepinephrine, dopamine, and serotonin reuptake inhibitor		
	NS2330 Tesofensine	

Marketed AchEInhibitors **[17, 18]**		
Sr. No	**Drug Name**	**Structure**
Naturally Derived		
1	Huperzine A	
2	Huperzine B	
3	Nelumbo nucifera	Aquatic plant
4	Himatanthuslancifolius	Shrub
5	Galangin	
Novel Flavonoid Derivatives		
Derivatives of four flavonoids		
1	Quercetin	
2	Rutin	
3	Kaempferol	
4	Macluraxthone	
Novel Compounds		
1	Pyridopyrimidine	
Hybrids (Donepezil hybrid)		
1	*Donepezil and AP2238*	
Synthetic Analogues		
1	*Ladostigil*	

efficacy. AChE inhibition has been studied recently, but only a few new medicines have been evaluated in people [18, 60]. Many of these inhibitors were investigated *in vitro*, *in silico*, and in animal models. More research is needed to assess the safety, efficacy, and toxicity of these medicines in humans. AChE inhibitors do not completely arrest the course of Alzheimer's disease, and several single-target medicines that have entered clinical trials have failed to treat the disease. As a result, multifunctional medications that target all pathogenetic components of AD, such as lower ACh levels, protein misfolding and aggregation, protein hyperphosphorylation, metal dyshomeostasis, and oxidative stress, are needed. Only a few research have looked at the development of multi-target medicines [19].

N-Methyl-D-Aspartate Receptor

Role and pathophysiology. Aβ-induced neuronal shrinkage and synaptic dysfunction is thought to be largely mediated by the glutamatergic system, including NMDA receptors [23]. The NMDA receptor plays a crucial role in cellular models of learning and neurotoxicity. The abnormal function of this receptor may contribute to AD pathophysiology [24]. The NMDA receptor may also play several roles in Aβ-related mechanisms like it may be an Aβ receptor or may interact with molecules that bind Aβ indirectly. It can mediate or act permissively, in Aβ's effect on synaptic transmission and plasticity. The function of NMDA receptors may be a downstream target of Aβ, in which Aβ may decrease or increase. Aβ formation may be controlled by NMDA receptor activity [24]. NMDA receptors are extremely permeable to calcium ions. The glutamate receptor (agonist) and the glycine receptor (co-agonist) are activated simultaneously by glutamate and glycine released from the presynaptic neurons. Glutamate also causes depolarization by activating the postsynaptic AMPA receptor. Magnesium blocks the channels of NMDA receptor at rest. When the NMDA receptor binds a co-agonist, a depolarizing impact on the postsynaptic cell occurs, which relieves the block. When NMDA receptor is activated potassium is excreted and sodium and calcium are influxed. The release of calcium from intracellular stores and the activation of the calcium/calmodulin-dependent kinase type II, in the hippocampus, are triggered by an increase in intracellular calcium concentrations [25]. While excess glutamate causes neurotoxicity by over-activating NMDARs, memantine works to restore the glutamatergic system and repair cognitive and memory deficits by blocking NMDA glutamate receptors [26].

Therapeutic approach. During ischemia and neurodegenerative diseases, glutamate receptors are thought to be over stimulated. As a result, NMDA receptor antagonists may be useful in the treatment of a variety of neurological illnesses, such as stroke, dementia, and neuropathic pain syndromes [27]. AD may be treated with glutamate-based strategies consisting of enhancing and normalizing of glutamatergic neurotransmission and/or protecting against glutamate mediated excitotoxicity [25]. Compared to placebo, memantine significantly improved cognitive and functional out comes after switching from placebo to open-label memantine. Donepezil is safe and effective for moderate to severe AD patients. The treatment of mild to moderate vascular dementia with memantine is also reported to be effective and safe in the UK [25]. Memantine has been reported to have a neuroprotective effect on both neurodegenerative and vascular processes. In both AD and PD combining memantine with other therapies is a valuable and feasible option [26]. It has been shown that galantamine is effective in treating Alzheimer's disease, and its dual mechanism of action makes it an excellent complement to other neurotransmitter modulators like memantine shown in Table 2. Although the two medications appear to have conflicting mechanisms of action, a physiologic examination of their activities could explain why they work together to improve cognition. Galantamine potentiates agonist-induced action by allosteric regulation, engaging nicotinic receptors and activating the glutamatergic system. Memantine reduces excitotoxicity, which causes neurodegeneration, as a result of this overstimulation both medications help to prevent Aβ-neurotoxicity, which is linked to neurodegeneration in AD [28].

Future perspectives. Other NMDA receptor antagonists are being developed as well. There's also neramexane, which has mechanisms comparable to memantine. NMDA antagonists are being researched for a variety of illnesses, including neuropathic pain, glaucoma, depression, alcoholism, and Parkinson's disease. A combination therapy is likely to become the new way to manage AD symptoms without a cure. Memantine is also being investigated when combined with other cholinesterase inhibitors (such as galantamine and rivastigmine). Memantine with cholinesterase inhibitors are anticipated to become the standard of care for all individuals with AD and associated dementias in the future [25].

Conventional drug target Tau

Role and pathophysiology. Tau is a microtubule-associated protein (MAP) with the ability to stabilize microtubules in neurons. It is abundant in the central nervous system and ocular neurons, also regulates and stimulates neuronal activity and tubulin assembly. Tau's importance in microtubule stabilization and axonal transport enhancement cannot be overstated, highlighting its crucial role in brain message transmission [29]. Tau in addition to its microtubule-binding capabilities, may be implicated in signal transduction, organelle transport, cell proliferation, and axonal outgrowth in non-microtubule related processes [30]. Cell development, cell polarity induction, and intracellular signal transduction are all aided by microtubules (MTs). Tactless signals produce a kinase/phosphate imbalance, which leads to tau hyperphosphorylation, MT instability, and microtubule disassembly. Hyperphosphorylated tau accumulates as paired helical filaments (PHFs) after MT breakdown, preventing intracellular transit and eventually leading to neuronal degeneration. As a result, this primary phospho-protein is moderately phosphorylated under normal physiological conditions, whereas aberrant or hyperphosphorylation causes severe pathogenic scenarios such as tau protein dissociation from microtubules and increased tau molecule aggregation. Overall, this aggregated form of tau has the potential to generate

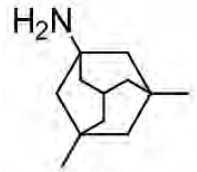
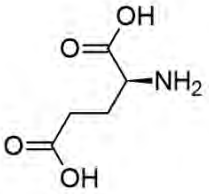
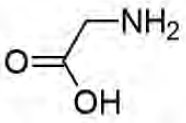
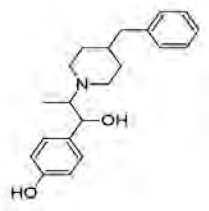
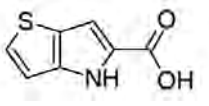
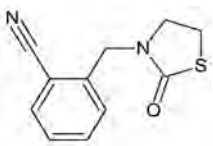
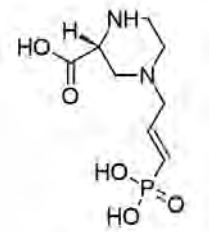
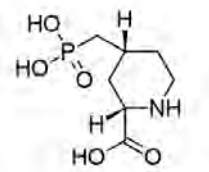
neuroinflammation and other negative effects that can lead to neurodegenerative disorders [29].

Therapeutic approach. Tau protein has gained a lot of attention as a potential therapy target for AD since it is the cause of a wide spectrum of neurodegenerative illnesses including tauopathies. Targeting tau has two pillars: post-translational modifications and protein interactions, as regulating these two processes can be an effective therapeutic step in treating AD. Tau, a protein that plays numerous functions in AD pathogenesis, is the most potential target for creating better-targeted therapeutics to cure the incurable disease [29]. The principal component of neurofibrillary tangles, tau protein, has just recently been discovered to be a better predictor of dementia severity than amyloid [31] shown in Table 3.

Future perspectives. The major component of neurofibrillary tangles Tau protein has just recently emerged as a stronger predictor of dementia severity than amyloid has only emerged in recent years. To begin, the tau protein should be targeted intracellularly because most tau protein diseases impact neurons within the cell. Second, as earlier anti-amyloid immunotherapy attempts have shown, developing second and third generation tau protein immunotherapy approaches is critical. Smaller antibodies that are fragments of full antibodies should have better access to the inside of the brain and the neurons in particular, as well as the ability to attach to multiple epitopes of the tau protein than complete antibodies, resulting in higher and more effective therapeutic advantages. They will be better suited for gene therapy than full antibodies because of their reduced size. Future preclinical research looking at antibody fragments is something we're looking forward to. Third, in recent years, there has been a strong focus on the adoption of drug-screening models aimed at preventing seeding or spreading aggregation. The identification of chemicals that prevent the neurotoxicity of these aggregates, which is not always connected with their seeding or spreading tendency, has received far less attention. All of these indicators should ideally be read as part of a single test or model. Fourth, the variety of conformer or strain of aggregates makes drug development for small molecule aggregation inhibitors more difficult, although this is unlikely to be an issue in antibody-based therapy. Fifth, other more general goals related to neurodegeneration should be pursued, although they are more difficult to achieve in many ways than removing amyloid and tau protein, which are characteristics of AD. Finally, long-term clinical investigations should include a change in treatment intervention time to the very early stages of AD. Because tau protein malfunction is more closely connected with performance on cognitive tests than amyloid, targeting the tau protein is anticipated to yield superior therapeutic effects at a later stage in the development of the disease. In the clinic, no drugs that target the tau protein have been authorized. We anticipate that the results of ongoing clinical trials will help us better understand the therapeutic efficacy of drugs that target the tau protein, putting them at the forefront of new medicines that patients and clinicians are eagerly anticipating. Treatments for amyloid and tau protein may be

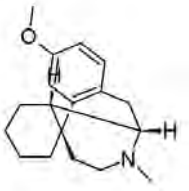
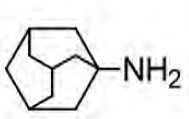
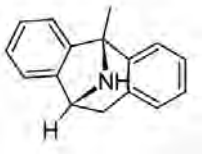
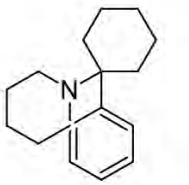
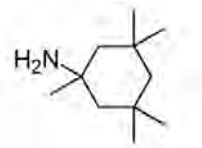
Table 2

N-Methyl-D-Aspartate receptor inhibitors

Marketed NMDA receptor antagonist **[25, 27]**		
Sr. No	**Drug Name**	**Structure**
1	Memantine (NMDA Antagonist)	
2	Glutamate (Agonist)	
3	Glycine (Co-agonist)	
4	Ifenprodil	
5	D-amino acid oxidase inhibitor (improved early phase AD)	
Novel Drugs		
1	Triazolylamidine derivatives	
Competitive N-methyl-D-aspartate receptor antagonists (in vitro binding affinities)		
1	Midafotel	
2	Selfotel	

Continued on Next Page

Table 2 Continued

Marketed NMDA receptor antagonist **[25, 27]**		
Sr. No	**Drug Name**	**Structure**
Uncompetitive N-methyl-D-aspartate receptor antagonists		
Low- to moderate-affinity antagonists		
1	Dextromethorphan	
2	Amantadine	
High-affinity antagonists		
1	Dizocilpin	
2	Phencyclidine	
3	Ketamine	
Other N-methyl-D-aspartate antagonists		
1	Neramexane	

beneficial on their own, but the convergent evolution of amyloid and tau protein disease suggests that combination therapy may be required in the end, especially when both are prominent [32].

Monoamine oxidase-B inhibitors (MAO-B)

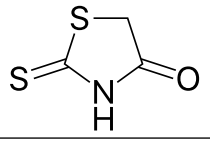
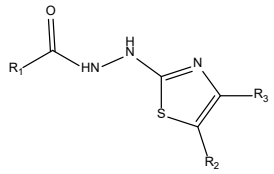
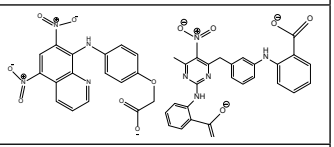
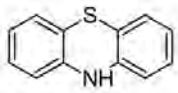
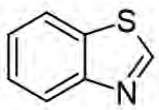
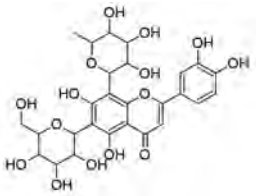
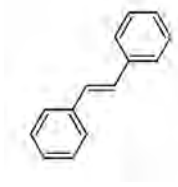
Role and pathophysiology. MAO-B inhibitors, which have a long history of clinical usage and are thought to be safe and nontoxic, may be a treatment option for Alzheimer's disease. The effects of L-deprenyl are responsible for a large amount of the clinical data and biological actions of MAO-B inhibitors. L-antidepressant deprenyl action has been linked to the inhibition of MAO-A as well as MAO-B. Because of its vasculoprotective properties, L-deprenyl may be useful in the treatment of vascular dementia [33]. MAO is classified into two forms, MAO-A and MAO-B, which are encoded by two different gene loci and have different tissue distribution patterns, substrate and inhibitor selectivity [34]. MAO-B causes a rise in hydrogen peroxide and oxidative free radicals, both of which contribute to the etiology of AD [35]. MAO-A deaminates serotonin (5-HT) and is more vulnerable to clorgyline inhibition, whereas it alsodeaminates β-phenylehtylamine and is inhibited by L-deprenylamine [33]. MAO-B activity increases as people become older, and it's particularly high around senile plaques in Alzheimer's sufferers. If MAO-B was blocked, the neurodegenerative processes that occur in AD brains would be reduced [35]. L-deprenyl is a monoamine oxidase inhibitor that can inhibit MAO-B selectively at low dosages while inhibiting MAO-A and MAO-B nonselectively at high levels [36].

Therapeutic approach. The therapeutic effects of L-deprenyl in AD have been attributed to a number of mechanisms. The most notable impact of L-deprenyl is the stimulation of central monoaminergic systems via inhibition of MAO-B. MAO-B medications may operate by reducing the production of oxygen radicals and restricting monoamine breakdown in Alzheimer's patients' brains. Other effects of L-deprenyl that may contribute to its neuroprotective qualities include antagonism of NMDA receptors via increased levels of N-acetylated polyamines, activation of antioxidant enzymes such as superoxide dismutase and catalase, and anti-apoptotic activity. L-deprenyl shown in Table 4 may boost NO-mediated processes in vascular and brain tissue, which could explain some of the drug's therapeutic efficacy and lead to new applications. MAO-B drugs could alleviate the decline in cerebral blood flow seen in AD and PD and improve cognitive performance by facilitating neuronal activation through NO-mediated vasodilation [33]. MAOIs are used to treat depressive, anxiety disorders, PD and AD [35]. MAO-A inhibitors have been shown to be effective antidepressants, whereas MAO-B blockers have been promoted for PD treatment [34]. L-deprenyl appears to primarily inhibit MAO-B and have modest antidepressant activity in humans at doses up to 10 mg/day, but it also inhibits MAO-A at doses of around 40 mg [36]. In those investigations, L-deprenyl 10 mg/day was found to be the optimal dose for attaining therapeutic efficacy in dementia in AD (DAD) patients without causing frequent or severe adverse effects [37]. Deprenyl medication not only delays the disabling progression of PD, but it also appears to decrease cognitive loss in AD, as measured by improved verbal memory ability and a longer interval between diagnosis and placement in a nursing home [38].

Future perspectives. In vivo investigations have shown that rasagiline is up to 10 times more effective than selegiline as an MAO-B inhibitor. Furthermore, rasagiline's optical (S)-isomer, which lacks MAO-A and MAO-B inhibitory action, has been shown to have neuroprotective and anti-apoptotic properties similar to rasagiline. Chronic oral therapy with TV3326 reduced neuronal degeneration and microgliosis while virtually

Table 3

Tau aggregation inhibitors

Tau aggregation Inhibitors **[32]**		
Sr. No	**Drug Name**	**Structure**
1	Rhodanine-based inhibitors	
2	Phenylthiazolyl-hydrazide inhibitors	
3	N-Phenylamines	
4	Phenothiazine	
5	Benzothiazoles	
Polyphenols and anthraquinones		
1	Flavonoids	
2	Stilbene	

completely prevented memory impairment in the streptozotocin rat model of AD [34]. Ladostigil and M30 are shown to have a wide range of neuroprotective action in a variety of settings, including cell culture and *in vivo* [39]. Lazabemide's antioxidant activity was much greater than that of Vitamin E or the MAO-B inhibitor selegiline. Lazabemide's preventive properties in AD are now being investigated, and some positive results appear to offer hope for the future [2]. The competitive and reversible MAO-B inhibitors AD3 and AD9 demonstrated IC50 values in the low micromolar range and high selectivity for MAO-B inhibition. Enamides' nontoxic qualities, as well as their selective, reversible, and competitive inhibition of MAO-B in AD3 and AD9, encourage their future development for the treatment of neurodegenerative illnesses such as AD and PD [40]. While modulating neuromodulatory monoamines, sembragiline lowered oxidative stress and astrocyte activation. Sembragiline treatment's safety has also been demonstrated in preclinical and clinical studies, where the drug was well tolerated with no side effects [41]. Sembragiline has completed a phase II research in people with moderate AD, and the results are being published now. While this phase II study reveals that adding sembragiline to standard-of-care medication (acetylcholinesterase inhibitors, memantine) does not enhance cognitive function in people with moderate AD, it may provide therapeutic benefit in patients with behavioral and neuropsychiatric symptoms (NPS) [42, 43].

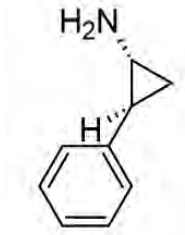
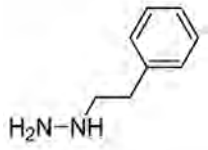
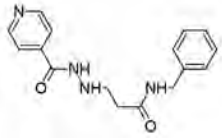
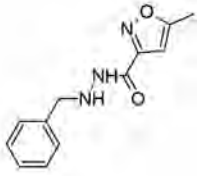
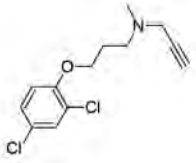
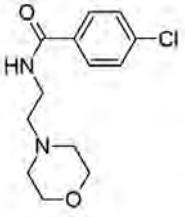
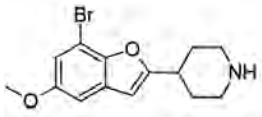
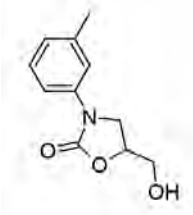
Butyrylcholinesterase (BuCHE)

Role and pathophysiology. BuChE is found in human brain neurons and glial cells, as well as neuritic plaques and tangles in Alzheimer's patients. Despite butyrylcholinesterase is thought to play only a minimal function in controlling brain acetylcholine levels, it has been linked to drug metabolism and detoxification. Both AChE and BuChE play a role in cholinergic signalling; BuChE has the ability to hydrolyze acetylcholine and can compensate for AChE deficit. In the AD brain, AChE levels fall while BuChE levels rise or stay stable, with the differences becoming more obvious as the disease advances. Additionally, the BuChE genotype may influence AD risk and development. Because both enzymes hydrolyze acetylcholine, and BuChE is elevated in the AD cerebral cortex, cholinesterase inhibitor therapy should target BuChE rather than AChE [48]. In the Alzheimer brain, butyrylcholinesterase activity increases by 40% to 90% over time. It primarily rises in the temporal cortex and hippocampus the brain areas most damaged by AD. BuChE activity has been found to be more prevalent among ChE-positive neurons in the human amygdala than AChE activity. AChE and BuChE are present in the same neuronal components. BuChE levels are high in AD neuritic plaques invitro; both AChE and BuChE appear to be involved in converting diffuse P-amyloid into compact neuritic plaques. BuChE hydrolyzes the ACh surrogate acetylthiocholine in the human brain in the presence of an AChE-specific inhibitor [44].

Therapeutic approach. BuChE plays a key part in the progression and development of AD. In addition to esterase activity, it exhibits peptidase activity. In AD it converts the amyloid precursor protein, which is abundant in normal brain, to β-amyloid protein, then deposit and form β-amyloid plaques. Selective BuChE inhibitors also prevent fresh β-amyloid plaque formation. Finding particular markers that aid in accurate and early AD diagnosis is crucial. The cerebrospinal fluid of Alzheimer's patients contains a specific form of BuChE with altered glycosylation [45]. Pharmacologists study butyrylcholinesterase because it is responsible for the hydrolysis of succinylcholine, a medication used in surgery as a short-acting cholinergic receptor blocker shown in Table 5. Rivastigmine is a carbamate inhibitor of both AChE and BChE that passes the blood-brain barrier with ease. Rivastigmine is the most widely prescribed carbamate in pharmacology. It is currently the only non-reversible inhibitor of AChE available for these disorders, as it

Table 4

Monoamine oxidase inhibitors

MAO Inhibitors **[34, 35]**		
Sr. No	**Drug Name**	**Structure**
	Non-Selective	
1	Tranylcypromine	
2	Phenelzine	
3	Nialamide	
4	Isocarboxazid	
	MAO-A Selective	
1	Clorgyline	
2	Moclobemide	
3	Brofaromine	
4	Toloxatone	

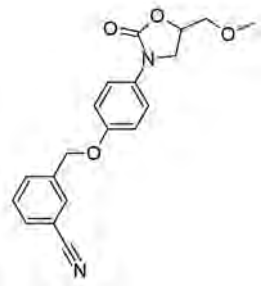
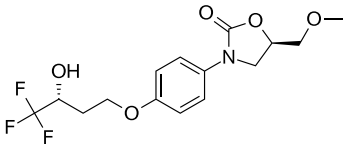
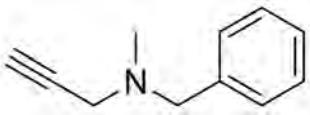
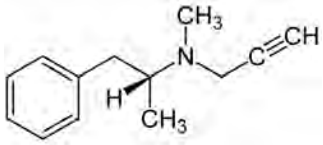
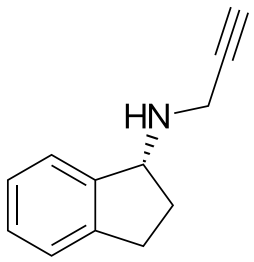
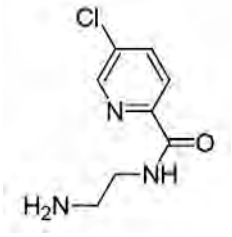
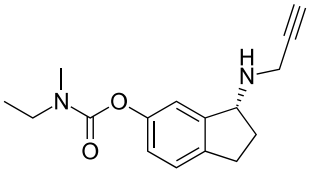
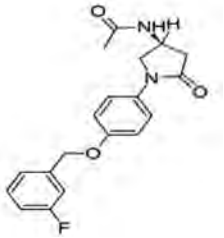
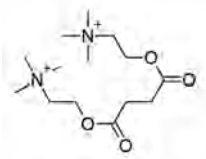
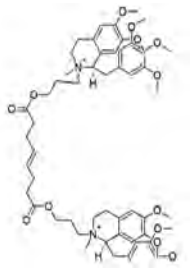
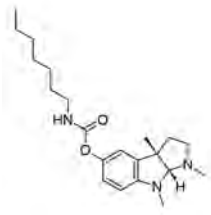
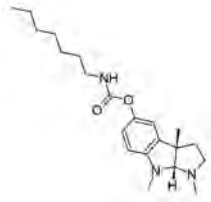
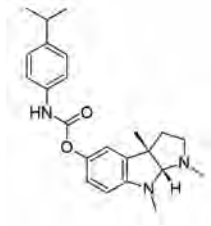
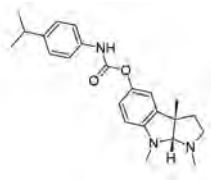
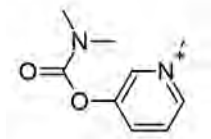
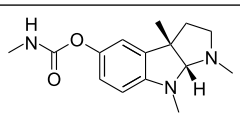
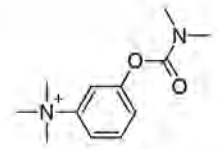
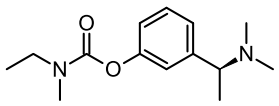
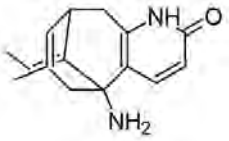
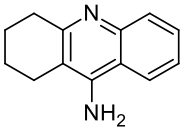
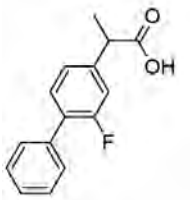
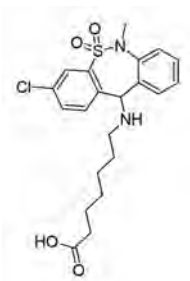
MAO Inhibitors **[34, 35]**		
Sr. No	**Drug Name**	**Structure**
5	Cimoxatone	
6	Befloxatone	
	MAO-B Selective	
1	Pargyline	
2	Selegillne (L-deprenyl)	
3	Rasagiline	
4	Lazabemide	
5	Ladostigil (TV3326)	
6	Sembragiline (Novel)	

Table 5

Butyrylcholinesterase inhibitors

BuCHE Inhibitors **[44, 46]**		
Sr. No	**Drug Name**	**Structure**
Human BCHE		
1	Succinylcholine	
2	Mivacurium	
Inhibitors with Carbamate structure		
1	Heptylphysostigmine	
2	Eptastigmine	
3	4'-Isopropylphenserine	
4	Cymserine	
5	Pyridostigmine	
6	Physostigmine	
7	Neostigmine	
8	Rivastigmine	
9	Huperzine A	
Tacrine-based inhibitors		
1	Tacrine	
2	Flurbiprofen	
3	Tianeptine	

inhibits cholinesterases in a pseudo-irreversible manner. Rivastigmine did not cause inflammation or have any additional side effects in clinical trials. As a result, rivastigmine is regarded as a relatively safe medication.

Future perspectives. Selective BuChE inhibitors may have certain advantages over selective or nonselective AChE inhibitors in the treatment of patients with advanced AD. To further understand the role of BuChE in normal and AD-affected brains, more study is needed at both the experimental and clinical levels. The measurement of serum BuChE should be part of normal clinical diagnostic procedures to assess patient clinical circumstances, especially *in situ*ations of inflammation and/or protein-energy deficiency. As AD proceeds, AChE levels in the hippocampus and temporal cortex drop, but BuChE levels rise rapidly. The development of effective and selective BuChE inhibitors to boost ACh levels in

advanced AD is critical to avoid the deleterious implications of AChE suppression. Crystal structure, along with appropriate structural modifications and precise evaluation procedures will surely be used to develop potent and selective BuChE inhibitors for the treatment of AD [46].

Cyclin-dependent kinase (Cdk5)

Role and pathophysiology. Cdk5 has multifaceted roles, influencing learning, memory, APP processing, β-amyloid production, dopamine signaling, and neurodevelopment. Recent findings suggest its involvement in neurodegenerative diseases. Targeting Cdk5 could prevent neuronal cell death and has therapeutic potential. It also impacts neuron formation, survival, synaptic plasticity, motility, and addiction. Notably, Cdk5's role extends to non-neuronal cells, affecting insulin production. As a serine/threonine kinase in the cyclin-dependent kinase family, Cdk5 is a candidate for AD treatment due to its neuronal localization. Cdk5-specific inhibitors offer neuron-focused action. However, caution is warranted for children and pregnant women. Cdk5's significance in neuronal growth, synaptic transmission, and neurodegenerative disorders, including Alzheimer's, is pivotal [47].

Therapeutic approach. Cdk5 inhibition not only protects tauopathies but also decreases Aβ-induced neurotoxicity, suggesting that targeting Cdk5 could be a new method in neuroprotection and AD treatment. It is thought to cause cell cycle reactivation and contribute to neuronal cell apoptotic death, suggesting a novel treatment avenue for AD. Cdk5 inhibitors shown in Table 6 (such as Roscovitine) and calpain inhibitors were the two main pharmacological inhibitors explored (such as MDL28170). Both can cross the blood-brain barrier, but because they are not totally specific, they can also alter other physiological and pathological pathways. Cdk5 appears to be a viable therapeutic target for the treatment of neurodegenerative disorders, drug misuse, and diabetes mellitus, according to current findings. Todate, several substances and peptides have been discovered as Cdk5 inhibitors. Purine analogues like roscovitine and olomoucine are the most commonly used chemical substances. These inhibitors compete with ATP for Cdk5 binding and generate hydrogen bonds with the protein [48]. Inhibition of the abnormal Cdk5/p25 complex, which prevents tau hyperphosphorylation and neurofibrillary tangle development, is thus a feasible target for treating AD. According to M.R. Shiradkar et al. suggested that, 2-aminothienyl derivatives are possible Cdk5/p25 inhibitors for the treatment of AD and other neurodegenerative illnesses [47, 48].

Future perspectives. The repercussions of Cdk5 dysregulation include the dysfunctioning of other pathways, which leads to neuroinflammation and neuron death. Inhibition of Cdk5/p25 has been shown to ameliorate circumstances and significantly diminish the pathological markers of AD. As a result, more research into Cdk5's role in AD is required in order to discover innovative treatments that may even cure the disease. Cdk1 and Cdk2 are inhibited by a roscovine derivative (R-roscovitine), which leads to cancer cell growth inhibition. R-roscovitine is now undergoing a phase II cancer clinical investigation. Furthermore, because the ATP binding site of Cdk5 is highly homologous to that of other Cdk's and glycogen synthase kinase 3-β (GSK3β), selectivity over these other kinases is another challenge in the search for a Cdk5 inhibitor. Key challenges in developing Cdk5 inhibitors for the treatment of AD include but are not

Table 6

Cycline- depended kinase inhibitors

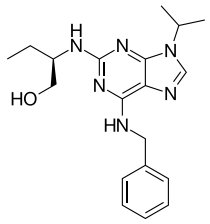
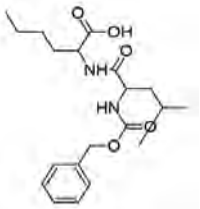
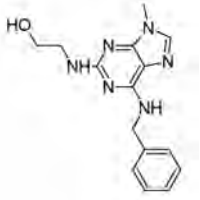
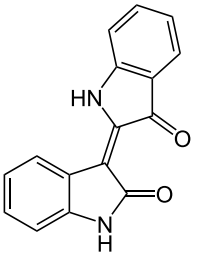
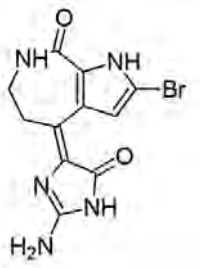
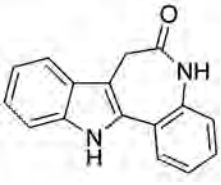
Cdk5 inhibitors **[47, 48]**		
Sr. No	**Drug Name**	**Structure**
Purine Analogues		
1	Roscovitine or flavopiridole	
2	Calpain	
3	Olomoucine	
4	Indirubins	
5	Hymenialdisine	
6	Paullones	

Table 7

Betasecretase inhibitors first generation peptide based mimetics (BACE 1) inhibitors

Sr. No	Drug Name
1	Peptidomimetics
2	MK-8931

limited to: 1) for *in vivo* research, highly selective and powerful Cdk5 inhibitors are being developed; 2) understanding the role of Cdk5 in animal models of tau hyperphosphorylation and NFT formation [49].

Betasecretase (BACE1)

Role and pathophysiology. Instead of being used to treat AD, BACE1 inhibitors could be used to prevent it. BACE1 belongs to the pepsin-like aspartyl proteases family. To reach the luminal BACE1 active site, BACE1 inhibitors must be lipophilic enough to pass plasma and endosomal membranes. The BACE1 inhibitor verubecestat (MK-8931), for example, showed significant promise in early human and animal trials, but Merck's recent statement that one of its trials will be halted raised concerns. The β-secretase and γ-secretase enzymes endoproteolyze APP in a stepwise manner to produce Aβ. β-secretase cuts the N-terminus of Aβ first, then cleaves to form the C-terminus of Aβ. Then, in the AD brain, Aβ is secreted from neurons, forming amyloid plaques. Inhibition of β-secretase should so reduce production of Aβ, the peptide's harmful formal though developing BACE1 inhibitors will be difficult, and it is likely that BACE1 medications will be developed some day [50]. BACE1 inhibitors that penetrate the brain have been produced, and clinical trials are underway, although their safety and efficacy remain unknown. BACE1 inhibition and other immunotherapy to lower brain Aβ are ineffective to improve cognition in AD, according to several clinical trials. Because physiologically relevant BACE1 substrates have been identified, full inhibition of BACE1 activity by BACE1 inhibitors may generate side effects.

Therapeutic approach. BACE1 is a prime target for anti-amyloid therapy, and biochemical purification of the enzyme has previously been done using powerful peptidic inhibitors inhibiting the formation of Aβ remains a top therapeutic target for BACE1. BACE1 is a promising therapeutic target for treating or preventing AD by reducing amyloidal beta levels in the brain. Data demonstrate that partial inhibition of BACE1 could effectively reduce Aβ deposition while avoiding mechanism-based toxicity [51]. There are five compounds which have reached phase III clinical trials verubecestat, lanabecestat, atabecestat, umibecestat and elenbecestat but now they are discontinued due to lack of cognitive or functional benefit. In mouse hamster and monkey models, potent nonpeptidic small molecule BACE1 inhibitors have been successful in decreasing cerebral Aβ levels shown in Table 7.

Future perspectives. Given the tremendous need for an effective AD treatment it is likely that substantial efforts toward development of β-secretase inhibitor drugs will be undertaken. The biopharmaceutical company CoMentis (USA) recently announced the completion of the first human phase I clinical trial of a BACE1 inhibitor drug. Other BACE1 inhibitor drug candidates will probably soon be entering into human clinical trials. Drug makers and physicians should keep in mind that BACE1 appears to have important physiological functions, perhaps requiring careful titration of the BACE1 inhibitor drug dose to minimize potential mechanism-based toxicity. BACE is an excellent target for anti-amyloid treatment, according to the research presented in this article. However, it is still feasible that BACE inhibitor development will halt before their effects on cognition in an AD trial can be evaluated. There are significant difficulties ahead in terms of blood-brain barrier penetration and inhibitor specificity. Further study on β-site APP cleaving enzyme 1 (BACE1) inhibitors is needed. First, significantly lowering Aβ levels by inhibiting BACE1 could have negative consequences. Second, BACE1 inhibitors have yet to complete phase II/III clinical trials, and no data on potential adverse effects in Alzheimer's patients is available. Finally, the clinical efficacy of BACE1 inhibitors is still debatable. Aβ plaques have already formed in mild AD patients. BACE1 inhibitors stop the formation of new Aβ plaques, but they have little effect on existing Aβ peptides. As a result, BACE1 inhibitors may be more effective at preventing AD than at treating it. BACE1 inhibitor medications have been difficult to produce, but the recent entry of several BACE1 inhibitors into clinical trials has refocused interest on this intriguing therapy option for AD. MK-8931 has progressed the furthest and is already in phase II/III, while the other medications are in phase I or nearing phase II. These chemicals are highly effective, lowering CSF Aβ levels by up to 90% [51].

Strategies for designing novel anti-Alzheimer drugs

Rational drug design methods using computer aided drug design (CADD) method. CADD strategies are influenced by the amount of structural and other information available about the target (enzyme/receptor) and the ligands. The computer's function in rational drug design is to integrate all of the relevant data, both problem-specific and general chemical knowledge. CADD is a fascinating and diverse discipline in which practical and basic research collide and stimulate one another. CADD is a powerful tool in the search of promising drug candidates, particularly when used in tandem with current chemical biology screening techniques [52]. Researchers may encounter little or no structural activity relationship (SAR) information early in the drug discovery process. The process of bringing a novel medication to market is known by several names, the most frequent of which is "development chain" or "pipeline" and it consists of several stages. To create a reasonable medicine, we must first determine which proteins in pathogenesis can be used as therapeutic targets. There have been some important advancements and enhancements in computational techniques used for Ligand-protein docking and rational drug-design applications over the last year. CADD has recently been used (as shown in Fig. 1) in the development of beta-secretase inhibitors, gamma-secretase inhibitors, amyloidal-inhibitors, and their radiotracers for the treatment and diagnostics of AD [53].

Drug repurposing. In the previous two decades, numerous attempts to discover drugs to treat AD have been impeded by generally unsuccessful clinical trials. Because of various impediments in the therapeutic drug development process, developing a new treatment from the ground up requires a huge amount of time, effort, and money [54]. By finding new uses and clinical indications for existing medications, the drug repurposing technique helps to resurrect the slow drug discovery process. Because conventional treatment medicines for AD only provide symptomatic relief and do not contribute to disease modification, an alternative repurposing technique can be employed to prevent neurodegeneration and other pathological consequences. Medication repurposing is one of the most recent advances in drug development, and it has a track record of successfully repurposing commercially accessible pharmaceuticals. Anticancer, antiepileptic, antibiotics, antidiabetes, and other medications are among the most commonly used in the treatment of AD. J. Bauzon et al. found 53 clinical studies involving 58 FDA-approved drugs. 78% of medications in clinical trials have putative disease-modifying mechanisms of action. Hematologic-oncologic agents account for 20% of the repurposed medications in development, while 18% are cardiovascular drugs, 14 percent are psychiatric drugs, 12 percent are diabetes therapies, 10% are neurologic drugs, and the remaining 26% are drugs with other indications [55]. The discovery of efficacy in an illness from existing treatments whose safety and pharmacokinetics have already been established in another disease in prior clinical research, or discontinued drugs repositioned for development, is known as drug repurposing, rediscovery, or rescue [56].

High throughput screening. The number of molecular targets available for therapeutic intervention expands as molecular biology, human genetics, and functional genomics progress. This, combined with the huge increase in compound collections generated by combinatorial technologies, has resulted in an urgent need for increased high-throughput screening (HTS) capabilities. As a result, HTS technology witnessed a revolution in the second part of the 1990s. HTS is now the major lead generation engine for most pharmaceutical businesses [57]. The availability of large compound collections from commercial sources, high-throughput technologies for combinatorial and multi-parallel chemical synthesis, and automation technologies for natural product isolation have increased the size and diversity of compound collections among most Pharma and Biotech companies in recent years, with some collections exceeding one million distinct chemical entities. Hundreds to thousands of potentially novel biological targets have emerged from the sequencing of the human genome, as well as the genomes of several pathogens such as germs, bacteria, and viruses, with little or no chemical precedent for lead optimization. While most traditional drug targets can be tackled using contemporary HTS readout technologies, the problem is with the hitherto untraceable drug target families. Future trends will place a heavy emphasis on these unique

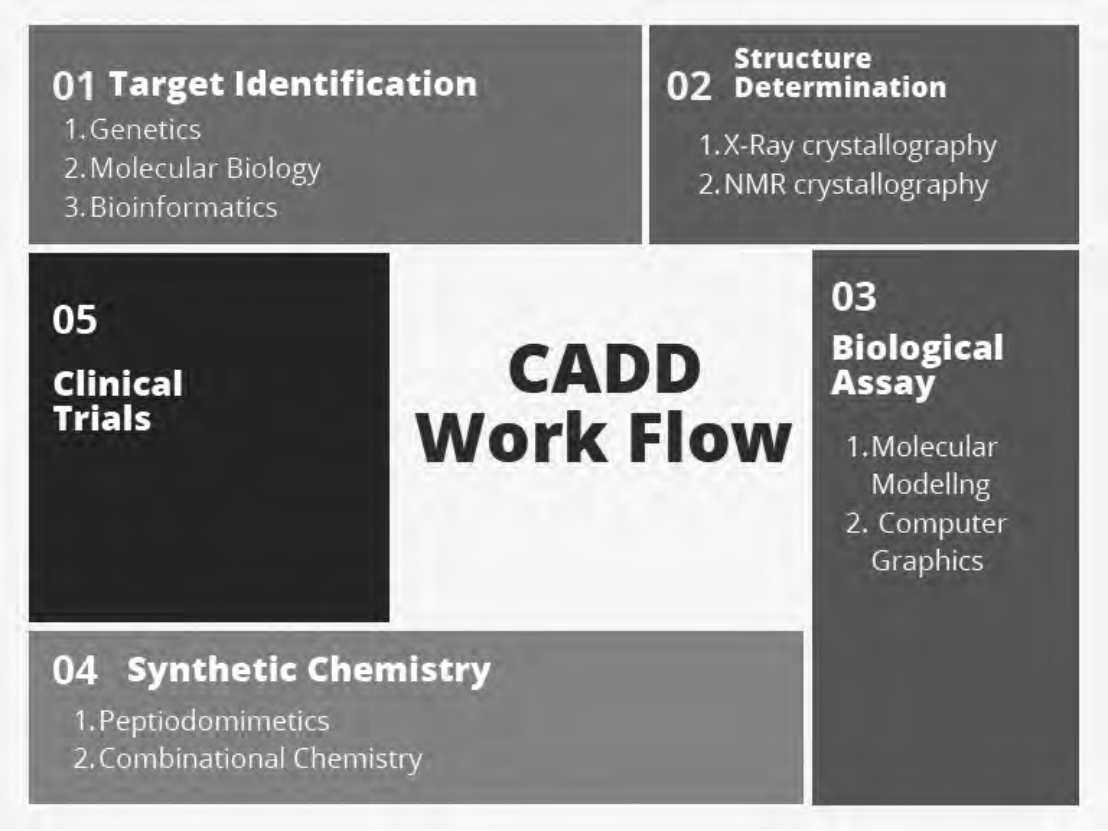


Fig. 1. CADD workflow
Рис. 1. Применение компьютера в рабочем процессе разработки лекарств

target classes, which include ion channels, transporters, protein-protein interactions, and many others. For these target classes, it will be critical to have appropriate readout technologies and chemical libraries. Better flexibility and inventiveness, as well as the utilization of project-specific, custom-tailored lead-finding methodologies in the discovery process, will be critical drivers for the future success of HTS in pharmaceutical, biotech, and academic drug development projects [58].

Drug discovery pipeline for Alzheimer's Drugs

In treatment of CNS disorders, drug discovery process is slow but progressing significantly due to advancement in molecular biology, drug design, bioinformatics, cheminformatics, machine learning and artificial intelligence. Drug discovery research has major focus on drugs to treat disorders of CNS due to its global occurrence and unavailability of potential drug candidates. Seven out of 49 drugs approved in 2021 were for the treatment of CNS disorders. Drug discovery pipeline for AD 2022 presents evaluation of 143 drug candidates in 172 Alzheimer clinical trials. These studies are highly promising and encouraging for the discovery of novel drugs; including 31 agents in phase 3, 94 agents in phase 2 and 30 agents in phase 1. Most of the agents reached in clinical trials are act by disease modifying therapies (83.2%), symptomatic cognitive enhancement treatment (9.8%) and by treating neuropsychiatric symptoms (6.9%). Drug repurposing also has major contribution (37%) in the drug discovery pipeline of AD [59].

Future perspective

Alzheimer's disease needs major focus of research from academia and drug discovery industries to gain in depth understanding of pathological conditions to identify molecular drug targets and promising drug candidate. From last few decades prominent progress has been observed in Alzheimer's drug discovery where the drug discovery shifting from symptomatic treatment to mechanism based disease modification. Additionally, genetic research helps in early diagnosis and prevention of disease conditions. Advancements in drug design, biotechnology, genetic engineering and molecular biology accelerates drug discovery process and provides more confidence on success rate. Although AD and other neurological disorders involve highly complex biochemistry and interconnections of pathological conditions, new technologies and scientific understanding of disease will surely help to solve the puzzle.

Conclusion. Aging is an important factor contributing in the development of Alzheimer; mainly responsible for progressive neuronal degeneration and impaired cognitive functions. Existing drug therapies are still struggling to achieve complete recovery from the disease. Thus knowledge of new drug targets and design of potential drug candidates is becoming an urgent need. Immunotherapeutic strategies that target the β amyloid (Aβ) and tau proteins were first believed to be almost certainly effective in clinical treatment due to the positive preclinical results.

Acetylcholine esterase inhibitors are mostly used in the treatment of mild to moderate AD whereas memantine (NMDA receptor inhibitor) is the only FDA-approved in the treatment of moderate to severe AD. Acetylcholine esterase inhibitors shows less and mild side effects hence they are most commonly used in treatment of AD as shown in Fig. 2. Tau and amyloid both proteins play important roles, their relationship to each other in the development of AD remains uncertain. However, it is feasible to develop treatments that target each protein individually. In later stages of the disease

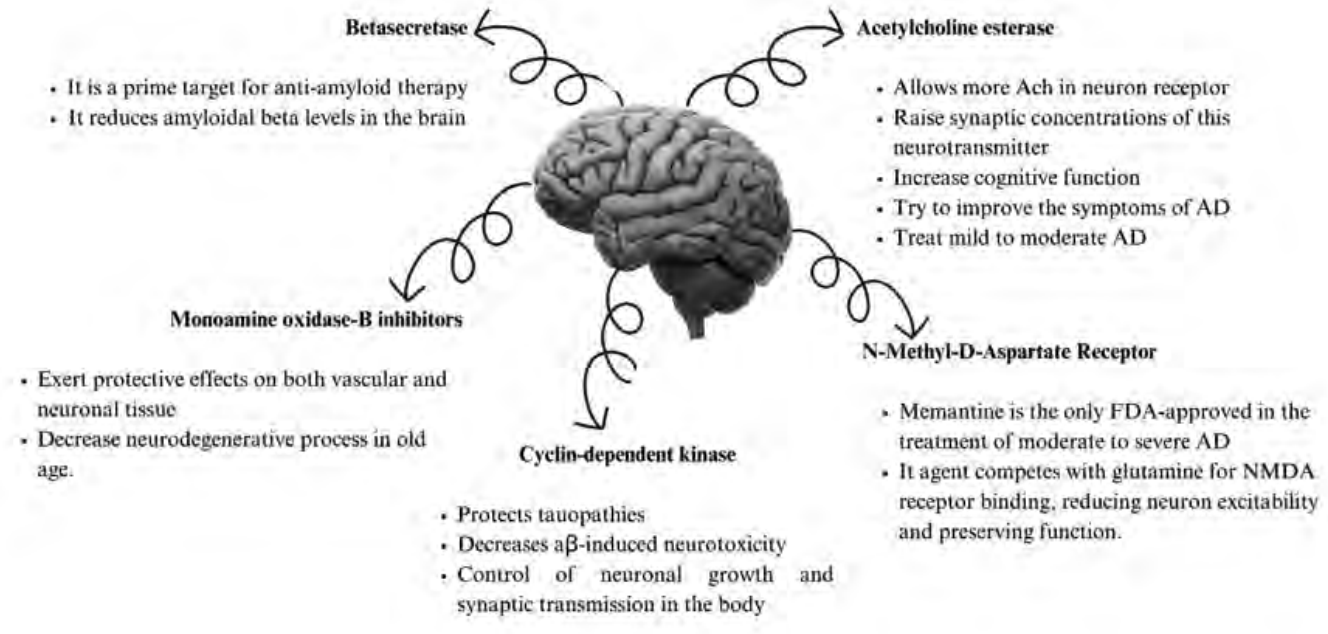


Fig. 2. Benefits of conventional drug target
Рис. 2. Преимущества традиционной мишени для лекарств

when both tau and amyloid proteins are abundant, it may become necessary to use a combination therapy to effectively treat Alzheimer's. The multiple failures of clinical investigations on vaccines and humanised anti-A and anti-tau monoclonal antibodies have raised doubts about this strategy, nevertheless. Recent approval of a novel anti-A monoclonal antibody (Aducanumab) by the US Food and Drug Administration demonstrate that the immunotherapy could be a promising therapeutic strategy. Tau pathology appears to play a major role in AD neurodegeneration and is not only a downstream consequence of the amyloid cascade. As a result, tau-target therapy has received more attention in recent years. Combination therapy is another recent strategy proposed by some authors. Given the complex pathology of AD and potential synergy between Aβ and tau, these combinations of treatments may be more effective than single therapy. Current review article compiled the information about novel and promising drug targets and lead data bases that will help to select appropriate target and design novel drug molecules for the treatment of Alzheimer.

Conflict of interest. The authors declare no conflict of interest.

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